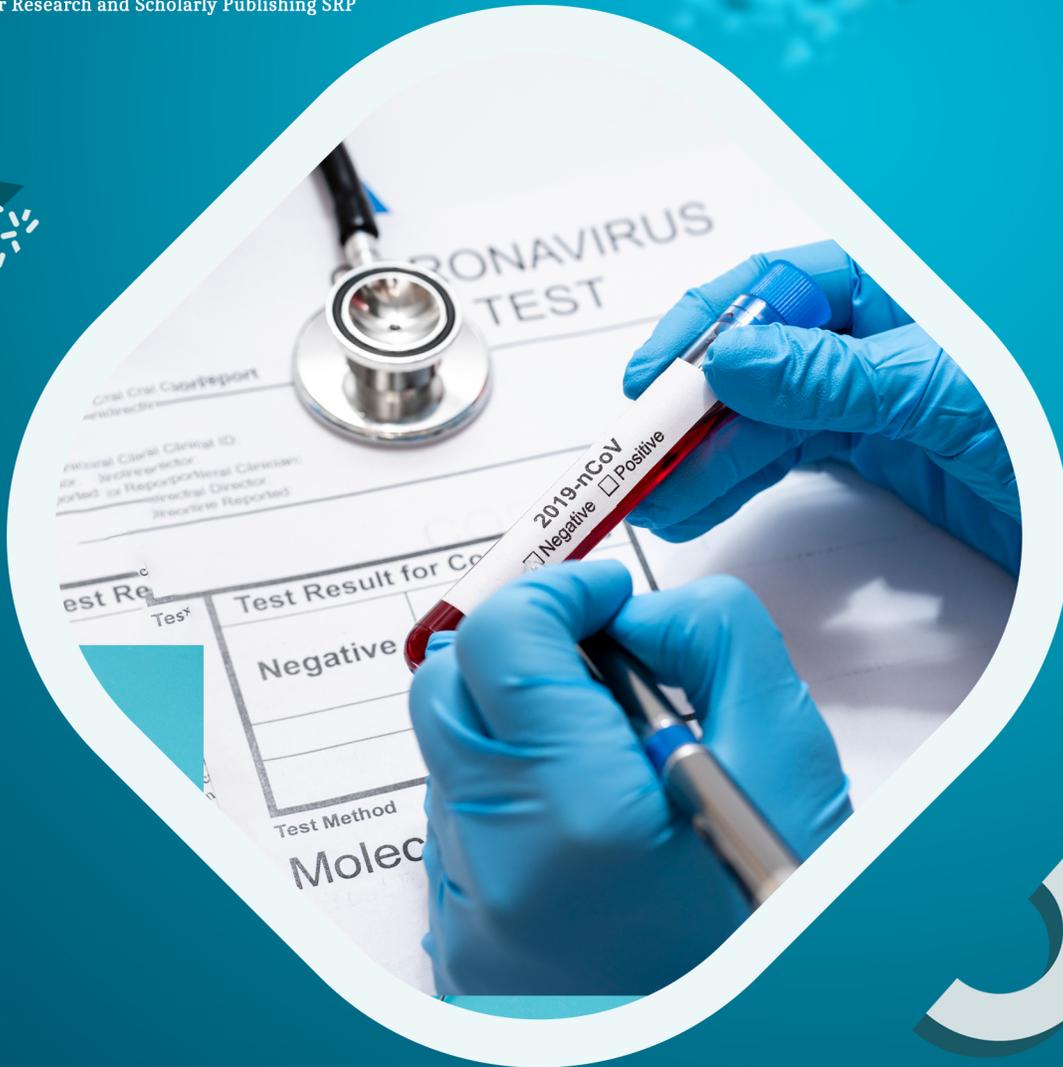




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Journey to Explore COVID-19 Infection

Dr.Dheaa Shamikh Zageer - Dr.Sundus Fadhil Hantoosh - Dr.Mustafa Nema A Ali

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***Journey to Explore COVID-19
Infection***

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CONTENTS

	INTRODUCTION	7
CHAPTER ONE		
SARS CORONAVIRUS-2 GENOMIC STRUCTURE and REPLICATION		
1.	Introductory View	13
2.	Evolutionary Phylogenetic Tree Analysis of Coronaviruses and Taxonomy	17
3.	Origins of SARS-Coronavirus-2	22
4.	Epidemiology	24
5.	Physicochemical Properties	25
6.	SARS-Coronavirus-2 Genome and Viral Cycle	26
CHAPTER TWO		
SYMPTOMS, DIAGNOSIS, ALTERED IMMUNITY , and RISK FACTORS		
1.	Modes of Transmission of COVID-19	56
2.	Symptoms of COVID-19 Infection	63
3.	COVID-19 Pathogenesis and Progression	66
4.	Pathology	71
5.	COVID-19 Pneumonia Phenotypes and Respiratory Treatments	75
6.	Diagnosis	78
7.	Altered Immunity and Convalescent Plasma Treatment in COVID-19 Infection	89
8.	Altered Biomarkers levels in COVID-19 Infection	111
9.	Chest Computed Tomography Scan	118
10.	Renin Angiotensin Aldosterone System	119
11.	Intensive Care Unit Admission in COVID-19 Infection	126
12.	Risk Factors	128
13.	Prevention	134
CHAPTER THREE		
COMPLICATIONS and THERAPY		
1.	Hypokalemia	141
1.1	Renin-Angiotensin Aldosterone System, Hypokalemia, and COVID-19 Infection	144
1.2	Hypokalemia in COVID-19 Infection	146
2.	Antiphospholipid Syndrome	151
2.1	Antiphospholipid Antibodies in COVID-19 Infection	158
3.	Hyperferritinemic Syndromes and Systemic Inflammation in COVID-19 Infection	165
4.	Coagulopathy	175
4.1	Thrombotic Burden in COVID-19 Infection	178
4.1.1	Inflammation	179
4.1.2	Endothelial Activation	180

4.1.3	Severe Hypoxemia	182
4.1.4	Pulmonary Microvascular Thrombosis	184
4.2	D-Dimer Generation in COVID-19 Infection	187
4.3	Role of Microparticles in COVID-19-Induced Coagulopathy	190
4.4	Complement Activation in COVID-19 Infection	192
4.5	Disseminated Intravascular Coagulation	199
4.5.1	Disseminated Intravascular Coagulation in COVID-19 Infection	204
4.6	Venous Thromboembolism	205
4.6.1	Venous Thromboembolism in COVID-19 Infection	207
4.7	Antithrombotic Therapy and COVID-19-Related Coagulopathy	209
5.	COVID Toes	210
6.	Autoimmune Hemolytic Anemia	214
6.1	Autoimmune Hemolytic Anemia in COVID-19 Infection	228
7.	Acute Porphyria	231
7.1	Acute Porphyria in COVID-19 Infection	241
8.	Kawasaki Disease	244
8.1	Kawasaki Disease in COVID-19 Infection	247
9.	Multisystem Inflammatory Syndrome in Children	254
10.	Respiratory Manifestations	268
10.1	Pneumonia	268
10.1.1	Pneumonia in COVID-19 Infection	276
10.2	Pulmonary Hypertension	284
10.2.1	Pulmonary Hypertension in COVID-19 Infection	297
10.3	Acute Respiratory Distress Syndrome	303
10.3.1	Acute Respiratory Distress Syndrome in COVID-19 Infection	326
10.4	Chronic Obstructive Pulmonary Disease	339
10.4.1	Chronic Obstructive Pulmonary Disease in COVID-19 Infection	358
11.	Pancreas Damage	363
11.1	Acute Pancreatitis in COVID-19 Infection	373
12.	Cardiac Injury	379
12.1	Cardiac Troponins	400
12.2	Cardiac Injury in COVID-19 Infection	402
13.	Liver Injury	419
13.1	Liver Injury in COVID-19 Infection	426
14.	Negative Impact of COVID-19 on Female Reproductive System	437
14.1	Angiotensin-Converting Enzyme2 in Ovary	437
14.2	Angiotensin-Converting Enzyme2 in Uterus and Vagina	438
14.3	Angiotensin-Converting Enzyme2 in Pregnancy	438
15.	Male Infertility in COVID-19 Infection	442
16.	Ocular Complications	446
16.1	Ocular Complications in COVID-19 Infection	480
17.	Kidney Injury	486
17.1	Kidney Injury in COVID-19 Infection	492
18.	Neurological Manifestations	501
18.1	Mechanisms of SARS-CoV-2 Infections on The Nervous System	505

	Damage	
18.2	Central Nervous System Manifestations	508
18.2.1	Intracranial Infection	511
18.2.1.1	Symptoms Related to Intracranial Infection in COVID-19 Infection	511
18.2.2	Seizures and Epilepsy	512
18.2.2.1	Seizures and Epilepsy in COVID-19 Infection	514
18.2.3	Acute Myelitis	517
18.2.3.1	Acute Myelitis in COVID-19 Infection	518
18.2.4	Cerebrovascular Disease	519
18.2.4.1	Cerebrovascular Disease in COVID-19 Infection	522
18.2.4.2	Stroke in COVID-19 Infection	522
18.2.5	Encephalopathy	527
18.2.5.1	Encephalopathy in COVID-19 Infection	528
18.2.5.2	Acute Necrotizing Encephalopathy	529
18.2.5.2.1	Acute Necrotizing Encephalopathy in COVID-19 Infection	534
18.2.5.3	Viral Encephalitis	535
18.2.5.3.1	Viral Encephalitis in COVID-19 Infection	538
18.2.5.4	Infectious Toxic Encephalopathy and COVID-19 Infection	539
18.2.6	Postencephalitic Parkinsonism	540
18.3	Peripheral Nervous System Manifestations and Complications	543
18.3.1	Anosmia and Chemosensory Dysfunction	543
18.3.1.1	Anosmia and Chemosensory Dysfunction in COVID-19 Infection	547
18.3.2	Guillain Barre Syndrome	548
18.3.2.1	Guillain Barre Syndrome in COVID-19 Infection	550
18.3.3	Skeletal Muscle Damage	554
18.3.3.1	Skeletal Muscle Damage in COVID-19 Infection	560
18.4	Neuropsychiatric Sequelae of COVID-19 Infection	561
18.4.1	Depression and Anxiety	561
18.4.2	Psychotic Disorders	562
18.5	Long Term Impact	562
18.6	Immunomodulatory Treatments	563
19.	Malnutrition in COVID-19 Infection	564
20.	Complications of COVID-19 Infection in Obese Patients	569
	GLOSSARY	572
	FOR FURTHER READINGS	689

INTRODUCTION

Wuhan was premier epicentre for coronavirus disease 2019 (COVID-19), where first 41 sick individuals experiencing severe pneumonia were reported after exposing to bats and pangolins at Huanan Seafood Wholesale market. Next sick individuals were recorded from same local place by Chen and colleagues. However, several ill individuals in outbreak did not expose to animals, indicates person to person droplets spread is highly possible. Few ill cases of heavy unexplained pneumonia were mentioned from Wuhan, China in December 2019. Bronchoalveolar lavage (BAL, also called bronchoalveolar washing) from a catalogue case was described as novel coronavirus (COVID-19) on 3rd January 2020 by Zhu and colleagues and thereafter World Health Organization (WHO) announced this disease as an epidemic. The disease quickly spread all over the world and the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease [named coronavirus disease 2019 (COVID-19)] a pandemic on 11th March 2020.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel, zoonotic, positive-sense, single-stranded ribonucleic acid (RNA) beta coronavirus (sub-genus *Sarbecovirus*, sub-family *Orthocoronaviridae*). This sub-family also includes severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), and the SARS-like (SL) viruses of bats: bat-SL-CoVZC45 and bat-SL-CoVZXC21. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is from a broad family of ribonucleic acid (RNA) viruses and has a single stand ribonucleic acid (RNA) genome with 32 kilobases length. It is regarded to be the largest ribonucleic acid (RNA) virus genome known to human being. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has an individual characteristic i.e., recombination frequency of positive-strand ribonucleic acid (RNA) is elevated. When host is infected with multiple coronaviruses (CoVs), they combine genetic information from different sources developing high mutation percent which makes main ambiguities during diagnosing and vaccine manufacturin.

Coronavirus disease 2019 (COVID-19) breakout has excessive hard impact on health; many infected individuals are symptomless or show a flu-like illness, but about 15-20% of sick individuals can progress a serious syndrome, presented by interstitial pneumonia with alveolar destruction and severe acute respiratory distress syndrome (ARDS), leading to about 5% of

patients to decrease. Most severe coronavirus disease 2019 (COVID-19) affected patients need intensive care and present an elevated risk of thromboembolic incidents, since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection cause hyperinflammatory immune response purposing endothelium and leading to a pro-coagulation condition, aggravated by hypoxia and prolonged immobilization. These ill individuals can develop pulmonary thrombosis and/or multi-organ dysfunction (MOD) due to thrombotic microangiopathy (TMA).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) binds its viral spike (S) proteins to angiotensin-converting enzyme 2 (ACE2) proteins for cell entry and uses cellular serine protease transmembrane protease serine 2 (TMPRSS2) for spike (S) protein priming. Cell entry receptor, angiotensin-converting enzyme 2 (ACE2), is broadly expressed across body, involving lungs (type II alveolar cells), gastrointestinal tract (GIT, esophageal epithelial cells and absorptive enterocytes of ileum and colon), hepatobiliary system (hepatocytes and cholangiocytes), cardiovascular (CV) system (myocardial cells), renal system (proximal tubule cells and urothelial bladder cells) and pancreas.

Angiotensin-converting enzyme 2 (ACE2) is much expressed in lung alveolar cells (principally type II alveolar cells) and functions in lung protection, and therefore viral binding to this receptor deregulates lung protective path, conferring viral pathogenic ability. Other noticeable loci involve endothelial cells of blood vessels and heart, pericytes, adipocytes, and neural cells.

The virus is believed to disperse primarily from human to human through respiratory droplets shed by infected persons. The primary way of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission is via respiratory droplets and close contact. In a comparatively closed environment, there is a possible way of aerosol transmission when exposed to high concentrations of aerosol for a long period of time. Coronavirus disease 2019 (COVID-19) ill individuals shed droplets temporarily staying in air within a radius of 4 m, through coughing, sneezing, talking, and so forth. This can cause infections in vulnerable persons, after inhalation. Droplets containing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are precipitated on surface objects. After hands of vulnerable persons contaminate by contact, the virus can then pass to mucous membranes of oral cavity, nasal cavity, eyes, and so forth, and cause infection. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been detected in the esophagus, gastrointestinal tract (GIT), and feces of infected persons, indicating

that the virus can replicate and survive in the digestive tract and presuming possibility of fecal-oral transmission. Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) can cause grave complications during pregnancy, and the similar pathogenicity and high degree of sequence homology between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome-coronavirus (MERS-CoV) suggests that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may also cause severe maternal and/or perinatal complications. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was detected in tears and conjunctival secretions. Rhesus macaques can be infected with this virus via conjunctival route. Zhong *et al.* (2020) also isolated novel coronavirus from a urine sample of a coronavirus disease 2019 (COVID-19) patient. Thus, these must also be considered as possible ways of transmission, via contamination of environment. Stating particular transmission routes aid in protecting healthy individuals, and thereby reducing infectious rate in people.

Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel described pathogenic agent, there is no pre-existing immunity to it in human community, also there is no conclusive medicate to interrupt or lower its astonishing breakout. These ambiguities make the situation more hazardous for vulnerable subjects including individuals with immune disturbances, co-existing comorbidity and elderly persons. In spite of novelty of the matter, there are a lot of proposed literature about history, transmission route, urgency of responding, pathogenic potential characteristics and protection plannings but there are still some underlying illnesses remaining not known.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a remarkable impedence to international public health. Although the virus presents to be only partially similar to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), all these viral infections are accountable for intense and potent fatal acute respiratory syndromes in human population. Since number of coronavirus disease 2019 (COVID-19) cases is rising around universe and it is associated with a notable number of mortality and morbidity, it has led to a new world phobia called Coro phobia.

Once reports concerning adult individuals with coronavirus disease 2019 (COVID-19) indicated a high predominance of comorbidities. For example, comorbidities were reported in 26.0% of 672 ascertained patients recorded by the Chinese Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. Most common comorbidities of adults were hypertension (HTN), diabetes mellitus (DM), cardiovascular disease (CVD), and chronic respiratory disease (CRD). The report did not give any information about prevalence of these illnesses in individuals of general population who were a similar age. However, 67.2% of those who deceased from coronavirus disease 2019 (COVID-19) had a comorbidity and this noticeable dominance supposes that comorbidity is a risk factor for poor prediction. Other risk factors lead to unwell consequences involve older age, pregnant, newborns, smoking, chronic obstructive pulmonary disease (COPD), lower lymphocyte counts, chronic kidney disease (CKD), malignant diseases, and raised D-dimer (DD) are possibly to develop more serious illness frequently necessitating nursing from an intensive care unit (ICU). These comorbidities solely or in combination with age were mentioned to be bound to unwell prediction. Among elderly ill individuals with medical comorbidities, coronavirus disease 2019 (COVID-19) is often aggravated. Moreover, males show a disproportionately noticeable number of decesses in bodies from China and Italy. United States Centers for Disease Control and Prevention (CDC) also involves immunocompromising statuses, severe obesity (body mass index ≥ 40), and liver disease as prime risk factors for heavy illness. Risk factors are associated with unwell predictions [decease and admission to intensive care unit (ICU)]. Persons with A blood group have a notably higher risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in comparison with non-A blood groups, whereas O blood group has a noticeably lower susceptibility for this infection compared with non-O blood groups. According to case analysis of 4,707 children with coronavirus disease 2019 (COVID19) in China and United States, it was found that rate of infant coronavirus disease 2019 (COVID19) was comparatively higher (accounting for 15% of the children), and 10.6% of the infant coronavirus disease 2019 (COVID19) was sorely or critically ill, which was much higher than average level of child group (5.8%). It is supposed that infants are more susceptible to coronavirus disease 2019 (COVID19) and this illness is more dangerous. Although incidence is higher in men than in women, the difference is not statistically noticeable. However, based on meta-analysis of 77,932 sick individuals, it was affirmed that morbidity, severity, and deaths of males were notably higher than females.

First reports from China showed incubation period of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was between 3 to 7 days and on occasion 2 weeks. The longest incubation period observed was 12.5 days .

A study recorded the actual signs and symptoms of coronavirus disease 2019 (COVID-19) which included fever (98.6%), fatigue (69.6%), dry cough (59.4%), anorexia (39.9%), myalgia (34.8%), dyspnea (31.2%), expectoration (26.8%), pharyngeal pain (17.4%), diarrhea (10.1%), nausea (10.1%) dizziness (9.4%), headache (6.5%), vomiting (3.6%) and abdominal pain (2.2%). Occurrence of pharyngeal pain, dyspnea, dizziness, abdominal pain and anorexia was more in intensive care unit (ICU) sick individuals. Respiratory rate, heart rate and mean arterial pressure (MAP) were comparable between sick individuals gaining intensive care unit (ICU) care and non-intensive care unit (ICU) sick individual. Common complications recognized were acute respiratory distress syndrome (ARDS) (19.6%), arrhythmia (16.7%), septic shock (8.7%), acute cardiac injury (ACI)(7.2%) and acute kidney injury (AKI) (3.6%). Sick individuals who necessitate intensive care unit (ICU) care were more frequently had these complicated conditions. Other complicated issues such as disseminated intravascular coagulation (DIC) and rhabdomyolysis were noticed. In addition, it was revealed that coronavirus disease 2019 (COVID-19) induced liver injury. Among sick individuals with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, pneumonia, respiratory failure, and acute respiratory distress syndrome (ARDS) are frequently faced complicated conditions. Although pathophysiology underlying severe coronavirus disease 2019 (COVID19) is still unsatisfactorily comprehended, accumulating proof discuss for hyperinflammatory syndrome causing fulminant and fatal cytokines production associated disease aggravity and unwell result.

Particular laboratory features have also been associated with worse results. These involve: lymphopenia, elevated liver enzymes, elevated lactate dehydrogenase (LDH), elevated inflammatory markers [e.g., C-reactive protein (CRP), ferritin], elevated D-dimer (DD) (>1 mcg/mL), elevated prothrombin time (PT), elevated troponin (Tn), and elevated creatine phosphokinase (CPK).

A study revealed that ill individuals with serious illness had been mentioned to have higher viral ribonucleic acid (RNA) levels in respiratory specimens than those with milder illness, although

this association was not seen in a different study that measured viral ribonucleic acid (RNA) in salivary samples.

It was recorded that among ill individuals who healed from severe acute respiratory syndrome coronavirus (SARS-CoV) infection, 68% continued experiencing anomalies of lipid metabolism at 12-years follow-up; cardiovascular (CV) disturbances were found in 40% and changed glucose (Glc) metabolism in 60%. Similar findings have also been recorded in ill individuals healing from other respiratory tract infections (RTIs). Taking this into account, observant follow-up of those healing from current coronavirus disease 2019 (COVID19) would be necessary to comprehend long-term impact of this illness and also to protect these ill individuals from future cardiovascular disease (CVD).

With limited therapeutic options, protection by social distancing seems to be backbone to lessen coronavirus disease 2019 (COVID-19) propagation. Virus transfer can be lowered in different methods described in World Health Organization (WHO) protocol. This involves, keeping secured social distance, regular hand washing for 20 seconds, using 60% alcohol hand rub, not to touch face, nostrils or mouth, evading congested locuses and public events. Countries have followed various measures to decrease viral transference and most of countries in the universe have imposed 'Lockdown' to reduce viral transference. As it is a virus in a big particle, a surgical face mask must give appropriate protection against inhalation of the virus. N-95 masks must be conserved to health care individuals. Personal Protective Equipment (PPE) should be worn according to institutional policy. All sick individuals with a history of transport to affected places must be screened for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) even if these passengers are asymptomatic. Persons with high temperature, dry cough, intense tiredness, diarrhoea or other not common symptoms with recent travel history must be subjected to lab exam for coronavirus disease 2019 (COVID-19). Nations need to make and modify their protection, lab examining and management strategies from period to period depending on Guidelines issued by World Health Organization (WHO).

CHAPTER ONE

SARS CORONAVIRUS-2 GENOMIC STRUCTURE and REPLICATION

1.Introductory View

Coronaviruses (CoVs) are a broad family of viruses that can cause a range of illnesses from common cold to serious illnesses such as Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV), which are reported causing serious respiratory and intestinal illnesses. Coronaviruses (CoVs) can be isolated from different animal species. These include fowls, domestic animals, and mammals such as camels, harpies, masked palm civets, mice, pooches, and cats. The diffused distribution and contractivity of coronavirus (CoV) emerge it a noticeable pathogenic agent. Human pathogenic subtypes of coronavirus (CoV) are associated with moderate clinical presentations. However, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two notable exemptions. In 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) was earlier detected in Saudia Arabia. It was responsible for 2,494 affirmed ill individuals, which led to 858 deceases. In 2002, a subtype of betacoronavirus (beta-COV) hastily propagated across Guangdong, China. This beakout resulted in 8,000 infections and 774 deaths in 37 countries. In late December 2019, sick individuals symptomizing with cough, fever, and dyspnea (i.e., difficult in breathing) with acute respiratory distress syndrome (ARDS) attributable to an obscured microbial infection were mentioned in Wuhan, China. Virus genome sequencing of five ill persons with pneumonia hospitalized from December 18 to December 29, 2019, revealed presence of a priorly unbeknown betacoronavirus (β -CoV) strain in all these ill persons. This isolated novel betacoronavirus (β -CoV) shows 88% symmetry to sequence of two harpy-derived severe acute respiratory syndromes (SARS)-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, and about 50% likeness to sequence of Middle East respiratory syndrome coronavirus (MERS-CoV). The International Committee on Taxonomy of Viruses named it as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This coronavirus (CoV), was initially named as the 2019novel coronavirus (2019-nCoV) on 12 January 2020 by World Health Organization (WHO). World Health Organization (WHO) officially named illness as coronavirus disease 2019 (COVID19) and Coronavirus Study Group (CSG) of the International Committee proposed to name the new coronavirus as severe acute

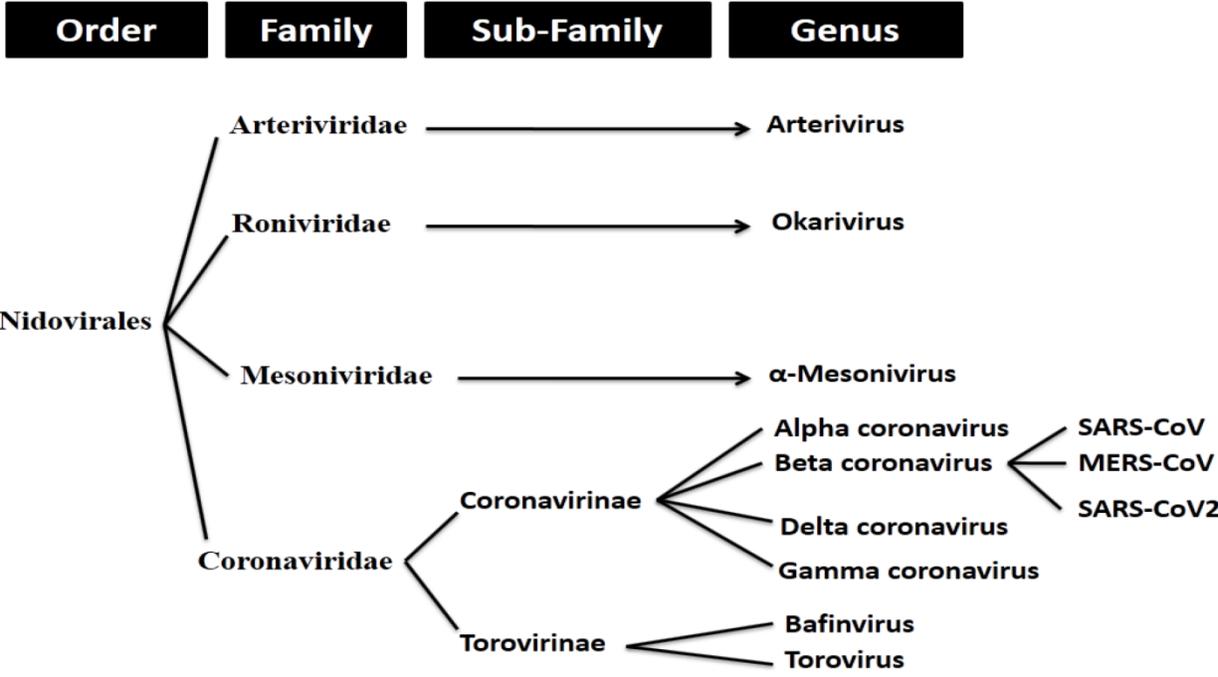
respiratory syndrome coronavirus-2 (SARS-CoV-2), both issued on 11 February 2020. The Chinese scientists hastily isolated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from an infected individual within a short time on 7 January 2020 and sequenced genome severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Recurring emergence and breakouts of coronaviruses (CoVs) indicate a public health impedence. This suggests possibility of animal-to-human and human-to-human transference of newly emerging coronaviruses (CoVs). Continuing alterations in ecology and weather lead to arising of such infections in time ahead. The virus is thought to be transferred from animals to humans at beginning, and then from humans to humans through airborne droplets of infected ill persons' fluids, which has made the virus to infect and kill thousands of commune and to emergence international interest.

Coronaviruses (CoVs) are a broad family of ribonucleic acid (RNA) viruses that are present diversifiedly in animal species. They are recognized to cause illnesses of respiratory, hepatic, nervous system, and gastrointestinal (GI) systems in human beings . Under electron microscope, they realize a crown-like appearance due to the presence of envelope spike (S) glycoproteins. Coronaviruses (CoVs) belong to subfamily Coronavirinae in the family of Coronaviridae of the order Nidovirales. The Coronaviridae family can be classified into four genera of alphacoronavirus (alpha-COV), betacoronavirus (beta-COV), deltacoronavirus (delta-COV), and gammacoronavirus (gamma-COV). Gene characterization has aided describe that harpies and rodents are the gene origin of alphacoronavirus (alpha-COV) and betacoronavirus (beta-COV). On the other hand, avian species are deemed as genetic origins of deltacoronavirus (delta-COV) and gammacoronavirus (gamma-COV). Within the genus beta-coronavirus (β -CoV), four lineages (A, B, C, and D) each with a distinguished set of accessory genes are commonly recognized. Lineage A includes HCoV-OC43 and HCoV-HKU1, beta-coronavirus 1 (more commonly known as bovine coronavirus, BCoV), murine coronavirus (MHV); Lineage B involves severe acute respiratory syndrome-related SARS-CoV, SARS-CoV-2, and different species got back from harpies; Lineage C includes Tylonycteris bat coronavirus HKU4 (BtCoV-HKU4), Pipistrellus bat coronavirus HKU5 (BtCoV-HKU5). Since April 2012, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) has arisen as a novel member in lineage C of the betacoronaviruses (β -CoVs), mostly related to bat coronaviruses HKU4 and HKU5. Middle East Respiratory Syndrome coronavirus (MERS-CoV) is premier betacoronavirus (β -CoV)

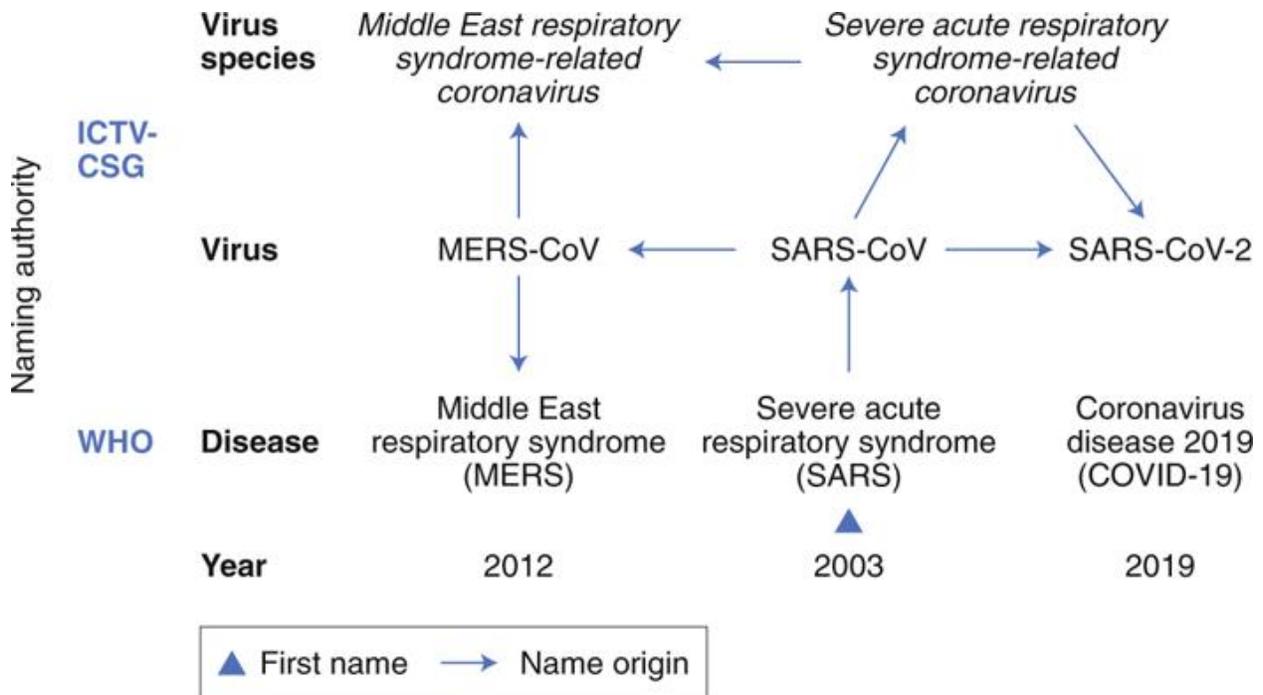
lineage C member isolated from human beings. Lineage D involves Rousettus bat coronavirus HKU9 (BtCoV-HKU9), which has only been detected in bats.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a β -coronavirus, which is enveloped non-segmented positive-sense ribonucleic acid (RNA) virus (subgenus sarbecovirus, Orthocoronavirinae subfamily).

Coronaviruses (CoVs) are accountable for 5-10% of serious respiratory infectious illnesses . It has been estimated that 2% of commune are deemed healthy carriers of these viral agents. Some common human coronaviruses (CoVs) involve HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63. In the immunocompetent, these coronaviruses (CoVs) clinically present with self-limiting respiratory infections and common colds. In elderly and immunocompromised, they can involve the lower respiratory tracts. Other human coronaviruses (CoVs) such as Middle East Respiratory Syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome-coronavirus (SARS-CoV), and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) present with pulmonary and extra-pulmonary characteristics. Genomic identification researches of the new strain of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have shown an 89% nucleotide match with bat SARS-like CoVZXC21 . There is also an 82% nucleotide match with the human severe acute respiratory syndrome (SARS) virus . Therefore, these findings think up the basis for the new strain to be called severe acute respiratory syndrome coronavirus-2 (SARS CoV-2).



Figure(1):Classification of coronaviruses [Rehman S.;Shafique L.; Ihsan A.; Liu Q. (2020). Evolutionary trajectory for the emergence of novel coronavirus SARS-CoV-2. Pathogens, 9(3), 240]

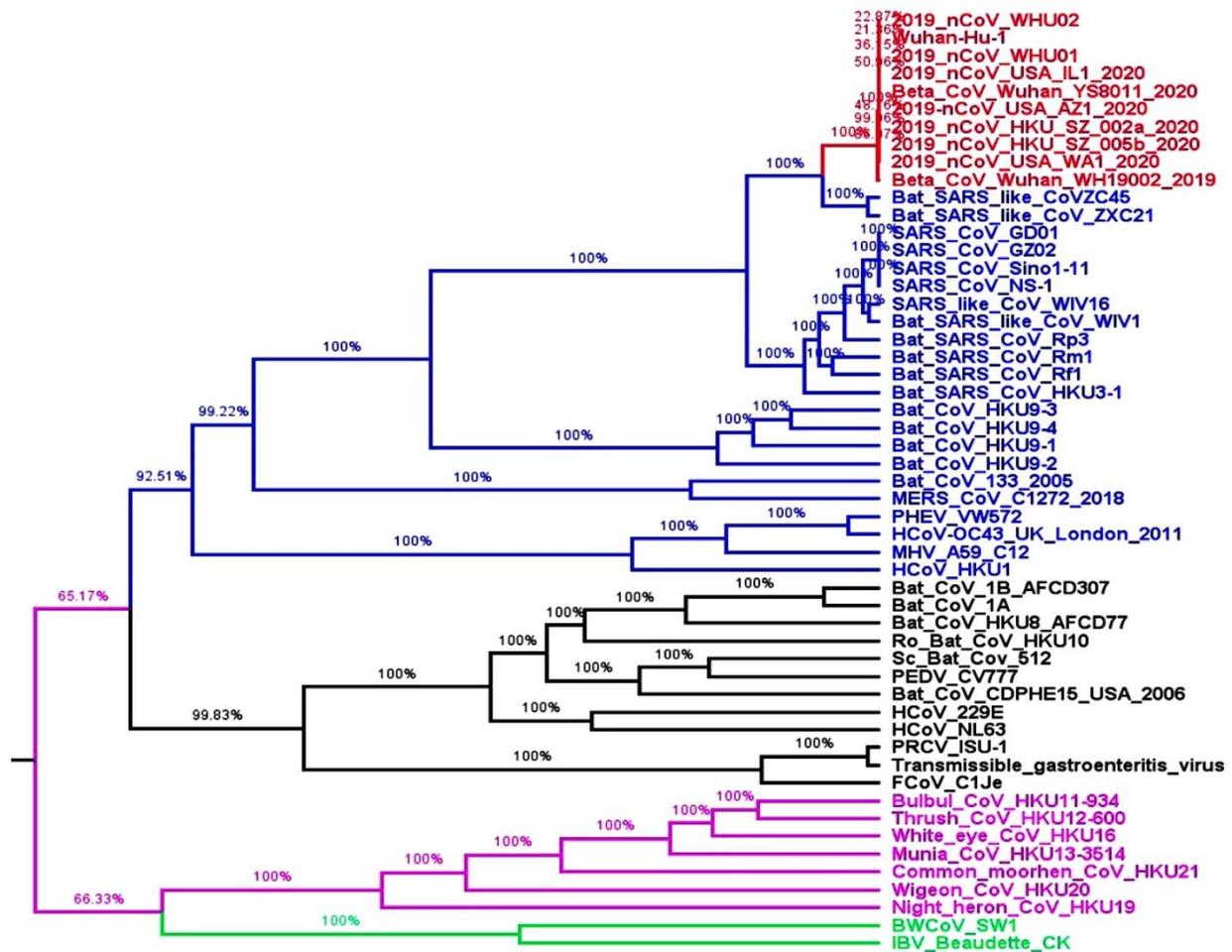


Figure(2): The species of severe acute respiratory syndrome coronaviruses and related diseases [Coronaviridae Study Group of International Committee on Taxonomy of Viruses. (2020). The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nature Microbiology*, 5:536-544]

2. Evolutionary Phylogenetic Tree Analysis of Coronaviruses and Taxonomy

It is the ultimate precedence of scientific group to reduce public health hazardous through tracking down the origin and natural denizens of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) to restrict human-to-human and cross-species transference. The phylogenetic tree results demonstrate that all coronaviruses (CoVs) account for breakout of concentrated pneumonia belong to genera *Betacoronavirus*. All severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) clade grouped with cluster of SARS/SARS-like CoVs, with harpy coronaviruses (CoVs) HKU9-1, HKU9-2 HKU9-3 and HKU9-4 as an immediate predecessor. The interior shared neighbors include SARS-CoV NS-1, SARS-CoV Sino1-11, SARS-CoV GZ02 and SARS-CoV GD01, and they were the human-infecting coronaviruses (CoVs). The whole genome-based phylogenetic analysis revealed that two Bat SARS-like CoVs (ZXC21 and ZC45) were the most affines of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). Most of the inner and outer joint neighbors of severe acute respiratory syndrome coronavirus-

2 (SARS-CoV-2) were found to have bats as their natural pool including Bat SARS-CoV WIV1 in *Rhinolophus sinicus*, Bat SARS-CoV HKU3-1, and Bat CoV HKU9-3 in *Rousettus* bats. In consequence, harpy would be proper native host of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), thus probable intermediate host for transference cascade used by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from harpies to human beings would be the same as that utilized by other severe acute respiratory syndrome-coronavirus (SARS-CoV).

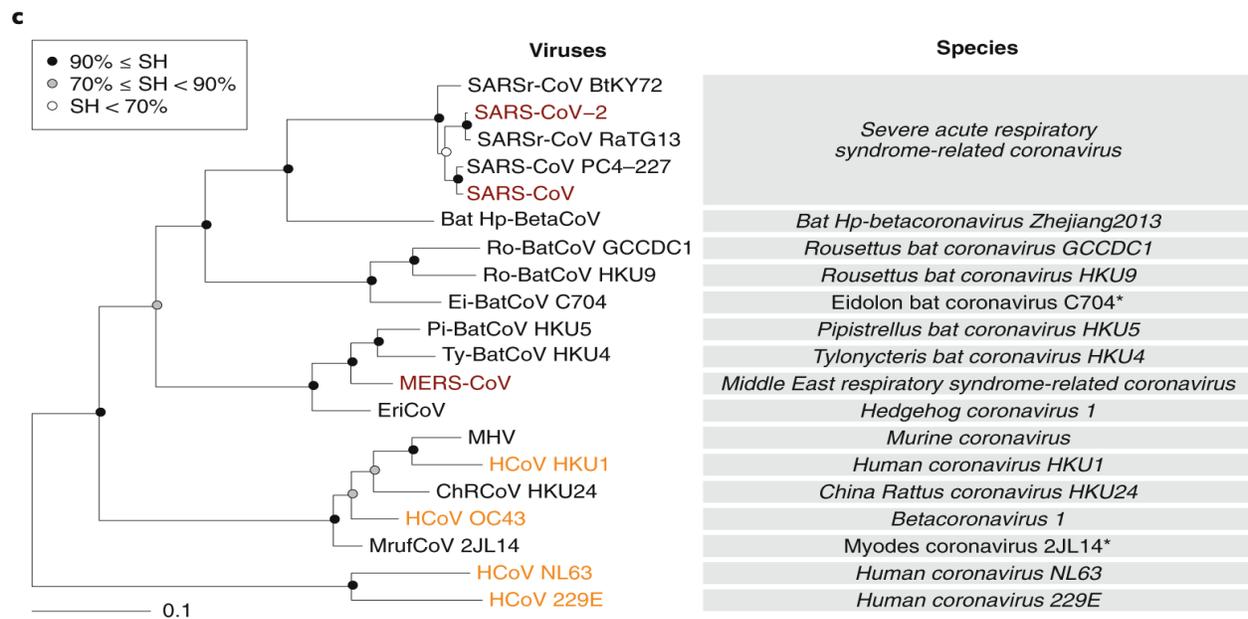
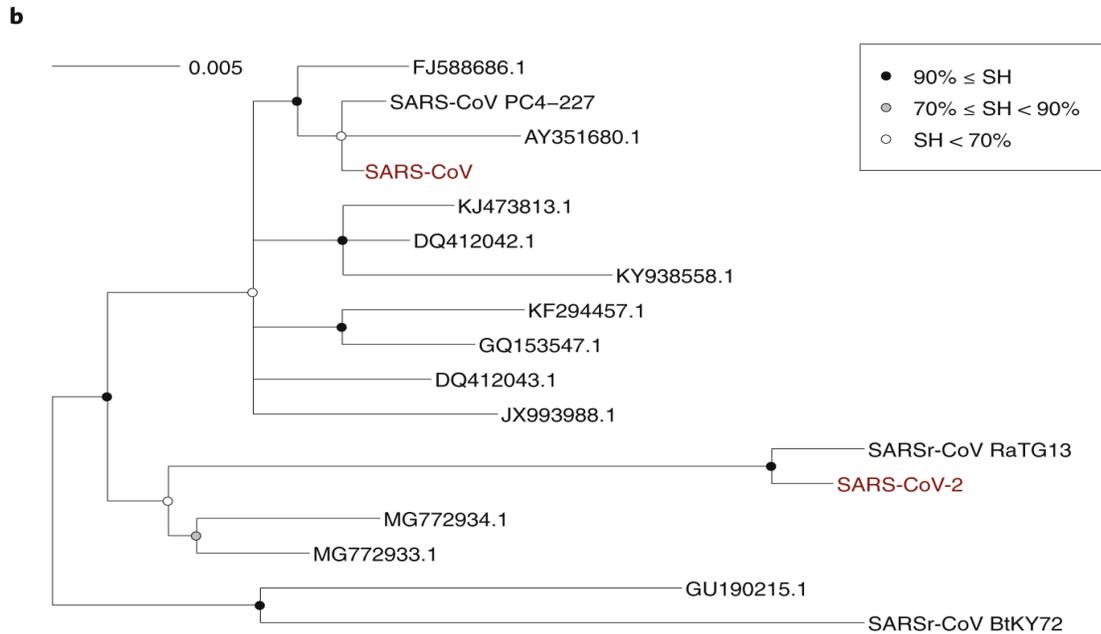
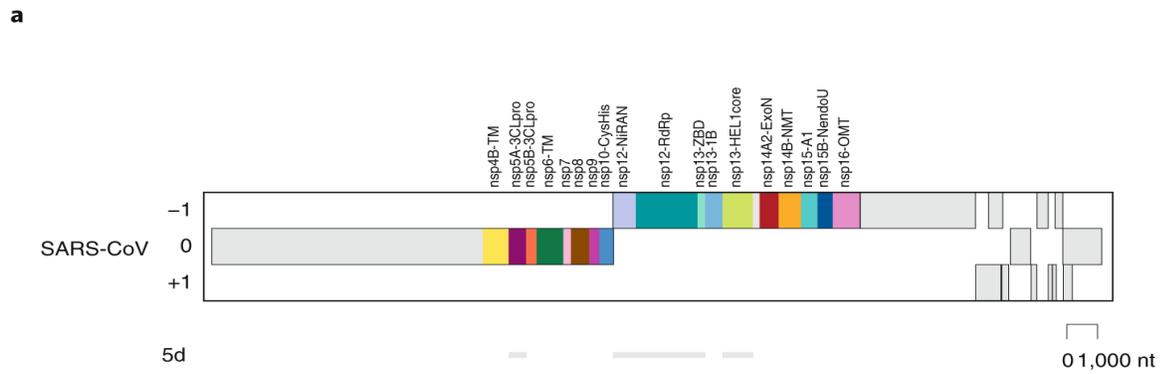


Figure(3): Evolutionary phylogenetic tree analysis of coronaviruses [Rehman S.;Shafique L.; Ihsan A.; Liu Q. (2020). Evolutionary trajectory for the emergence of novel coronavirus SARS-CoV-2. Pathogens, 9(3), 240]

Figure (3) shows evolutionary phylogenetic tree analysis of Coronaviruses: whole-genome sequences built on phylogenetic tree of coronaviruses (CoVs) was structured with maximum-likelihood method using BEAST with GTR+I+G as nucleotide substitution model with an

applied posterior probability value of 0.5. Branches with different colors represent various genera of coronaviruses; black, alpha coronavirus, blue, beta coronavirus; red, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); green, delta coronavirus; purple, gamma coronavirus.

In figure (4) below in part (a) it reveals concatenated multiple sequence alignments (MSAs) of the protein domain combination used for phylogenetic and DEmARC analyses of the family *Coronaviridae*. Shown are the locations of replicative domains reserved in order *Nidovirales* in relation to several other ORF1a/b-encoded domains and other main open reading frames (ORFs) in severe acute respiratory syndrome-coronavirus (SARS-CoV) genome. 5d, 5 domains: nsp5A-3CLpro, two beta-barrel domains of the 3C-like protease; nsp12-NiRAN, nidovirus RdRp-associated nucleotidyltransferase; nsp12-RdRp, RNA-dependent RNA polymerase; nsp13-HEL1 core, superfamily 1 helicase with upstream Zn-binding domain (nsp13-ZBD); nt, nucleotide. In figure(4) below in part (b) it shows maximum-likelihood tree of severe acute respiratory syndrome coronavirus (SARS-CoV) was reconstructed by IQ-TREE v.1.6.1 using 83 sequences with best being the right evolutionary model. Thereafter, the tree was cleared out from most similar sequences and midpoint-rooted. Branch support was evaluated using the Shimodaira–Hasegawa (SH)-like approximate likelihood ratio test with 1,000 replicates. GenBank IDs for all viruses except four are shown; SARS-CoV, AY274119.3; SARS-CoV-2, MN908947.3; SARSr-CoV_BtKY72, KY352407.1; SARS-CoV_PC4-227, AY613950.1. Also in figure (4) below in part (c) shows an IQ-TREE maximum-likelihood tree of single virus representatives of thirteen species and five representatives of the species severe acute respiratory syndrome-related coronavirus of the genus *Betacoronavirus*. The tree is rooted with HCoV-NL63 and HCoV-229E, representing two species of the genus *Alphacoronavirus*. Purple text highlights zoonotic viruses with varying pathogenicity in human beings; orange text points to common respiratory viruses that circulate in human beings. Asterisks indicate two coronavirus species whose demarcations and names are pending consent from the International Committee on Taxonomy of Viruses (ICTV) and, thus, these names are not italicized.



Figure(4):Phylogeny of coronaviruses (www.google.com)

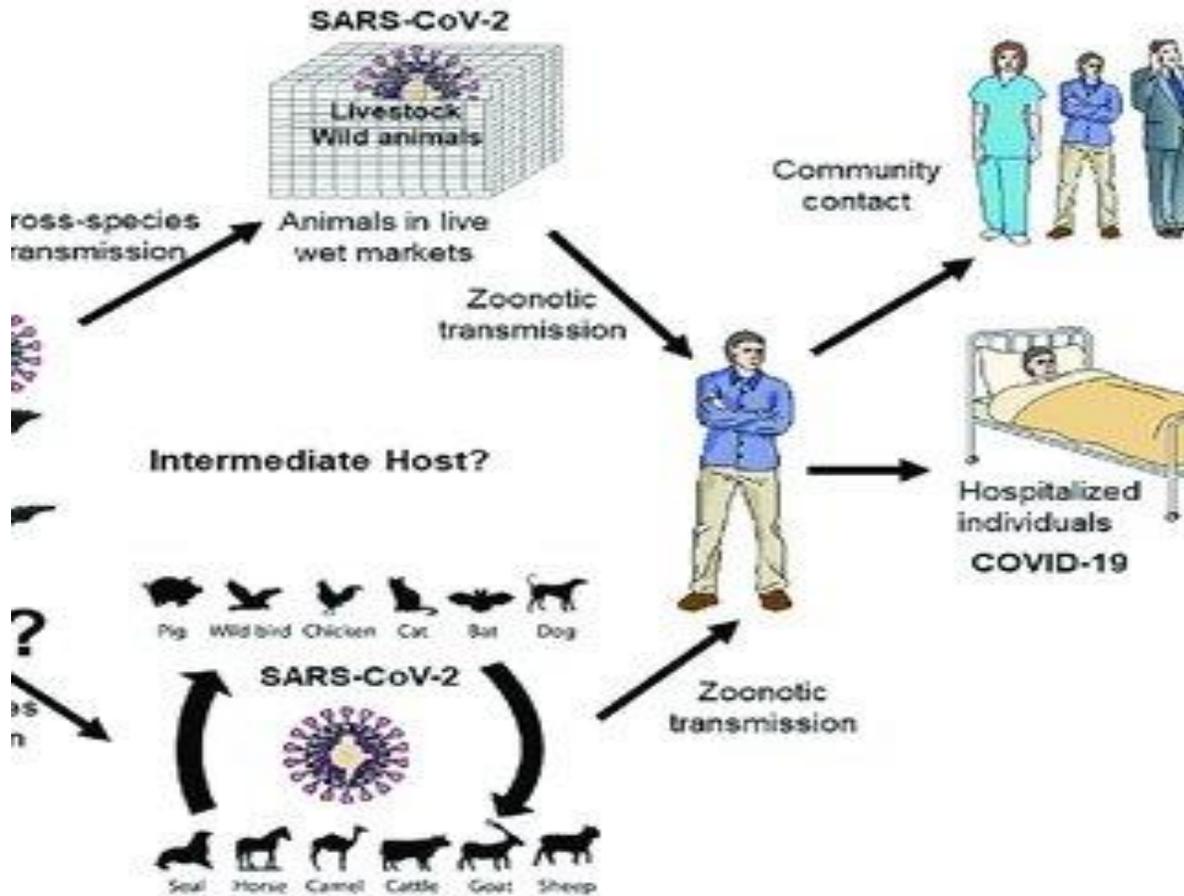
At first, classification of coronaviruses (CoVs) was widely depended on serological (cross-) reactivities to the viral spike (S) protein, but is now built on comparative sequence analyses of replicative proteins. The choice of proteins and the methods used to analyze them have progressively evolved since the beginning of this century. The Coronaviridae Study Group (CSG) currently analyses 3CLpro, NiRAN, RdRp, ZBD and HEL1, two domains less than formerly served in analyses conducted between 2009 and 2015. Based on our current knowledge, these five crucial domains are only ones conserved in all viruses of order *Nidovirales*. They are thus used for classification by all International Committee on Taxonomy of Viruses (ICTV) nidovirus study groups (coordinated by the NSG).

Category	Coronaviruses	Humans	Divergence
Realm	<i>Riboviria</i>		●
Order	<i>Nidovirales</i>	Primates	●
Suborder	<i>Cornidovirineae</i>		●
Family	<i>Coronaviridae</i>	Hominidae	●
Subfamily	<i>Orthocoronavirinae</i>	Homininae	●
Genus	<i>Betacoronavirus</i>	<i>Homo</i>	●
Subgenus	<i>Sarbecovirus</i>		●
Species	<i>Severe acute respiratory syndrome-related coronavirus</i>	<i>Homo sapiens</i>	●
Individuum	SARS-CoVUrbani, SARS-CoVGZ-02, Bat SARS CoVRf1/2004, Civet SARS CoVSZ3/2003, SARS-CoVPC4-227, SARSr-CoVBtKY72, SARS-CoV-2 Wuhan-Hu-1, SARSr-CoVRatG13, and so on.	Dmitri Ivanovsky, Martinus Beijerinck, Friedrich Loeffler, Barbara McClintock, Marie Curie, Albert Einstein, Rosalind Franklin, Hideki Yukawa, and so on.	●

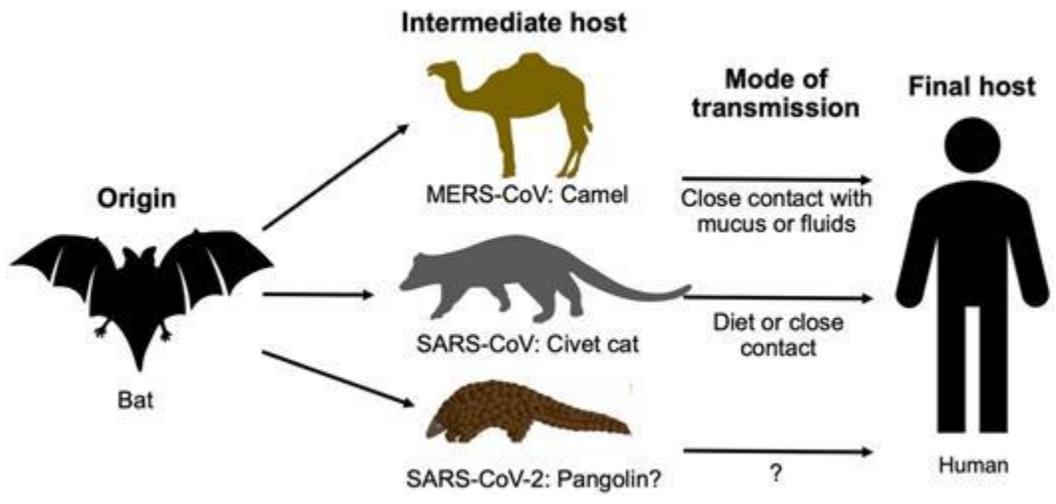
Figure(5): Taxonomy of selected coronaviruses [Coronaviridae Study Group of International Committee on Taxonomy of Viruses. (2020). The species severe acure respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature Microbiology, 5:536-544]

3.Origins of SARS-Coronavirus-2

All coronaviruses (CoVs) that have caused illnesses to human beings have had animal descents- generally either in harpies or rodents. Prior breakout of betacoronaviruses (β -CoVs) in human beings involved direct exposing to animals other than harpies. In case of severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV), they were transferred directly to human beings from civet cats and dromedary camels, respectively. Severe acute respiratory syndrome (SARS)-related coronaviruses are enveloped by spike (S) proteins that contain a variable receptor-binding domain (RBD). This receptor-binding domain (RBD) attaches to angiotensin-converting enzyme-2 (ACE-2) receptor found in heart, lungs, kidneys, and gastrointestinal tract (GIT) thus easing viral entrance into target cells. On basis of genomic sequencing, the receptor-binding domain (RBD) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) seems to be a mutated version of its most closely related virus, RaTG13, specimened from harpies (*Rhinolophus affinis*). It is, therefore, thought that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) also had its origin from harpies and, after mutating, was able to contract other animals. Mutation increased receptor-binding domain (RBD) affinity to angiotensin-converting enzyme 2 (ACE-2) in human beings, but also other animals such as ferrets and Malayan pangolins (*Manis javanica*; a long-snouted, ant-eating mammal sold illegally for use in traditional Chinese medicine), but also decreased receptor-binding domain (RBD) affinity to angiotensin-converting enzyme 2 (ACE-2) in rodents and civets. Pangolin is deemed to be intermediate host of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). There was coming early speculation that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) arose from a manmade manipulation of an existing coronavirus, but there is no proof to support such a theory. In fact, it was presumed that particular mutation that was found in the receptor-binding domain (RBD) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is different to what would have been predicted on basis of precedingly used genetic systems. Authors, stated that “it is currently impossible to prove or disprove the other theories of [the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)]origin”.



Figure(6): Origins of SARS-CoV-2 (www.google.com)



Figure(7): Origins of MERS-CoV, SARS-CoV and SARS-CoV-2 (www.google.com)

4.Epidemiology

Coronavirus disease (COVID-19) was detected in Wuhan, China, in December 2019. Epidemic of unknown acute respiratory tract infection surged in the beginning in Wuhan, China, since 12 December 2019, possibly related to a seafood market. Several articles suggested that harpy may be the possible reservoir of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). However, there is no proof yet that the source of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was from the seafood market. Harpies are the natural reservoir of a broad variety of coronaviruses (CoVs), involving severe acute respiratory syndrome-coronavirus (SARS-CoV)-like and Middle East Respiratory Syndrome coronavirus (MERS-CoV)-like viruses. Upon virus genome sequencing, coronavirus disease (COVID-19) was analyzed throughout the genome to Bat CoV RaTG13 and exerted 96.2% thorough genome sequence identity, suggesting that bat coronavirus (CoV) and human severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) might partake same ancestor, although harpies are not obtainable for sale in this seafood market. Besides, protein sequences alignment and phylogenetic analysis showed that similar residues of receptor were observed in many species, which gave more possibility of alternate intermediate hosts, such as tortoise, pangolin and appetizers. Human-to-human transference of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is incident mainly between family members, including akins and mates who were in intimate contact with ill individuals or incubation carriers. It is mentioned that 31.3% of ill individuals recently tripped to Wuhan and 72.3% of ill individuals contacting with persons from Wuhan among the ill persons of nonresidents of Wuhan. Transmission between healthcare workers happened in 3.8% of coronavirus disease 2019 (COVID-19) sick persons, issued by the National Health Commission of China on 14 February 2020. On contrary, transportation of severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) is documented to occur mainly through nosocomial transference. Contagions of healthcare workers in 33–42% of severe acute respiratory syndrome (SARS) sick persons and transference between sick persons (62–79%) was most common way of contagion in Middle East respiratory syndrome coronavirus (MERS-CoV) sick persons. Direct contract with intermediate host animals or eating wild animals was suspected to be major way of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transference. However, the

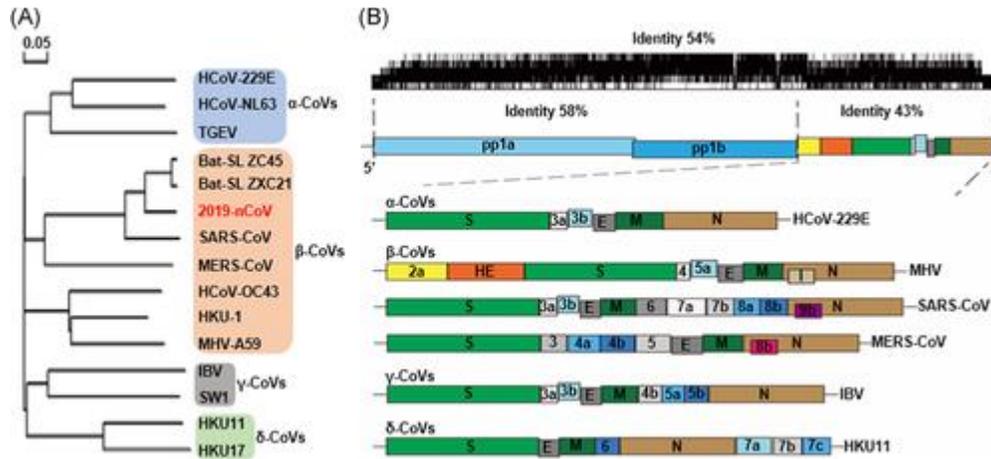
source(s) and transmission routine(s) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) remain elusive.

With no efficient control measures, the illness has propagated across the globe with more than one hundred countries reported asserted infected persons. Having realized that the number of new affirmed sick individuals outside China has elevated 13-folds, the World Health Organization eventually decided to characterize coronavirus disease (COVID-19) as a pandemic on 11 March 2020 and ordered member states to tabulate their emergency response mechanisms.

5. Physicochemical Properties

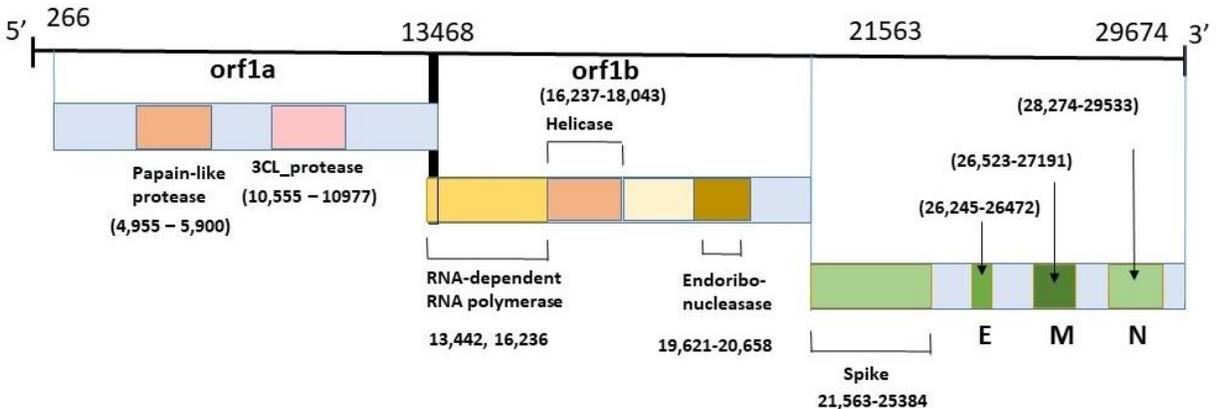
The virus particle has a diameter of 60~100 nm and takes shape round or oval. Most of data about physicochemical properties of coronaviruses (CoVs) comes from severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be inactivated by ultraviolet (UV) or heated at 56°C30min, and also sensitive to most disinfectants such as diethyl ether, 75% ethanol, chlorine, peracetic acid, and chloroform. It has been mentioned that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 h after application to these surfaces. On cardboard, half-life of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was longer than that of severe acute respiratory syndrome-coronavirus (SARS-CoV) and the longest viability of both viruses was on stainless steel and plastic.

6.SARS-Coronavirus-2 Genome and Virus Cycle



Figure(8):The genomic structure and phylogenetic tree of coronaviruses [Chen Y.; Liu Q.; Guo D. (2020). Emerging coronaviruses: genome structure, replication, and pathogenesis. Journal of Medical Virology. 92(4):418-4231

Figure (8) shows genomic structure and phylogenetic tree of coronaviruses (CoVs). A, phylogenetic tree of representative coronaviruses (CoVs), with new coronavirus 2019-nCoV highlighted in red. B, genome structure of four genera of coronaviruses. Pp1a and pp1b represent the two long polypeptides that are processed into 16 nonstructural proteins. S, E, M, and N indicate the four structural proteins spike, envelope, membrane, and nucleocapsid. 2019-nCoV, 2019 novel coronavirus; CoVs, coronavirus; HE, hemagglutinin-esterase. Viral names: HKU, coronaviruses identified by Hong Kong University; HCoV, human coronavirus; IBV, infectious bronchitis virus; MHV, murine hepatitis virus; TGEV, transmissible gastroenteritis virus.



Figure(9): Coronavirus genome (www.google.com)

All coronaviruses (CoVs) are pleomorphic ribonucleic acid (RNA) viruses peculiarly containing crown-shape peplomers with 80-160 nm in size and 27-32 kb [making it the largest RNA

genome of the ribonucleic acid (RNA) virus family] and with positive polarity enclosed in a nucleocapsid of helical symmetry. Coronaviruses (CoVs) are viruses whose genome structure is best known among all ribonucleic acid (RNA) viruses. Coronaviruses (CoVs) have an unsegmented, single-stranded (ss) positive-sense ribonucleic acid (RNA) genome. Human coronavirus (CoV) particles are usually globular and decorated with large (~20 nm), club- or petal-shaped surface projections [the peplomers or spikes (S)], which confer an image looking like the solar crown or corona on electron micrographs of infected tissues and hence to the family name. Coronaviruses (CoVs) genomes are usually composed of a 5'-methylguanosine cap at beginning, a 3'-poly-A tail at end, and in between there are 6-10 genes. It is shown that genome of coronaviruses (CoVs) has a varying number (6–11) of open reading frames (ORFs). The order of their genes is typically highly conserved, with first one being replication-and transcription-related, and the rest, structural. The 5'-most gene of the coronavirus (CoV) genome, gene1, lodges about two-thirds of the genome and is composed of two large overlapping open reading frames (ORFs), open reading frame 1a (ORF1a) and open reading frame 1b (ORF1b), with a ribosomal frameshifting signal at the junction of the two open reading frames (ORFs). The first open reading frames (ORFs) of coronaviruses (CoVs), open reading frame 1a/b (ORF1a/b), encode 16 nonstructural proteins (nsps) [nonstructural proteins (nsp1-16)], except *Gammacoronavirus* that lacks nonstructural protein 1 (nsp1). There is a –1 frameshift between open reading frame 1a (ORF1a) and open reading frame 1b (ORF1b), leading to production of two polypeptides: polyprotein 1a (pp1a) and polyprotein 1b (pp1ab). Two-thirds of viral ribonucleic acid (RNA), principally found in the first open reading frame (ORF) [open reading frame 1a/b (ORF1a/b)] translates two polyproteins, polyprotein 1a (pp1a) and polyprotein 1b (pp1ab), and encodes 16 non-structural proteins (nsp), while the remaining open reading frames (ORFs) encode accessory and structural proteins. The remaining part of virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins, that interfere with host innate immune response (IIR). Main genomic encoded proteins of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) are alike to severe acute respiratory syndrome- coronaviruses (SARS-CoVs), as well as present particular differences. At protein level, there are no amino acid (AA) substitutions that occurred in nsp7, nsp13, envelope (E), matrix (M), or accessory proteins p6 and 8b, except in nsp2, nsp3, spike (S)

protein, underpinning subdomain, i.e., receptor-binding domain (RBD). Another research supposed that mutation in nonstructural proteins nsp2 and nsp3 participate in infectious capability and differentiation mechanism of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The genotypes of coronavirus disease 2019 (COVID-19) were analyzed in different sick persons from different districts and revealed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had been mutated in various sick persons in China. Genome alterations coming from recombination, gene exchange, gene insertion, or deletion are usual amongst coronaviruses (CoVs), and this will occur in time ahead breakouts as in previous pestilences. Recombination percents of coronaviruses (CoVs) are very high because of on and on developing transcription errors and RNA dependent RNA polymerase (RdRP) leapings. It was conducted a population genetic analyses of 103 severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) genomes and classified out two prevailing development types of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), L type (~70%) and S type (~30%). Strains in L type, derived from S type, are developmentarily more antagonistic and infectious. Thus, virologists and epidemiologists need to closely keep an eye on novel coronavirus, in order to investigate virulence and pestilence. First step in virus infection is interaction of sensitive human cells with spike (S) protein. Genome encoding happens after entering to cell and eases expression of genes, that encode necessary accessory proteins, which progress adaptability of coronaviruses (CoVs) to their human host.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) single-stranded RNA (ssRNA) genome possesses 29891 nucleotides, encoding for 9860 amino acids (AAs). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) genome is of 29.891 kb long, with a G + C content of 38%. These viruses are enclosed with an envelope containing viral nucleocapsid. Nucleocapsids in coronaviruses (CoVs) are ordered in helical coordination, which reflects an odd attribute in positive-sense ribonucleic acid (RNA) viruses. Electron micrographs of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) revealed a disclosing spherical outline with some degree of pleomorphism, virion diameter varying from 60 to 140 nm and distinct spikes of 9 to 12 nm, giving the virus a semblance of a solar crown. Genome of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is similar to ordinary coronaviruses (CoVs) and possesses at least ten open reading frames (ORFs). The initial open reading frames (ORFs) open reading frame 1a/b (ORF1a/b), about two-thirds of viral ribonucleic acid (RNA), are

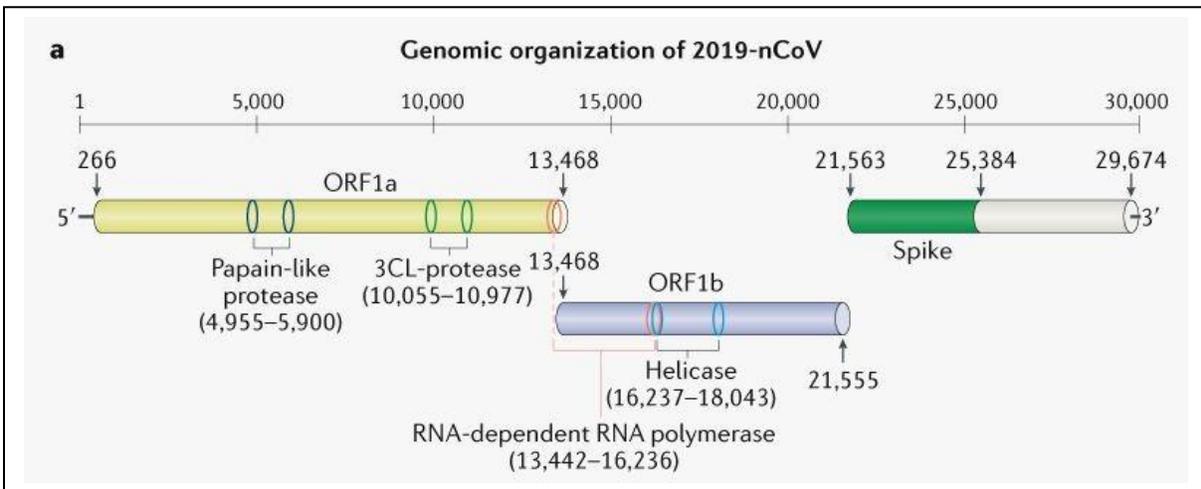
translated into two large polyproteins. In severe acute respiratory syndrome-coronavirus (SARS-CoV), two polyproteins, polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), are processed into 16 non-structural proteins (nsp1-nsp16), which construct viral replicase transcriptase complex (RTC). Those nonstructural proteins (nsps) rearrange membranes arising from rough endoplasmic reticulum (RER) into double-membrane vesicles where viral replication and transcription happen. Other open reading frames (ORFs) of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on the one-third of the genome encode four main structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins, as well as several accessory proteins.

Whole corona viruses (CoVs) share resemblances in organization and expression of their genome, in which 16 non-structural proteins (nsps) (nsp1 through nsp16), encoded by open reading frame(ORF) 1a/b at the 5' end, are followed by structural proteins spike (S), envelope (E), membrane (M) and nucleocapsid (N), which are encoded by other open reading frames (ORFs) at the 3' end. Coronaviruses (CoVs) genome is ordered linearly as 5'-leader-untranslated region (UTR)-replicase-structural genes-(S-E-M-N)-3' untranslated region (UTR)-poly (A). Accessory genes such as 3a/b, 4a/b, hemagglutinin-esterase gene (HE) are also recognized mingled within structural genes. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has also been found to be ordered the same and encodes several accessory proteins. Main 5' end is lodged by open reading frame 1a/b (ORF1a/b), which produces 16 nonstructural proteins (nsps). The two polyproteins, polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), are primarily produced from open reading frame 1a/b (ORF1a/b) by a -1 frameshift between open reading frame 1a (ORF1a) and open reading frame 1b (ORF1b). Viral encoded proteases split polyproteins into particular nonstructural proteins (nsps) [main protease (Mpro), chymotrypsin-like protease (3CLpro), and papain-like protease (PLPs)]. Noticeably, a variety between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and other coronaviruses (CoVs) is the identification of a novel short assumed protein within open reading frame 3b (ORF3b), and a secreted protein with an alpha helix and beta-sheet with six strands encoded by open reading frame 8 (ORF8).

As mutation percents in replication of ribonucleic acid (RNA) viruses are much higher than that of deoxyribonucleic acid (DNA) viruses, genomes of ribonucleic acid (RNA) viruses are often

less than 10kb in length. However, coronavirus (CoV) genome is much larger, with roughly 30kb in length, the largest recognized ribonucleic acid (RNA) viruses. Conservation of such a large genome of coronaviruses (CoVs) may be attributable to certain features of coronavirus (CoV) replication/transcription complex (RTC), which contains several ribonucleic acid (RNA) processing enzymes such as the 3'-5' exoribonuclease of nonstructural protein 14 (nsp14). The 3'-5' exoribonuclease is specific to coronaviruses (CoVs) between whole ribonucleic acid (RNA) viruses, possibly giving a proofreading function of the replication/transcription complex (RTC).

Sequence analysis demonstrates that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) possesses a model genome structure of coronavirus (CoV) and belongs to cluster of betacoronaviruses (β -CoVs) that involves Bat SARS-like (SL)-ZC45, Bat-SL ZXC21, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). On the basis of phylogenetic tree of coronaviruses (CoVs), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is more relatively related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more far related to severe acute respiratory syndrome-coronavirus (SARS-CoV).



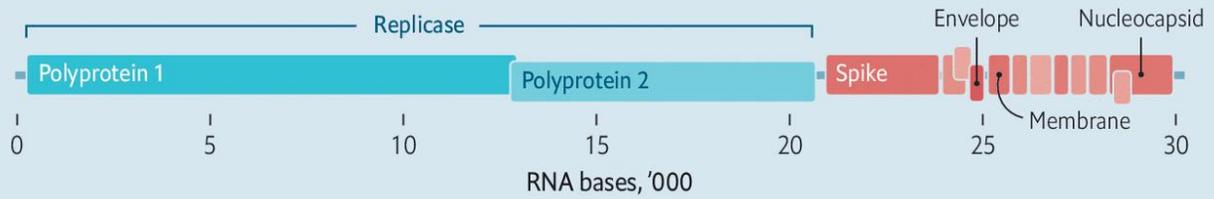
Figure(10): Genomic structure of 2019-nCoV (SARS-CoV-2) (www.google.com)

Ripped genes

Genome of SARS-like coronaviruses*

Genes for non-structural proteins
20 kilobases

Genes for structural and
accessory proteins 10 kilobases

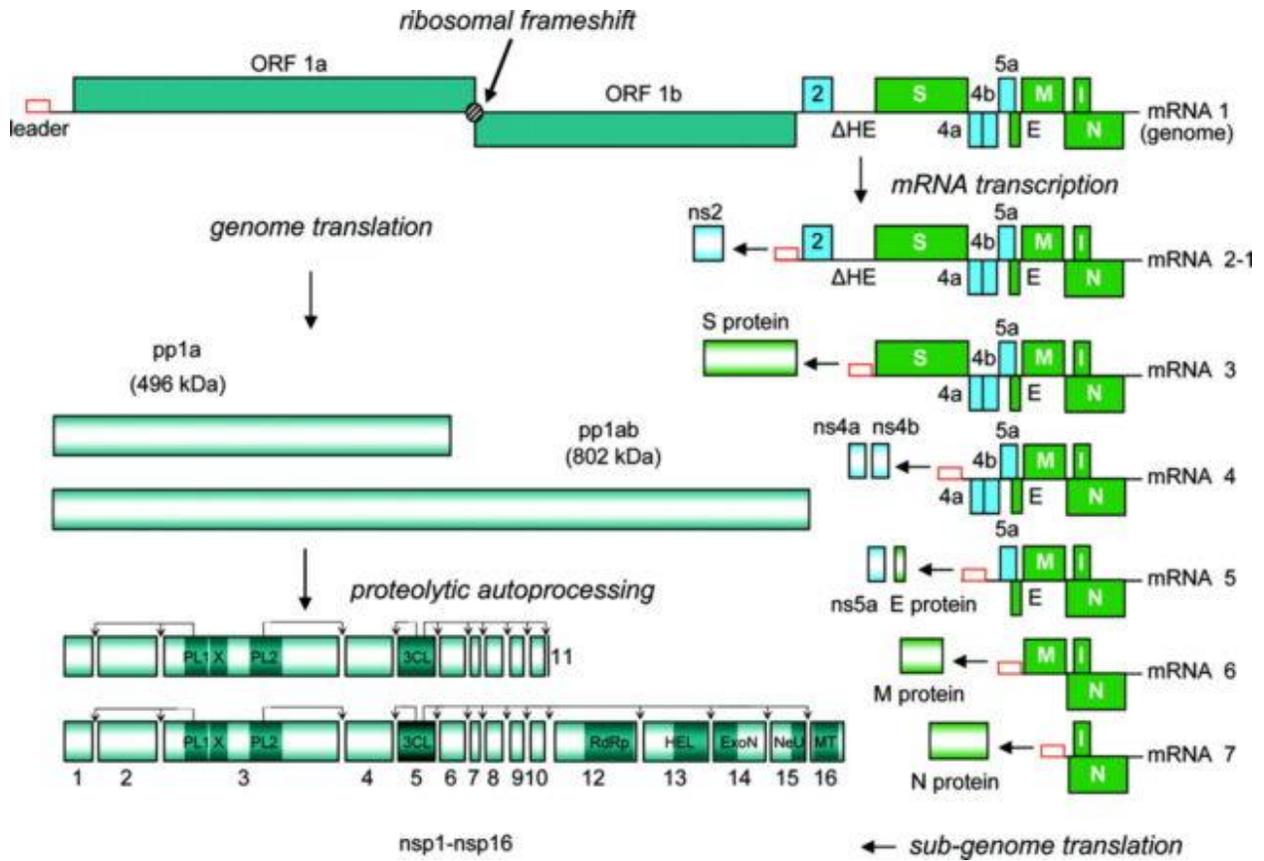


Source: Anthony R. Fehr and Stanley Perlman, *Methods Mol. Biol.*, 2015

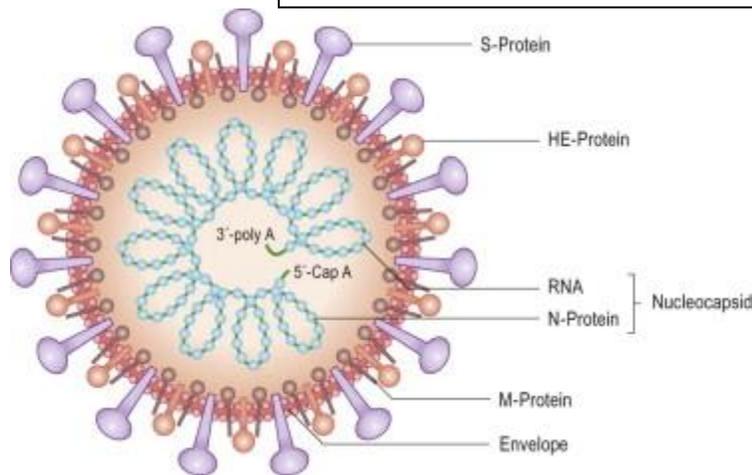
*Gene sizes are approximate

The Economist

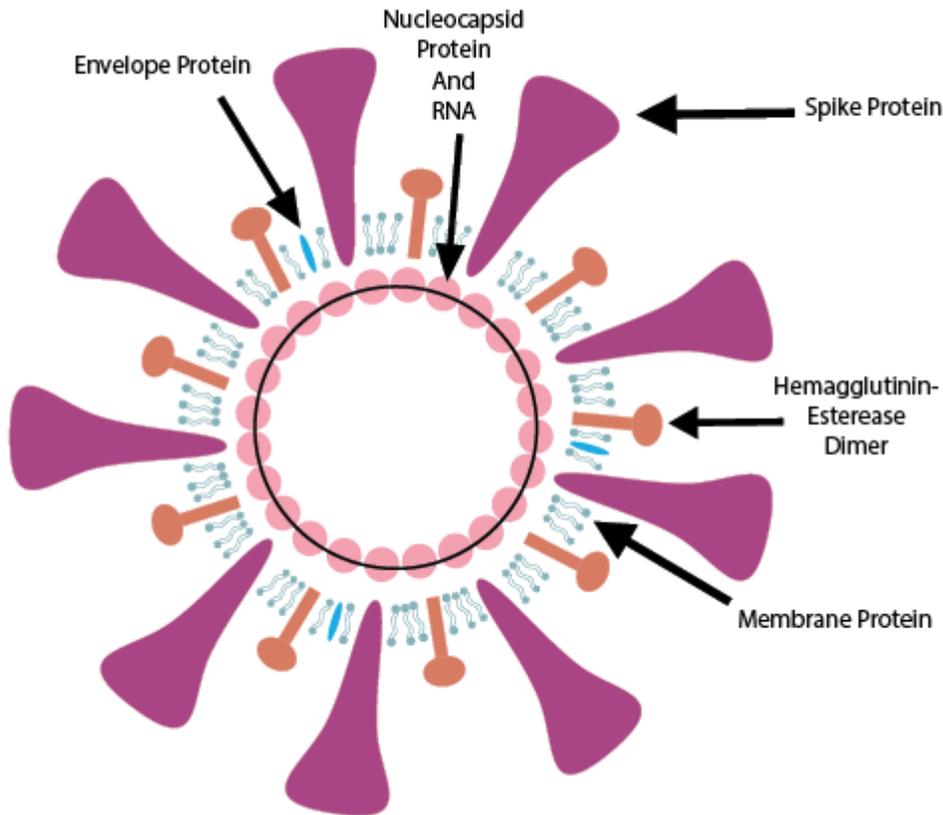
Figure(11):SARS-like coronaviruses genomic structure (www.google.com)



Figure(12): SARS-CoV-2 genome (www.google.com)



Figure(13):Structure of Human Coronavirus [Korsman S. (2012). Virology, Pub Churchill Livingtone]



Figure(14): SARS-CoV-2 structure (www.google.com)

Severe acute respiratory syndrome-coronavirus (SARS-CoV) genome has an enveloped, single, positive-stranded ribonucleic acid (ssRNA) genome that encodes four major viral structural proteins, namely spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins, that follow typical gene order [5' -replicase (rep gene), spike (S), envelope (E), membrane (M), nucleocapsid (N)-3'] with short untranslated loci at both endings. All structural and accessory proteins are translated from subgenomic ribonucleic acid (sgRNAs) of coronaviruses (CoVs). Four main structural proteins are encoded by open reading frames (ORFs) 10, 11 on one-third of the genome near 3'-terminus. Some of these proteins subject to glycosylation in Golgi apparatus to produce glycoproteins. Viral membrane contains spike (S), envelope (E), and membrane (M) proteins, and spike (S) protein functions a vital actual role in viral entrance.

Besides these main structural proteins, different coronaviruses (CoVs) encode particular structural and accessory proteins, such as hemagglutinin-esterase (HE) protein, 3a/b protein, and

4a/b protein. These mature proteins are accountable for some notable functions in genome conservation and virus replication.

Replicase (rep) gene encodes the non-structural protein (nsp) and exemplifies nearly two-thirds of genome at 5' end. In detail, spike (S) protein is in charge of receptor-binding and subsequent viral entrance into host cells, and is therefore a primary therapeutic target. Membrane (M) and envelope (E) proteins function notable roles in viral collection, and nucleocapsid (N) protein is vital for ribonucleic acid (RNA) synthesis.

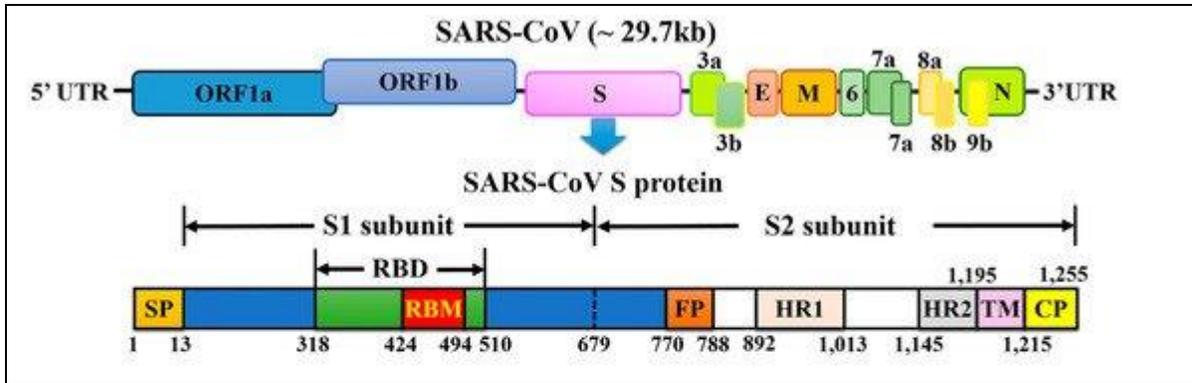
According to recent research, a spike (S) mutation, which possibly happened in late November 2019, provoked leaping to humans. In particular, authors in a significant study compared severe acute respiratory syndrome-coronavirus-2 (SARS-Cov-2) gene sequence with that of severe acute respiratory syndrome-coronavirus (SARS-Cov). They analyzed transmembrane helical parts in open reading frame 1ab (ORF1ab) encoded 2 nonstructural protein 2 (nsp2) and nonstructural protein 3 (nsp3) and demonstrated that site 723 presents a serine (Ser) instead of a glycine (Gly) residue, while site 1010 is lodged by proline (Pro) instead of isoleucine (Ile). State of viral mutations is guide for interpreting probable illness falls.

Comparing genome of severe acute respiratory syndrome-coronavirus-2 (SARS-Cov-2) with that of exceedingly related severe acute respiratory syndrome/severe acute respiratory syndrome-like coronavirus (SARS/SARS- like CoV) showed that sequence coding for spike (S) protein with a total length of 1,273 amino acids (AAs) indicated 27 amino acid (AA) exchanges. Six of these exchanges are in locus of receptor binding domain (RBD), and another six exchanges are in underpinning subdomain (SD).

Trimers of spike (S) protein constitute spikes of severe acute respiratory syndrome-coronavirus (SARS-CoV) and provide the formation of a 1255-amino-acids (AAs)-length surface glycoprotein precursor. Most of protein and amino terminus are positioned on outside of virus particle or cell surface. Predictable construction of spike (S) protein comprises four sites: a signal peptide situated at N terminus from amino acids (AAs) 1 to 12, an extracellular domain from amino acids (AAs) 13 to 1195, a transmembrane domain from amino acids (AAs) 1196 to 1215, and an intracellular domain from amino acids (AAs) 1216 to 1255. Proteases such as factor Xa, trypsin, and cathepsin L split severe acute respiratory syndrome-coronavirus (SARS-CoV) spike

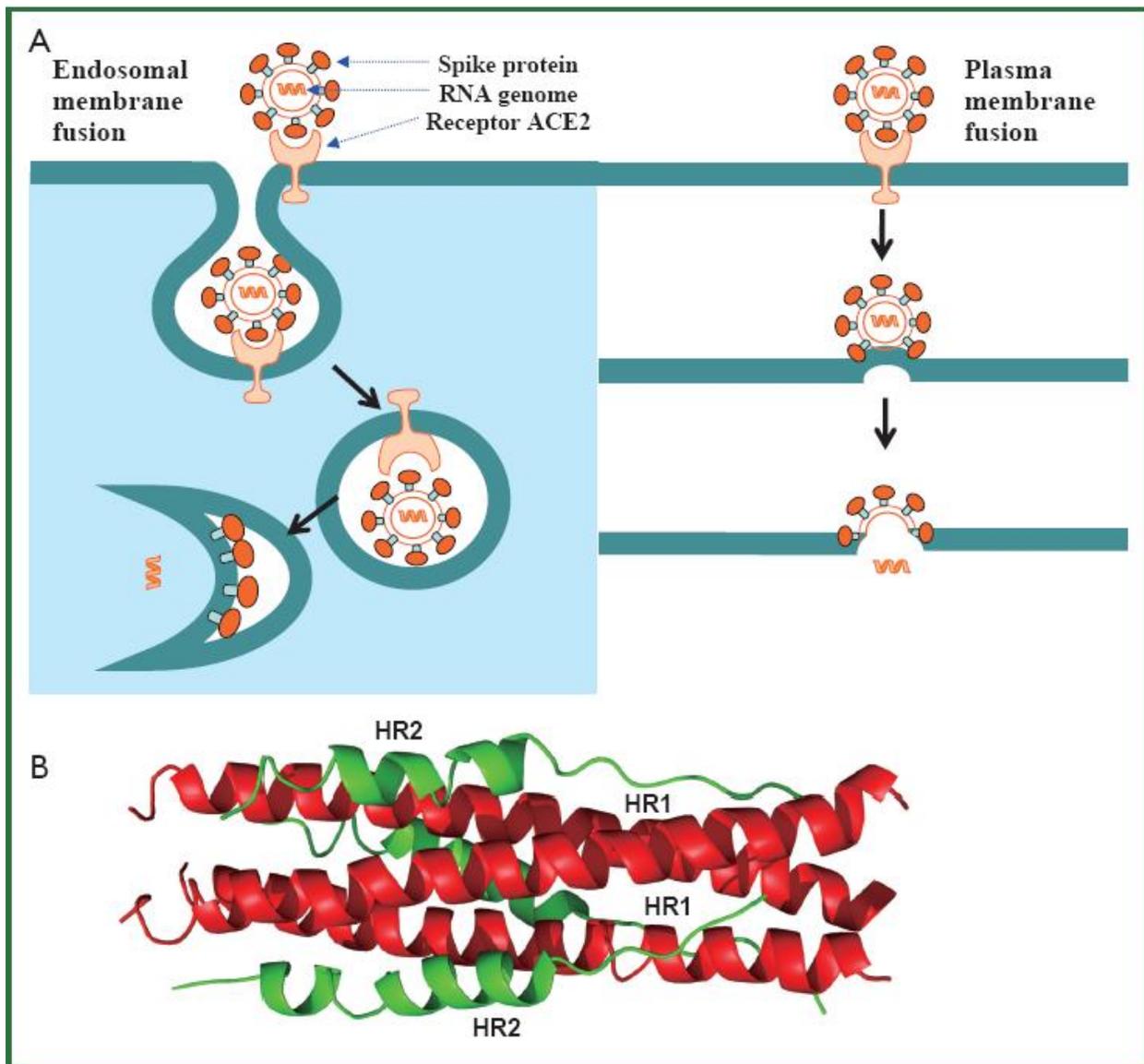
(S) protein into two subunits, S1 and S2 subunits. Minimum receptor-binding domain (RBD) situated in S1 subunit (amino acids 318–510) can attach host cell receptor, angiotensin converting enzyme 2 (ACE2), a transmembrane receptor which is broadly expressed in lung, heart, kidney and gastrointestinal (GI) tissue. Human serine protease transmembrane protease, serine2 (TMPRSS2) is capable of priming spike (S) protein of both severe acute respiratory syndrome-coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and angiotensin-converting enzyme 2 (ACE2) is regarded a receptor for entrance of these two viruses. The features of cellular receptor angiotensin-converting enzyme 2 (ACE2) can also interpret pathogenesis characteristics of severe acute respiratory syndrome-coronavirus (SARS-CoV) and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). It has been revealed that attachment of viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2) promotes a negative feedback loop that eventually results in downregulation of angiotensin-converting enzyme 2 (ACE2). Decrease of angiotensin-converting enzyme 2 (ACE2) thereafter orients its substrate angiotensin I towards its related enzyme, angiotensin-converting enzyme 2 (ACE2). Increased angiotensin-converting enzyme 2 (ACE2) activity consequently results in elevated concentrations of angiotensin II. Once angiotensin II binds to its receptor, angiotensin II receptor, type 1a (AGTR1A), pulmonary vascular permeability is elevated. Receptor-binding domain (RBD) shows a concave surface during interaction with the receptor. The entire receptor-binding loop, called the receptor-binding motif (RBM) (amino acids 424–494), is situated on receptor-binding domain (RBD) and is accountable for full attachment with angiotensin-converting enzyme 2 (ACE2). Of importance, two residues in the receptor-binding motif (RBM) at sites 479 and 487 specify progression of the severe acute respiratory syndrome (SARS) illness and tropism of severe acute respiratory syndrome-coronavirus (SARS-CoV). Studies using civets, mice, and rats indicated that any substitution in these two residues might enhance animal-to-human or human-to-human transference and ease effective cross-species contagion. The S2 subunit mediates fusion between severe acute respiratory syndrome coronavirus (SARS-CoV) and target cells, and involves heptad repeat 1 (HR1) and heptad repeat 2 (HR2) domains, whose heptad repeat 1 (HR1) locus is longer than heptad repeat 2 (HR2) locus. Severe acute respiratory syndrome-coronavirus (SARS-CoV) spike (S) protein function actual roles in viral contagion and pathogenesis. The S1 subunit recognizes and attaches host receptors, and thereafter conformational modification in S2 subunit mediate binding between viral

envelope and host cell membrane. Receptor-binding domain (RBD) in S1 subunit is accountable for virus attachment to host cell receptors. Angiotensin converting enzyme 2 (ACE2) is a active receptor for severe acute respiratory syndrome-coronavirus (SARS-CoV) that makes contact with 14 amino acids (AAs) in the receptor-binding domain (RBD) of severe acute respiratory syndrome-coronavirus (SARS-CoV) among its 18 residues. Receptor-binding domain (RBD) in S1 subunit is accountable for virus attachment to host cell receptors. Locus R453 in receptor-binding domain (RBD) and locus K341 in angiotensin converting enzyme 2 (ACE2) play requisite roles in complex formation. Further, N479 and T487 in receptor-binding domain (RBD) of spike (S) protein are indispensable loci for affinity with angiotensin-converting enzyme 2 (ACE2), and R441 or D454 in receptor-binding domain (RBD) influences antigenic construction and binding activity between receptor-binding domain (RBD) and angiotensin-converting enzyme 2 (ACE2). From a pre-fusion construction to a post-fusion construction, attachment of receptor-binding domain (RBD) in S1 subunit to receptor angiotensin converting enzyme 2 (ACE2) induces a fixed change in S2. In accordance, the proposed fusion peptide (amino acids 770–788) constructs in target cell membrane of host. Meanwhile, a six-helix bundle fusion core construction is constituted by heptad repeat 1 (HR1) and heptad repeat 2 (HR2) domains for letting viral envelope and target cell membrane be into nearby vicinity and contributing to attachment. Furthermore, severe acute respiratory syndrome-coronavirus (SARS-CoV) displays an alternative method of fusing to host cell via other probable receptors. Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) and/or liver/lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin (L-SIGN) are two examples of such receptors. Seven residue positions, at loci 109, 118, 119, 158, 227, 589, and 699 of spike (S) protein displaying asparagine (Asn)-linked glycosylation are fundamental for dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) or liver/lymph node-specific intercellular adhesion molecule-3-grabbing non-integrin (L-SIGN)-mediated virus entrance. These residues, not like those of angiotensin-converting enzyme 2 (ACE2)-binding domain, serve independently of angiotensin-converting enzyme 2 (ACE2).



Figure(15): Schematic representation of the genome organization and functional domains of S protein for SARS-CoV [Song Z.; Xu Y.; Bao L.; Zhang L.; Yu P.; Qu Y.; Zhu H.; Zhao W.; Han Y.; Qin C. (2019). From SARS to MERS, thrusting coronaviruses into the spotlight. *Viruses*, 11, 59]

In figure(15): the construction of spike (S) protein is shown beneath genome organization. Spike (S) protein primarily contains S1 and S2 subunits. The residue numbers in each locus exemplify their situations in spike (S) protein of severe acute respiratory syndrome coronavirus (SARS-CoV). The S1/S2 cleavage sites are highlighted by dotted lines. SARS-CoV, severe acute respiratory syndrome coronavirus; CP, cytoplasm domain; FP, fusion peptide; HR, heptad repeat; RBD, receptor-bonding domain; RBM, receptor-binding motif; SP, single peptide; TM, transmembrane domain.



Figure(16):The models of SARS-CoV entry into the target cell[Zhu X.; Liu Q.; Du L.; Lu L.; Jiang S. (2013). Receptor-binding domains as a target for developing SARS vaccines. Journal of Thoracic Disease, 5(Supplement2).

In figure (16): part (A): severe acute respiratory syndrome-coronavirus (SARS-CoV) enters into target cell majorly through endosomal membrane fusion (left side) and alternatively via plasma membrane fusion (right side); in part (B): fusion core structure formed by heptad repeat 1 (HR1) and heptad repeat 2 (HR2) domains in severe acute respiratory syndrome-coronavirus (SARS-CoV) spike (S) protein; Fusion core is a six-helix bundle (6-HB) with three heptad repeat 2 (HR2) α -helices packed in an oblique antiparallel manner against hydrophobic grooves on surface of central heptad repeat 1 (HR1) trimer.

Identical to other betacoronaviruses (β -CoVs), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virion possesses a nucleocapsid composed of genomic ribonucleic acid (RNA) and phosphorylated nucleocapsid (N) protein. The nucleocapsid is inhaled inside phospholipid bilayers and covered by two various types of spike (S) proteins: spike glycoprotein trimmer(S) that is present in all coronaviruses (CoVs), and hemagglutinin-esterase (HE) only shared among some coronaviruses (CoVs). Nucleocapsid protein (N) proteins attach viral genome in beads on a string type structure. The N protein of coronavirus (CoV) is multipurpose. Two viral proteins have been shown to attach to coronavirus 5'UTR, nucleocapsid (N) protein and nonstructural protein 1 (nsp1). Amongst different functions, nucleocapsid N protein takes part in complex formation with viral genome, eases membrane (M) protein interaction necessary during virion collection, and enhances transcription efficacy of virus. It plays an important role in virion construction, replication and transcription of coronaviruses (CoVs), because nucleocapsid (N) protein situates in both replication/ transcriptional region of coronaviruses (CoVs) and endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) site where the virus is accumulated. This protein probably supports binding viral genome to replicase-transcriptase complex (RTC), and thereafter packs encapsulated genome into viral particles. It contains three highly conserved and distinguished domains, called an N-terminal domain (NTD), RNA-binding domain or a linker region (LKR), and a C-terminal domain (CTD). N proteins contain two constructionally independently ribonucleic acid (RNA) binding domains, the N-terminal RNA binding domain (NTD) and a C-terminal domain (CTD), residues (256–385) which also has ribonucleic acid (RNA) binding activity, joined by a charged linker region rich in serine (Ser) and arginine (Arg) residues (SR linker). N-terminal RNA binding domain (NTD) creates a particular and high affinity complex with the transcription-regulating sequence (TRS) or its complement transcription-regulating sequence (cTRS) and completely unwinds a transcription-regulating sequence (TRS)- complement transcription-regulating sequence (cTRS) (TRS-cTRS) duplex that serves a critical role in subgenomic ribonucleic acid (sgRNA) synthesis and other processes necessitating ribonucleic acid (RNA) rebuilding. In addition a study revealed that N3 domain (residues 409–454) which extends to the true C-terminus of N protein serves a role in specifying N-membrane protein interaction in murine hepatitis virus (MHV). A study showed that N-terminal RNA binding domain (NTD)-transcription-regulating sequence (TRS) (NTD–TRS) interaction includes N residues R125,

Y127, and Y190 and anchors adenosine-rich region in the 3' end of the transcription-regulating sequence ribonucleic acid (TRS RNA) to β -platform of N and that this interaction is necessary for effective subgenomic ribonucleic acid (sgRNA) production. N-terminal RNA binding domain (NTD) attaches 3' end of the viral genome, possibly through electrostatic interactions, and is highly differed both in length as well as sequence. Charged linker region (LKR), as mentioned, serine (Ser) and arginine (Arg)- rich, is also known as SR (Serine and Arginine) domain. Linker region (LKR) is capable of direct interaction with in vitro ribonucleic acid (RNA) interaction and is also accountable for cell signaling. It is reported that nucleocapsid (N) protein can attach nonstructural protein 3 (nsp3) protein in order to support tethering genome to replication/transcription complex (RTC), and pack encapsidated genome into virions. It serves a recognizable role in virion build, replication and transcription of coronaviruses (CoVs), because nucleocapsid (N) protein situates in both replication/ transcriptional region of coronaviruses (CoVs) and endoplasmic reticulum (ER)-Golgi intermediate compartment (ERGIC) region where virus is accumulated. It has also been proposed that nucleocapsid (N) protein binding to leader transcription regulating sequence (TRS-L) approves translation of viral viral ribonucleic acids (RNAs). Nucleocapsid (N) modulates antiviral response of host as it functions as an antagonist of interferon (IFN) and viral encoded repressor of ribonucleic acid (RNA) interference, which appears to be of benefit for viral replication. In comparison to severe acute respiratory syndrome-coronavirus (SARS-CoV), nucleocapsid (N) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) possess five amino acid (AA) mutations, where two are in intrinsically dispersed region (IDR, 25 and 26 positions), one each in N-terminal RNA binding domain (NTD) (103 position), linker region (LKR) (217 position) and C-terminal domain (CTD) (334 position).

Coronaviruses (CoVs) envelope (E) protein is the most enigmatic and smallest among the major structural proteins. Envelope (E) glycoproteins are small proteins that are consisted of about 76 to 109 amino acids (AAs). Approximately 30 amino acids (AAs) in N-terminus of envelope (E) proteins give binding to membrane of viruses. Coronavirus envelope (E) protein is found in small amounts within the virus. It is most probable a transmembrane protein and with ion channel activity. It is a small integral membrane polypeptide that serves as viroporin (ion-channel). The protein eases gathering and release of the virus and has other vital acts such as ion channel activity. It is not necessary for viral replication but it is for pathogenesis. Amongst

functions of constructional proteins, envelope (E) protein has a crucial role in virus pathogenicity as it induces viral collection and release. Inactivation or absence of this protein is attributable to altered virulence of coronaviruses (CoVs) due to changes in morphology and tropism. Envelope (E) protein is composed of three domains, namely short hydrophilic amino-terminal, a large hydrophobic transmembrane domain, and an excellent C terminal domain. The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) envelope (E) protein reveals a similar amino acid (AA) construction without any interchange.

All envelope (E) proteins and nucleocapsid (N) protein are present in all virions but hemagglutinin (HE) is only found in some beta coronaviruses. In addition to that, it is thought the virus particles are bunched together owing to interaction between these proteins.

Membrane protein (M) is most copious building protein. Membrane (M) proteins are glycosylated in Golgi apparatus. Modification of membrane (M) protein is crucial for the virion to fuse into cell and to create protein antigenic. Membrane (M) protein serves a guide role in regenerating virions in cell. It does not contain signal sequence and is found as a dimer in the virion. It may have two various figures to promote membrane curvature as well as attach to nucleocapsid. Nucleocapsid (N) protein constitutes a complex by binding to genomic ribonucleic acid (RNA) and membrane (M) protein provokes making of interacting virions in this endoplasmic reticulum-Golgi apparatus intermediate compartment (ERGIC) with this complex. Membrane (M) glycoprotein spans membrane bilayer three times, leaving a short NH₂-terminal domain outside virus and a long COOH terminus (cytoplasmic domain) inside virion. Coronaviruses (CoVs) membrane (M) proteins are highly diverse in accordance to amino acid (AA) constituents but conserve overall structural similarity within different genera. Membrane (M) protein has three transmembrane domains, flanked by short amino-terminal outside virion, and a long carboxy-terminal inside virion. Membrane (M) protein three transmembrane domains configure virions, promote membrane curvature, and attaches to nucleocapsid. As a whole, viral scaffold is kept by membrane-membrane (M-M) interaction. Between envelope (E) proteins exist a molecular interaction that probably particulates construction and constitution of coronaviral membrane. Membrane (M) protein plays a predominant role in intracellular synthesis of virus particles without requiring spike (S) protein. In the presence of tunicamycin coronavirus (CoV) grows and produces spikeless, noninfectious virions that contain membrane (M) protein but

devoid spike (S) protein. Membrane (M) protein acts as a central organizer of coronavirus (CoV) collection. To the note, membrane (M) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) does not have any amino acid (AA) exchange in comparison to severe acute respiratory syndrome-coronavirus (SARS-CoV).

Hemagglutinin-esterase dimer protein (HE) is detected in a subset of betacoronaviruses (β -CoVs). The protein attaches to sialic acids (derivatives of neuraminic acid) on surface glycoproteins. The protein vitalities are thought to promote spike (S) protein-mediated cell entrance and virus disperse through mucosa.

All structural and accessory proteins are translated from subgenomic ribonucleic acids (sgRNAs) of coronaviruses (CoVs). da Silva et al. (2020) used several calculation tools to analyze open reading frame (ORF) 1a and 1b of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Authors record that ORF1a/b comprises about two-thirds of viral genome and codes for 16 nonstructural proteins (nsp1-16) and they interpret that there is a -1 frameshift between ORF1a and ORF1b, leading to production of two polypeptides (pp1a and pp1ab), which are further processed by viral-encoded proteases into 16 nonstructural proteins (nsp). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) genome contains 8 accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and orf14). All these proteins function a particular role in viral replication. Several accessory proteins interfere with host innate immune response (IIR). Severe acute respiratory syndrome-coronavirus (SARS-CoV) possesses five and eight accessory proteins, respectively, which might support the virus to devoid immune system by being mischievous to innate immune response (IIR). Difference in respect to accessory proteins with severe acute respiratory syndrome-coronavirus (SARS-CoV), severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)(2019-nCoV) does not contain 8a protein and longer 8b, and shorter 3b proteins. Nonstructural protein 7 (nsp7), nonstructural protein 13 (nsp13), envelope (E), matrix (M), or accessory proteins p6 and 8b have not been realized with any amino acid (AA) changes in comparison to coronaviruses (CoVs).

Coronavirus (CoV) messenger ribonucleic acid 1 (mRNA 1), which is genome length, containing two overlapping reading frames (ORFs), i.e., open reading frame 1a (ORF1a) and open reading frame 1b (ORF1b), orients synthesis of two precursor polyproteins, i.e., polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab), via a -1 frameshifting machinery involving a pseudoknot

construction. Polyproteins are then processed by two or three virus-encoded [in open reading frame 1a (ORF1a)] proteinase domains to develop a membrane-bound replicase-transcriptase complex (RTC). Two large precursor polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab) are processed by open reading frame 1a (ORF1a)-encoded viral proteinases, papain-like proteinase (PL^{pro}) and 3C-like proteinase (3CL^{pro}), into 16 mature nonstructural proteins [nsp1-nsp16, numbered according to their order from the N-terminus to the C-terminus of the open reading frame 1 (ORF1) polyproteins]. In accordance to proteolytic processing, frameshifted open reading frame 1ab (ORF 1ab) polypeptide generates 15–16 nonstructural proteins, many of which are included in either ribonucleic acid (RNA) synthesis or proteolytic processing necessary for viral replication: nonstructural protein1-nonstructural protein11 (nsp1–nsp11) encoded in open reading frame 1a (ORF 1a) and nonstructural protein12-nonstructural protein16 (nsp12–nsp16) encoded in open reading frame 1b (ORF1b). Open reading frame 1a (ORF 1a) encodes three protease domains, one or two papain-like domains in nonstructural protein 3 (nsp3) depending on particular coronavirus (CoV), and one picornavirus 3C-like domain in nonstructural protein 5 (nsp5). Nonstructural protein 8 (nsp8) in open reading frame 1a (ORF 1a) contains a second RNA-dependent RNA polymerase (RdRp) domain that is proposed to act as a primase and synthesize primers utilized by primer-dependent nonstructural protein 12 RNA-dependent RNA polymerase (nsp12 RdRp). Open reading frame 1b (ORF 1b) encodes an RNA-dependent RNA polymerase (RdRp) core unit in nonstructural protein 12 (nsp12) [although a differed number of nucleotides (nts) of nonstructural protein 12 (nsp12) coding sequence locates within open reading frame 1a (ORF 1a), depending on particular virus], a superfamily 1 helicase in nonstructural protein 13 (nsp13), an exonuclease and N-methyltransferase in nonstructural protein 14 (nsp14), an endoribonuclease in nonstructural protein 15 (nsp15), and an S-adenosylmethionine-dependent 2'-O-methyl transferase in nonstructural protein 16 (nsp16). Enzymatic activities of the exonuclease, endoribonuclease and S-adenosylmethionine-dependent 2'-O-methyl transferase encoded by nonstructural protein (nsp)14, 15 and 16 are particular to Nidoviruses. Many of nonstructural proteins (nsps) perform essential functions in viral ribonucleic acid (RNA) replication and transcription. Besides RNA-dependent RNA polymerase (RdRp), helicase and proteases, some of nonstructural proteins (nsps) are ribonucleic acid (RNA)-processing enzymes such as poly (U)-specific endoribonuclease, 3'-5' exoribonuclease, ribose 2'-O methyltransferase, adenosine diphosphate-ribose-1"-phosphatase and cyclic

nucleotide phosphodiesterase. The enzymatic activities and the functional domains of many of these fundamental nonstructural proteins (nsps) are predicted to be kept between different genera of coronaviruses (CoVs), indicating their noticeability in viral replication. In addition to these nonstructural proteins (nsps) with described actions, there are several nonstructural proteins (nsps) whose biological servings and roles in coronavirus (CoV) life cycle still remain to be illucidated.

While nonstructural protein3-nonstructural protein16 (nsp3-nsp16) from different coronavirus (CoV) genera share several protected functional domains, N-terminal region of open reading frame 1 (ORF1) polyprotein, primarily nonstructural protein 1 (nsp1) sequence, is highly differed amongst coronaviruses (CoVs). Nonstructural protein 1 (nsp1) is most N-terminal cleavage yield released from open reading frame 1a (ORF1a) polyprotein by activity of papain-like proteinase (PL^{pro}). In severe acute respiratory syndrome-coronavirus (SARS-CoV), papain-like proteinase (PL^{pro})–mediated cleavage at consensus cleavage site LXGG in open reading frame 1a (ORF1a) polyprotein liberates comparable nonstructural protein 1 (nsp1) and nonstructural protein 2 (nsp2) as 20-KDa and 70-KDa proteins, respectively. Severe acute respiratory syndrome-coronavirus (SARS-CoV) nonstructural protein 1 (nsp1) is positioned exclusively in cytoplasm of virus-infected cells. Severe acute respiratory syndrome-coronavirus (SARS-CoV) nonstructural protein 1 (nsp1) also attaches to a stem-loop structure, SL1, in 5' untranslated region (5'UTR) of severe acute respiratory syndrome-coronavirus (SARS-CoV) genome and it has suggested that this interaction enhances virus replication. Using transient gene expression in mammalian cells, severe acute respiratory syndrome-coronavirus (SARS-CoV) nonstructural protein 1 (nsp1) was initial coronavirus (CoV) nonstructural protein1 (nsp1) that was shown to block expression of reporter gene under control of constitutive promoters as well as inducible interferon-beta (IFN- β) promoter. A study by Tanaka *et al.* (2012) suggested that a particular interaction of nonstructural protein1 (nsp1) with 5' untranslated region (5'UTR) of severe acute respiratory syndrome-coronavirus (SARS-CoV) messenger ribonucleic acid (mRNA) conserves viral messenger ribonucleic acids (mRNAs) from nonstructural protein 1 (nsp1)-mediated translational shutoff in severe acute respiratory syndrome-coronavirus (SARS-CoV)-infected cells. In addition, the researchers speculated that nonstructural protein 1 (nsp1) stimulates viral protein synthesis and viral ribonucleic acid (RNA) replication through this interaction because this influence was not observed with a mutated nonstructural protein 1 (nsp1) protein, carrying

R124A mutation that abolished its interaction with the 5' untranslated region (5' UTR) of viral messenger ribonucleic acid (mRNA). In the study by Tanaka *et al.* (2012), nonstructural protein 1 (nsp1)-mediated enhancement of viral protein synthesis could be an indirect consequence of decay of host messenger ribonucleic acids (mRNAs), provoked by nonstructural protein 1 (nsp1) but not by nonstructural protein 1 (nsp1)R124A mutant, that would eliminate the competition between viral and host messenger ribonucleic acids (mRNAs) for finite amounts of translationally-competent 40S subunits, thereby tiling balance in favor of viral messenger ribonucleic acid (mRNA) translation. Furthermore, nonstructural protein 1 (nsp1)-induced deterioration of host messenger ribonucleic acids (mRNAs) could also liberate translation initiation factors from host messenger ribonucleic acids (mRNAs) that can be utilized by intact viral messenger ribonucleic acids (mRNAs) in severe acute respiratory syndrome-coronavirus (SARS-CoV)-infected cells. Therefore, it is believable that split of host messenger ribonucleic acids (mRNAs) by nonstructural protein1 (nsp1) and resistance of viral messenger ribonucleic acids (mRNAs) to nonstructural protein1 (nsp1)-induced ribonucleic acid (RNA) split are strategies that severe acute respiratory syndrome-coronavirus (SARS-CoV) could have developed to compensate for blocking of viral messenger ribonucleic acid (mRNA) translation by nonstructural protein1 (nsp1) thereby easing production of viral proteins in severe acute respiratory syndrome-coronavirus (SARS-CoV)-infected cells.

Pathophysiology and virulence mechanics of coronaviruses (CoVs), and therefore also of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) have links to function of nonstructural proteins (nsps) and structural proteins. For instance, research underlined that nonstructural protein (nsp) is able to block host innate immune response (IIR).

Among four coronavirus (CoV) genera, only alpha-coronavirus (α -CoVs) and beta-coronaviruses (β -CoVs) encode nonstructural protein1 (nsp1), whereas gamma-coronaviruses (γ -CoVs) and delta-coronaviruses (δ -CoVs) lack nonstructural protein1 (nsp1) and thus, their gene1 encode only 15nonstructural proteins (nsps) (nonstructural protein2-nonstructural protein16) (nsp2-nsp16). Nonstructural protein1 (nsp1) of alpha-coronaviruses (α -CoVs) share no considerable sequence resemblance with beta-coronavirus (β -CoV) nonstructural protein1 (nsp1) and their sizes are also differed. On the basis of comparative sequence analysis of the genomes of different

coronaviruses (CoVs), nonstructural protein1 (nsp1) could be considered as one of the genus-specific markers.

Severe acute respiratory syndrome-coronavirus (SARS-CoV) is a single, nonsegment and positive-stranded ribonucleic acid (RNA) virus with envelope. Its genomic ribonucleic acid (RNA) is composed of 29,736 nucleotides, two thirds of its 5'-encoding nonstructural ribonucleic acid (RNA) replicase polyprotein and one third of its 3'-encoding structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (11). Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) genome has 5' and 3' terminal sequences [265 nucleotides (nts) at the 5' terminal and 229 nucleotides (nts) at the 3' terminal region], which is usual of beta-coronaviruses (β -CoVs), with a gene order 5'-replicase open reading frame (ORF) 1ab-spike (S)-envelope(E)-membrane(M)-nucleocapsid (N)-3'. The predicted spike (S), open reading frame 3a (ORF3a), envelope (E), membrane (M), and nucleocapsid (N) genes of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) are 3822, 828, 228, 669, and 1260 nucleotides (nts) in length, respectively. Alike to severe acute respiratory syndrome-coronavirus (SARS-CoV), severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) carries a predicted open reading frame 8 (ORF8) gene (366 nucleotides (nts) in length) situated between membrane (M) and nucleocapsid (N) open reading frame (ORF) genes.

Angiotensin-converting enzyme 2 (ACE2) is a type I transmembrane protein consisted of 805 amino acids (AAs) and is primarily expressed in the gastrointestinal tract (GIT), heart, kidney and lung. As a negative regulator of the renin-angiotensin system (RAS), angiotensin-converting enzyme 2 (ACE2) plays a notable role in keeping homeostasis of cardiovascular (CV) system and regulating absorption of amino acids (AAs) in kidney and gastrointestinal tract (GIT). Genetic studies also reveal the role of angiotensin-converting enzyme 2 (ACE2) in preventing stroke. Angiotensin-converting enzyme 2 (ACE2), expressed the lower respiratory tract of human beings, is known as cell receptor for severe acute respiratory syndrome-coronavirus (SARS-CoV) and regulates both the cross-species and human-to-human transference. Isolated from the bronchoalveolar lavage fluid (BALF) of a coronavirus disease-19 (COVID)-19 sick person, it has been asserted that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) uses the same cellular entry receptor, angiotensin-converting enzyme 2 (ACE2), as severe acute respiratory syndrome-coronavirus (SARS-CoV). In order for the virus to complete entrance into

the cell following this initial process, spike (S) protein has to be primed by an enzyme called a protease. similar to severe acute respiratory syndrome-coronavirus (SARS-CoV), severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (COVID-19) uses a protease called transmembrane protease, serine 2 (TMPRSS2) to complete this process. In order to attach virus receptor [spike (S) protein] to its cellular ligand (ACE2), activity by transmembrane protease, serine 2 (TMPRSS2) as a protease is needed. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can also construct a novel short protein encoded by open reading frame 3b (ORF3b) and a secreted protein encoded by open reading frame 8 (ORF8). Open reading frame 3b (ORF3b) of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) may play a role in viral pathogenicity and block expression of interferon-beta (IFN β); however, open reading frame 8 (ORF8) does not contain any known functional domain or motif. Å resolution in complex with the sodium-dependent neutral amino acid transporter B0AT1 (SLC6A19), they found that the complex, which had open and closed conformations, was collected as a dimer and angiotensin-converting enzyme 2 (ACE2)-B0AT1 complex can attach two spike (S) proteins, which gives proof for coronavirus (CoV) recognition and contagion. Sodium-dependent neutral amino acid transporter B0AT1 (SLC6A19) may become a therapeutic target for drug screening to suppress severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) contagion. Virion spike (S)-glycoprotein on surface of coronavirus (CoV) can attach to the receptor, angiotensin-converting enzyme 2 (ACE2) on surface of human cells. However, spike (S) protein of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) attaches to human angiotensin-converting enzyme 2 (ACE2) more weakly than that of severe acute respiratory syndrome-coronavirus (SARS-CoV), which is coincident with the fact that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes less severe infection in sick persons than severe acute respiratory syndrome-coronavirus (SARS-CoV). Spike (S) protein is split by endosomal acid proteases (cathepsin L) to activate its fusion activity. After the fusion peptide (FP) inserts into the endosomal membrane, the heptad repeat 1 and 2 (HR1 and HR2) domains in spike (S) protein interact with each other to construct a six-helix bundle (6-HB) core, which brings viral envelope and the cellular plasma membrane into close vicinity for fusion. Spike (S) glycoprotein involves two subunits, S1 and S2. S1 determines the virus-host range and cellular tropism with the key function domain –receptor-binding domain (RBD), while S2 mediates virus-cell membrane fusion by two tandem domains, heptad repeat 1 (HR1) and heptad

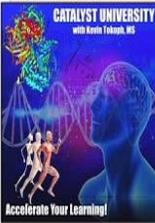
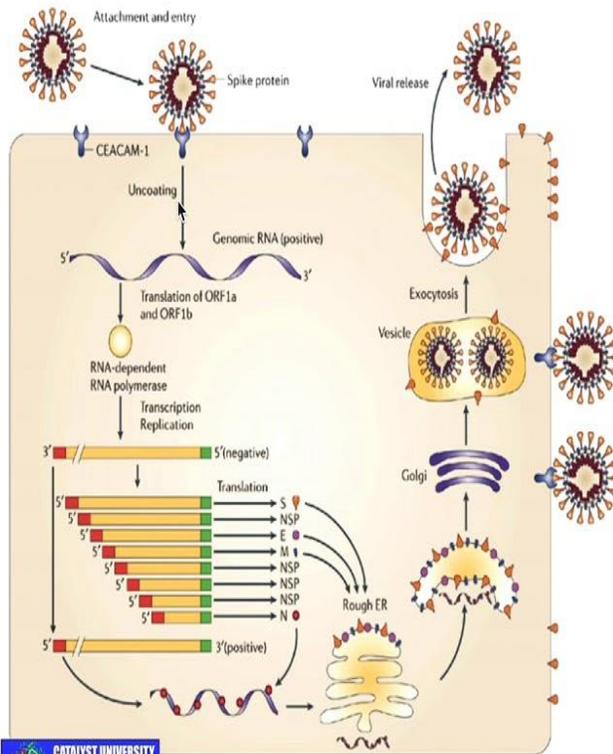
repeat 2 (HR2). The receptor binding domain (RBD) on S1 subunit interacts with angiotensin-converting enzyme 2 (ACE2) to construct a virion-angiotensin-converting enzyme 2 (ACE2) complex. The virion-angiotensin-converting enzyme 2 (ACE2) complex is then transferred and enters endosome of target cells. After that, the structure domain of heptad repeats (HR)1 and HR2 in spike (S) proteins interact with one another to construct a six-helix bundle core. This core promotes fusion of the viral envelope (E) with cellular membrane. The ribonucleic acids (RNAs) of virus are then released into the cytoplasm of target cells. Alternatively, severe acute respiratory syndrome-coronavirus (SARS-CoV) may also enter target cell through plasma membrane fusion in a manner resembling to human immune virus (HIV). After S1 subunit of severe acute respiratory syndrome-coronavirus (SARS-CoV) spike (S) protein attaches to angiotensin-converting enzyme 2 (ACE2), S2 subunit changes conformation by inserting the fusion peptide into plasma membrane. Heptad repeat 2 (HR2) domain interacts with heptad repeat 1 (HR1) trimer to construct six-helical bundle (*6-HB*) core, leading to fusion between viral envelope (E) and cellular plasma membrane. Coronaviral ribonucleic acid (RNA) synthesis happens in the cytoplasm on double-walled membrane vesicles. During coronaviral ribonucleic acid (RNA) replication and transcription of subgenomic ribonucleic acids (sgRNAs), the genomic ribonucleic acid (RNA) acts as a template for the synthesis of full-length and subgenomic negative-strand ribonucleic acids (RNAs), the latter through a discontinuous transcription mechanism. In turn, full-length negative-strand ribonucleic acids (RNAs) function as templates for synthesis of genome ribonucleic acid (RNA) and negative strand subgenomic ribonucleic acids (sgRNAs) act as templates for subgenomic messenger ribonucleic acid (mRNA) synthesis. Infected cells contain seven to nine virus specific messenger ribonucleic acids (mRNAs) with coterminal 3' ends, the largest of which is the genomic ribonucleic acid (RNA). All of the messenger ribonucleic acids (mRNAs) carry identical 70–90 nucleotides (nts) leader sequences at their 5' ends. The 3' end of the leader sequence contains transcriptional regulatory sequence (TRS-L), which is also present in the genome just upstream of the coding sequence for each transcription unit [TRS-B (body)], where it acts as a cis-regulator of transcription. All coronavirus transcription regulatory sequences (TRSs) include conserved 6–8 nucleotides core sequence (CS) plus variable 5' and 3' flanking sequences. Betacoronaviruses (β -CoVs) contain a consensus heptameric sequence, 5'-UCUAAAC-3', with the severe acute respiratory syndrome-coronavirus transcription regulatory

sequence (SARS-CoV TRS) having 5'-ACGAAC-3' as the core sequence. Replicative process happens shortly after entrance and uncoating of the virion through production of full-length genomic and subgenomic negative strand intermediates. Genomic ribonucleic acid (RNA) is used as template to directly translate polyprotein 1a/1ab (pp1a/pp1ab), which encodes nonstructural proteins (nsps) to make replication-transcription complex (RTC) in double-membrane vesicles (DMVs). Continuously replication-transcription complex (RTC) replicate and synthesize a nested set of subgenomic ribonucleic acids (sgRNAs), which encode accessory proteins and structural proteins. Nested set of subgenomic ribonucleic acids (sgRNAs) are synthesized by replication-transcription complex (RTC) in a pattern of discontinuous transcription. These subgenomic messenger ribonucleic acids (sgmRNAs) possess common 5'-leader and 3'-terminal sequences. Transcription termination and subsequent acquisition of a leader ribonucleic acid (RNA) occurs at transcription regulatory sequences (TRSs), positioned between open reading frames (ORFs). These minus-strand subgenomic ribonucleic acids (sgRNAs) serve as templates for production of subgenomic messenger-ribonucleic acids (sgmRNAs). Genome and subgenomes of a typical coronavirus (CoV) contain at least six open reading frames (ORFs). The premier open reading frames (ORFs) (open reading frame 1a/b)(ORF1a/b), about two-thirds of whole genome length, encode 16 nonstructural proteins (nsps) (nonstructural protein 1-16) (nsp1-16). There is a -1 frameshift between open reading frame 1a (ORF1a) and open reading frame 1b (ORF1b), leading to production of two polypeptides: polyprotein 1a (pp1a) and polyprotein 1ab (pp1ab). These polypeptides are processed by virally encoded chymotrypsin-like protease (3CL^{pro}) or main protease (M^{pro}) and one or two papain-like protease (PL^{pro}) into 16 nonstructural proteins (nsps). Many of the nonstructural proteins (nsps) carry out fundamental functions in viral ribonucleic acid (RNA) replication and transcription. Some nonstructural proteins (nsps) construct a replication/transcription complex (RTC) (RNA-dependent RNA polymerase, RdRp), which use (+) strand genomic ribonucleic acid (RNA) as a template. Besides RNA-dependent RNA polymerase (RdRp), RNA helicase, and protease activities, which are usual to ribonucleic acid (RNA) viruses, coronavirus (CoV) replicase was recently predicted to employ a variety of ribonucleic acid (RNA) processing enzymes that are not (or extremely rarely) expressed in other ribonucleic acid (RNA) viruses and involve putative sequence-specific endoribonuclease, 3'-to-5' exoribonuclease, 2'-O-ribose methyltransferase, ADP ribose 1'-phosphatase and, in a subset

of group 2 coronaviruses, cyclic phosphodiesterase activities. Enzymatic activities and functional domains of many of these essential nonstructural proteins (nsps) are predicted to be kept between different genera of coronaviruses (CoVs), referring their necessity in viral replicative process. Multiple lines of proof have proposed the role of coronavirus nonstructural protein1 (CoV nsp1) in regulating viral replicative process and gene expression. These 16 nonstructural proteins (nsps) form double-membrane vesicles (DMV). At the same time, this double-membrane vesicle (DMV) is virus replication and transcription complex (RTC). Nonstructural proteins (nsps), particularly non-structural protein3 (nsp3), has a necessary role in virion construction, the replication and transcription of coronavirus (CoV). Other open reading frames (ORFs) on the one-third of the genome close to 3'terminus encodes at least four prime constructional proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. In other words, the genes 2 to 7 are translated from subgenomic messenger ribonucleic acid (sgmRNA), where subgenomic ribonucleic acids (sgRNAs) encode the prime viral constructional proteins and accessory proteins, which are fundamental for virus-cell receptor attachment. The newly constructional produced proteins are released into endoplasmic reticulum (ER). All of these proteins, along with nucleocapsid (N) protein, are linked to viral genomic ribonucleic acid (RNA) and localized in endoplasmic reticulum-Golgi intermediate compartment (ERGIC) part. Although, nucleocapsid (N) protein is known to be fundamental for coronavirus (CoV) replicative process, the particular role that this protein functions in this process remains not known. But, many studies presume that nucleocapsid (N) protein interaction with nonstructural protein 3 (nsp3) serves a critical role in virus replicative process initially in contagion. Besides the four prime structural proteins, different coronaviruses (CoVs) encode particular structural and accessory proteins, such as hemagglutinin (HE) protein, 3a/b protein, and 4a/b protein. All structural and accessory proteins are translated from subgenomic ribonucleic acids (sgRNAs) of coronaviruses (CoVs). Mediating endoplasmic reticulum (ER) and Golgi, recently synthesized genomic ribonucleic acid (RNA), nucleocapsid (N) proteins and envelope (E) glycoproteins assemble and form viral particle buds. Spike (S), envelope (E) and membrane (M) proteins enter endoplasmic reticulum (ER), and the nucleocapsid (N) protein is combined with (+) strand genomic ribonucleic acid (RNA) to lead to a nucleoprotein complex. They merge into the entire virus particle in endoplasmic reticulum-Golgi apparatus compartment. Viruses bud into smooth walled vesicles in endoplasmic reticulum-Golgi intermediate compartment (ERGIC).

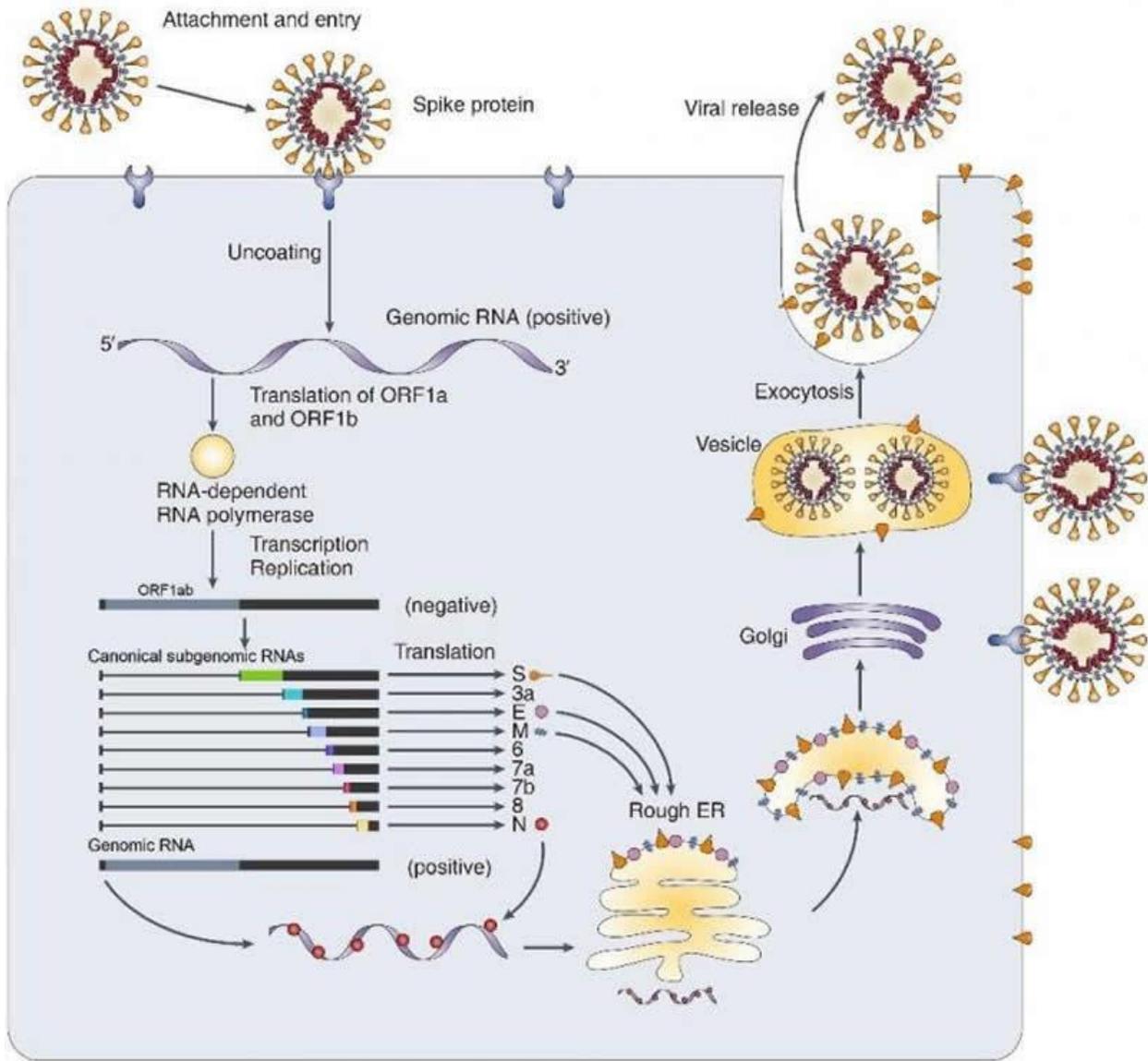
Subsequent budding, virus particles mature in Golgi apparatus, with a compact, electron-dense internal core. Viruses traverse Golgi and are transported in exocytic vesicles which ultimately fuse with plasma membrane to release virus into the extracellular area .

Since mutation rates in replication of ribonucleic acid (RNA) viruses are much higher than that of deoxyribonucleic acid (DNA) viruses, genomes of ribonucleic acid (RNA) viruses are in usual less than 10 kb in length. However, coronavirus (CoV) genome is much larger, with about 30 kb in length, the largest known ribonucleic acid (RNA) viruses. Conservation of such a large genome of coronaviruses (CoVs) may be attributable to particular features of coronavirus (CoV) replication/transcription complex (RTC), which contains several ribonucleic acid (RNA) processing enzymes such as 3'-5' exoribonuclease of nonstructural protein 14 (nsp14). The 3'-5' exoribonuclease is specific to coronaviruses (CoVs) amongst all ribonucleic acid (RNA) viruses, possibly giving a proofreading function of replication/transcription complex (RTC).

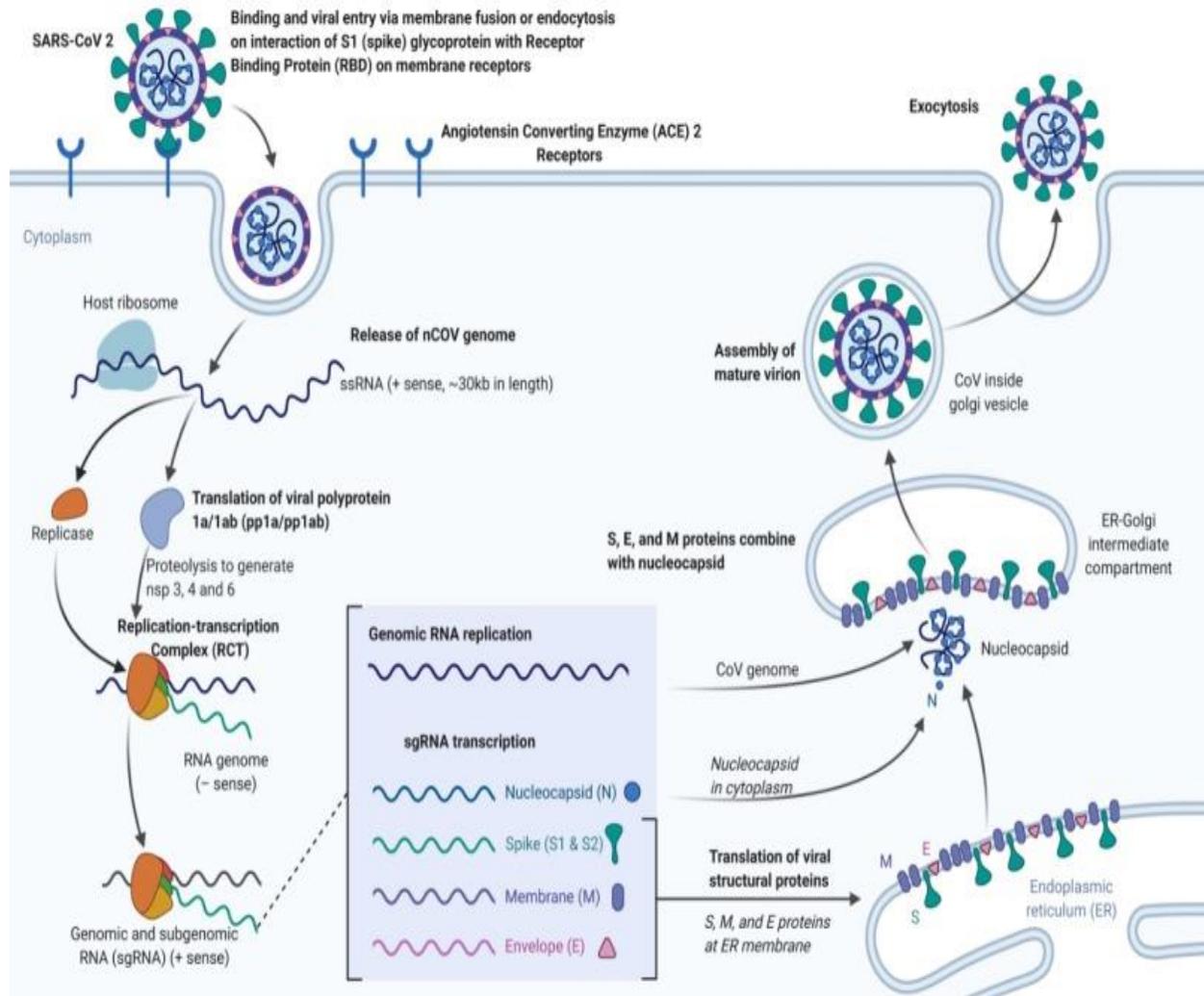


- *Coronaviruses* utilize **RNA-dependent RNA synthesis** to generate mRNAs to be transcribed by the host genome.
- The RNA(+) strand is used to make the enzyme, **RNA-dependent RNA polymerase**.
 - The RNA(+) strand is replicated to RNA(-).
- The RNA(-) strand is used to:
 - [1] make **subgenomic mRNAs** by transcribing from the RNA(-) strand from multiple start sites and in multiple open reading frames (ORFs).
 - [2] Make more RNA(+) via replication.
- Virion progeny is made via the secretory pathway (Rough ER, Golgi apparatus, and exocytosis).

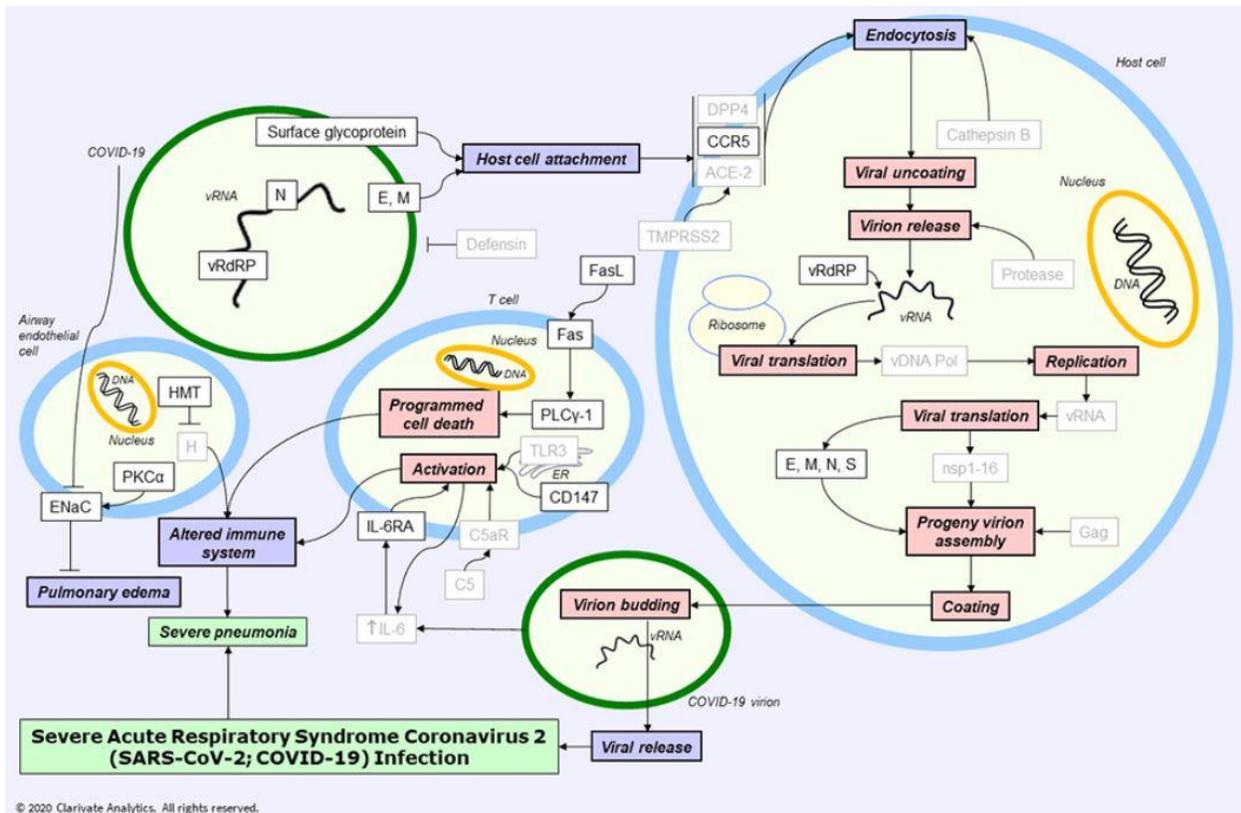
Figure(17): SARS-CoV replication (www.google.com)



Figure(18): SARS-coronavirus-2 life cycle in infected cell (www.google.com)



Figure(19): SARS-coronavirus-2 replication, transcription and translation in infected tissue (www.google.com)



Extracellular	Eukaryotic Plasma Membrane	Validated Protein Target	Recombinant Molecule
Intracellular	Prokaryotic Membrane / Viral Cell Wall	Non Validated Protein Target	Intracellular Effect
Positive Effect	Eukaryotic Nuclear Membrane	Validated Gene Target	Extracellular Effect
Negative Effect		Non Validated Gene Target	Related Condition / Symptom
		MicroRNA	

Figure(20): SARS-CoV-2 infection (www.google.com)

CHAPTER TWO

SYMPTOMS, DIAGNOSIS, ALTERED IMMUNITY , and RISK FACTORS

1.Modes of Transmission of COVID-19

Epidemiologic search in Wuhan at beginning of breakout described a premier association with a seafood market that sold live animals, where most ill individuals had worked or visited and which was thereafter closed for disinfection. However, as breakout progressed, person-to-person spread became the principal way of transference.

Direct person-to-person transference is principal way of transmission of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is thought to be incident through close-range contact, particularly via respiratory droplets; virus released in respiratory secretions when an infected person coughs, sneezes, or talks can contract another person if it makes direct contact with mucous membranes; contagion might also happen if a person's hands are contaminated by droplets or by touching contaminated surfaces and then they touch their eyes, nose, or mouth. Droplets usually do not transmit more than six feet (about two meters).

The range to which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be transferred through airborne way (through particles smaller than droplets that remain in air over time and distance) under natural conditions and how much this way of transfer has contributed to pandemic are argumentative. A study showed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) grown in tissue culture remained viable experimentally generated aerosols for at least three hours; some studies have detected viral ribonucleic acid (vRNA) in ventilation systems and in air specimens of hospital rooms of ill individuals with coronavirus disease 2019 (COVID-19), but cultures for viable virus were negative or not performed in these researches. Other literature using specialized imaging to visualize respiratory exhalations have supposed that respiratory droplets may get aerosolized or carried in a gas cloud and have horizontal trajectories beyond six feet (two meters) with speaking, coughing, or sneezing. However, direct link of these results to epidemiology of coronavirus disease 2019 (COVID-19) and their clinical implications are vague. Although some studies of clusters of cases have presumed a probable for short-range airborne transference of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) within enclosed indoor spaces, long-range airborne transference of

severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has not obviously been recorded. Moreover, in a few articles of health care workers exposed to ill individuals with undiagnosed contagion while using only contact and droplet precautions, no secondary contagions were described despite absence of airborne precautions. Reflecting current suspect regarding transfer mechanisms, recommendations on airborne precautions in health care setting vary by location; airborne precautions are internationally recommended when aerosol-generating procedures are performed.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been detected in non-respiratory specimens, involving feces, blood, ocular secretions, and seminal fluid, but the role of these sites in transference is unsettled. Several researches have shown detection of severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) from feces specimens, even after viral ribonucleic acid (vRNA) could no longer be detected from upper respiratory specimens, and live virus has been cultured from feces in seldom infected persons. Although it would be difficult to state, fecal-oral transfer has not been clinically described, and according to a joint World Health Organization (WHO)-China report, did not appear to be an observable factor in contagion disperse.

Detection of severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) in blood has also been mentioned in some but not all articles that have examined for it. However, possibility of blood borne transfer (e.g., through blood products or needle sticks) seems low; respiratory viruses are in general not transferred through blood borne way, and transfusion-transmitted contagion has not been mentioned for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or for the related Middle East respiratory syndrome coronavirus (MERS-CoV) or severe acute respiratory syndrome coronavirus (SARS-CoV).

There is also no proof that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be transferred through contact with non-mucous membrane loci (e.g., abraded skin).

Coronavirus disease 2019 (COVID-19) ill individuals are main source of contagion, and serious ill persons are regarded to be more contagious than mild ones. Asymptomatically infected persons or ill persons in incubation who exhibit no signs or symptoms of respiratory contagion proven to shed infectious virus, may also be possible sources of contagion. In addition, specines

obtained from ill persons healed from coronavirus disease 2019 (COVID-19) continuously show a positive real-time reverse transcription–polymerase chain reaction (RT-PCR) lab exam, which has never been related in history of human contagious illnesses. In other words, asymptotically contracted persons and sick persons in incubation or healed from coronavirus disease 2019 (COVID-19) may pose grave encounters for illness prevention and control. In other words, it seems that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be transferred prior to the development of symptoms and throughout course of illness, particularly premier in the course. However, most data informing this issue are from studies evaluating viral ribonucleic acid (vRNA) detection from respiratory and other specimens; detection of viral ribonucleic acid (vRNA) does not necessarily indicate presence of contagious virus, and thus prolonged viral ribonucleic acid (vRNA) detection following resolution of illness does not necessarily indicate infectiousness.

Largely indirect data presume that contracted persons are more possibly to be contagious in earlier stages of contagion. Viral ribonucleic acid (vRNA) concentrations from upper respiratory specimens looks to be higher soon after symptom onset in comparison with later in illness. Furthermore, in a study of nine ill persons with moderate coronavirus disease 2019 (COVID-19), contagious virus was isolated from naso/oropharyngeal and sputum specimens during first eight days of illness, but not after this interval, despite continued high viral ribonucleic acid (vRNA) concentrations at these spaces. One modeling search, based on timing of contagion among 77 transported pairs in China (with a mean serial interval of 5.8 days between emergence of symptoms in each pair) and assumptions about incubation period, proposed that infectiousness started 2.3 days prior to symptom rise, peaked 0.7 days before symptom emerge, and declined within seven days; however, most affected individuals with coronavirus disease 2019 (COVID-19) were isolated following symptom emergence, which would reduce risk of transference later in illness regardless of infectiousness. In another search that evaluated over 2500 close contacts of 100 patients with coronavirus disease 2019 (COVID-19) in Taiwan, all of the 22 secondary contracted individuals had their first expose to index case within six days of symptom onset; there were no contagions documented in the 850 contacts whose expose was after this interval. Transport of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from asymptomatic ill persons (or ill persons within incubation period) has also been well stated. Biologic basis for this is supported by a research of a severe acute respiratory syndrome

coronavirus-2 (SARS-CoV-2) breakout in a long-term care facility, in which contagious virus was cultured from real-time reverse transcription–polymerase chain reaction (RT-PCR)-positive upper respiratory tract specimens in presymptomatic and asymptomatic ill persons as early as six days prior to development of usual symptoms. However, the extent to which asymptomatic or presymptomatic transfer happens and how much it contributes to pandemic remain unknown. In an analysis of 157 locally acquired coronavirus disease 2019 (COVID-19) patients in Singapore, transfer during incubation period was evaluated to account for 6.4 percent; in such ill patients, exposures occurred one to three days prior to symptom development.

How long a person remains infectious is also uncertain, but available data suppose that prolonged viral ribonucleic acid (vRNA) shedding after symptom resolution is not obviously associated with prolonged infectiousness. Duration of viral ribonucleic acid (vRNA) shedding is variable; there seems to be a wide extent, which may depend on gravity of illness. In one study, asymptomatic contagion was associated with a higher possibility of nasopharyngeal viral ribonucleic acid (vRNA) clearance within first week of diagnosis compared with symptomatic contagion. In another study of 21 patients with mild illness (no hypoxia), 90 percent had repeated negative viral ribonucleic acid (vRNA) lab exams on nasopharyngeal swabs by 10 days after beginning of symptoms; lab exams were positive for longer in sick persons with more serious illness. On contrary, in another study of 56 ill persons with mild to moderate illness [none required intensive care unit (ICU) admission], median period of viral ribonucleic acid (vRNA) shedding from naso- or oropharyngeal samples was 24 days, and the longest was 42 days.

Detectable viral ribonucleic acid (vRNA) does not always associate with isolation of contagious virus, and there may be a threshold of viral ribonucleic acid (vRNA) concentration below which infectivity is improbable. In the study of nine ill individuals with mild coronavirus disease 2019 (COVID-19), contagious virus was not detected from respiratory specimens when viral ribonucleic acid (vRNA) concentration was $<10^6$ copies/mL. In another study, contagious virus was only detected on stored respiratory specimens that had a high concentration of viral ribonucleic acid (vRNA) [real-time reverse transcription–polymerase chain reaction (RT-PCR) positive at cycle threshold (Ct) <24]. According to information from United States Centers for Disease Control and Prevention (CDC), when sick persons keep to have detectable viral ribonucleic acid (vRNA) in upper respiratory specimens following clinical healing, by three days after healing, ribonucleic acid (RNA) concentrations are mostly at or below the concentrations at

which replication-competent virus can be reliably isolated; additionally, isolation of contagious virus from upper respiratory specimens more than ten days after illness start has only scarcely been documented in ill individuals who had non-serious contagion and whose symptoms have resolved. Contagious virus has also not been isolated from respiratory specimens of ill individuals who have a repeat positive ribonucleic acid (RNA) lab exam following clinical improvement and initial viral riddance.

Occasional searches have described isolation of contagious virus from respiratory or stool specimens more than 10 days after symptom start, principally in individuals with severe or critical coronavirus disease 2019 (COVID-19).

Risk of transfer from a sick person with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion differs by type and period of exposure, use of preventive measures, and likely individual factors (e.g., the amount of virus in respiratory secretions).

Risk of transfer after contact with a sick individual suffering from coronavirus disease 2019 (COVID-19) increases with vicinity and period of contact and appears highest with prolonged contact in indoor settings. Thus, most secondary infections have been described in following settings: amongst household contacts, in health care settings when personal preventive equipment was not used (involving hospitals and long-term care facilities), and in other congregate settings where persons are residing or working in near quarters (e.g., cruise ships, homeless shelters, and detention facilities).

However, reported patients after social or work gatherings also shed light on hazard of transfer through close, non-household contact. Although outdoor settings are mostly indicated lower risk for transport than indoor settings, vicine contact with a contracted individual with coronavirus disease 2019 (COVID-19) continues a risk outdoors.

Contact tracing in premier stages of pestilences at differed locations supposed that generally secondary contagions were amongst household contacts, with a secondary attack percent of up to 15; some studies have presumed even higher household contagion percents. A large seroprevalence survey from Spain also underlined elevated danger of contagion with household contacts. Percent of detectable antibodies (Abs) to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was 31 to 37 (depending on serologic procedure used) among

persons who reported having a household member with affirmed coronavirus disease 2019 (COVID-19), compared with percents of 10 to 14 amongst those who showed a co-worker, non-household family member, or friend with assured coronavirus disease 2019 (COVID-19).

Coronavirus disease 2019 (COVID-19) patients have been frequently reported following family, work, or social assemblances where near personal contact can happen. As an example, epidemiologic analysis of patients in state of Illinois showed probable transport through two family assemblance at which communal food was consumed, hugs were shared, and extended face-to-face conversations were exchanged with symptomatic patients who were thereafter assured to have coronavirus disease 2019 (COVID-19). A report of a breakout amongst a choir group, with 33 affirmed and 20 probable individuals described among 61 members who attended a practice session, raised likelihood of a high transport daanger through singing in close vicinity.

Transporting with a sick individual with coronavirus disease 2019 (COVID-19) is a high-risk expose, as it mostly results in near contact for a prolonged time. An analysis from China looked at risk amongst persons who transported by train and were exposed within three rows to persons later affirmed to have coronavirus disease 2019 (COVID-19). The study described 2334 primary and 234 secondary individuals for a thorough attack percent 0.32. The gravity of secondary contagion was highest (3.5 percent) for persons in seats adjacent to the index sick person, and higher for those seated in same row than for those in front or behind. Seriousness also increased over time of transport. This study could not account for probability that persons seated next to one another could have been from same household or shared other exposes.

Danger of transport with more indirect contact (e.g., passing someone with contagion on the street, handling items that were previously handled by someone with contagion) is not well established and is possibly low. However, many sick persons with coronavirus disease 2019 (COVID-19) do not report having had a specific vicine contact with coronavirus disease 2019 (COVID-19) in the weeks prior to diagnosing of illness.

Virus present on contaminated surfaces may be another source of contagion if susceptible persons touch these surfaces and then transport contagious virus to mucous membranes in mouth, eyes, or nose. The frequency and relative importance of this type of transfer are still obscure. It

may be probable to be a possible source of contagion in settings where there is heavy viral contamination (e.g., in an infected person's household or in health care settings).

Extensive severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) contamination of environmental surfaces in hospital rooms and residential areas of individuals with coronavirus disease 2019 (COVID-19) has been described. In a study from Singapore, viral ribonucleic acid (vRNA) was detected on nearly all surfaces examined (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of an individual with symptomatic mild coronavirus disease 2019 (COVID-19) prior to routine cleaning. Viral ribonucleic acid (vRNA) was not detected on similar surfaces in rooms of two other symptomatic ill individuals following routine cleaning (with sodium dichloroisocyanurate). Viral ribonucleic acid (vRNA) detection notably does not necessarily indicate the presence of contagious virus.

It is unbeknown how long severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can persist on surfaces; other coronaviruses (CoVs) have been examined and may survive on inanimate surfaces for up to six to nine days without disinfection. In a study estimating survival of viruses dried on a plastic surface at room temperature, a specimen containing severe acute respiratory syndrome coronavirus (SARS-CoV) [a virus mostly related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] had detectable infectivity at six but not nine days. However, in a systematic review of similar studies, different disinfectants (including ethanol at concentrations between 62 and 71%) inactivated a number of coronaviruses (CoVs) related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) within one minute. Simulated sunlight has also been observed to inactivate severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) over duration of 15 to 20 minutes in experimental situations, with higher levels of ultraviolet-B (UVB) light associated with more haste inactivation. On the basis of information concerning other coronaviruses (CoVs), time of viral persistence on surfaces also possibly depends on ambient temperature, relative humidity, and size of the primary inoculum.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is believed to have originally been transported to human beings from an animal host, but the ongoing risk of transfer through animal contact is not conclusive. There is no proof supposing animals (involving domesticated animals) as a major source of contagion in humans. Severe acute respiratory

severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion has been described in animals in both natural and experimental settings. There have been scarce reports of animals with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion (including asymptomatic contagions in canines and symptomatic contagions in cats) following too proximate contact with a human with coronavirus disease 2019 (COVID-19). Further, asymptomatic, experimentally infected domestic cats may transport severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to cats they are in the same crate. Seriousness of contagion may be different by species. In one study estimating contagion in animals after intranasal viral inoculation, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) replicated effectively in ferrets and cats; viral replication was also detected in canines, but they seemed to be less susceptible grossly to experimental contagion. Pigs and fowls were not susceptible to contagion. Mink look highly susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); breakouts on mink farms have been mentioned in Netherlands, and in this setting, a suspected case of mink to human transfer was described. Given the unaffirmed transfer risk and apparent susceptibility of some animals to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion, it is recommended that pets be remaining away from other animals or persons outside of household and that persons with affirmed or suspected coronavirus disease 2019 (COVID-19) try to avoid vicine contact with household pets, as they should with human household members, for time of their self-isolation. There have been no reports of domesticated animals transporting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion to human beings.

2.Symptoms of COVID-19 Infection

Like previous coronaviruses (CoVs), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes respiratory illness, and symptoms affect respiratory hygiene. According to Centers for Disease Control and Prevention (CDC), primary symptoms of coronavirus disease 2019 (COVID-19) can be very mild to serious and comprise fever, cough, and dyspnea (shortness of breath). Other symptoms can involve: tiredness, aches, runny nose, sore throat, headache, diarrhea, vomiting, and some persons have experienced loss of smell or taste. Many persons are asymptomatic. Symptoms may onset 2 to 14 days after exposing to the illness. It is suggested that the virus can cause mild, flu-like symptoms, as well as more grave illness. Most

infected individuals look to have mild illness, and about 20% seem to develop more grave illness, involving pneumonia, respiratory failure, and, in some cases, decease.

However, common presenting symptoms involve:

1-Fever

-Incidence differes depending on study (~40-90%).

-Inclines to be high and persistent.

2-Cough

3-Breathlessness

-Dyspnoea onset tends to be around Day 6.

-Multiple reports, particularly in elderly, show silent hypoxia–severe hypoxaemia without breathlessness.

4-Anosmia

-Olfactory and/or taste disturbance is in approximately one third of sick persons.

-In South Korea, 30% of those testing positive had anosmia as their primary apparent symptom in otherwise mild infected persons.

The less common or scarce symptoms involve:

1-Rhinorrhoea, i.e., free discharge of a thin nasal mucus fluid. The presentation, commonly known as a runny nose, happens almost frequently.

2-Sore throat

3-Myalgia which describes muscle aches and pain, which can involve ligaments, tendons and fascia, the soft tissues that connect muscles, bones and organs.

4-Gastrointestinal (GI) presentations (e.g., diarrhea)

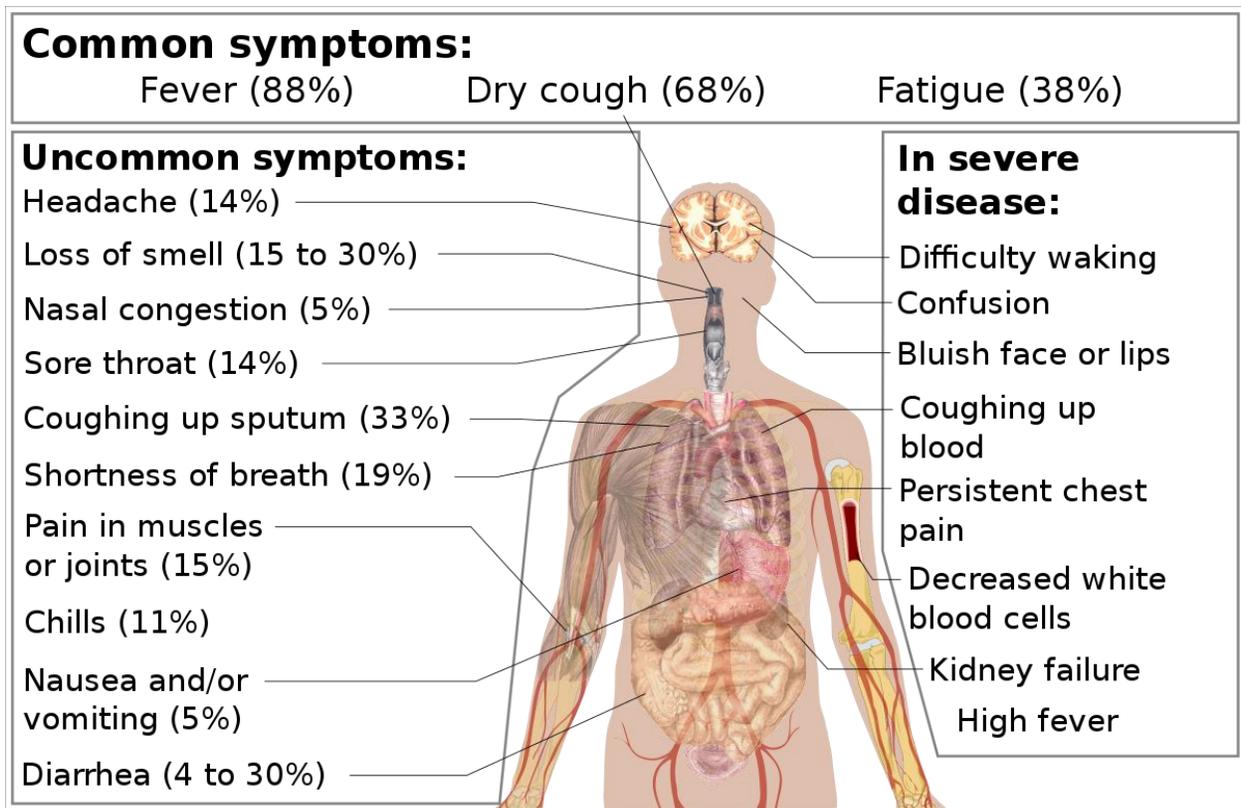
5-Other neurological features

-Meningitis/ encephalitis and hemorrhagic necrotizing encephalopathy (involving altered mental state and coma). It is worthy to define the followings: first, meningitis is an inflammation (swelling) of protective membranes covering brain and spinal cord; second, encephalitis is an inflammation of brain; and acute necrotizing encephalopathy (ANE) is a rare central nervous system (CNS) complication secondary to particular viral contagions which is exemplified by changed mental status and seizures, and frequently this further progresses to profound disability or decease and it is in general regarded as a parainfectious illness secondary to immune response

that is provoked majorly by these viral contagions, i.e., it has been related to intracranial cytokine storms, which result in blood-brain barrier (BBB) breakdown but without direct viral invasion or parainfectious demyelination.

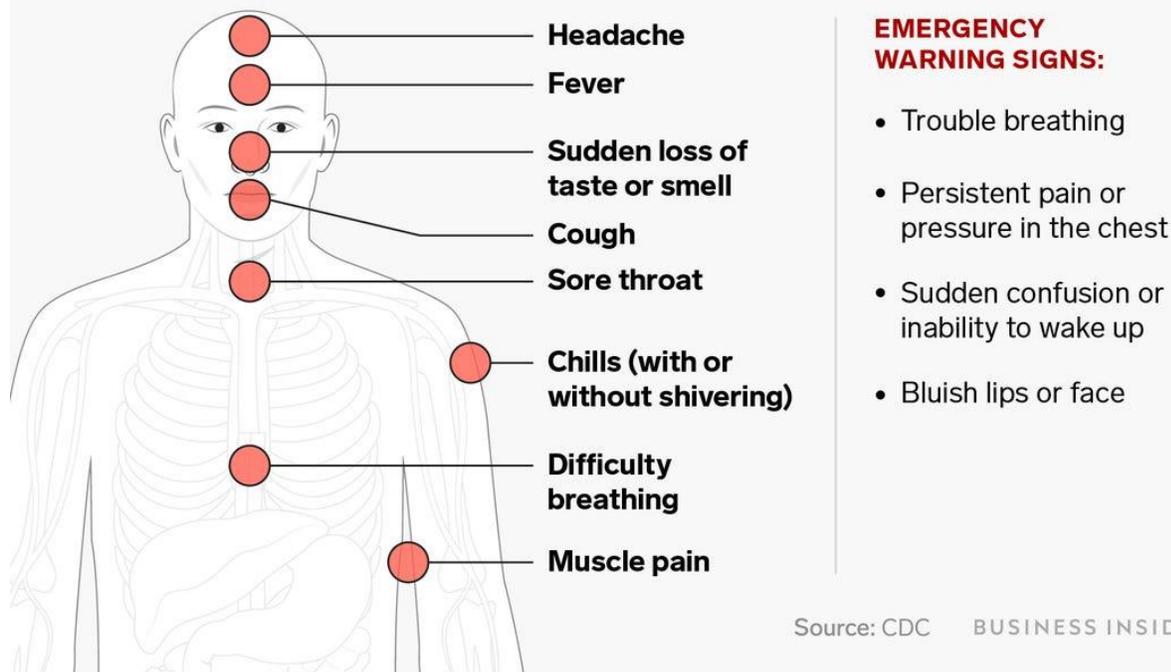
-Guillain-Barre Syndrome (GBS) which is a scarce but grave autoimmune disturbance in which immune system attacks healthy nerve cells in peripheral nervous system (PNS). This leads to weakness, numbness, and tingling, and can eventually cause paralysis.

-Others are encephalopathy, agitation, confusion, and corticospinal tract signs in coronavirus disease 2019- intensive care unit (COVID-19-ICU) ill individuals with acute respiratory distress syndrome (ARDS).



Figure(21): COVID-19 symptoms (www.google.com)

Coronavirus symptoms



Figure(22): COVID-19 symptoms and emergency warning signs (www.google.com)

3.COVID-19 Pathogenesis and Progression

Coronavirus disease 2019 (COVID-19) has been described as a pattern of self-limiting contagious illness, and most affected persons with mild symptoms can heal in 1-2 weeks. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion can cause five different outcomes: asymptotically infected individuals (1.2%); mild to medium infected individuals (80.9%); severely infected individuals (13.8%); critical state of infected individuals (4.7%); and decease (2.3% in all reported infected individuals). A study shows that proportion of asymptomatic contagion in children under 10-years old is as high as 15.8%.

Coronaviruses (CoVs) express trans-membrane glycoproteins [spike (S) proteins] which allow the virus to attach to and gain entrance to target cell. Spike (S) proteins on severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) share many resemblances with those of

severe acute respiratory syndrome coronavirus (SARS-CoV) and attach to surface angiotensin-converting enzyme 2 (ACE2) receptors. Angiotensin-converting enzyme 2 (ACE2) is expressed predominantly on type II pneumocytes but also on upper respiratory tract epithelial cells and small intestine enterocytes. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein seems to attach angiotensin-converting enzyme 2 (ACE2) with higher affinity than severe acute respiratory syndrome coronavirus (SARS-CoV), which may account for its greater transfer. Other cofactors are possibly required, involving transmembrane protease, serine 2 (TMPRSS2). Viral ribonucleic acid (vRNA) replication happens within target cell, utilizing RNA-dependent RNA polymerase (rdRp).

Median incubation period is 4-5 days. Symptoms develop:

- Between 2 and 7 days in 75% of infected persons
- After 14 days in less than 1% of infected persons

Asymptomatic viral shedding may happen at some stage in up to 50% of contracted individuals, although this remains debatable. Most (80%) coronavirus disease 2019 (COVID-19) ill individuals experience mild-to-moderate upper respiratory tract infection (URTI) symptoms for the first 7 days followed by healing. Approximately 20% of contracted individuals experience dyspnea necessitating hospital admission, usually at day 6-8. A small proportion of individuals with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion experience life threatening lung illness exemplified by severe pneumonitis that may progress to acute respiratory distress syndrome (ARDS), involves diffuse, direct and indirect decay to alveoli. However, it is worthy to describe acute respiratory distress syndrome (ARDS) as a severe lung condition. It happens when fluid fills up air sacs in lungs. Too much fluid in lungs can lower amount of oxygen or increase amount of carbon dioxide in bloodstream. Acute respiratory distress syndrome (ARDS) can hinder organs of body from getting oxygen they need to work, and it can eventually lead to organ failure. Profound hypoxemia with relatively preserved lung compliance appears common early. Hypoxemia is mostly described as an abnormally low level of oxygen in blood. More particularly, it is oxygen deficiency in arterial blood. Hypoxemia has many causes, and usually leads to hypoxia as blood is not supplying enough oxygen to tissues of body. Some severely contracted individuals also develop:

- Cytokine storm-a severe reaction akin to hemophagocytic lymphohistiocytosis (HLH) ;

-Myocarditis/ cardiomyopathy (rare): myocarditis is an inflammation of heart muscle (myocardium), while cardiomyopathy indicates illnesses of heart muscle; and

-Disseminated intravascular coagulation (DIC) which is a condition in which small blood clots develop throughout bloodstream, blocking small blood vessels. Increased clotting depletes platelets and clotting factors urgent to control bleeding, causing excessive bleeding. It portends a poor prognosis, and thrombotic complications.

-Post-mortem findings involve:

1-Diffuse alveolar damage usual for acute respiratory distress syndrome (ARDS);

2-Lymphocytic infiltration;

3-Microvascular and large vessel thrombosis;

4-In some cases, a secondary bacterial pneumonia with or without underlying diffuse alveolar damage;

5-Extrapulmonary features involving lymphocytic myocarditis. Any chronic inflammation in a heart biopsy for new-onset heart failure (HF) is considered diagnostic of myocarditis. Lymphocytic myocarditis as seen at autopsy is rich in T cells and macrophages ($M\Phi$), and the inflammation is usually diffuse, with focal myocyte necrosis; and

6-Presence of severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) in lung and other tissues.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion may cause illness ranging in gravity from no symptoms, to mild, moderate or severe coronavirus disease 2019 (COVID-19):

1-Asymptomatic: a small proportion may remain asymptomatic though exact proportion is not known;

2-Proportion of gravity experienced in one large cohort of patients was:

-Mild or moderate – 81%

-Severe – 14 % [dyspnea, respiratory rate (RR) ≥ 30 , oxygen saturation $\leq 93\%$, (arterial pO_2 divided by the FIO_2 (PF ratio) is less than 300, and/or lung infiltrates]. Respiratory rate (RR) is rate at which breathing happens. This is often measured in breaths per minute. Oxygen saturation is a measure of the amount of hemoglobin that is attached to molecular oxygen at a given time point. PaO_2/FiO_2 ratio is the ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2 expressed as a fraction, not a percentage) also called

the Horowitz index for Lung Function, the Carrico index, and (most conveniently) the P/F ratio. A pulmonary infiltrate is a substance denser than air, such as pus, blood, or protein, which lingers within the parenchyma of the lungs. Pulmonary infiltrates can be correlated with pneumonia. Pulmonary infiltrates can be shown on a chest radiograph.

-Critical – 5% [respiratory failure (RF), septic shock and/or multi organ dysfunction (MOD)]. Respiratory failure (RF) is a syndrome in which the respiratory system fails in one or both of its gas exchange actions: oxygenation and carbon dioxide elimination. In practice, it may be classified as either hypoxemic or hypercapnic. Hypoxemic respiratory failure (type I) (HRF type I) is characterized by an arterial oxygen tension (PaO₂) lower than 60 mm Hg with a normal or low arterial carbon dioxide tension (PaCO₂). This is most common form of respiratory failure (RF), and it can be associated with virtually all serious illnesses of lung, which generally involve fluid filling or collapse of alveolar units. Hypercapnic respiratory failure (type II) is characterized by an arterial carbon dioxide tension (PaCO₂) higher than 50 mm Hg. Hypoxemia is common in ill individuals with hypercapnic respiratory failure who are breathing room air. Potential of hydrogen (or power of hydrogen, pH) depends on level of bicarbonate, which, in turn, is dependent on duration of hypercapnia. Common etiologies involve drug overdose, neuromuscular illness, chest wall anomalies, and severe airway disturbances [e.g., asthma and chronic obstructive pulmonary disease (COPD)]. Septic shock (namely, contagion throughout body) is a potentially grave medical condition that happens when sepsis, which is organ injury or destruct in response to contagion, leads to dangerously low blood pressure and anomalies in cellular metabolism.

In case severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2):

(a)-Person not presenting any clinical features supposing a complex course of illness.

(b)-Mild illness features:

-No symptoms or mild upper respiratory tract (URT) symptoms.

-Stable clinical picture

Stable patient presenting with respiratory and/or systemic symptoms or signs, able to preserve oxygen saturation above 92% [or above 90% for ill individuals with chronic lung disease (CLD, or bronchopulmonary dysplasia (BPD))] with up to 4L/min oxygen via nasal prongs.

(c)-Moderate illness characteristics:

-Prostration, severe asthenia, fever $>38^{\circ}\text{C}$ or persistent cough. However, it is important to describe the following: first, prostration indicates a condition in which a person is so tired or weak that he or she is unable to do anything; and second, asthenia, is an ill-defined condition characterized by generalized weakness and usually involves mental and physical fatigue.

-Clinical or radiological signs of lung involvement

-No clinical or laboratory indicators of clinical seriousness or respiratory impairment

(d)-Severe illness: patient meeting any of the following criteria:

-Respiratory rate (RR) ≥ 30 breaths/min

-Oxygen saturation $\leq 92\%$ at a rest state

-Arterial partial pressure of oxygen (PaO₂)/inspired oxygen fraction (FiO₂) ≤ 300

(e)-Critical illness: sick person meets any of following criteria:

-Respiratory failure (RF)

-Occurrence of severe respiratory failure [Arterial partial pressure of oxygen (PaO₂)/inspired oxygen fraction (FiO₂) < 200], respiratory distress or acute respiratory distress syndrome (ARDS).

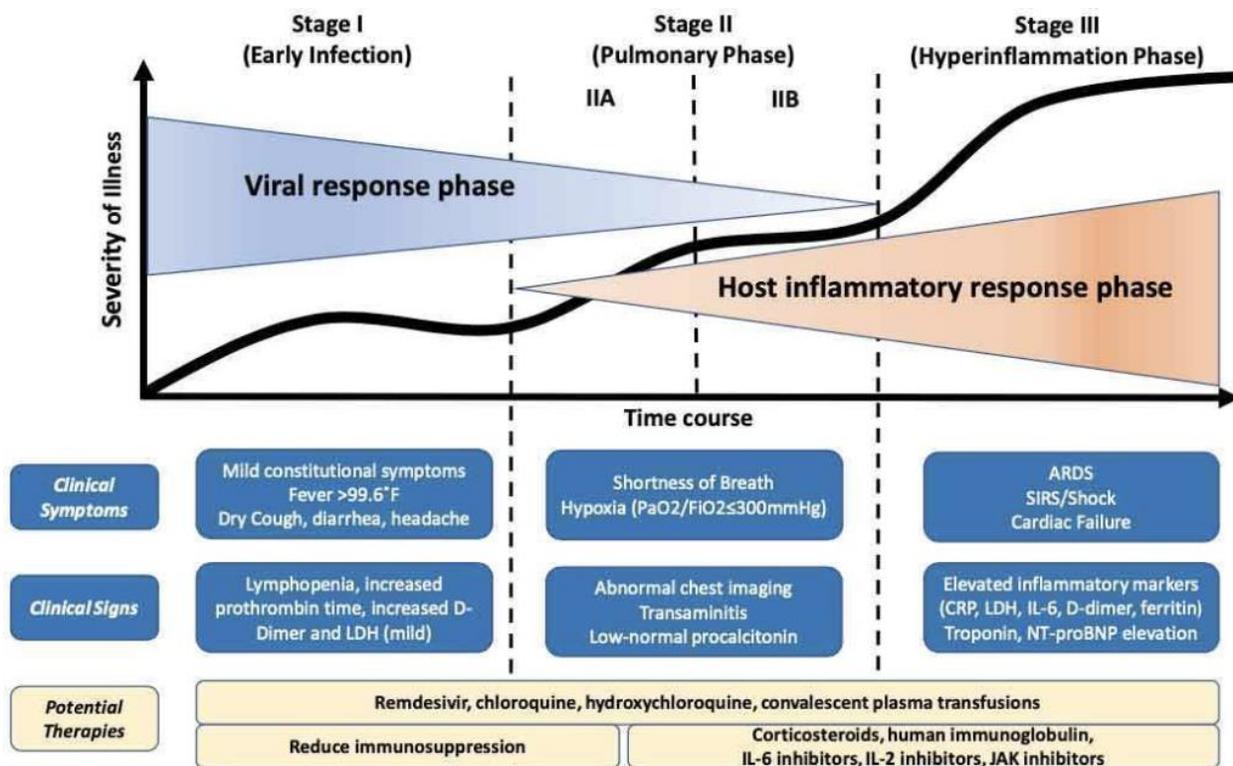
Critical illness involves:

-Patients are deteriorating despite advanced forms of respiratory support (NIV, HFNO). It is regarded to define the followings: first, non-invasive ventilation (NIV) is use of breathing support administered through a face mask, nasal mask, or a helmet, air, usually with added oxygen, is given through mask under positive pressure, generally amount of pressure is alternated depending on whether someone is breathing in or out, and it is termed non-invasive because it is delivered with a mask that is tightly fitted to face or around head, but without a need for tracheal intubation (a tube through mouth into windpipe); and second, high-flow nasal oxygen therapy (HFNO) represents an alternative to conventional oxygen therapy, high-flow nasal oxygen therapy (HFNO) provides humidified, titrated oxygen therapy matching or even exceeding patients' inspiratory demand.

-Sick persons are needing mechanical ventilation. Mechanical ventilation can be described as technique through which gas is moved toward and from lungs through an external device connected directly to sick person. Clinical objectives of mechanical ventilation can be highly diverse: to maintain gas exchange, to reduce or substitute respiratory effort, to diminish consumption of systemic and/or myocardial O₂, to obtain lung expansion, to allow sedation,

anesthesia and muscle relaxation, and to stabilize thoracic wall, etc. Ventilation can be carried out by negative extrathoracic pressure or intermittent positive pressure. According to cycling mechanism, positive-pressure ventilators are classified as pressure-cycled, flow-cycled, or mixed, and according to type of flow in continuous-flow ventilators, as intermittent flow or constant basic flow. Finally, high-frequency ventilators are classified according to their high-frequency mechanism as intermittent positive pressure, oscillatory high-frequency and high-frequency jet ventilators.

-Other signs of significant deterioration, hypotension or shock, impairment of consciousness, or other organ failure



Figure(23):Proposed staging of COVID19 and potential therapies [Brogan G.; Campbell N.; Durie M.; Nickson C. (2020). Coronavirus disease 2019 (COVID-19). LIFE IN THE FASTLANE]

4.Pathology

Pathology autopsy or biopsy studies will always be key to understanding biological characteristics of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). A study showed histological exams of two sick persons who underwent lung lobectomies for adenocarcinoma revealed edema, proteinaceous exudate, and focal hyperplasia of pneumocytes

with only patchy inflammatory cellular infiltration without prominent hyaline membranes. Since both sick persons had not presented symptoms of coronavirus disease 2019 (COVID-19) pneumonia at time of operation, these changes likely exemplify a premier phase of lung pathology of coronavirus disease 2019 (COVID-19) pneumonia. Qian *et al.* (2020) first mentioned pathological features of a sick person who deceased from coronavirus disease 2019 (COVID-19). General observation from fresh eyes demonstrated less fibrosis and consolidation, and instead more exudative lesions in coronavirus disease 2019 (COVID-19) than severe acute respiratory syndrome (SARS). Microscopic exam revealed bilateral diffuse alveolar decay with cellular fibromyxoid exudates, indicating acute respiratory distress syndrome (ARDS). Interstitial mononuclear inflammatory infiltrates were dominated by lymphocytes. Multinucleated syncytial cells with atypical enlarged pneumocytes indicated viral cytopathic-like changes, without notable intranuclear or intracytoplasmic viral inclusions. Results from flow cytometric analysis showed that counts of peripheral CD4⁺ and CD8⁺ T cells were substantially reduced, while their status was hyper-activated. This indicated severe immune injury in later stages of coronavirus disease 2019 (COVID-19), but not by virus direct destruction. However, T helper cells (Th cells), also known as CD4⁺ cells, are a type of T cell that play a crucial role in immune system, primarily in adaptive immune system. They help the activity of other immune cells by releasing T cell cytokines. These cells help suppress or regulate immune responses. They are crucial in B cell antibody (Ab) class switching, in activation and growth of cytotoxic T cells, and in maximizing bactericidal activity of phagocytes such as macrophages (MΦ). Mature T helper (Th) cells express surface protein CD4 and are referred to as CD4⁺ T cells. Such CD4⁺ T cells are mostly treated as having a pre-defined role as helper T cells within immune system. For example, when an antigen-presenting cell (APC) expresses an antigen (Ag) on major histocompatibility complex (MHC) class II, a CD4⁺ cell will aid those cells through a combination of cell to cell interactions [e.g., CD40 (protein) and CD40L] and through cytokines. CD154, also called CD40 ligand or CD40L, is a cell surface protein that mediates T cell helper function in a contact-dependent process and is a member of tumor necrosis factor (TNF) superfamily of molecules. It attaches to CD40 on antigen-presenting cells (APC), which develops many effects depending on target cell type. CD154 acts as a costimulatory molecule and is particularly important on a subset of T cells called T follicular helper cells (TFH cells). On T follicular helper cells (TFH cells), CD154 promotes B cell maturation and serve by engaging

CD40 on B cell surface and therefore easing cell-cell communication. CD8⁺ (cytotoxic) T cells, like CD4⁺ helper T cells, are generated in thymus and express T-cell receptor. However, rather than CD4 molecule, cytotoxic T (T_c) cells express a dimeric co-receptor, CD8, usually composed of one CD8 α and one CD8 β chain. CD8⁺ T cells recognize peptides presented by major histocompatibility complex (MHC) class I molecules, found on all nucleated cells. The CD8 heterodimer attaches to a conserved portion (the $\alpha 3$ region) of major histocompatibility complex (MHC) class I during T cell/antigen presenting cell (APC) interactions. CD8⁺ T cells (often called cytotoxic T lymphocytes, or CTLs) are very important for immune defense against intracellular pathogenic agents, involving viruses and bacteria, and for tumor surveillance. When a CD8⁺ T cell recognizes its antigen (Ag) and becomes activated, it has three major mechanisms to kill infected or malignant cells. First is secretion of cytokines, primarily tumor necrosis factor-alpha (TNF- α) and interferon-gamma (IFN- γ), which have anti-tumor and anti-viral microbial effects. Second major function is production and release of cytotoxic granules. These granules, also found in natural killer (NK) cells, contain two families of proteins, perforin, and granzymes. Perforin forms a pore in membrane of target cell, resemble to membrane attack complex (MAC) of complement. This pore allows granzymes also contained in cytotoxic granules to enter infected or malignant cell. Granzymes are serine proteases (or serine endopeptidases) which cleave proteins inside cell, blocking production of viral proteins and eventually result in apoptosis of target cell. Cytotoxic granules are released only in direction of target cell, aligned along immune synapse, to avoid non-specific bystander destruct to healthy surrounding tissue. CD8⁺ T cells are able to release their granules, kill an infected cell, then move to a new target and kill again, often referred to as serial killing. Third main function of CD8⁺ T cell destruction of infected cells is via Fas/FasL interactions. Activated CD8⁺ T cells express FasL on cell surface, which binds to its receptor, Fas, on surface of target cell. This binding causes Fas molecules on surface of target cell to trimerise, which pulls together signaling molecules. These signaling molecules result in activation of caspase cascade, which also results in apoptosis of target cell. Because CD8⁺ T cells can express both molecules, Fas/FasL interactions are a mechanism by which CD8⁺ T cells can kill each other, called fratricide, to eliminate immune effector cells during contraction phase at end of an immune response (IR). In addition to their critical role in immune defense against viruses, intracellular bacteria, and tumors, CD8⁺ T cells

can also contribute to an excessive immune response (IR) that leads to immunopathology, or immune-mediated damage.

On the basis of public database and single-cell ribonucleic acid (RNA)-Seq technique, pathological searches showed that male donors had a higher angiotensin-converting enzyme 2 (ACE2)-expressing cell ratio than their female counterparts. Only Asian male specimens have five more times as much angiotensin-converting enzyme 2 (ACE2) expressing as white and African American donors. This might explain why severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and previous severe acute respiratory syndrome coronavirus (SARS-CoV) pandemic were concentrated in Asian population and heightened susceptibility of male ill persons, although more proof is needed to draw such conclusions.

Pathological manifestations of severe acute respiratory syndrome (SARS) and Middle East Respiratory syndrome coronavirus (MERS-CoV) contracted individuals may focus on controlling current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. Histology examination revealed a realizable higher viral load of severe acute respiratory syndrome coronavirus ribonucleic acid (SARS-CoV RNA) in lung and small bowels than other organs of body, supposing a reason for manifestation of pneumonia and diarrhea in severe acute respiratory syndrome (SARS) contracted persons. Living severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was also detected positive in fecal specimens and rectal swabs of affected persons, considering a possible oral-fecal transport path. Proper handling of infected corpse and disposal of human excreta of affected persons were of great importance. Thrombi were observed in all six autopsies of severe acute respiratory syndrome coronavirus (SARS-CoV) affected persons, with huge thrombus formation in part of pulmonary vessels. Coagulation function disturbances were recorded in most of severe coronavirus disease 2019 (COVID-19) sick persons, by higher concentrations of D-dimer (DD) and prolonged prothrombin time (PT), some of whom ended in disseminated intravascular coagulation (DIC). This may explain some sudden deceases of clinical healing affected individuals and serve as an indication for illness gravity. In an autopsy study, the only patient without usage of corticosteroids (CSs) showed increased CD3⁺ lymphocyte compared with five other specimens treated with corticosteroids (CSs). This suggested an inhibition of immune system and careful usage of corticosteroids (CSs) in coronavirus disease 2019 (COVID-19) management.

5.COVID-19 Pneumonia Phenotypes and Respiratory Treatments

A debatable report proposed that coronavirus disease 2019 (COVID-19) affected persons seem to have at least two phenotypes, from the perspective of intensive care unit (ICU) management. However, this classification is largely based on anecdote, remains preliminary and management should be optimized for each individual patient as clinically indicated.

1-Coronavirus disease 2019 (COVID-19) pneumonia, Type L

At the beginning, coronavirus disease 2019 (COVID-19) pneumonia presents with following characteristics:

-Low elastance. The nearly normal compliance indicates that amount of gas in lung is nearly normal.

-Low ventilation-to-perfusion (VA/Q) ratio. Since gas volume is nearly normal, hypoxemia may be best explained by loss of regulation of perfusion and by loss of hypoxic vasoconstriction. Accordingly, at this stage, pulmonary artery pressure (PAP) should be near normal.

-Low lung weight. Only ground-glass densities are present on computed tomography (CT) scan, primarily positioned subpleurally and along the lung fissures. As a consequence, lung weight is only moderately increased.

-Low lung recruitability. Amount of non-aerated tissue is very low; thus, recruitability is low.

To conceptualize these phenomena, it is hypothesized the following sequence of events: viral contagion leads to a modest local subpleural interstitial edema (ground-glass lesions) particularly positioned at interfaces between lung structures with different elastic properties, where stress and strain are concentrated. Vasoplegia accounts for severe hypoxemia. Vasoplegia is syndrome of pathological low systemic vascular resistance, the dominant clinical characteristic of which is reduced blood pressure in presence of a normal or raised cardiac output. Normal response to hypoxemia is to increase minute ventilation, primarily by increasing tidal volume (up to 15–20 ml/ kg), which is associated with a more negative intrathoracic inspiratory pressure. Undetermined factors other than hypoxemia markedly stimulate, in these sick persons, the respiratory drive. Near normal compliance, however, explains why some of ill persons present without dyspnea as ill person inhales volume person expects. This increase in minute ventilation causes a decrease in the partial pressure of carbon dioxide (PaCO₂).

2-COVID-19 pneumonia, Type H

The Type H patient:

-High elastance. Decrease in gas volume due to increased edema accounts for increased lung elastance.

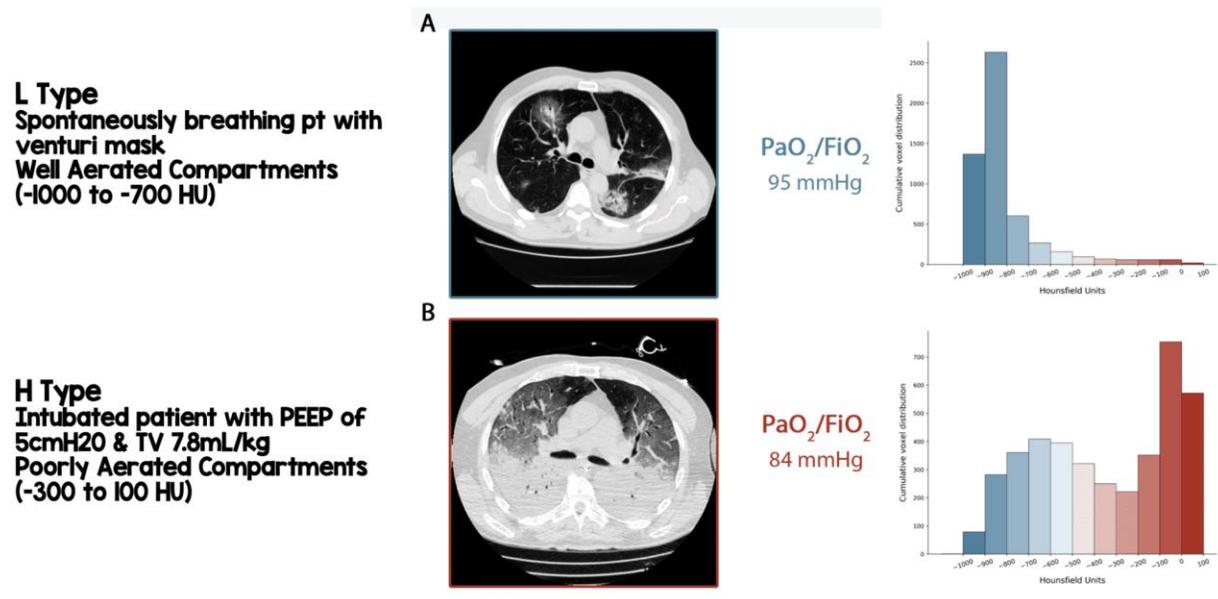
- High right-to-left shunt. This is due to fraction of cardiac output perfusing non-aerated tissue which develops in dependent lung regions due to increased edema and superimposed pressure.

-High lung weight. Quantitative analysis of computed tomography (CT) scan shows a considerable increase in lung weight (>1.5 kg), on the order of magnitude of severe acute respiratory distress syndrome (ARDS).

-High lung recruitability. Increased amount of non-aerated tissue is associated, as in severe acute respiratory distress syndrome (ARDS), with increased recruitability.

Type H pattern, 20–30% of sick persons in the series, fully fits severe acute respiratory distress syndrome (ARDS) criteria: hypoxemia, bilateral infiltrates, decreased respiratory system compliance, increased lung weight and potential for recruitment.

Near Same P/F Ratio But Different Phenotype of COVID-19 Pneumonia



Figure(24): COVID-19 L type and H type (www.google.com)

Respiratory treatment offered to Type L and Type H patients must be different. The proposed management is consistent with what showed in coronavirus disease 2019 (COVID-19), even though overwhelming number of sick persons observed in this pandemic may restrict its broad applicability.

1-First step to reverse hypoxemia is through an increase in fraction of inspired oxygen (F_{iO_2}) to which Type L patient responds well, particularly if not yet breathless.

2-In Type L patients with dyspnea, several noninvasive options are available: high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV). At this stage, measurement (or estimation) of inspiratory esophageal pressure swings is imperative. In absence of esophageal manometry, surrogate measures of work of breathing, such as swings of central venous pressure or clinical detection of excessive inspiratory effort, should be evaluated. In intubated patients, $P_{0.1}$ and $P_{occlusion}$ should also be determined. High positive end-expiratory pressure (PEEP), in some sick persons, may decrease pleural pressure swings and stop vicious cycle that exacerbates lung injury. However, high positive end-expiratory pressure (PEEP) in sick persons with normal compliance may have detrimental effects on hemodynamics. In any case, noninvasive options are questionable, as they may be associated with high failure percents and delayed intubation, in an illness which as usual lasts several weeks.

3-Magnitude of inspiratory pleural pressures swings may determine transition from Type L to Type H phenotype. As esophageal pressure swings increase from 5 to 10 cmH₂O-which are mostly well tolerated-to above 15 cm H₂O, risk of lung injury increases and therefore intubation should be performed as soon as possible.

4-Once intubated and deeply sedated, Type L patients, if hypercapnic, can be ventilated with volumes greater than 6 ml/kg (up to 8–9 ml/kg), as high compliance results in tolerable strain without seriousness of ventilator-induced lung injury (VILI). Ventilator-induced lung injury (VILI) is when mechanical ventilation caused acute lung injury (ALI). Prone positioning should be used only as a rescue maneuver, as lung states are too good for prone position effectiveness, which is based on improved stress and strain redistribution. End-expiratory pressure (PEEP) should be reduced to 8–10 cmH₂O, given that recruitability is low and gravity of hemodynamic failure increases at higher levels. An early intubation may avert transition to Type H phenotype.

5-Type H patients should be treated as severe acute respiratory distress syndrome (ARDS), including higher end-expiratory pressure (PEEP), if compatible with hemodynamics, prone positioning and extracorporeal support.

6.Diagnosis

Reverse transcription polymerase chain reaction (RT-PCR) is a laboratory technique combining reverse transcription of ribonucleic acid (RNA) into deoxyribonucleic acid

(DNA) (called complementary deoxyribonucleic acid or cDNA) and amplification of particular deoxyribonucleic acid (DNA) targets using polymerase chain reaction (PCR). It is primarily used to measure amount of a certain ribonucleic acid (RNA). This is achieved by watching amplification reaction using fluorescence, a technique called real-time PCR or quantitative PCR (qPCR). Combined reverse transcription polymerase chain reaction (RT-PCR) and quantitative polymerase chain reaction (qPCR) are routinely used for analysis of gene expression and quantification of viral ribonucleic acid (vRNA) in search and clinical settings. Diagnosis reverse transcription polymerase chain reaction (RT-PCR) is a diagnostic lab exam that uses nasal swab, tracheal aspirate or bronchoalveolar lavage (BAL) specimens. Primary, and preferred, method for diagnosis is collection of upper respiratory specimens via nasopharyngeal and oropharyngeal swabs. Use of bronchoscopy as a diagnostic method for coronavirus disease 2019 (COVID-19) is not recommended as aerosol that is generated poses a crucial serious issue for both sick individuals and healthcare staff. Bronchoscopy can be considered only for intubated sick individuals when upper respiratory specimens are negative and other diagnostic tools would considerably change clinical medicate. However, bronchoscopy may be indicated when clinical and safety criteria are met and in case of unstated diagnosis. Alternatively, tracheal aspiration and nonbronchoscopic bronchoalveolar lavage (BAL) can be used to collect respiratory specimens in intubated sick persons. Nonbronchoscopic bronchoalveolar lavage (NB-BAL) is a simple technique and as performed by Schindler and Cox in 1994 involved blindly wedging a 5 or 8F infant feeding catheter endobronchially and lavaging one millilitre per kg saline using a syringe. Appropriate samples were collected in 87% of the nonbronchoscopic bronchoalveolar lavage (NB-BAL) specimens. Several methods of non-bronchoscopic bronchoalveolar lavage (NB-BAL) have been illustrated. However, they all involve use of specialized catheters such as balloon-tipped²⁴ or double-lumen catheters, specialized bronchial catheters, mucosity aspirators, and catheters containing a sterile brush and plug. Many require radiological affirm of catheter position prior to performing bronchoalveolar lavage (BAL).

Severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) has been extracted from upper and lower respiratory tract specimens, and virus has been isolated in a cell culture of upper respiratory tract (URT) secretions and bronchoalveolar lavage (BAL) specimens. In one case series, Zou *et al.* (2020) found that concentrations of severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) were higher in

samples collected from upper respiratory tract (URT) (as demonstrated by lower cycle threshold values in the nose) and in first 3 days after symptom beginning, and high concentrations of severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) were also found in specimens collected from upper respiratory tract (URT) specimens from an asymptomatic sic person. Several studies have shown that severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) can also be detected in blood and fecal specimens. It is reasonable that viral ribonucleic acid (vRNA) would be detectable for weeks, as observed in some cases of contagion with severe acute respiratory syndrome coronavirus (SARS-CoV) or Middle East respiratory syndrome coronavirus (MERS-CoV). Viable severe acute respiratory syndrome coronavirus (SARS-CoV) has been isolated from respiratory, blood, urine and fecal samples. Specificity of reverse transcription polymerase chain reaction (RT-PCR) lab exam looks to be very high, although there may be false-positive results due to swab contamination, particularly in asymptomatic sick individuals. Sensitivity rate is not clear, but is estimated to be around 66–80%. Test validity in asymptomatic ill individuals who have been in vicine contact with symptomatic ill individuals is even less clear; the rate of positivity could reach 50% without any proof of symptoms or affirmed contagion. A single negative test does not exclude severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion, particularly in highly exposed individuals, if the test is performed using a nasopharyngeal swab specimen and at start of contagion. In this case, it may be advisable to repeat the test or collect a deeper respiratory tract specimen, such as bronchoalveolar lavage (BAL).

Currently, most coronavirus disease 2019 (COVID-19) examining is performed in laboratory environment. Accurate and scalable point-of-care (POC) lab exams for diagnosis of coronavirus disease 2019 (COVID-19) would increase scope for diagnosis to be made in community and outside laboratory setting.

Current reference test of point-of-care (POC) tests for diagnosis of active contagion by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a real time reverse transcriptase polymerase chain reaction (rRT-PCR) assay. Real time reverse transcriptase polymerase chain reaction (rRT-PCR) assay utilizes viral ribonucleic acid (vRNA) extracted from ill individual specimens [e.g. material collected by nasopharyngeal/oropharyngeal (NP/OP) swab], synthesizes complementary deoxyribonucleic acid (cDNA) through action of reverse transcriptase (RT) enzyme, and amplifies target sequences of viral genome from complementary deoxyribonucleic

acid (cDNA) template. Real time reverse transcriptase polymerase chain reaction (rRT-PCR) can be interpreted in a semi-quantitative manner, with speed of target amplification dependent on concentration and quality of viral ribonucleic acid (vRNA) in first specimen, and thus amplification percent can be used as a proxy for sample viral load. Failure to amplify can be explained as a negative result, but could also be attributable to bad quality of clinical specimen or to early illness status. These assays can be run on standard real time reverse transcriptase polymerase chain reaction (rRT-PCR) thermocyclers or large automated or semi-automated diagnostic platforms. Examining in individuals suspected of having coronavirus disease 2019 (COVID-19) involves sending a respiratory specimen [e.g. oropharyngeal (OP)/nasopharyngeal (NP) swab, sputum or bronchoalveolar lavage (BAL) in seriously unwell ill individuals] to a reference laboratory for real time reverse transcriptase polymerase chain reaction (rRT-PCR) testing. Time between sample gathering and display of results can range from 24 to 72 hours, but could be much faster with a streamlined approach from specimen to answer for urgent clinical scenarios.

A point-of-care (POC) test is performed at or near site where a sick person initially encounters health care system, has a haste turnaround time (approximately 15 min), and provides actionable information that can lead to a change in sick person management. Haste results reduce need for multiple sick person visits, enable timely medicate, and ease containment of contagious illness propagation. However, there are emerging molecular technologies that enable nucleic acid-based approaches at point-of-care (POC). Molecular point-of-care (POC) lab exams utilize same basic methodology as laboratory procedure, but fundamentally automate a differed number of the steps required. As they could be operated in near-patient settings rather than on laboratory bench, they might be expected to provide a shorter time to result. Many of these point-of-care (POC) examinations are molecular-based polymerase chain reaction (PCR)-type tests, but others are serological assays, which detect presence of antibodies (Abs) in a blood sample. Serological assays, using enzyme-linked immunosorbent assays (ELISA), detect presence of antibodies (Abs) to coronavirus (CoV) in a whole blood, plasma or serum sample. These procedures detect immunoglobulins M and G (IgM and IgG). Immunoglobulin M (IgM) is the largest immunoglobulin, and is the first to appear after initial exposure to an antigen (Ag). Immunoglobulin G (IgG) is most common antibody (Ab) found in body, which will appear later but will be generated in abundance. These tests can determine whether an ill individual has

previously been infected with coronavirus (CoV), as they will stay positive after active contagion has gone. Currently, serological checking is not routinely offered as part of screening or diagnosis of coronavirus disease 2019 (COVID-19), as no validated methods are available. These lab exams will not be positive until body has started to make antibodies (Abs) to fight the virus, usually 5-10 days post-contagion. Widespread use of such a lab exam could indicate what percentage of population has had the virus, but these lab exams are less probable to detect contracted persons in early stages of illness. In ill persons where molecular lab exam is negative but there is a strong clinical suspicion of coronavirus disease 2019 (COVID-19), serological checking could support a diagnosis once validated assays become at hand. Antigen (Ag) lab exams may also offer additional information before or at time of taking a specimen for molecular screening, but there are no commercially available antigen (Ag) lab exams for coronavirus disease 2019 (COVID-19) at time of writing.

Most of six molecular point-of-care (POC) lab exams have either got CE marking or emergency the Food and Drug Administration (FDA) approbation.

Almost all point-of-care lab exams are portable, bench top-sized analyzers, apart from the Microsens Dx RapiPrep©COVID-19 test and the MesaBioTech Accula Test, which are smaller, handheld devices.

Usual validated specimen types include nasal, throat, oral or nasopharyngeal swabs. MicrosensDx also supports sputum specimens.

All lab exams require sample preparation, which involves placing swab sample into a viral transport media and pipetting a proportion of sample into a single-use cartridge. Preparation step is typically quoted to take approximately two minutes but may take 5-10 minutes for some devices. The Abbot ID Now kit indicates a 1-2 minute preparation time, as swab is mixed with viral transport media within cartridge in analyzer.

Most point-of-care (POC) devices are single-access and operate with single-use cartridges. Cepheid Xpert SARS-CoV-2 can run 2-4 specimens per run in a random access manner, and GenMark EPlex can run 3 specimens per run in a random access manner.

Storage of most cartridges requires refrigeration plus some time to equilibrate to room temperature, apart from the Cepheid Xpert SARS-CoV-2, Mesa BioTech Accula severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and Abbott ID NOW COVID-19 tests, which can be stored at room temperature prior to use. Time to result varies from 13 minutes (Abbott ID NOW) to 45 minutes (Cepheid Xpert Xpress).

Of five antibody-based tests, two are lateral flow immunoassays (BioMedomics rapid test and Surescreen rapid test cassette), one is a time-resolved fluorescence immunoassay (TRFICA) (Goldsite diagnostics kit) and two are colloidal gold immunoassays (Assay Genie rapid POC kit and VivaDiag COVID-19 IgG-IgM test). All assays detect presence of immunoglobulin G (IgG) and immunoglobulin M (IgM) from whole blood, serum or plasma. They involve pipetting a few drops of blood from a fingerprick or vein onto immunoassay, followed by a couple of drops of buffer solution, with result displayed (as lines similar to a pregnancy test) within 10-15 minutes. All use single-use disposable cartridges, and most can be stored at room temperature.

The reference standard used for comparison in these researches was reverse transcription polymerase chain reaction (RT-PCR) testing. Some diagnostic accurate data was collected from clinical, rather than laboratory exam, the largest such research article being evaluation of BioMedomics IgM-IgG rapid lab exam, which estimates 89% sensitivity and 91% specificity among 525 sick individuals specimens. Being based on published clinical data, this assessment constitutes stronger affirm. It is also found a registered clinical trial protocol for VivaDiag and expect that further clinical accuracy data will become available as coronavirus disease 2019 (COVID-19) pandemic progresses.

Most common laboratory anomalies reported on admission amongst hospitalized sick individuals with pneumonia included leucopenia (9– 25%) or leucocytosis (24–30%), lymphopenia (63%) and elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (37%). Amongst 1099 coronavirus disease 2019 (COVID-19) sick individuals, lymphocytopenia was present in 83%; in addition, 36% had thrombocytopenia and 34% had leucopenia. A mild thrombocytopenia, hypertransaminasaemia and an increase in lactate dehydrogenase (LDH, also known as lactic acid dehydrogenase) have also been recorded. Increased inflammation indices, usually including reduced procalcitonin (PCT) and increased C-reactive protein (CRP) levels, are associated with clinical gravity. It was documented an average C-reactive protein (CRP)

concentration of 1.1 mg/dL in sick individuals with normal percentage oxygen saturation (SatO₂) and of 6.6 mg/dL in hypoxemic sick individuals. A study noticed a correlation between C-reactive protein (CRP) and disease risk. Increased troponin (Tn) was also reported in 7% of sick individuals who in the end deceased because of fulminant myocarditis (FM). Troponin (Tn) seems to be a potent prognostic indicator of disease. Finally, it was noticed that D-dimer (DD) and ferritin concentrations were usually high in hospitalized sick individuals.

Usual computed tomography (CT) findings in individuals with coronavirus disease 2019 (COVID-19) were ground-glass opacities, especially on the peripheral and lower lobes, and bilateral multiple lobular and subsegmental areas of consolidation, especially in intensive care unit (ICU) ill individuals. Number of lung segments involved was found to be related to illness seriousness. These opacities tended to flow together and thicken with progression of illness. Non-usual computed tomography (CT) findings involved pleural effusion (only about 5%), masses, cavitations and lymphadenopathies; therefore, these would propose alternative diagnostic route. In one study, time period from symptom start to initial computed tomography (CT) scan was assessed and authors found that 56% of sick individuals who presented symptoms within 2 days had normal computed tomography (CT) images. Computed tomography (CT) sensitivity looks to be high in sick individuals with positive reverse transcription polymerase chain reaction (RT-PCR) (86–97% in different case studies) and lower in sick individuals with only constitutional and nonrespiratory symptoms (about 50%). Conventional chest X-ray sensitivity is lower at around 59%. Usual chest computed tomography (CT) findings in coronavirus disease 2019 (COVID-19) involve bilateral infiltrates with multiple ground-glass opacities or consolidation, but no edema. Some sick individuals exhibit asymmetrical edematous lesions and atelectasis, or scattered fibrosis. Given the low resolution of plain radiography, it is recommended that chest computed tomography (CT) be performed in all serious sick persons. However, unfortunately, computed tomography (CT) scanning is not available in all emergency departments, and may require transfer of sick person to a radiology suite.

Ultrasound has been used as a diagnostic tool in a very limited number of sick persons. Ultrasound has a very low specificity, and, despite being affected by factors such as illness seriousness, contracted individual weight and operator skill, sensitivity is estimated to be around 75%. Nevertheless, ultrasound may play a role in predicting progression of illness through detection of interstitial lung disease (ILD, another term for pulmonary fibrosis) features, such as

B lines and subpleural consolidations. Lung ultrasound (LU) is a developing technique which has been used extensively in acute respiratory distress syndrome (ARDS) affected persons over last decades and may be useful for safe, noninvasive bedside diagnosis of coronavirus disease 2019 (COVID-19) pneumonia; specific lung ultrasound (LU) patterns have been defined. Nevertheless, this technique has several limitations, such as need for formal training, interobserver variability, and limited accuracy [especially in obese sick persons and in presence of subcutaneous emphysema (SCE, SE)].

There have been few reports of chest computed tomography (CT) findings in coronavirus disease 2019 (COVID-19). Computed tomography (CT) imaging demonstrates five stages in accordance to time since onset and illness progression:

1-Very early phase [asymptomatic, positive nasopharyngeal (NP) swab]: single, double, or scattered focal ground-glass opacity, nodules located in central lobule surrounded by patchy ground-glass opacities, patchy consolidation and air bronchogram sign;

2-Early phase: (1–3 days after clinical manifestations): dilatation and congestion of alveolar septal capillaries, exudation of fluid in alveolar cavity, interlobular interstitial edema;

3-Rapid progression phase (3–7 days after clinical manifestations): massive accumulation of cell-rich exudates in the alveolar cavity, vascular expansion and exudation in the interstitium, large-scale light consolidation with air bronchogram sign;

4-Consolidation phase (7–14 days after clinical manifestations): fibrous exudation of alveolar cavity with multiple patchy consolidations; and

5-Dissipation phase (2–3 weeks after clinical manifestations): grid-like thickening of interlobular septum, thickening and strip-like twisting of bronchial walls, and a few scattered patchy consolidations.

Monitoring of chest computed tomography (CT) features is of extreme importance in these ill individuals to personalize medication strategies and mechanical ventilator settings. Chest computed tomography (CT) scan particularly can help in evaluation of areas of atelectasis or overperfusion and shunting, as well as assessment of risk of pulmonary embolism (PE). It has

been described three main chest computed tomography (CT) patterns in coronavirus disease 2019 (COVID-19) sick persons, representing three different phenotypes:

1-Multiple, focal, possibly overperfused ground-glass opacities mainly in subpleural region;

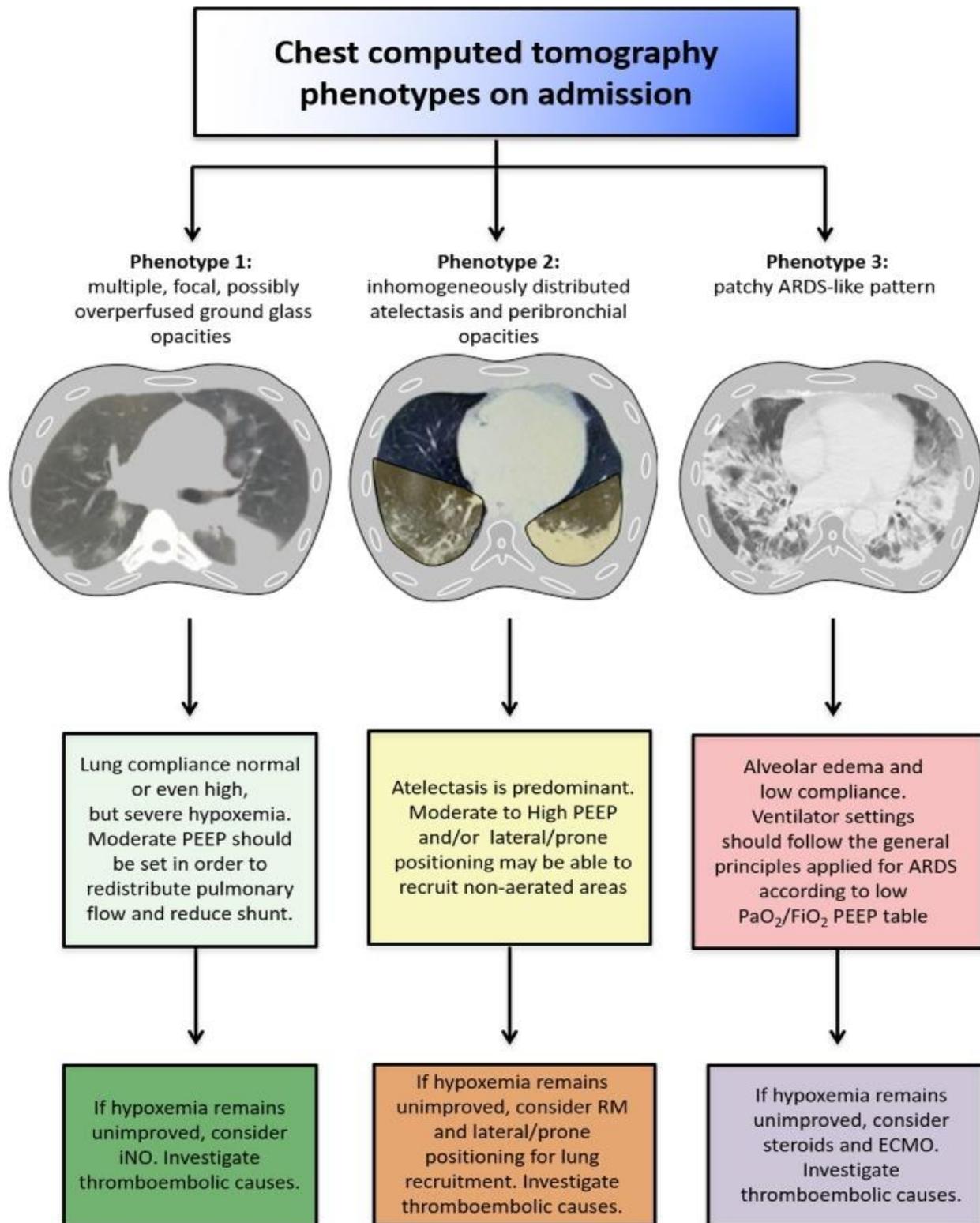
2-Inhomogeneously distributed atelectasis and peribronchial opacities; and

3-A patchy ARDS-like pattern.

These differing phenotypes are attributable to different pathophysiological mechanisms, and therefore require different ventilatory strategies; however, the phenotypes proposed look to be in agreement with Gattinoni *et al.* (2020), who presumed a phenotype L (low elastance, low ventilation to perfusion ratio, and low lung reclinability) compatible with the phenotype 1, a phenotype H (high elastance, and similar ARDS pattern), compatible with the phenotype 3, and a transitioning phenotype, which reflects the evolution of the disease.

Computed tomography (CT) and ultrasound findings appear to be superimposable; computed tomography (CT) appears to be more precise in detecting apical intraparenchymal lesions, whilst ultrasound can describe smallest subpleural lesions and pleural effusions. Sensitivity for subpleural lesions increases when a linear probe is used. Main ultrasound findings involve isolated or confluent B lines, and irregular or interrupted pleural line thickening with dynamic air bronchogram.

Most of these pathological findings are located in lower and posterior areas. It is possible to scan in color Doppler mode in order to detect a reduced blood supply in the (usually increased in other inflammatory illnesses). Use of computed tomography (CT) for all ill individuals seems to be unreasonable in terms of time, cost and radiation exposure, particularly as management and therapeutic approach would not depend substantially on results. However, it is suggested that computed tomography (CT) scanning should be reserved for ill individuals with an undefined clinical picture, as well as differential diagnosis.



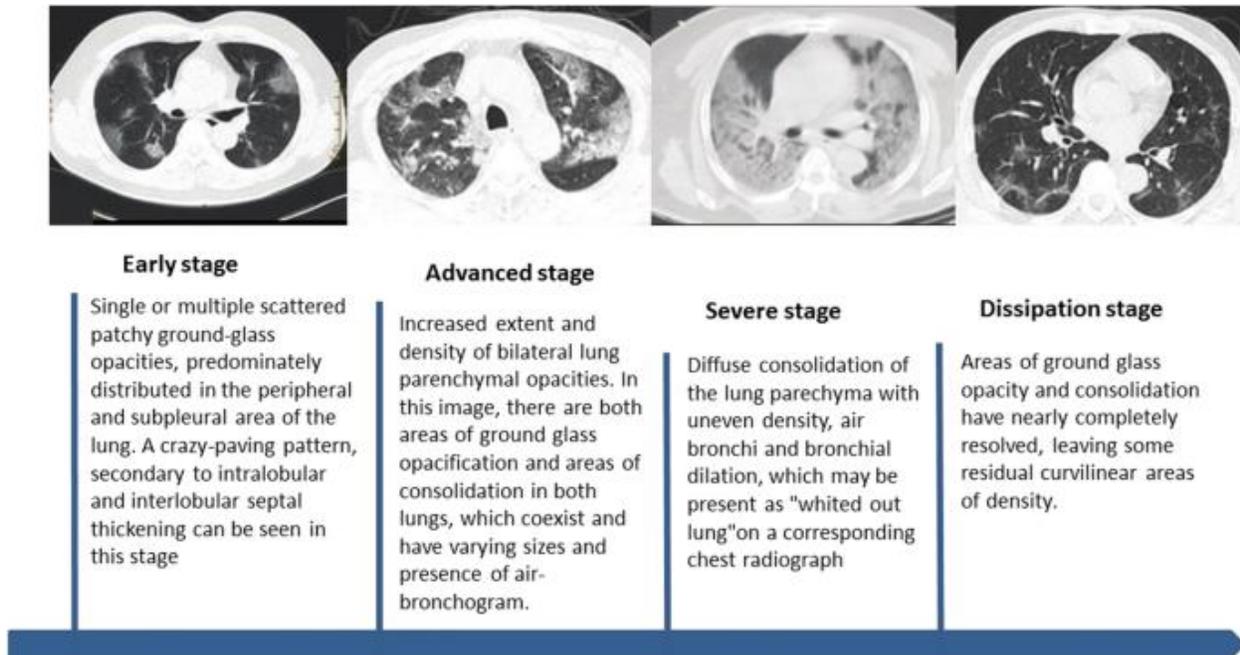
Figure(25):Chest CT finding in COVID-19[Robba et al. (2020). Distinct phenotypes require distinct respiratory management strategies in severe COVID-19. Respir Physiol Neurobiol, 279, 103455. doi:10.1016/i.resn.2020.103455

In figure(25) above: summary of key points for respiratory management of coronavirus disease 2019 (COVID-19) ill individuals according to three distinct phenotypes.

Phenotype 1: good compliance, but severe hypoxemia. Positive end-expiratory pressure (PEEP) should be set with aim to redistribute pulmonary flow and reduce shunting. In this case, using principles generally applied in acute respiratory distress syndrome (ARDS), and thus setting positive end-expiratory pressure (PEEP) according to best driving pressure, will probably lead to use of lower positive end-expiratory pressure (PEEP) (as compliance is good), resulting in less oxygenation. Inhaled nitric oxide (iNO) could be considered in these cases, and prone positioning can redistribute perfusion, but is generally not very useful at this stage.

Phenotype 2: atelectasis and derecruitment are predominant. In this case, high positive end-expiratory pressure (PEEP) and prone positioning can recruit non-aerated areas of the lung. Recruitment maneuvers (RMs) may play a role in these cases, whereas inhaled nitric oxide (iNO) is less useful.

Phenotype 3: typical computed tomography (CT) pattern of moderate-to-severe acute respiratory distress syndrome (ARDS), with alveolar edema and low compliance. Respiratory settings should follow general principles applied for acute respiratory distress syndrome (ARDS). Positive end-expiratory pressure (PEEP) should be set according to best driving pressure; eventually, recruitment maneuvers (RMs), prone positioning, and extracorporeal membrane oxygenation (ECMO) may be considered. Extracorporeal membrane oxygenation (ECMO) is a procedure where a critical ill individual gets life support from a modified heart lung machine which can provide respiratory, circulatory or both respiratory and circulatory support.



Figure(26):CT manifestations of different stages of COVID-19 [Yang W.; Sirajuddin A.; Zhang X.; Liu G.; Teng Z.; Zhao S.; Lu M. (2020). The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). Springer. European Radiology. <https://doi.org/10.1007/s00330-020-06827-4>]

7. Altered Immunity and Convalescent Plasma Treatment in COVID-19 Infection

Immune response is vital for control and resolution of coronavirus (CoV) contagions, while it can also lead to immunopathogenesis, associated with immune response out of control. Spike (S) proteins of coronavirus (CoV) binds to host cells by angiotensin-converting enzyme 2 (ACE2), fusing to membrane and release viral ribonucleic acid (vRNA). Viral ribonucleic acids (vRNAs), as pathogen-associated molecular patterns (PAMPs), are detected by pattern recognition receptors (PRRs). Usually, Toll-like receptor3 (TLR3), Toll-like receptor7 (TLR7), Toll-like receptor8 (TLR8), and Toll-like receptor9 (TLR9) sense viral ribonucleic acid (vRNA) and deoxyribonucleic acid (DNA) in endosome. It is important to refer that Toll-like receptors (TLRs), a superfamily of transmembrane interleukin-1 receptor (IL-1R)-like molecules, serve in innate immune system by distinguishing different pathogenic agents depending on molecular signatures; Toll-like receptors (TLRs) are pattern recognition receptors (PRRs). They contain leucine (Leu)-rich motifs and a cytoplasmic region, Toll/interleukin-1 receptor (TIR) domain, that is necessary for cell signaling. These receptors are largely expressed on cell surface, although Toll-like receptors (TLRs) 7 to 9 have been found intracellularly. Signaling through these receptors initiates formation of Toll-like receptor (TLR) homodimers and heterodimers, leading to production of proinflammatory cytokines/chemokines and other mediators. Toll-like receptors (TLRs) are expressed in monocytes/macrophages (MΦ), dendritic cells (DCs), B cells, and mast cells, but some are found in certain nonimmune cells, involving cells lining mucosal surfaces (e.g., intestinal epithelial cells). Also, receptor expression is modulated by microbial invasion, microbial components, and cytokines. Viral ribonucleic acid (vRNA) receptor retinoic-acid inducible gene I (RIG-I), cytosolic receptor melanoma differentiation-associated gene 5 (MDA5), and nucleotidyltransferase cyclic GMP-AMP synthase(cGAS) are responsible for recognition of viral ribonucleic acid (vRNA) and deoxyribonucleic acid (DNA) in cytoplasm. These complex signaling recruit adaptors, including TIR-domain-containing adapter-inducing interferon-β (TRIF), mitochondrial antiviral-signaling protein (MAVS), and stimulator of interferon genes protein (STING) to induce downstream cascades molecules, including adaptor molecule myeloid differentiation primary response 88 (MYD88) and result in activation of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon regulatory factor 3 (IRF3) and production of type I interferons (IFN-α /β), and by some growth factors and cytokines. Many biological activities have been demonstrated such as

direct antiviral effects, regulation of immune responses, antiproliferation, and modulation of expression of major histocompatibility class I (MHC I) and major histocompatibility class II (MHC II) and a series of pro-inflammatory cytokines. Hence, virus-cell interactions produce a diverse set of immune mediators against invading virus. Innate immunity is needed in a precise regulation to eliminate virus, otherwise will result in immunopathology. A few plasma cytokines and chemokines were shown elevated in coronavirus disease 2019 (COVID-19) affected individuals, involving interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-4 (IL4), interleukin-7 (IL-7), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13), interleukin-17 (IL-17), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), interferon gamma-induced protein 10 [IP-10, also called as C-X-C motif chemokine ligand 10 (CXCL10) or small-inducible cytokine B10], monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1 α (MIP-1 α), hepatocyte growth factor (HGF), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α). An anatomy report of coronavirus disease 2019 (COVID-19) pneumonia corpse notably demonstrated that coronavirus disease 2019 (COVID-19) caused an inflammatory response in lower airway and led to lung injury. Collectively, virus particles invade respiratory mucosa firstly and infect other cells, provoking a series of immune responses and production of cytokine storm in body, which may be associated with critical condition of coronavirus disease 2019 (COVID-19) sick individuals. By retrospectively tracking dynamic changes of lymphocyte (LYM)% in deceased cases and cured cases, this study presumes that lymphocyte count is an efficient and reliable indicator for disease classification and prognosis in coronavirus disease 2019 (COVID-19) patients. A high correlation of blood lymphocytes (LYM) with illness progression proposed that lymphocyte (LYM) deficiency or incapacity is the key cellular pathology of coronavirus disease 2019 (COVID-19). Protection, maintenance or promotion of lymphocyte (LYM) concentrations might have a well effect on prevention and management of coronavirus disease 2019 (COVID-19).

During development of mild illness into severe condition, proportion of lymphocytes (LYM) in blood gradually decreased and maintained at a low level. By the time the illness began to improve, lymphocyte (LYM)% in blood gradually rose to normal or nearly normal levels. Sick persons with persistently low levels of blood lymphocytes (LYM), especially less than 5%, usually had a poor prognosis. Therefore, it is presumed that lymphocyte (LYM)% should be used as an indicator for assessing effectiveness of clinical drugs or therapies.

Lymphocytes (LYM) play a decisive role in keeping immune homeostasis and inflammatory response throughout body. Understanding mechanism of decreased blood lymphocyte (LYM) concentrations is anticipated to provide an efficient strategy for therapy of coronavirus disease 2019 (COVID-19). There are four possible mechanisms leading to lymphocyte (LYM) deficiency and as following:

1-Virus might directly infect lymphocytes (LYM), causing lymphocyte death. Lymphocytes (LYM) express coronavirus (CoV) receptor angiotensin-converting enzyme2 (ACE2) and may be a direct target of viruses.

2-Virus might directly destroy lymphatic organs. Acute lymphocyte decline might be related to lymphocytic dysfunction, and direct damage of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to organs such as thymus and spleen cannot be ruled out.

3-Inflammatory cytokines continued to be disordered, perhaps leading to lymphocyte (LYM) apoptosis. Basic researches confirmed that tumor necrosis factor-alpha (TNF α), interleukin-6 (IL-6) and other pro-inflammatory cytokines could trigger lymphocyte (LYM) deficiency.

4-Inhibition of lymphocytes (LYM) by metabolic molecules that are produced by metabolic disturbances, such as hyperlactic acidemia. Lactate concentrations greater than 2 mmol/L represent hyperlactatemia, whereas lactic acidosis is in general described as serum lactate concentration above 4 mmol/L. Lactic acidosis happens when lactic acid (LA) production exceeds lactic acid (LA) clearance. Increase in lactate production is usually caused by impaired tissue oxygenation, either from decreased oxygen delivery or a defect in mitochondrial oxygen utilization. Severe type of coronavirus disease 2019 (COVID-19) ill individuals had elevated blood lactic acid (LA) concentrations, which might suppress proliferation of lymphocytes (LYM). Multiple mechanisms mentioned above or beyond might work together to cause lymphopenia.

A study presumed that lymphocytes (LYM)% can be used as a reliable indicator to classify moderate, severe and critical ill types independent of any other auxiliary indicators. Lymphopenia is an efficient and reliable indicator of severity and hospitalization in coronavirus disease 2019 (COVID-19) ill individuals. It is suggested that Time-LYM% model (TLM) should be involved in diagnosis and therapeutic guidelines of coronavirus disease 2019 (COVID-19).

Time-LYM% model (TLM) is defined as follows: ill individuals have varying lymphocytes (LYM)% after start of coronavirus disease 2019 (COVID-19).

Effective antiviral responses of host innate and adaptive immunity, involving production of various pro-inflammatory cytokines, activation of T cells, CD4 and CD8+ T cells, are necessary for controlling viral replication, limiting spread of virus, inflammation and cleaning infected cells. Nevertheless, tissue injury caused by the virus could stimulate exaggerated production of proinflammatory cytokines, the recruitment of pro-inflammatory macrophages (MΦ) and granulocytes. This results in cytokine storm termed as a macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH), thus leading to further tissue damage. Data obtained from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contracted ill persons have shown that severe cases may be characterized by a cytokine storm inexorably developing to acute respiratory distress syndrome (ARDS). Several features of coronavirus disease 2019 (COVID-19), such as cytokine profile, serological markers, and clinical symptoms, resemble secondary hemophagocytic lymphohistiocytosis (sHLH) usually stimulated by viral contagion. Moreover, another important proof is that severity of coronavirus disease 2019 (COVID-19) is related to concentration of proinflammatory cytokines and subsets of immune cells. Coronavirus disease 2019 (COVID-19) possesses different concentrations of various cytokines and chemokines through mild to severe stage of illness. In severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contracted individuals, retrospective analysis has demonstrated that initial plasma concentrations of interleukin-1beta (IL-1β), interleukin-1 receptor antagonist (IL-1RA), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-10 (IL-10), interferon-gamma (IFN-γ), monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein-1alpha (MIP-α), macrophage inflammatory protein-1beta (MIP-1β), granulocyte colony stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-α) are elevated in ill individuals with coronavirus disease 2019 (COVID-19). Further analysis has indicated that plasma levels of interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-17 (IL-17), interleukin-10 (IL-10), monocyte chemoattractant peptide-1 (MCP-1), macrophage inflammatory protein-1alpha (MIP-1α), and tumor necrosis factor-alpha (TNF-α) in intensive care unit (ICU) contracted individuals are higher than non-intensive care unit (ICU) ill individuals. In addition, plasma concentrations of interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α), recognized

in severe contagion, are distinguishably greater than those in non-severe contagion. Few retrospective studies have demonstrated that lung injury reported with Murray score is potently correlated with concentration of interleukin-1alpha (IL-1 α), interleukin-1 receptor antagonist (IL-1RA), interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-10 (IL10), interleukin-17 (IL-17), interferon-gamma (IFN- γ), interferon-gamma (IFN- γ) inducible protein-10 (IP-10), granulocyte colony stimulating factor (G-CSF), and monocyte-chemotactic protein 3 (MCP-3) and these cytokines and chemokines excluding monocyte-chemotactic protein 3 (MCP-3) are positively related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral load. It was found that plasma concentration of interleukin-6 (IL-6), regarded as a noticeable cytokine contributing to macrophage activation syndrome (MAS), elevated both in mild and severe sick person groups of coronavirus disease 2019 (COVID-19), severe sick persons had a considerable higher concentration of interleukin-6 (IL-6) than mild or nonsevere sick persons. Moreover, based on evaluation of pulmonary infiltration in sick persons with acute respiratory distress syndrome (ARDS), large area of lung injury ($\geq 50\%$) was closely correlated with increased concentration of interleukin-6 (IL-6) and subgroup of lymphocytes (LYM) in peripheral blood. During contagion, both innate and adaptive immune cells synergistically participate in anti-viral response. The important increment in number of neutrophils, leukocytes, and the neutrophil-lymphocyte ratio (NLR) has been realized in severe coronavirus disease 2019 (COVID-19) in comparison with mild cases. Prominent lymphopenia, referring to impairment of immune system, develops in most coronavirus disease 2019 (COVID-19) sick persons particularly in severe ones. Therefore, it looks that neutrophils and leukocytes might reinforce cytokine storm other than lymphocytes (LYM) in coronavirus disease 2019 (COVID-19). Concentration of lymphocytes (LYM) and subsets of T cells which play a noticeable role in balancing of immune response (IR) varies according to type of virus due to possible viral pathologic mechanism. Previous investigations have shown that total count of lymphocytes (LYM) and subset of T cells are decreased in ill individuals with severe acute respiratory syndrome coronavirus (SARS-CoV) disease. Data from later studies have supposed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion can cause immune dysregulation through affecting subsets of T cells. Considerable alleviation of T cells is recognized in coronavirus disease 2019 (COVID-19) and more pronounced in severe cases. In ill individuals with coronavirus disease 2019 (COVID-19), concentration of helper T cells (CD3+, CD4+) and cytotoxic suppressor T

cells (CD3+, CD8+), and regulatory T (Treg) cells are below normal concentration while helper T (Th) cells and regulatory T (Treg) cells in severe ill individuals are significantly lower than nonsevere ill individuals. Regulatory T (Treg) cells are responsible for keeping immune homeostasis with suppressing activation, proliferation, and proinflammatory function of most lymphocytes (LYM) including CD4+ T cells, CD8+ T cells, natural killer (NK) cells, and B cells. Further, percentage of naïve helper T cells amplifies while percentage of memory helper T cells and CD28+ cytotoxic suppressor T (Tc) cells decreases in severe coronavirus disease 2019 (COVID-19). Equilibrium between naïve T cells and memory T cells is essential for mediating effective immune response (IR). In addition to T cells, decrease of B cells and natural killer (NK) cells are observed in coronavirus disease 2019 (COVID-19). Another potent finding is affirmed strong relationship between inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) and subset of lymphocytes. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for immune dysregulation with induction of aberrant cytokine and chemokine response, alteration in concentration of subgroup of lymphocytes all of which might develop cytokine storm and further tissue damage. Excessive inflammatory response with characteristics of cytokine storm cause severe illness course and worsens prognosis in coronavirus disease 2019 (COVID-19). Definitive and most effective therapies for coronavirus disease 2019 (COVID-19) drugs would be antiviral agents that directly target severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Considering lack of proven antiviral drugs and hyperinflammation caused by virus, anti-inflammatory medications used in daily rheumatology practice may constitute possible treatment options in treatment of coronavirus disease 2019 (COVID-19). Following anti-inflammatory treatments are potential candidates for coronavirus disease 2019 (COVID-19) with their preclinical or limited clinical evidence.

Severe lung inflammation and impaired pulmonary gas exchange in coronavirus disease 2019 (COVID-19) has been proposed to be attributed to upregulation of pro-inflammatory cytokines. In healthy individuals, angiotensin 1-7 (Ang-1-7) limits the synthesis of pro-inflammatory and pro-fibrotic cytokines. Thus, downregulation of angiotensin-converting enzyme 2 (ACE2) by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), with consequent decrease in angiotensin 1-7 (Ang-1-7) concentrations, may exaggerate cytokine storm leading to overwhelming inflammatory response. Cytokines have been extensively studied in sick persons

with heart failure (HF) due to their role in inflammatory modulation, myocyte stress/stretch, myocyte injury and apoptosis, fibroblast activation and extracellular matrix (ECM) remodeling.

A study performed by Guo *et al.* (2020) showed that plasma troponin (Tn) concentrations had a noticeable positive linear correlation with plasma high-sensitivity C-reactive protein (CRP) concentrations, exhibiting that myocardial injury may be closely associated with inflammatory pathogenesis during the progress of illness. In addition to their direct effects on cardiomyocytes, high concentrations of circulating cytokines also develop functional reprogramming of endothelial cells, endothelial dysfunction, and atherogenesis (i.e., formation of fatty deposits in arteries). In fact, endothelial cells are thought to play a notable role in inflammatory response in viral contagions.

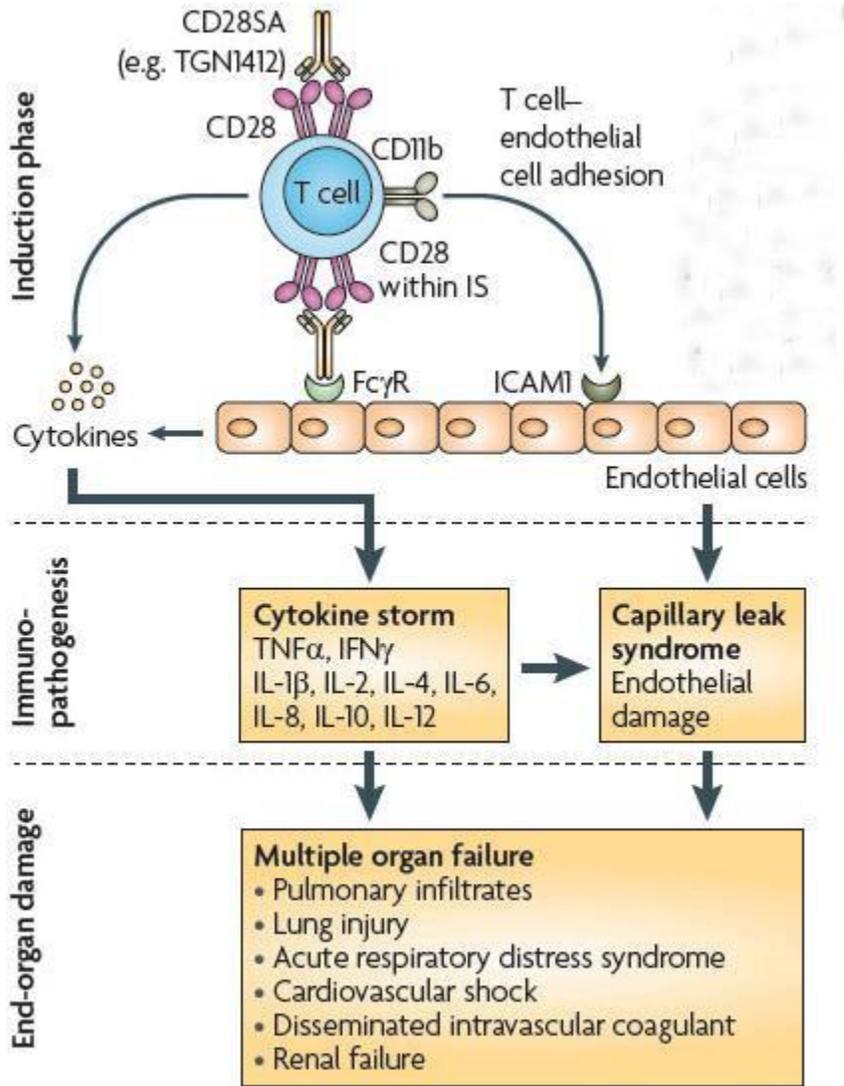
Thus, systemic inflammatory response (SIR) with cytokine storm is rational cause of myocardial injury in late phases of illness, usually associated with acute respiratory distress syndrome (ARDS), multiorgan failure (MOF) and decease. However, high cytokine concentrations may represent key player of myocardial injury in coronavirus disease 2019 (COVID-19), being related to direct myocardial injury, endothelial dysfunction, destabilization of coronary plaque, and microthrombogenesis.

During incubation period, often ranging from 1 to 14 days, and during early phase of illness, when non-specific symptoms are present, peripheral blood leukocyte and lymphocyte (LYM) counts are normal or slightly decreased. Following viraemia (i.e., presence of viruses in blood), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) fundamentally affects tissues expressing high levels of angiotensin-converting enzyme2 (ACE2) comprising lungs, heart and gastrointestinal tract (GIT). Approximately 7 to 14 days from beginning of initial symptoms, there is surge in clinical manifestations of illness with pronounced systemic increase of inflammatory mediators and cytokines, which may even be characterized as cytokine storm. At this point, noticeable lymphopenia becomes obvious. Several factors may contribute to coronavirus disease 2019 (COVID-19) associated lymphopenia. It has been demonstrated that lymphocytes (LYM) express angiotensin-converting enzyme2 (ACE2) receptor on their surface; thus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may directly infect those cells and eventually cause their lyses. Moreover, cytokine storm is characterized by considerably elevated concentrations of interleukins [mostly interleukin-6 (IL-6), interleukin-2 (IL-2),

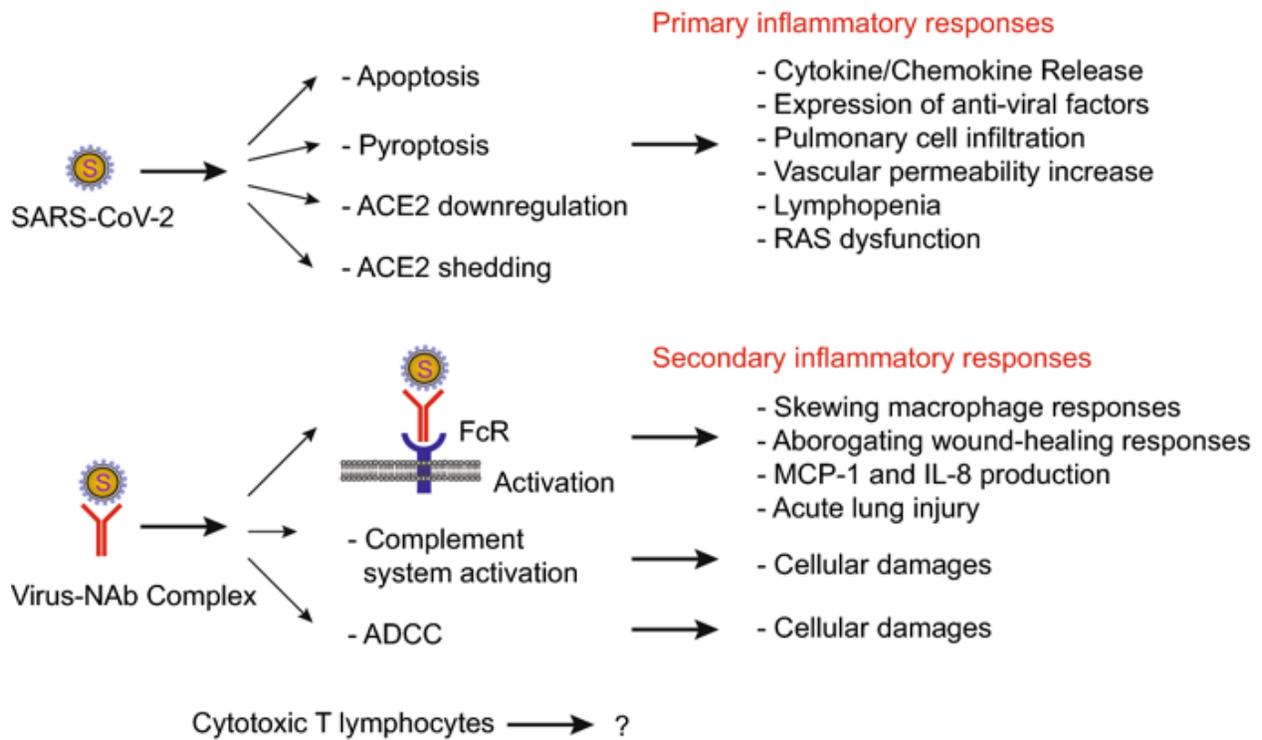
interleukin-7 (IL-7), granulocyte colony stimulating factor (G-CSF), interferon- γ inducible protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1alpha (MIP1 α) and tumor necrosis factor-alpha (TNF- α), which may induce lymphocyte (LYM) apoptosis. Actual cytokine activation may be also associated with atrophy of lymphoid organs, involving spleen, and further impairs lymphocyte (LYM) turnover. Coexisting lactic acid acidosis, which may be more obvious among cancer ill individuals who are at increased risk for complications from coronavirus disease 2019 (COVID-19), may also inhibit lymphocyte (LYM) proliferation. Guan *et al.* (2020) administered data on clinical characteristics of 1,099 coronavirus disease 2019 (COVID-19) individuals with laboratory affirm during first two months of pestilence in China. On admission, vast majority of ill individuals presented with lymphocytopenia (83.2%), whereas 36.2% had thrombocytopenia, and 33.7% showed leukopenia. Thrombocytopenia is deficiency of platelets in blood and this causes bleeding into tissues, bruising, and slow blood clotting after injury, while leukopenia is reduction in number of white blood cells (WBCs) in blood, typical of various illnesses. However, they found hematological disturbances were more obvious among severe versus non-severe cases (96.1% versus 80.4% for lymphocytopenia, 57.7% versus 31.6% for thrombocytopenia and 61.1% versus 28.1% for leukopenia). These results were consistent in four other descriptive studies that were conducted during same period in China and included 41, 99, 138 and 201 confirmed cases with coronavirus disease 2019 (COVID-19), respectively. Valuable studies highlighted association between lymphopenia and need of intensive care unit (ICU) care, and a notable study showed association between lymphopenia and acute respiratory distress syndrome (ARDS) development. Specifically, Wu *et al.* (2020) retrospectively analyzed possible peril factors for developing acute respiratory distress syndrome (ARDS) and decease among 201 ill individuals with coronavirus disease 2019 (COVID-19) pneumonia in Wuhan, China. Increased peril of acute respiratory distress syndrome (ARDS) during illness course was noticeably associated with elevated neutrophils levels ($p < 0.001$), reduced lymphocytes levels ($p < 0.001$) in a bivariate Cox regression analysis. Elevated levels of neutrophils ($p = 0.03$) were associated with increased risk of decease. Of interest, 69% of ill individuals with low lymphocyte (LYM) count showed reactive lymphocyte (LYM) population involving a lymphoplasmacytoid subset, which was not common in peripheral blood of ill individuals with severe acute respiratory syndrome coronavirus (SARS-CoV) contagion in 2003. Flow cytometry (FC) did not reveal any inversion in the CD4+/CD8+

lymphocyte (LYM) ratio. However, functional studies have presumed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may deteriorate function of CD4+ helper (Th) and regulatory T (Treg)-cells and induce initial hyperactivation which is followed by rapid exhaustion of cytotoxic CD8+ T (Tc)-cells. In Singapore, it was also found that ill individuals requiring intensive care unit (ICU) support had considerably lower lymphocyte (LYM) levels ($p<0.001$) at baseline. In another retrospective study including 52 critically ill individuals from Wuhan, China, lymphopenia was reported in 85% of contracted individuals. Lymphopenia was also clear among critically ill individuals with coronavirus disease 2019 (COVID-19) in Washington, United States of America. During hospitalization, non-survivors demonstrated more significant deterioration in lymphopenia compared with those who survived ($p<0.05$). It has also been reported that ill individuals with severe illness and fatal outcomes present with reduced lymphocyte (LYM)/white blood cell (WBC) ratio both in admission ($p<0.001$) and during hospitalization ($p<0.001$) compared with those who survived. Contrary to non-survivors, survivors showed nadir (i.e., minimum value) of lymphocytes (LYM) count on day 7 from symptom start and thereafter restoration. Therefore, serial assessment of lymphocyte (LYM) count dynamics may be predictive of ill individual outcome. It has been proposed a model based on lymphocyte (LYM) counts at two time points; ill individuals with less than 20% lymphocytes (LYM) at days 10-12 from beginning of symptoms and less than 5% at days 17-19 which showed worst prognosis. Studies have shown that myocardial injury among inpatients with coronavirus disease 2019 (COVID-19) is combined with increased deaths. In a prospective study in Wuhan, China including 416 consecutive ill persons 82 (19.7%) had documented myocardial injury. Compared with others, these ill persons with myocardial injury had higher leukocyte ($p<0.001$), lower lymphocyte ($p<0.001$) and lower platelet counts ($p<0.001$). A retrospective study including 187 ill persons with coronavirus disease 2019 (COVID-19) from another hospital in Wuhan showed that ill persons with high troponin-T (TnT) concentrations had leukocytosis ($p<0.001$), elevated neutrophils ($p<0.001$) and reduced lymphocytes (LYM) ($p=0.01$). A meta-analysis of nine studies has presumed that thrombocytopenia is significantly associated with gravity of coronavirus disease 2019 (COVID-19), with very high between-studies heterogeneity though; a more sizeable drop in platelet counts was noticed particularly in nonsurvivors. Of interest, a study showed that among 30 hospitalized sick persons with coronavirus disease 2019 (COVID-19), those presenting with a peak in platelet count during illness course had worse

outcomes. Interestingly, platelet to lymphocyte (LYM) ratio at time of platelet peak emerged as an independent prognostic factor for prolonged hospitalization in multivariate analysis. It was observed that a high platelet to lymphocyte (LYM) ratio may indicate more pronounced cytokine storm due to enhanced platelet activation.



Figure(27):Cytokine storm (www.google.com)



Figure(28): SARS-CoV-2 mediated inflammatory responses (www.google.com)

Antibodies (Abs) to virus are induced in those who have become infected. Preliminary proof supposes that some of these antibodies (Abs) are protective, but this remains to be definitively established. Moreover, it is unknown whether all contracted individuals mount a protective immune response and how long any protective effect will last. Data on protective immunity following coronavirus disease 2019 (COVID-19) are arising. A case series assessing convalescent plasma (CP) for treatment of coronavirus disease 2019 (COVID-19) described neutralizing activity in plasma of recovered sick persons that seemed to be transferred to recipients following plasma infusion. Similarly, in another study of 23 sick persons who healed from coronavirus disease 2019 (COVID-19), antibodies (Abs) to receptor-binding domain (RBD) of spike (S) protein and nucleocapsid (N) protein were detected by enzyme-linked immunosorbent assay (ELISA), in most sick persons by 14 days following beginning of symptoms; enzyme-linked immunosorbent assay (ELISA) antibody (Ab) titers associated with neutralizing activity. However, some data propose that magnitude of antibody (Ab) response

may be related to gravity of illness and that sick persons with mild contagion may not mount detectable neutralizing antibodies (Nabs).

In addition, durability of neutralizing activity following contagion is uncertain. In a study of 37 sick individuals who had symptomatic coronavirus disease 2019 (COVID-19), by eight weeks following hospital discharge, neutralizing activity decreased by a median of 12 percent in 62 percent. In another study of 149 convalescent sick individuals, 7 percent of whom had required hospitalization, only 1 percent had high titers of neutralizing antibodies (Nabs) a mean of 39 days after illness start. Nevertheless, receptor-binding, domain-specific B cells were identified in six sick individuals (all of those studied), and strong neutralizing antibodies (Nabs), regardless of serum-neutralizing titer, were also identified, supposing that highly protective vaccines could be designed to stimulate production of such antibodies (Abs).

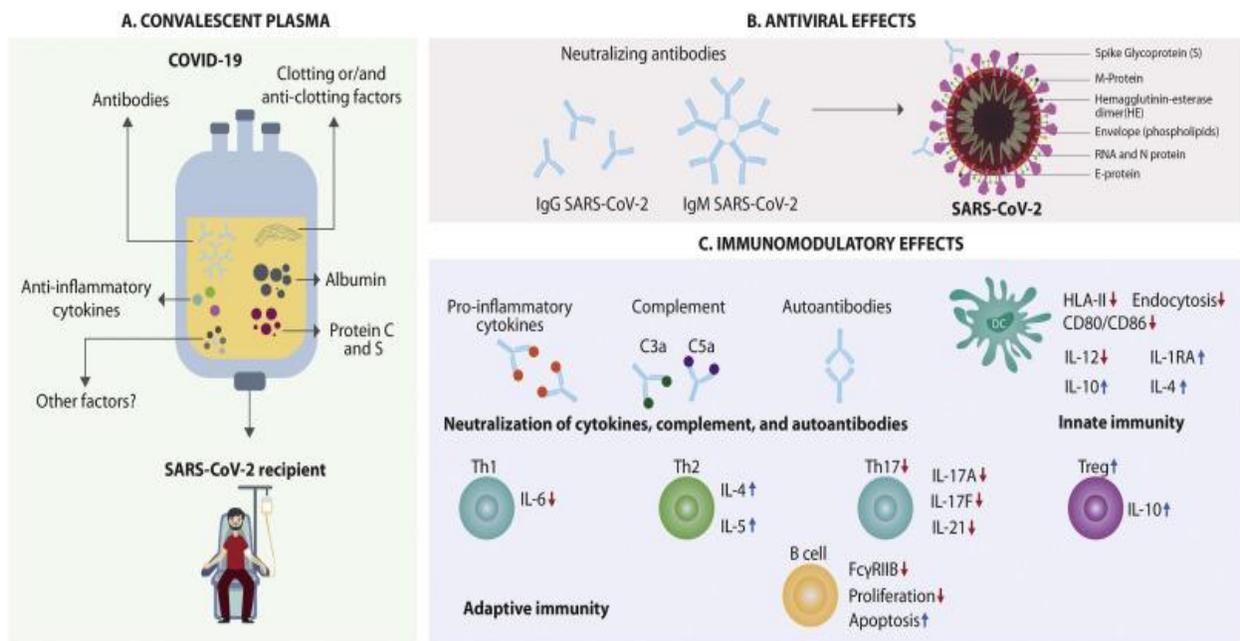
Animal studies have presumed that immune response (IR) to contagion may provide some protection against reinfection, at least in short term. In one study of nine rhesus macaques experimentally infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), all animals developed neutralizing antibodies (Nabs); upon rechallenge with same viral dose 35 days later, all had amnestic immune (or recall) responses and, on nasal swab, had lower viral ribonucleic acid (vRNA) concentrations and more rapid viral ribonucleic acid (vRNA) decline compared with initial challenge and with challenged naïve control animals. Studies assessing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine candidates in macaques have also supposed that immune responses (IR) to vaccination lead to lower concentrations or more rapid clearance of viral ribonucleic acid (vRNA) in respiratory tract samples following viral challenge compared with unvaccinated controls.

Studies have also described severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-specific CD4 and CD8 T cell responses in sick individuals who had healed from coronavirus disease 2019 (COVID-19) and in persons who had received investigational severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine, which suggest possibility for durable T cell immune response (IR).

Some studies have reported positive reverse transcription polymerase chain reaction (RT-PCR) lab exams for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in individuals with laboratory-confirmed coronavirus disease 2019 (COVID-19) following clinical improvement and negative results on two consecutive lab exams. However, these positive lab

exams occurred shortly after negative lab exams, were not associated with worsening symptoms, may not represent contagious virus, and probably did not reflect reinfection. Specifically, in a report from Korea Centers for Disease Control and Prevention of individuals with coronavirus disease 2019 (COVID-19) who had a repeat positive ribonucleic acid (RNA) lab exam after being previously cleared from isolation, contagious virus could not be isolated in cell culture in any of 108 sick persons subjected to testing. Among 790 contacts, there were no newly affirmed cases that were traced to exposure during period of repeat positive lab exam.

Food and Drug Administration (FDA or USFDA) has granted emergency use authorization for exams that identify antibodies (Abs) against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in serum or plasma. Should proof affirm that presence of these antibodies (Abs) reflects protective immune response (IR), serologic screening will be important tool to understand population immunity and distinguish people who are at lower risk for reinfection.



Figure(29): Scheme of convalescent plasma components and its mechanism of action [Rojas M.; Rodriguez Y.; Monsalve D.; Acosta-Ampudia Y.; Camacho B.; Gallo J.; Rojas-Villarraga A.; Ramirez-Santana C.; Diaz-Coronado J.; Manrique R.; Mantilla R.; Shoenfeld Y.; Anaya JM.(2020). Convalescent plasma in COVID-19: possible mechanisms of action. Elsevier. Autoimmunity Reviews, 19(7), 102554. <https://doi.org/10.1016/j.autrev.2020.102554>]

In figure (29): schematic representation of convalescent plasma components and its mechanisms of action. A. Main convalescent plasma components. B. Antiviral effects of neutralizing

antibodies (Nabs). Immunoglobulin G (IgG) and immunoglobulin M (IgM) are major isotypes, although immunoglobulin A (IgA) may be also important, especially in mucosal viral contagions. Other non-neutralizing antibodies (non-Nabs) may exhibit protective effect. Humoral immune response (HIR) is mostly directed towards spike (S) protein. C. Anti-inflammatory effects of convalescent plasma (CP) involve network of autoantibodies (AAbs) and control of overactive immune system (*i.e.*, cytokine storm, Th1/Th17 ratio, complement activation and regulation of hypercoagulable state). Abbreviations: N: Nucleoprotein; M: Membrane; E: Envelope.

Safety of use of convalescent plasma (CP) is another issue that has been historically relevant in epidemics. In pestilences of Influenza A (H1N1), severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), studies did not find any adverse event associated to convalescent plasma (CP) administration. In case of Ebola, convalescent plasma (CP) administration was associated with mild adverse reactions such as nausea, skin erythema, and fever. In coronavirus disease 2019 (COVID-19), reports have indicated that administration of convalescent plasma (CP) is safe, and it was not associated with major adverse events. Thus, due to tolerability and possible efficiency, convalescent plasma (CP) is better candidate to be assessed as treatment option to control coronavirus disease 2019 (COVID-19) pandemic.

Convalescent donors must undergo standard pre-donation assessment to ensure compliance with current regulations regarding plasma donation. Currently, convalescent donors between 18 and 65 years old are considered as persons without contagious symptomatology and negative examination for coronavirus disease 2019 (COVID-19) after 14 days of recovery. These examinations must be repeated 48 h later and at moment of donation. Donors from pestilence areas for tropical illnesses (*e.g.*, malaria) should be excluded. In addition to molecular lab exams, it is critical to recognize emotional situation, to explore susceptibilities, and guarantee not exploitation of donors.

Apheresis is recommended procedure to obtain plasma. This procedure is based on continuous centrifugation of blood from donor to allow selective collection plasma. Efficacy of this technique is around 400–800 mL from single apheresis donation. This amount of plasma could be storage in units of 200 or 250 mL, and frozen within 24 h of collection to be used in further transfusions.

As convalescent plasma (CP) production requires high quality standards, it must be free of any contagion, so examinations for human immunodeficiency virus (HIV), hepatitis B, hepatitis C,

sypilis, human T-cell lymphotropic virus type 1 (HTLV-1, also called human T-cell leukemia type 1), and human T-cell lymphotropic virus type 2 (HTLV-II, also called human T-cell leukemia type 1), and *Trypanosoma cruzi* (if living in pestilence area) should be carried out. In this sense, nucleic acid lab exam for human immunodeficiency virus (HIV) and hepatitis viruses is mandatory to guarantee safety of recipients. Other protocols suppose inactivation of pathogenic agents with riboflavin or psoralen plus exposure to ultraviolet (UV) light to improve safety of convalescent plasma (CP).

There is not a standard transfusion dose of convalescent plasma (CP). In different studies for coronaviruses (CoVs) administration of convalescent plasma (CP) ranges between 200 and 500 mL in single or double scheme dosages. Currently, recommendation is to administrate 3 mL/kg per dose in two days. This strategy facilitates distribution of plasma units (250 mL per unit) and provide standard option of delivery in public health strategies.

Composition of convalescent plasma (CP) is variable and include wide variety of blood derived components. Plasma contains mixture of inorganic salts, organic compounds, water, and more than 1000 proteins. Also it was found albumin (alb), immunoglobulins (Igs), complement, coagulation and antithrombotic factors among others. Interestingly, it is suggested that plasma from healthy donors provides immunomodulatory effects via infusion of anti-inflammatory cytokines and antibodies (Abs) that blockade complement, inflammatory cytokines and autoantibodies (AAbs). These factors may influence immunomodulatory effect of convalescent plasma (CP) in ill persons with coronavirus disease 2019 (COVID-19).

Neutralizing antibodies (Nabs) are crucial in virus clearance and have been considered essential in protecting against viral illnesses. Passive immunity (PI) driven by convalescent plasma (CP) can provide these neutralizing antibodies (Nabs) that restrain contagion. Efficiency of this management has been correlated with the level of neutralizing antibodies (Nabs) in plasma from recovered donors . In severe respiratory syndrome coronavirus (SARS-CoV) and Middle East coronavirus (MERS-CoV) were discovered that neutralizing antibodies (Nabs) bind to spike1-receptor binding protein (S1-RBD), S1-N-terminal domain (NTD) and S2, thus inhibiting their entry, limiting viral amplification. Moreover, other antibody (Ab)-mediated pathways such as complement activation, antibody-dependent cellular cytotoxicity (ADCC) and/or phagocytosis may also promote therapeutic effect of convalescent plasma (CP).

A pseudotyped-lentiviral-vector-based neutralization assay to measure specific neutralizing antibodies (Nabs) in plasma from healed ill persons with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) showed variations in neutralizing antibodies (Nabs) titers, approximately 30% of ill persons did not develop high neutralizing antibodies (Nabs) titers after contagion. These variations are associated with age, lymphocyte (LYM) count, and C reactive protein (CRP) levels in blood, suggesting that other components from plasma contribute to healing of these ill persons.

In plasma, in addition to neutralizing antibodies (Nabs), there are other protective antibodies (Abs), including immunoglobulin G (IgG) and immunoglobulin M (IgM). Non-neutralizing antibodies (non-Nabs) that attach to virus, but do not affect its capacity to replicate, might contribute to prophylaxis and/or healing improvement.

Shen *et al.* (2020), revealed that healed donors from coronavirus disease 2019 (COVID-19) contagion had severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-specific antibody (Ab) titers ranging between 1.800 and 16.200 and neutralizing antibodies (Nabs) titers were between 80 and 480. Plasma obtained from donors and transfused in recipients on same day lead to viral load decreased. After transfusion of convalescent plasma (CP), titers of immunoglobulin G (IgG) and immunoglobulin M (IgM) in recipients increased in time-dependent manner. Moreover, presence of neutralizing antibodies (Nabs) in recipients played vital role in restriction of viral contagion. Another study evaluated kinetics of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-specific neutralizing antibodies (Nabs) development during course of illness. Titers of neutralizing antibodies (Nabs) in ill individuals contracted with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were low before day 10 post-disease beginning and then increased, with a peak 10 to 15 days after disease start, remaining stable thereafter in all ill individuals.

A report in ill individuals with coronavirus disease 2019 (COVID-19), showed that critically ill individuals exhibited positivity for anti-cardiolipin immunoglobulin A (IgA) antibodies as well as for anti- β 2-glycoprotein I IgA and IgG antibodies. This evidence may suggest that convalescent plasma (CP)-coronavirus disease 2019 (COVID-19) may neutralize this type of autoantibodies (AAbs) reducing odds of suffering from thrombotic events (i.e., antiphospholipid syndrome-like disease), especially in critically ill contracted individuals. In same line, report of sick person with Sjögren's syndrome (SjS, SS) and coronavirus disease 2019 (COVID-19)

successfully treated with convalescent plasma (CP) may suppose that this strategy is safe and efficient in autoimmune conditions.

In addition, some antibodies (Abs) inhibit complement cascade (i.e., C3a and C5a), and limit formation of immune complexes. A study showed that complement-deficient mice with induced severe acute respiratory syndrome coronavirus (SARS-CoV) contagion exhibited high viral titers, secretion of inflammatory cytokines and chemokines, and immune cell infiltration within lung. These results propose that complement activation widely contribute to systemic inflammation and migration of neutrophils to lungs, causing tissue damage. Additional studies have revealed that immunoglobulin G (IgG) transferred by plasma neutralize cytokines such as interleukin-1beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α). In this sense, passive immunity (PI) by infusion of convalescent plasma (CP)-coronavirus disease 2019 (COVID-19) may restrict inflammatory cascade driven by pathogenic antibodies (Abs), as well as cellular damage stimulated by complement cascade activation in excessive inflammatory conditions.

Antibody-dependent enhancement (ADE) is mechanism in which intensity of contagion increases in presence of preexisting poorly neutralizing antibodies (Nabs), favoring replication of virus into macrophages (M Φ) and other cells through interaction with fragment crystallizable region (Fc region) and/or complement receptors (CR). In vitro assays with human promonocyte cell lines revealed that severe acute respiratory syndrome coronavirus (SARS-CoV) antibody-dependent enhancement (ADE) was primarily mediated by antibodies (Abs) against spike (S) proteins, considerably elevating rate of apoptosis in these cells. This is of major importance in regions in which coronaviruses (CoVs) are endemic. Vaccines development should take into account this phenomenon in sick individuals with coronavirus disease 2019 (COVID-19), and administration of convalescent plasma (CP)-coronavirus disease 2019 (COVID-19) in these areas should be conducted with caution since antibody dependent enhancement (ADE) may arise as mischievous reaction in sick individuals with active contagion. If one suspects of this phenomenon following convalescent plasma (CP)-coronavirus disease 2019 (COVID-19) administration, clinicians must soon notify health authorities and assess safety according to endemic coronaviruses (CoVs) in the region.

The neonatal Fc receptor (also FcRn, IgG receptor FcRn large subunit p51, or Brambell receptor) is critical regulator of immunoglobulin G (IgG) half-life. It is important to define neonatal Fc receptor (FcRn) as protein that in humans is encoded by *FCGRT* gene. It is fragment

crystallizable (Fc) receptor which is similar in construction to major histocompatibility complex (MHC) class I molecule and also associates with beta-2-microglobulin (B2M). Other studies showed similar receptor in human beings, leading to naming as neonatal Fc receptor (FcRn). In humans, however, it is found in placenta to help ease transport of mother's immunoglobulin G (IgG) to growing fetus. It has also been demonstrated to play role in checking immunoglobulin G (IgG) and serum (alb) albumin turnover. Neonatal Fc receptor (FcRn) expression is up-regulated by proinflammatory cytokine, tumor necrosis factor-alpha (TNF- α), and down-regulated by interferon-gamma (IFN- γ). This receptor works by preventing degradation and clearance of immunoglobulin G (IgG) by pinocytotic mechanism that allow antibody (Ab) circulation within cell for its posterior excretion. The neonatal Fc receptor (FcRn) inhibitor rozanolixizumab demonstrated reduction of immunoglobulin G (IgG) levels in phase 1 study, and it proved to be critical in intravenous immunoglobulin (IVIg) catabolism in common variable immunodeficiency ill persons. It has been indicated that saturation of this receptor by intravenous immunoglobulin (IVIg) may consider as most possible mechanism to clear autoantibodies (AAb) in autoimmune environments by shortening their lifetime. Whether antibodies (Abs) play critical role in coronavirus disease 2019 (COVID-19) pathogenesis still remains to be interpreted, however, saturation of neonatal Fc receptor (FcRn) may offer additional immunomodulatory pathway in ill persons receiving convalescent plasma (CP).

Fc γ receptors, i.e. receptors for Fc region of immunoglobulin G (IgG), are found in about all immune cells and are important in both promoting and regulating immune response (IR) and inflammatory immune response (IIR) to immune complexes. These receptors are critical factors in modulating or inhibiting activity of immune cells, including lymphocytes (LYM). Fc γ receptor activation by immunoglobulin G (IgG) triggers upregulation of FC γ RIIB. FC γ RIIB is an Fc receptor which has been associated with inhibitory effects and which blocks B cell activation. FC γ RIIB is the only inhibitory Fc receptor. It controls many aspects of immune responses (IR) and inflammatory immune responses (IIR). It has been presumed that sialylation of this receptor is critical for inhibitory effects in immune cells. However, study of T helper 17 (Th17) cells in model of autoimmune encephalomyelitis [EAE, a T-cell-mediated autoimmune disease of central nervous system (CNS)] revealed that this process is dispensable for immunomodulatory effect of intravenous immunoglobulin (IVIg) medication. Despite these results, convalescent plasma (CP)

infusion may help modulation of immune response (IR) via Fc γ receptors (Fc γ R), and accounts for attention in current treatment of coronavirus disease 2019 (COVID-19).

Dendritic cells (DCs), antigen-presenting cells (APCs, also known as accessory cells) of mammalian immune system, are key regulators of innate immune response (IIR) and work as specialized antigen presenting cells (APCs). In vitro studies have shown that administration of intravenous immunoglobulin (IVIg) may abrogate maturation of dendritic cells (DCs), as well as reduction in production of interleukin-12 (IL-12). Importantly, production of interleukin-10 (IL-10) was enhanced. A study found that intravenous immunoglobulin (IVIg) induced production of interleukin-33 (IL-33) that thereafter expanded interleukin-4 (IL-4)-producing basophils. Another study considered that intravenous immunoglobulin (IVIg) could induce production of interleukin-4 (IL-4) and interleukin-13 (IL-13) which correlated with concentrations of interleukin-33 (IL-33). T helper 2 (Th2) cytokine-mediated downregulation of Fc γ RIIa (a human platelet Fc receptor) and interferon gamma receptor 2 [IFN- γ R2, a cytoplasmic β subunit of interferon- γ receptor (IFN- γ R)] was proposed to be possible mechanisms for this phenomenon. Moreover, it was administered that intravenous immunoglobulin (IVIg) activated β -catenin in an immunoglobulin G (IgG)-sialylation independent manner, which was found critical for reducing inflammation.

Down regulation of human leukocyte antigen class II (HLA-II) and costimulation molecules such CD86, CD80, and CD40 have been reported in dendritic cells (DCs) after stimulation with intravenous immunoglobulin (IVIg). It is important to say that human leukocyte antigen class II (HLA-II) molecules, encoded within human major histocompatibility complex (MHC), play central role in immune response (IR) by presenting peptide antigens (Ags) to helper (T4+) lymphocytes. These molecules are expressed on surface of antigen presenting cells (APCs) such as monocytes, B cells, and dendritic cells (DCs). Much worthy is to add that co-stimulatory molecules are a heterogenous group of cell surface molecules that act to amplify or counteract initial activating signals provided to T cells from the T cell receptor (TCR) following its interaction with an antigen (Ag)/major histocompatibility complex (MHC), thereby influencing T cell differentiation and fate. In ill persons with systemic lupus erythematosus (SLE), which exhibit high pro-inflammatory condition, administration of intravenous immunoglobulin (IVIg) abrogated interferon-alpha (IFN- α)-mediated maturation. Data presume that infusion of plasma from healed coronavirus disease 2019 (COVID-19) donors may enhance

anti-inflammatory properties of dendritic cells (DCs), which could be critical in phases of excessive inflammatory stimuli in ill persons with coronavirus disease 2019 (COVID-19).

Despite ability of enhancing T helper2 (Th2) cells via interleukin-33 (IL-33) in dendritic cells (DCs), it has been mentioned that intravenous immunoglobulin (IVIg) modulates balance between CD4⁺/CD8⁺ T cells, as well as inducing proliferation and survival of T regulatory (Treg) cells. Management with intravenous immunoglobulin (IVIg) looks to decrease antigenic presentation of T cells via modulation and inhibition of dendritic cells (DCs). This process was independent of FC γ RIIB, and other reports indicated that decreased activation of T cells was independent of immunoglobulin G (IgG) sialylation, monocytes or B cells.

Moreover, ill persons managed with intravenous immunoglobulin (IVIg) exhibited decrease in T helper (Th1) cells and low concentrations of interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α) with elevation of T helper2 (Th2) cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10). Clinically, it has been observed that ill persons with Influenza A (H1N1) managed with convalescent plasma (CP) demonstrated decrease in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), with elevation in interleukin-10 (IL-10). This boost concept of an anti-inflammatory effect of convalescent plasma (CP) in individuals with acute viral contagions.

Cytotoxicity is also regulated by administration of intravenous immunoglobulin (IVIg). A study presented that ill persons with chronic inflammatory demyelinating polyneuropathy (CIPD) managed with intravenous immunoglobulin (IVIg), exhibited decrease in CD8⁺ T cells with high concentrations of CD4⁺ T effector memory and T central memory cells. In another study, intravenous immunoglobulin (IVIg) was affirmed to reduce activation of CD8⁺ T cells correlated with a T-cell receptor (TCR) blockade, thus reducing interaction between effector and target cells. A study demonstrated that in individuals experienced Kawasaki disease (KD, an inflammatory illness in arteries, veins, and capillaries), a high proportion of CD8⁺ cells was correlated with resistance to intravenous immunoglobulin (IVIg), thus presuming that these cells could be taken into account a predictive factor for intravenous immunoglobulin (IVIg) response. Studies have administered that intravenous immunoglobulin (IVIg) decreases proliferation of T helper17 (Th17) cells, as well as decreases production of interleukin-17A (IL-17A), interleukin-17F (IL-17F), interleukin-21 (IL-21), and chemokine (C-C motif) ligand 20 (CCL20) [also called liver activation regulated chemokine (LARC) or Macrophage Inflammatory Protein-3 (MIP3A)].

In another study, intravenous immunoglobulin (IVIg) were observed to modulate Thelper17/T regulatory (Th17/Treg) ratio which is related to recurrent pregnancy loss. It is understood that convalescent plasma (CP) may function in a similar way in individuals with coronavirus disease 2019 (COVID-19).

B cells are critical in adaptive (acquired or specific) immunity via production of antibodies (Abs) and cytokines. In ill persons with demyelinating polyneuropathy (inflammation of nerve roots and peripheral nerves and destruction of the fatty protective covering (myelin sheath) over the nerves), administration of intravenous immunoglobulin (IVIg) exhibited overexpression of Fc γ RIIB receptors on B cells. Intravenous immunoglobulin (IVIg) inhibited Toll-like receptor 9 (TLR-9)-dependent B cell responses. This was combined with intravenous immunoglobulin (IVIg) inhibitions of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway, decrease in CD25 and CD40 expression, and reduced interleukin-6 (IL-6) and interleukin-10 (IL-10) secretion by B cells. This process looks to be regulated by Src-homology 2 (SH2) domain-containing phosphatase 1. Tyrosine-protein phosphatase non-receptor type 6, also known as Src homology region 2 domain-containing phosphatase-1 (SHP-1), is an enzyme that in human beings is encoded by *PTPN6* gene. Tyrosine-protein phosphatase non-receptor type 6, also known as Src homology region 2 domain-containing phosphatase-1 (SHP-1), is an enzyme that in human beings is encoded by the *PTPN6* gene. Protein encoded by this gene is member of protein tyrosine phosphatase (PTP) family. protein tyrosine phosphatases (PTPs) are known to be signaling molecules that regulate variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation. N-terminal part of this protein tyrosine phosphatase (PTP) contains two tandem Src homolog (SH2) domains, which act as protein phospho-tyrosine binding (PTB) domains, and mediate interaction of this protein tyrosine phosphatase (PTP) with its substrates. This protein tyrosine phosphatase (PTP) is expressed primarily in hematopoietic cells, and functions as an important regulator of multiple signaling pathways in hematopoietic cells.

Proliferation and survival of B cells is mediated by the B cell-activating factor (BAFF), which is member of tumor necrosis factor (TNF) family, and this protein is best known for its role in creation and maintenance of healthy B cells, while excessive production of it is often linked to autoimmune conditions. A worthy study showed that intravenous immunoglobulin (IVIg) contained neutralizing antibodies (Nabs) for B cell-activating factor (BAFF). This could explain

decrease in proliferation, as well as elevated rates of apoptosis of B cells. Regarding latter process, it was found that anti-Fas (anti-CD95) antibodies, present in intravenous immunoglobulin (IVIg) preparations, triggered apoptosis in B cells.

In dendritic cells (DCs), downregulation of costimulatory molecules following administration of intravenous immunoglobulin (IVIg) has been recognized. This is similar to B cells which showed reduction in antigen-presentation activity secondary to immunoglobulin G (IgG) internalization, in concordance with decreased interleukin-2 (IL-2) secretion by T cells. In addition, intravenous immunoglobulin (IVIg) administration modulates B-cell receptor (BCR) signaling. It was found that interaction between B-cell receptor (BCR) and CD22 resulted in down-regulation of tyrosine (Tyr) phosphorylation of Lyn and the B-cell linker proteins which resulted in a sustained activation of extracellular-signal-regulated protein kinase (Erk) 1/2 and arrest of the cell cycle at the gap 1 phase (G1 phase) and thus leading to immunomodulation of the inflammatory response in coronavirus disease 2019 (COVID-19) secondary to convalescent plasma (CP) administration. However, it is important to say that Lyn is non-receptor tyrosine-protein kinase transporting signals from cell surface receptors and plays a notable role in regulation of innate and adaptive immune responses, hematopoiesis, responses to growth factors and cytokines, integrin signaling, but also responses to deoxyribonucleic acid (DNA) destruction and genotoxic agents. It acts principally as negative regulator, but can also serve as activator, depending on context. It is necessary for beginning of B-cell response, but also for its down-regulation and termination. It plays a noticed role in regulation of B-cell differentiation, proliferation, survival and apoptosis, and is crucial for immune self-tolerance. In addition, it is important to mention that activation of extracellular-signal-regulated protein kinase (Erk) is central to growth-factor-receptor-mediated signaling including that originating from T cell antigen receptor (TCR). It integrates cytoplasmic signals to effect changes in transcription associated with differentiation, proliferation, and survival. Extracellular-signal-regulated protein kinase (Erk)1/2 constitute a focal point of MAP-kinase-pathway signaling in mammalian cells. These two highly homologous serine-threonine kinases are activated by tyrosine (Tyr) and threonine (Thr) dual phosphorylation and, in turn, broadcast this activation to both cytoplasmic signaling complexes and nuclear transcription factors.

Reports suggest production of antiphospholipid antibodies (APAs) in ill persons with coronavirus disease 2019 (COVID-19) together with antiphospholipid-like syndrome (APS), and

regulation of this cascade could be critical to avoid deleterious outcomes in these group of ill persons [*i.e.*, thrombosis, disseminated intravascular coagulopathy (DIC)].

Major immunological factor suspected to be associated with inflammation and lung destruction in coronavirus disease 2019 (COVID-19) is activation of macrophages (MΦ). It has been supposed that ill persons with coronavirus disease 2019 (COVID-19) may experience macrophage activation syndrome-like disease associated to innate immune migration to lung tissues. In this context, inhibition of this immunological pathway may help to control excessive cytokine production and prevent pulmonary damage (*i.e.*, fibrosis). This was supported by study of Blanco-Melo *et al.* (2020) who illustrated an up regulation of chemokines for innate immune cells in ferrets as well as in individuals suffering from coronavirus disease 2019 (COVID-19). Interestingly, results indicated that this scenario mainly occurred in first 7 days post contagion, whereas at day 14th, other cytokines such as interleukin-6 (IL-6) and interleukin-1 (IL-1) persisted activated.

It was found that macrophages (MΦ) treated with intravenous immunoglobulin (IVIg) showed increased production of interleukin-10 (IL-10), with decrease in interleukin-12 (IL-12)/23p40, thus suggesting induction of anti-inflammatory macrophage (MΦ) profile. Although there is no proof of macrophage (MΦ) pulmonary migration inhibition by intravenous immunoglobulin (IVIg), a study on induced peripheral neurotoxicity showed that this treatment reduced nerve macrophage (MΦ) infiltration in rats. These observations deserve attention in those affected persons managed with convalescent plasma (CP)-coronavirus disease 2019 (COVID-19) since they may consider for positive results encountered in critically ill persons with coronavirus disease 2019 (COVID-19). In this line, it is advised for convalescent plasma (CP)- coronavirus disease 2019 (COVID-19) administration in early stages of illnesses to prevent innate immune cells migration and avoid lung damage.

8. Altered Biomarkers Levels in COVID-19 Infection

Biomarkers, such high serum procalcitonin (PCT) and ferritin have also displayed as bad prognostic factors. Moreover, blood hypercoagulability is common amongst hospitalized coronavirus disease 2019 (COVID-19) sick persons. Higher D-Dimer (DD) concentrations are consistently recorded, whereas their gradual increase during illness course is particularly correlated with illness worsening. Other coagulation abnormalities such as prothrombin time (PT) and activated partial thromboplastin time (aPTT or APTT) prolongation, fibrin degradation

products elevate, with severe thrombocytopenia lead to life-threatening disseminated intravascular coagulation (DIC) which necessitates continuous vigilance and prompt intervention. Coronavirus disease 2019 (COVID-19) contracted cases whatever hospitalized or ambulatory are at high seriousness for venous thromboembolism (VTE) and an early and prolonged pharmacological thromboprophylaxis with low molecular weight heparin (LMWH) which is a class of anticoagulant medications, is highly recommendable.

Coagulation disturbances are relatively often encountered among coronavirus disease 2019 (COVID-19) contracted individuals, particularly amongst those with severe illness. In a multicenter retrospective study during first two months of pestilence in China, 260 out of 560 contracted subjects (46.4%) with laboratory affirmed coronavirus disease 2019 (COVID-19) contagion had elevated D-dimer (DD) (≥ 0.5 mg/L), whereas elevation was more observed amongst severe contracted subjects (59.6% versus 43.2% for non-severe ones). D-dimer (DD) dynamics can reflect seriousness and their elevated levels are correlated with adverse results among ill persons with community-acquired pneumonia (CAP), which is defined as pneumonia that is acquired outside hospital. Elevated D-dimer (DD) (> 1.5 $\mu\text{g/L}$) was detected in 36% of ill persons in a descriptive study of 99 coronavirus disease 2019 (COVID-19) affected subjects in Wuhan, China. Another retrospective study in China comprising 41 subjects revealed that D-dimer (DD) and prothrombin time (PT) levels were elevated notably on admission among subjects requiring intensive care unit (ICU) support. It was found that ill persons requiring intensive care unit (ICU) management had considerably higher D-dimers (DD) in comparison with less serious cases. Affected individuals presenting with cardiac injury in context of coronavirus disease 2019 (COVID-19) contagion are more prone to coagulation disturbances in comparison with those without cardiac illnesses. Sick persons with high troponin-T (TnT) concentrations may show more often higher prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer (DD) levels. A study presented that among 201 sick persons with coronavirus disease 2019 (COVID-19) pneumonia, increased prothrombin time (PT) was related to increased risk of acute respiratory distress syndrome (ARDS), and additionally increased concentrations of D-dimer (DD) were significantly correlated with increased risk of acute respiratory distress syndrome (ARDS) and decease. Difference in median concentrations of D-dimer (DD) between survivors and non-survivors was larger than that between acute respiratory distress syndrome (ARDS) and non- acute respiratory distress

syndrome (ARDS) groups, which might suppose that disseminated intravascular coagulation (DIC)-related complications may have led subset of contracted persons to decease independently of acute respiratory distress syndrome (ARDS). In a multicenter retrospective cohort study from China, elevated D-dimer (DD) concentrations ($>1\mu\text{g/mL}$) were considerably associated with in-hospital decease in multivariable analysis. In another retrospective study encompassing data from 183 consecutive sick persons with coronavirus disease 2019 (COVID-19), non-survivors had considerably higher D-dimer (DD), fibrin degradation products (FDP) levels, and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT, also known as partial thromboplastin time, PTT) in comparison with survivors at initial assessment. By late hospitalization, fibrinogen and antithrombin (AT) concentrations were also noticeably lower in non-survivors. Of interest, 71.4% of non-survivors versus 0.6% of survivors fulfilled clinical criteria for disseminated intravascular coagulation (DIC) during illness course. Median time from admission to disseminated intravascular coagulation (DIC) manifestation was 4 days (range: 1-12 days). Therefore, it is indicated that D-dimer (DD) elevation and disseminated intravascular coagulation (DIC) may be common in sick persons with severe form of coronavirus disease 2019 (COVID-19) contagion. Scoring system for compensated and overt disseminated intravascular coagulation (DIC) endorsed by International Society on Thrombosis and Hemostasis should be followed for early disseminated intravascular coagulation (DIC) identification. Venous thromboembolism (VTE) risk in hospitalized coronavirus disease 2019 (COVID-19) infected persons is an emerging matter. Rate of symptomatic venous thromboembolism (VTE) in acutely ill hospitalized medical ill subjects raises up to 10%. Prolonged immobilization during illness, dehydration, an acute inflammatory state, presence of other cardiovascular (CV) risk factors [i.e., hypertension (HTN), diabetes mellitus (DM), obesity] or cardiovascular disease [CVD, i.e., coronary artery disease (CAD), history of ischemic stroke or peripheral artery disease (PAD)], previous history of venous thromboembolism (VTE) and classical genetic thrombophilia, such as heterozygous Factor V Leiden mutation are common comorbidities in hospitalized coronavirus disease 2019 (COVID-19) infected subjects, which possibly increase venous thromboembolism (VTE) risk. Possibility of endothelial cell activation/damage due to virus attachment to angiotensin-converting enzyme2 (ACE2) receptor may further increase venous thromboembolism (VTE) gravity. Release of large amount of inflammatory mediators and application of hormones and immunoglobulins (IG) in severe or critically ill infected persons

may lead to increased blood viscosity. Furthermore, mechanical ventilation (MV), central venous catheterization, and surgery may promote vascular endothelial dysfunction (VED). Combination of all above factors may lead to deep vein thrombosis (DVT) occurrence or even possibility of lethal pulmonary embolism (PE) due to thrombus migration. Thus, facing such venous thromboembolism (VTE) hazard, application of pharmacological thromboprophylaxis is mandatory in hospitalized coronavirus disease 2019 (COVID-19) sick persons. In this context, venous thromboembolism (VTE) risk increase must be evaluated in all acutely ill infected persons admitted to hospital, and thromboprophylaxis should be given to all these high-risk infected persons according to current clinical practice guidelines. In coronavirus disease 2019 (COVID-19) infected individuals with clinical manifestations of sudden deterioration of oxygenation, respiratory distress, or hypotension is of major importance for improvement of clinical outcomes. Although published data are very limited, it looks reasonable that D dimer (DD) estimation as well as kinetics of their increase could offer useful information for research of deep vein thrombosis (DVT) and/or pulmonary embolism(PE), along with recommended imaging techniques such as ultrasound venous echo-Doppler or bedside echocardiography. A small study in 25 pulmonary embolism (PE) suspected ill persons explored with computed tomography pulmonary angiography (CTPA) administered that those with affirmed pulmonary embolism (PE) had D-dimer (DD) concentrations higher than 7000 ng/ml compared to those without pulmonary embolism (PE) with significantly lower D-dimer (DD) concentrations.

Low molecular weight heparins (LMWH), or unfractionated heparin (UFH) should be preferred over direct oral anticoagulants (DOACs) due to possible drug-drug interactions with concomitant antiviral (especially anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin) treatment. Such therapies interfering with cytochrome P450 family 3 subfamily A member 4 (CYP3A4) and/or P-glycoprotein (P-gp) pathways may increase bleeding risk or reduce antithrombotic effect in case of direct oral anticoagulant (DOAC) use. In a retrospective Chinese study, involving 449 severe coronavirus disease 2019 (COVID-19) infected persons in Wuhan, low molecular weight heparin (LMWH) administration amongst infected persons with noticeably elevated D-dimers (DD) or in those meeting criteria for sepsis-induced disseminated intravascular coagulation (DIC) was considerably associated with improved 28-day overall survival. Moreover, clinicians should routinely assess all coronavirus disease 2019 (COVID-19) infected persons under heparin treatment for indices of heparin-induced thrombocytopenia (HIT)

syndrome performing 4T score (thrombocytopenia, timing of platelet count fall, thrombosis or other sequelae, other causes for thrombocytopenia). Although heparin-induced thrombocytopenia (HIT) incidence in this patient group has not been determined yet, there is possibly increased risk due to immune deregulation and massive inflammatory syndrome induced by viral contagion, with significant neutrophil extracellular traps (NETS) and platelet factor 4 (PF4) release.

Hematological changes are common in sick persons with coronavirus disease 2019 (COVID-19), which involve decreased lymphocyte (LYM) count and platelet count but normal white blood cell (WBC) count. A study indicated that prolonged activated partial thromboplastin time (aPTT), 26% had elevated D-dimer (DD) concentrations, and most sick persons had normal prothrombin time (PT). Of seven sick persons in University of Hong Kong-Shenzhen Hospital (Shenzhen, Guangdong province, China), two had thrombocytopenia, and two had elevated D-dimer (DD) concentrations. A study involving 1099 ill persons from 31 provinces/direct-controlled municipalities in China revealed that 82.1% of ill persons had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia. These laboratory marker disturbances were more considerable in severe illness cases. In 13 patients from 3 hospitals in Beijing, 72.5% experienced thrombocytopenia. Statistics from 41 ill persons in designated hospital in Wuhan demonstrated that 5% of ill persons had thrombocytopenia on admission. In most infected persons, platelet count did not reduce to concentration at which bleeding occurs. However, mechanisms by which this coronavirus (CoV) interferes with hematopoietic system are unclear.

A study presented results from various provinces in China, interesting biochemical findings were described; C-reactive protein (CRP) was elevated in 60.7% of infected persons, elevated procalcitonin (PCT), which may also be suggestive of secondary bacterial infection (SBI) complicating clinical course of coronavirus disease 2019 (COVID-19), was present in 5.5% and elevated lactate dehydrogenase (LDH) in 41% of infected persons. More severe infected persons exhibited more noticeable increase in comparison with the non-severe ones [81.5% versus 56.4% for C-reactive protein (CRP), 13.7% versus 3.7% for procalcitonin (PCT) and 58.1% versus 37.2% for lactate dehydrogenase (LDH)]. Accordingly in a retrospective cohort study including 191 sick persons with coronavirus disease 2019 (COVID-19) from Wuhan, China, non-survivors, as compared with survivors, presented mostly with elevated lactate dehydrogenase (LDH), elevated procalcitonin (PCT), high serum ferritin levels and higher interleukin-6 (IL-6). In a

notable study 40% of infected individuals showed higher lactate dehydrogenase (LDH). Elevated lactate dehydrogenase (LDH) has been combined also with higher risk of acute respiratory distress syndrome (ARDS), intensive care unit (ICU) support and decease across published studies. Elevated C-reactive protein (CRP) has been bound to disadvantageous aspects of coronavirus disease 2019 (COVID-19) contagion, such as acute respiratory distress syndrome (ARDS) development, elevated troponin-T (TnT) concentrations and myocardial injury, and decease. A meta-analysis of four published studies showed that elevated procalcitonin (PCT) levels were correlated with about 5-fold higher risk of severe contagion. Regarding ferritin, a study showed that elevated serum ferritin was correlated with acute respiratory distress syndrome (ARDS) development; trend of association with survival did not reach significance. At their univariate analysis, it was supported association between elevated serum ferritin levels and decease, but no multivariate analysis was presented. An outstanding biomarker for coronavirus disease 2019 (COVID-19) course is interleukin-6 (IL-6). In study by Chen *et al.* (2020) 52% (51/99) of affected individuals had higher interleukin-6 (IL-6) concentrations at admission. Elevated interleukin-6 (IL-6) concentrations have been bound to increased risk of decease, and gradual increase during hospitalization has been reported in non-survivors.

Coronaviruses (CoVs) can infect bone marrow (BM) cells, leading to abnormal hematopoiesis. It is considered that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) similarly obstacles hematopoiesis in bone marrow (BM) through certain receptors to cause reduced primary platelet formation and develop thrombocytopenia. secondary hemophagocytic lymphohistiocytosis (sHLH) is resulted from excessive proliferation and activation of mononuclear macrophage system, in which large number of inflammatory cytokines are secreted and large number of blood cells are swallowed. This reactive illness has rapid response with high deaths, and its basic characteristics involve persistent fever, hyperferremia (also called siderosis, excess of iron in blood.), cytopenia (i.e., reduction in number of mature blood cells), and lung involvement. In retrospective analysis of 150 affected individuals with coronavirus disease 2019 (COVID-19) in Wuhan, China, it was found that increased ferritin was one of predictors of decease. After analyzing blood samples of 33 severe and critical type coronavirus disease 2019 (COVID-19) ill individuals, WeiHaiming's team presented that after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion, T cells were overactivated to produce granulocyte-macrophage colony-stimulating factor (GMCSF) and interleukin-6 (IL-6).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) induced CD14⁺ CD16⁺, inflammatory mononuclear macrophages to produce more interleukin-6 (IL-6), and other inflammatory factors, thus forming inflammatory storm and resulting in immune damage to lungs and other organs. This is identical to clinical manifestation and laboratory examination of ill persons with secondary hemophagocytic lymphohistiocytosis (sHLH). Moreover, studies have shown that cytokine spectrum identical to secondary hemophagocytic lymphohistiocytosis (sHLH) is related to these variety of coronavirus disease 2019 (COVID-19) illness. It is considered that after cytokine storm, hematopoietic progenitor cells in bone marrow (BM) of sick persons with pneumonia infected by severe acute respiratory syndrome coronavirus-2 were destroyed, primary production of platelets reduced, and at the same time, too many blood cells were swallowed, which resulted in decrease of peripheral blood platelet count. Proof has shown that large number of megakaryocytes which are large multinucleated cells of bone marrow (BM) dynamically secrete platelets during pulmonary circulation. Persistent hypertension (HTN) and oxygen toxicity exacerbate lung injury, leading to consolidation changes such as fibrosis. Damaged pulmonary capillary beds cause the process of megakaryocyte rupture and platelet secretion to be blocked, which impacts secretion of platelets into pulmonary circulation and indirectly causes decreased platelet synthesis in systemic circulation.

It is advised that sick persons with excessive activation of inflammatory response, recommended dose of glucocorticoid can be used in short period of time. This is consistent with studies to improve thrombocytopenia. Reverse transcriptase inhibitors (RTIs, a class of antiretroviral drugs) are effective in therapy of human immunodeficiency virus (HIV)-related thrombocytopenia. For example, zidovudine increased platelet synthesis. Furthermore, drug promotion of megakaryocyte synthesis can increase platelet synthesis. Proof shows that chemokine CXCR4 can be expressed in megakaryocytes. Because severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and human immunodeficiency virus (HIV) are both ribonucleic acid (RNA) viruses, reverse transcriptase inhibitors (RTIs) and chemokine receptor antagonists (antiviral agents) may improve illness course of coronavirus disease 2019 (COVID-19). At the same time, it is supposed that Shenmai injection can be used to manage immunosuppression in therapy of traditional Chinese medicine (TCM) in Shenmai injection has a scavenging effect on all kinds of pathological substances. It can improve anticoagulation and thrombocytopenia in sick individuals with coronavirus disease 2019 (COVID-19) efficiently. In

addition, immunotherapy scheme of monoclonal antibody (mAb or moAb) drug topirazumab+ routine therapy is also enrolled in Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) as valid option treating severe and critical ill coronavirus disease 2019 (COVID-19) infected person. Monoclonal antibody (mAb or moAb) against interleukin-6 (IL-6) receptor tocilizumab can efficiently block coronavirus disease 2019 (COVID-19) inflammatory storm, thus improving prognosis of ill individuals.

Coronavirus disease 2019 (COVID-19) may increase concentrations of autoantibodies (AAB) and immune complexes, leading to particular destruction of platelets by immune system. A study reported that phenomenon of immune-mediated thrombocytopenia in subjects infected with human immunodeficiency virus-1 (HIV-1) is widespread. Although pathogenesis is unknown, this was proven to be associated with circulating immune complexes containing platelet membrane components and anti-platelet membrane GPIIIa49-66 IgG antibodies. Anti-platelet membrane GPIIIa49-66 IgG antibodies can cross-react with the HIV-1GP 160/120 antigen. Antibodies (Abs) and immune complexes deposited on surfaces of platelets will be recognized by reticuloendothelial cells (RECs), and platelets will be destroyed as target tissues, causing excessive platelet destruction. Platelets with similar antigens (Ags) may be coated by anti-platelet antibodies and immune complexes, which may result in immune-mediated damage. Furthermore, antibodies (Abs) produced during viral contagion may specifically attach to antigens (Ags) on platelets through molecular mimicry, leading to increased platelet destruction.

9. Chest Computed Tomography Scan

Chest radiography (also known as chest x-ray or CXR) and chest computed tomography (CT) of infected individuals show bilateral lung involvement; findings may differ according to illness stage, patient age, and immune status at time of imaging. With computed tomography (CT) scanning using thinner layers is revealed thickening of interlobular septa which are delicate strands of connective tissue separating adjacent pulmonary acini and primary pulmonary lobules which are part of acinus that comprises alveolar ducts, sacs, and alveoli but does not involve respiratory bronchioles. High-resolution computed tomography (HRCT) revealed small, honeycomb-like condensation of interlobular septa in a study of 45 infected subjects. The resolution of radiographic examination was not as good as that of computed tomography (CT) imaging, which revealed ground-glass opacities (GGOs) with fuzzy edges in 9 infected persons.

Song *et al.* (2020) described chest computed tomography (CT) observations in 51 ill persons infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), including pure ground-glass opacities (GGOs) in 77%, ground-glass opacities (GGOs) with interstitial and/or interlobular septal thickening in 75%, and ground-glass opacities (GGOs) with consolidation in 59% of cases. More consolidated lung lesions were found in ill persons aged ≥ 50 years compared with younger ill individuals. Kanne *et al.* (2020) concluded that chest computed tomography (CT) imaging findings are key focus points for radiologists in sick individuals with severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) contagion. It was defined usual computed tomography (CT) imaging findings, which incorporated consolidative pulmonary opacities and bilateral pulmonary parenchymal ground-glass opacities (GGOs). However, computed tomography (CT) imaging also depicts peripheral lung distribution and, occasionally, rounded morphology. On the basis of computed tomography (CT) imaging, Jin *et al.* (2020) described 5 stages according to body condition during viral contagion and time of illness onset. Ultra-early stage has no clinical manifestations and negative laboratory investigation results, but positive results for severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) is seen when throat swabs are examined. Chest computed tomography (CT) imaging characteristics include dotted focal ground-glass opacities (GGOs) or single or double focal ground-glass opacities (GGOs), patchy consolidation, and nodules positioned in central lobule area enclosed by patchy ground-glass opacities (GGOs). Early stage, which refers to phases at 1-3 days after beginning of clinical signs and symptoms, is characterized by fever and dry cough, among other symptoms. Chest computed tomography (CT) imaging features involve single or numerous agglomerated or scattered patchy ground-glass opacities (GGOs) segregated by grid-like condensed or honeycomb-like interlobular septa. Rapid progression stage occurs approximately 3-7 days after beginning of clinical signs and symptoms. Pathological signs and symptoms include fibrous exudation attached to every alveolus throughout inter-alveolar space, creating fusion situation. Chest computed tomography (CT) imaging characteristics involve pulmonary consolidation with air bronchogram. Consolidation stage occurs approximately 6-15 days after appearance of clinical signs and symptoms. Chest computed tomography (CT) imaging reveals numerous patchy pulmonary consolidations of lower density and range is then observed in rapid progression stage. Finally, dissipation stage occurs at approximately 14-21 days. This stage is

observed after beginning of clinical signs and symptoms, and chest computed tomography (CT) imaging characteristics involve strip-like opacity and patchy consolidation.

10. Renin Angiotensin Aldosterone System

In human physiology, peptides are degraded by limited number of non-specific extracellular enzymes known as peptidases or proteases. These are membrane proteins, active sites of which face extracellular space. Endopeptidases cut within peptide chain, while exopeptidases release C- or N-terminal amino acids. Angiotensin-converting enzymes (ACEs) are exopeptidases (carboxypeptidases), comparatively particular to amino acids (AAs) surrounding cut site, although these may be common to several peptides. It is therefore important to be aware that given peptidase is not as such specific to given peptide. Angiotensin-converting enzyme 2 (ACE2) is an enzyme (carboxypeptidase) mainly found in membrane, circulating forms being created by enzyme splicing of membrane anchor; it is homologous to angiotensin-converting enzyme (formerly simply known as ACE but now better denoted ACE1) first described in 2000 . Angiotensin-converting enzyme 2 (ACE2) down-regulates renin-angiotensin system (RAS) and acts as deactivator of angiotensin II (AngII) , converting it into angiotensin-(1-7), an active peptide with opposite properties to angiotensin II (Ang II) . Several animal studies showed that angiotensin-(1-7), by attaching to mitochondrial assembly receptor (MasR), induced vasodilatation and showed anti-fibrosis and anti-inflammatory properties. Angiotensin II (AngII) is also deactivated by aminopeptidase which converts angiotensin II (Ang II) into angiotensin III (Ang III), which induces vasodilatation and increases natriuresis and bradykinin by preferential attaching to angiotensin II receptors (AT2Rs) with 30-fold greater affinity than for angiotensin I receptors (AT1Rs). Angiotensin-converting enzyme 2 (ACE2) also converts angiotensin 1 [Ang1, also known as angiotensin-(1-10)] into angiotensin-(1-9) [Ang(1-9)], of not known action, which is further converted into angiotensin-(1-7) [Ang(1-7)] by angiotensin-converting enzyme 1 (ACE1). Renin angiotensin aldosterone system (RAAS) can thus be divided into activator system comprising classical and historical angiotensin II/ACE1/AT1R/aldosterone pathway, and an inhibitor system comprising angiotensin-(1-7)/ACE2/MasR pathway, the latter able both to deactivate angiotensin II (Ang II) and counter its effects. Pharmacology of angiotensin-(1-7)/ACE2/MasR pathway, in contrast to angiotensin II/ACE1/AT1R/aldosterone pathway, has been little explored, but some in-vitro

studies showed beneficial cardiovascular (CV) impact when activated, potentially involving cyclic guanosine monophosphate (cGMP)- elevation. Angiotensin-converting enzyme 2 (ACE2) has also been reported to interact with angiotensin-1 receptor (AT1R), targeted by angiotensin II receptor blockers (ARB). Angiotensin II receptor blockers (ARBs) counter angiotensin-1 receptor (AT1R)-mediated effects of angiotensin II (Ang II), thus inducing angiotensin II (Ang II) liberation; in response to this increase in angiotensin II (Ang II), they thus increase angiotensin-converting enzyme 2 (ACE2) expression. Angiotensin-converting enzyme 2 (ACE2) seems to be expressed by cells of various organs, including heart, kidney, vessels, digestive tract, testicles, ENT region (i.e., areas in ear, nose, and throat) and lung .

Angiotensin-converting enzyme 2 (ACE2) is human homolog of angiotensin-converting enzyme (ACE), composed of 805 amino acids (AAs) including 17-amino acid N-terminal signal sequence and C-terminal membrane binding domain and hydrolyzes angiotensin II (Ang II) into angiotensin1–7 [Ang (1-7)]. Angiotensin II (Ang II), major component of ACE/Ang II/AT1(angiotensin II type 1) axis, allows vasoconstriction, contributes to cell proliferation, and keeps hydro-salinity balance. Angiotensin 1-7 [Ang (1-7)] is endogenous ligand for G protein-coupled receptor Mas (GPCR Mas) and particularly inhibits angiotensin II (Ang II) by the antagonism of angiotensin II type 1 receptors (AT1Rs), which is regarded as a key modulator of the human renin-angiotensin system (RAS). Moreover, angiotensin 1-7 [Ang(1-7)] enhances vasodilation, protects heart and alleviates metabolic syndrome (MS).

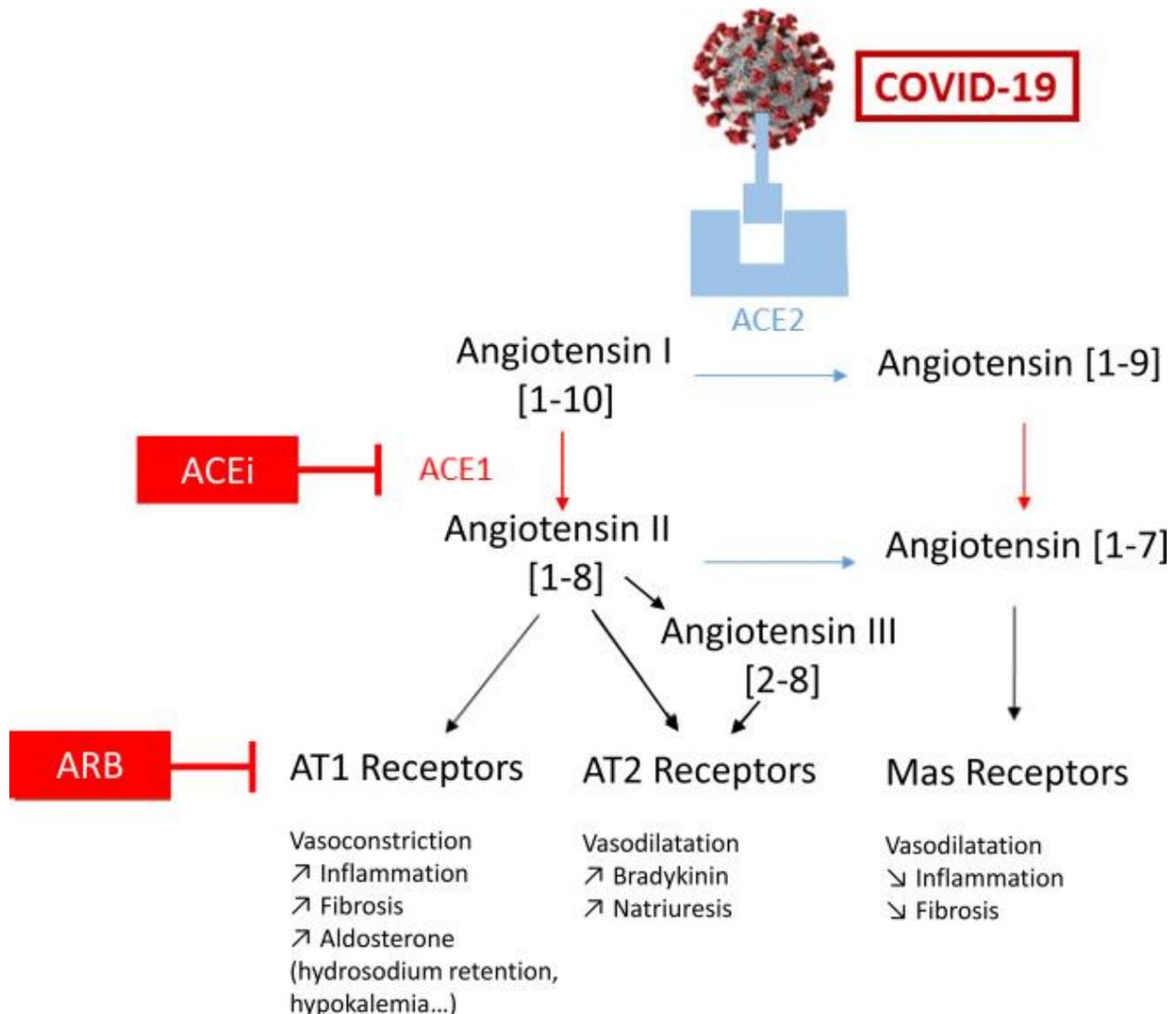
To enter and infect cells, coronavirus (CoV) has to recognize [via their spike (S) surface glycoprotein] and to attach to a membrane receptor (a transmembrane protein mediates signal transduction for cellular responses to extracellular stimuli). This depends on prior activation of spike (S) protein by human proteases including transmembrane protease, serine 2 (TMPRSS2). As a membrane enzyme with extracellular domain, angiotensin-converting enzyme 2 (ACE2) seems to provide entrance into human cells of coronavirus disease 2019 (COVID-19), and therefore acts as a receptor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) . Precise identification of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) glycoproteins and their angiotensin-converting enzyme 2 (ACE2) binding site shows the latter to be identical to that of severe acute respiratory syndrome coronavirus (SARS-CoV), despite the two viruses being distinguished and showing no more than 80% homology. Moreover, affinity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) for

angiotensin-converting enzyme 2 (ACE2) is greater than that of severe acute respiratory syndrome coronavirus (SARS-CoV). This spike (S) protein activation by transmembrane protease, serine 2 (TMPRSS2) followed by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) attaching to extracellular domain of membrane angiotensin-converting enzyme 2 (ACE2) explains how the virus attaches to and penetrates cell. Conversely, circulating soluble angiotensin-converting enzyme 2 (ACE2), while it can attach to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is unable to induce cell contagion. Experimentally, antibodies (Abs) targeting severe acute respiratory syndrome coronavirus (SARS-CoV) seem also to block severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) binding to angiotensin-converting enzyme 2 (ACE2), supposing potential therapeutic strategies, noticeably by repositioning certain protease inhibitors (PIs).

Certain in-vitro studies reported positive correlation between membrane expression and/or tissue activity of angiotensin-converting enzyme 2 (ACE2) and risk of coronavirus disease 2019 (COVID-19) contagion . In addition, by attaching to angiotensin-converting enzyme 2 (ACE2), virus induces decrease in angiotensin-converting enzyme 2 (ACE2) tissue activity, thus aggravating coronavirus disease 2019 (COVID-19)-induced inflammation in organs such as, considerably, lung. A study reported reduced membrane expression of angiotensin-converting enzyme 2 (ACE2) in mouse lung following severe acute respiratory syndrome coronavirus (SARS-CoV) administration, concomitant with respiratory impairment . In this context, administration of angiotensin II receptor blocker (ARB) (losartan) improved respiratory function, perhaps by restoring angiotensin-converting enzyme 2 (ACE2) membrane expression and tissue activity. Thus, level of angiotensin-converting enzyme 2 (ACE2) membrane expression and/or tissue activity may influence start of coronavirus disease 2019 (COVID-19) contagion and thus hazard of developing more severe inflammatory tissue injuries. Likewise, in recent retrospective study of 175 Chinese coronavirus disease 2019 (COVID-19) sick persons requiring hospital admission, 62% showed hypokalemia, i.e. a low level of potassium (K^+) in blood serum, which authors explained by altered angiotensin II (Ang II) deactivation by shift in angiotensin-converting enzyme 1 (ACE1) / angiotensin-converting enzyme 2 (ACE2) balance [reduced angiotensin-converting enzyme 2 (ACE2) tissue activity under coronavirus disease 2019 (COVID-19)] in favor of angiotensin-converting enzyme 1 (ACE1) , thus inducing aldosterone synthesis and hypokalemia occurrence . If this hypothesis is

affirmed, mineralocorticoid receptor blockers (MRBs) may be able to contribute to correcting this hypokalemia.

Therefore, it is clear that angiotensin-converting enzyme 2 (ACE2) and particularly its membrane expression and tissue activity play key role in coronavirus disease 2019 (COVID-19) contagion. Exact roles, however, are complex and may be deleterious in contamination phase, as angiotensin-converting enzyme 2 (ACE2) acts as receptor to coronavirus disease 2019 (COVID-19) (and severity may correlate with membrane expression and tissue activity) while being beneficial in inflammatory lesion phase.



Figure(30):Renin-angiotensin-aldosterone system in COVID-19 infection [Alexandre J.; Cracowski JL.; Richard V.; Bouhanick B.; Drugs, COVID-19 working group of the French Society of Pharmacology, Therapeutics. (2020). Renin-angiotensin-aldosterone system and COVID-19 infection. Elsevier. Annales d'Endocrinologie]

In figure (30): ACE1: angiotensin-converting enzyme 1; ACE2: angiotensin-converting enzyme 2; ARB: angiotensin II receptor blocker; ACEi: angiotensin-converting enzyme inhibitor.

Viral spike (S) proteins are well established as significant determinant of host tropism and represents key target for therapeutic and vaccine development against coronavirus disease 2019 (COVID-19) contagion. In addition, host cell proteases are important for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) entrance and contagion of cells as both spike (S) proteins and angiotensin-converting enzyme 2 (ACE2) are proteolytically modified during process. Binding affinity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with angiotensin-converting enzyme 2 (ACE2) looks stronger than severe acute respiratory syndrome coronavirus (SARS-CoV), with alterations in several amino acid (AA) residues allowing for enhanced hydrophobic interactions and salt bridge building, which may interpret noticeably larger global influence of coronavirus disease 2019 (COVID-19) than initial severe acute respiratory syndrome coronavirus (SARS-CoV). Furthermore, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has evolved to utilize broad array of host proteases including cathepsin L (CTSL, a lysosomal cysteine protease), cathepsin B (CTSB, a lysosomal cysteine protease), trypsin (a serine protease), factor X (a serine endopeptidase enzyme of coagulation cascade), elastase (a serine protease enzyme), furin (a cellular endoprotease), and transmembrane protease serine 2 (TMPRSS2) for spike (S) protein priming and facilitating cell entrance following receptor attachment. Transmembrane protease serine 2 (TMPRSS2) and cathepsin L/B mediates spike (S) protein priming of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and camostat mesylate (a potent serine protease inhibitor), a serine protease inhibitor combined with cathepsin L/B inhibitor, E-64d (an epoxysuccinyl peptide and an inhibitor of cysteine protease cathepsin B, calpains 1 and 2) blocked severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) entrance. Entry of both severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into cells is promoted by interaction between viral spike (S) protein with extracellular domains of transmembrane angiotensin-converting enzyme 2 (ACE2) proteins, followed by thereafter downregulation of surface angiotensin-converting enzyme 2 (ACE2) expression. In a cohort of 12 coronavirus disease 2019 (COVID-19) sick persons, circulating angiotensin II (Ang II) concentrations were noticeably increased compared with healthy controls (linearly correlated with viral load), providing direct link between tissue

angiotensin-converting enzyme 2 (ACE2) downregulation with systemic renin-angiotensin system (RAS) imbalance, and allowing development of multiorgan damage (MOD) from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagions.

Entrance of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into cells is facilitated by interaction between viral spike (S) protein with extracellular domains of transmembrane angiotensin-converting enzyme 2 (ACE2) proteins, followed by subsequent downregulation of surface angiotensin-converting enzyme 2 (ACE2) expression.

In a cohort study of 12 coronavirus disease 2019 (COVID-19) contracted persons, circulating angiotensin II (Ang II) concentrations were noticeably increased in comparison with healthy controls (linearly correlated with viral load), providing a direct link between tissue angiotensin-converting enzyme2 (ACE2) downregulation with systemic renin angiotensin system (RAS) imbalance, and facilitating development of multiorgan damage (MOD) from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagions.

Angiotensin-converting enzyme 2 (ACE2) works as master regulator of renin-angiotensin system (RAS) primarily by converting angiotensin I (Ang I) and angiotensin II (Ang II) into angiotensin 1-9 (Ang 1-9) and angiotensin 1-7 (Ang 1-7), respectively. Both loss-of-function and gain-of-function approaches in experimental models of human illnesses have described critical role for angiotensin-converting enzyme 2 (ACE2) in heart failure (HF), systemic hypertension (sHTN) and pulmonary hypertension (PH), myocardial infarction (MI), and diabetic cardiovascular (CV) complications. Gut dysbiosis and changed gut permeability have arisen as a notable mechanism of illness controlled by angiotensin-converting enzyme 2 (ACE2) axis in both vascular and lung illnesses, as well as in diabetes mellitus (DM). It is remarkable to define gut dysbiosis, also known as intestinal or gastrointestinal dysbiosis, as a state in which there is imbalance of microorganisms (MOs) within intestines. Clinical and experimental studies support physiological and pathophysiological role for angiotensin-converting enzyme 2 (ACE2) in cardiovascular disease (CVD), and increasing/activating angiotensin-converting enzyme 2 (ACE2) may evolve protective effects against hypertension (HTN) and cardiovascular disease (CVD). Angiotensin-converting enzyme 2 (ACE2) has garnered broad interest as cellular receptor of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causative virus of coronavirus disease 2019 (COVID-19) pandemic, which emerged from Wuhan, China, in late 2019. Angiotensin-

converting enzyme 2 (ACE2) provides protection in acute lung injury (ALI), presuming that, although it facilitates viral entrance at epithelial surface, angiotensin-converting enzyme 2/angiotensin 1-7 (ACE2/Ang 1–7) axis can be carefully manipulated to mitigate severe acute respiratory syndrome (SARS)-induced tissue injuries, which represents possible target for therapeutic intervention. Therapeutic intervention is an effort performed by persons or groups to enhance well-being of someone else who either needs help but refuses it or is otherwise not able to initiate or accept help. In experimental models of lung illness, catalytically active angiotensin-converting enzyme 2 (ACE2) alleviates pulmonary injury and vascular destruct and prevent pulmonary hypertension (PH), decreased lung fibrosis [or pulmonary fibrosis (PF) meaning scarring in lungs], arterial remodeling, and improved right ventricular performance due to combination of direct action in lungs and via angiotensin-converting enzyme 2 (ACE2)-dependent gut-lung axis. In phase II clinical trials, administration of angiotensin-converting enzyme 2 (ACE2) was shown to decrease systemic inflammation(SI, the result of release of pro-inflammatory cytokines from immune-related cells)and shifted renin-angiotensin system (RAS) peptide balance away from angiotensin II (Ang II) toward angiotensin 1-7 (Ang 1–7). Ongoing global efforts are concentrated on manipulating angiotensin-converting enzyme 2/ angiotensin 1-7 (ACE2/Ang 1–7) axis to limit severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion while granting maximal protective effects against lung and cardiovascular (CV) destruct in sick persons with coronavirus disease 2019 (COVID-19).

Severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2) majorly invades alveolar epithelial cells (AECs), leading to respiratory symptoms. These symptoms are more severe in ill individuals with cardiovascular disease (CVD), which might be correlated with elevated release of angiotensin- converting enzyme 2 (ACE2) in these ill individuals in comparison with healthy subjects. Angiotensin- converting enzyme 2 (ACE2) levels can be elevated by use of renin–angiotensin–aldosterone system (RAAS) inhibitors, which are a group of drugs that serve by inhibiting renin-angiotensin-aldosterone system (RAAS) and involve angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and direct renin inhibitors (DRIs). Given that angiotensin- converting enzyme 2 (ACE2) is actual receptor for severe acute respiratory syndrome coronavirus-2 (SARS- CoV-2), safety and possible effects of anti-hypertension treatment with angiotensin- converting enzyme 2 (ACE2) inhibitors (ACEIs) or angiotensin- receptor blockers (ARBs) in ill individuals with coronavirus disease-19 (COVID-

19) should be carefully taken into account. Hypertension (HTN), diabetes mellitus (DM) and cardiac diseases (CD) are often treated with angiotensin- converting enzyme 2 (ACE2) inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) which can increase expression of angiotensin- converting enzyme 2 (ACE2); hence, enhancing contagion with coronavirus (CoV) and be responsible for increased seriousness of illness in these group of ill individuals. Whether ill persons with coronavirus disease2019 (COVID-19) and hypertension (HTN) who are taking angiotensin- converting enzyme 2 (ACE2) inhibitor (ACEI) or angiotensin-receptor blocker (ARB) should switch to another antihypertensive drug remains debatable, and further proof is demanded.

11.Intensive Care Unit Admission in COVID-19 Infection

Several considerable results have been noticed amongst severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) affected persons and admitted to intensive care unit (ICU). Intensive care unit (ICU) individuals show higher neutrophil and white blood cell (WBC) counts, in addition to higher levels of D-dimer (DD), creatine (Cr), and creatine kinase (CK). Median time from symptom start to intensive care unit (ICU) admission has been reported to be 10 days. Median Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure Assessment (SOFA) scores on day of intensive care unit (ICU) admission have been calculated by investigators. It seems that median Glasgow Coma Scale (GCS) score is 15 (IQR, 9-15), Sequential Organ Failure Assessment (SOFA) score is 5 (IQR, 3-6), and Acute Physiology and Chronic Health Evaluation (APACHE) II is 17 (IQR, 10-22). Other factors, such as median partial pressure of oxygen (PaO₂) and median of ratio of partial pressure of oxygen to the fraction of inspired oxygen PaO₂/FiO₂, have also been evaluated [68 mmHg (IQR, 56-89) and 136 mmHg (IQR, 103-234), respectively]. However, it is noticeable to describe ratio of partial pressure arterial oxygen and fraction of inspired oxygen, known as the Horowitz index or Carrico index, as comparison between oxygen level in blood and oxygen concentration that is breathed. This helps to define degree of any problems with how lungs transport oxygen to blood. It was reported that ventilator-assisted breathing was administered to intensive care unit (ICU) contracted individuals. They provided extracorporeal membrane oxygenation (ECMO) and anti-infection treatment after admission to intensive care unit (ICU). It is important to refer that in extracorporeal membrane oxygenation (ECMO), blood

is pumped outside of body to heart-lung machine that removes carbon dioxide and sends oxygen-filled blood back to tissues in body. Blood flows from right side of heart to membrane oxygenator in heart-lung machine, and then is rewarmed and sent back to body. This method allows blood to bypass heart and lungs, allowing these organs to rest and heal. Extracorporeal membrane oxygenation (ECMO) is used in critical care situations, when person's heart and lungs need help so that one can heal. It may be used in care for coronavirus disease 2019 (COVID-19), acute respiratory distress syndrome (ARDS) and other contagions. It was reported that infected persons admitted to intensive care unit (ICU) showed high decrease rates. They noted that intensive care unit (ICU) cases had higher plasma levels of granulocyte-colony stimulating factor (G-CSF or GCSF), interferon gamma (IFN- γ)-inducible protein 10 (also called CXCL10/IP-10), interleukin-10 (IL-10), interleukin-7 (IL-7), interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF- α), monocyte chemoattractant protein-1(MCP1), and macrophage inflammatory protein-1alpha (MIP-1 α /CCL3) than non-intensive care unit (ICU) cases. They also determined D-dimer (DD) levels and prothrombin time (PT) during admission. Median D-dimer (DD) level and median prothrombin time (PT) were 2.4 mg/L (IQR, 0.6-14.4) and 12.2s (IQR 11.2-13.4), respectively. Authors also described secondary contagions that developed in intensive care unit (ICU) ill persons. Elevated concentrations of some cytokines were noticed by some clinicians.

12.Risk Factors

Goodman (2020) shows that risk from coronavirus disease 2019 (COVID-19) contagion increases with advancing age. In general, persons in their fifties are at higher risk than persons in their forties. Likewise, persons in their sixties and seventies are at higher risk than those who are in their fifties.

Conditions in which there's strong proof of increased risk involve: chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) (like emphysema), persons with lower immune health because of solid organ transplantation (SOT), obesity - those with body mass index (BMI) greater than 30Kg/m², serious heart conditions like heart failure (HF) and coronary artery disease (CAD), sickle cell disease (SCD), and type 2 diabetes mellitus (T2DM).

Conditions that might place a person at greater danger for a severe outcome from coronavirus disease 2019 (COVID-19) are: asthma, dementia, cerebrovascular diseases (CBVD, such as stroke), cystic fibrosis (CF), high blood pressure [HBP, also called hypertension (HTN)], lower immune health, pregnancy, liver disease, pulmonary fibrosis [PF, a form of interstitial lung disease(ILD)], smoking, type 1 diabetes mellitus (T1DM), and thalassemia (inherited blood disorder).

Rod *et al.* (2020) described total of 17 studies, with most of them relying on retrospective cross-sectional design and reporting data using descriptive statistics. Only three studies performed multivariate analysis adjusting for confounding factors. Sixteen of studies reported laboratory-affirmed infected persons with coronavirus disease 2019 (COVID-19) and one reported clinically diagnosed contracted persons. There were 60 risk factors described for coronavirus disease 2019 (COVID-19) seriousness. Of these, 7 were regarded of high, 40 of medium and 13 of low consistency. Increase in the followings: age, D-dimer (DD), C-reactive protein (CRP), sequential organ failure assessment (SOFA) score, and body temperature while decrease in albumin (alb), and history of diabetes mellitus (DM) were risk factors with highest consistency as predictors for coronavirus disease 2019 (COVID-19) seriousness. In addition, elevated levels of white blood cells (WBCs) count, procalcitonin (PCT), lactate dehydrogenase (LDH), cardiac troponins (cTn), prothrombin time (PT), interleukin-6 (IL-6), serum ferritin, neutrophils count, creatine kinase MB (CK-MB), CURB-65 score with decreased lymphocyte (LYM) count, and dyspnea were classified as medium consistency risk factors with at least positive difference of two studies reporting statistically considerable difference between non-severe and CSF groups. There was high heterogeneity in definition of CSF, ranging from need for supplemental oxygen to development of acute respiratory distress syndrome (ARDS), intensive care unit (ICU) admission and decease. However, Rod *et al.* (2020) findings also suggested that diabetes mellitus (DM) is one of most critical comorbidities in terms of illness seriousness. Diabetes mellitus (DM) has been previously correlated with other respiratory virus illness severities in cross national specimens. This might be interpreted by immunosuppressive effects of hyperglycemia and could also explain why contracted persons that develop acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) were found to have statistically significant higher glucose (Glc) concentrations. This finding has important implications given high global prevalence of diabetes mellitus.

Chen *et al.* (2020) described eight hospital admission covariates which are independent risk factors for decease in almost 2000 contracted persons with coronavirus disease 2019 (COVID-19) involving older age, smoking history, higher body temperature ($^{\circ}\text{C}$), and levels of D-dimer (DD), activated partial thromboplastin time (aPTT), serum creatinine (sCr), platelet, and neutrophil-lymphocyte ratio (NLR) on admission. Several are reported by others; however, authors were unable to assure other risk factors mentioned in smaller datasets. Chen *et al.* (2020) identified Log_{10} NLR as independent risk factor for decease with $\text{HR} = 14.1$ (3.2, 61.2) with Log_{10} values ≥ 0.4 to ≤ 1.0 but not otherwise. Although higher neutrophil and lower lymphocyte (LYM) concentrations and higher neutrophil-lymphocyte ratio (NLR) were previously mentioned, Log_{10} NLR has not.

A notable study showed that pregnancy can make course of coronavirus disease 2019 (COVID-19) more serious for women, though it doesn't seem to increase their risk of decease. In a study that compared coronavirus disease 2019 (COVID-19) outcomes among women between ages of 18 and 44 by pregnancy status, nearly one-third of pregnant women were hospitalized for their contagions, while only about 6% of the non-pregnant women had to be admitted to hospital. Pregnant women were also more likely to need intensive care unit (ICU) care and to receive breathing support from a ventilator, but they were not more likely to pass away. About 0.2% of both pregnant and non-pregnant women passed away of coronavirus disease 2019 (COVID-19) during study period. Study authors stress that women who are pregnant during pandemic should take extra care by staying at home whenever possible, wearing mask in public, standing or sitting at least 6 feet away from others when they do have to go out, and washing their hands often.

A study conducted by Almazeedi *et al.* (2020) found association between several risk factors and admission to intensive care unit (ICU): namely, age above 50 years old, smoking, elevated quick sepsis related organ failure assessment (qSOFA, also known as quickSOFA) score, elevated C-reactive protein (C-RP) and procalcitonin (PCT) levels. Also, following risk factors were identified as having correlation with decease in study sample: asthma, smoking and elevated procalcitonin (PCT) levels.

A study conducted by Almazeedi *et al.* (2020) in Kuwait mentioned that only 19% of study's sick individuals were females, which is lower but in keeping with findings by Guan *et al.* (2020) and

Richardson *et al.* (2020) who also documented lower admission percent for women compared to men (41.9% and 39.7%, respectively). Contributing factor to lower proportion of women in Almazeedi *et al.* (2020) study sample, may be high percents of coronavirus disease 2019 (COVID-19) detected in manual laborer of Indian ethnicity, who tend to be both male and younger. A breaking out in two main epicenters, Al-Jileeb and Mahboula areas in Kuwait, both of which house high concentrations of Indian male manual laborers may also account for large proportion of young, male, Indian infected persons in this study sample (48.1%). Also, South Asian ethnicity and lower socio-economic state have been hypothesized to be associated with higher percents of coronavirus disease 2019 (COVID-19) and poorer outcomes, based on epidemiological observations. Mean body mass index (BMI) for study sample was 26.6 kg/m², with 41.5% of infected persons in overweight category, which is reflective of normal weight demographics in Kuwait. As reported by other studies, hypertension (HTN) (16.1%) and diabetes mellitus (DM) (14.1%) were most common comorbidities demonstrated in Almazeedi *et al.* (2020) cohort study. For symptomatic persons, most common symptom was cough (57.5%), which is in keeping with several other retrospective cohort studies. Of interest, almost half of study sample were asymptomatic on admission (46.3%) and had no signs of contagion on clinical examination (59.7%).

Other retrospective cohort studies in coronavirus disease 2019 (COVID-19) contracted persons reported much higher percents of temperature, i.e. studies conducted by Richardson *et al.* (2020) 30.7%, Guan *et al.* (2020) 59.2%, and Wu *et al.* (2020) 38.3% above 39 °C, while Zhou *et al.* (2020) 94% above 37.3 °C, as almost all their contracted individuals were symptomatic. Interestingly, Almazeedi *et al.* (2020) revealed that large proportion of affected persons had sodium and calcium levels below reference range on admission (28.7% and 20.6%, respectively). Hong *et al.* (2020) reported comparable findings, where 50% of coronavirus disease 2019 (COVID-19) contracted persons they examined had hyponatremia and hypokalemia and they supposed there was correlation with degree of renal injury in those infected persons. Comparably, Sun *et al.* (2020) presented high percents of hypocalcaemia (74.7%) in their coronavirus disease 2019 (COVID-19) contracted persons, on admission. Elevated C-reactive protein (CRP), D-dimer (DD), and procalcitonin (PCT) concentrations were found in large percentage of affected individuals, as noted by other studies. In addition, prothrombin concentrations below reference range were present in over half Almazeedi *et al.* (2020) study

population (53.4%). Implications of these findings are not clear, but authors presume it may be associated with procoagulant state that is thought to occur in coronavirus disease 2019 (COVID-19) infected persons. As almost all infected persons enrolled in Almazeedi *et al.* (2020) cohort study had a chest x-ray on admission, authors determined that 76.3% infected persons either had a normal chest-ray or benign findings such as prominent broncho-vascular markings, as reported by a radiologist. Conversely, Wong *et al.* (2020) demonstrated that in a cohort of 64 infected subjects they studied, only 31% of coronavirus disease 2019 (COVID-19) infected subjects had normal initial chest x-ray. In Almazeedi *et al.* (2020) cohort study infected subjects with abnormal chest x-ray findings, 16.6% had unilateral local patchy shadowing or opacification, as most common pathological finding. Deaths rates and intensive care unit (ICU) admission rates are comparable to Guan *et al.* (2020) [death, 1.4% and intensive care unit (ICU) admission, 5%], but much lower than other large retrospective cohort studies as studies performed by Wu *et al.* (2020), 21.9% death , 26.4% intensive care unit (ICU) admission, and Zhou *et al.* (2020) 28.3% death, 26% intensive care unit (ICU) admission. This may reflect that research article by Guan *et al.* (2020) was one of earliest coronavirus disease 2019 (COVID-19) retrospective cohort studies so included ill persons may have had milder symptoms, compared to research articles that were published later, when health resources became more limited. In addition, multivariable analysis of Almazeedi *et al.* (2020) cohort study, indicated an association between death rate and being a smoker, having asthma and elevated procalcitonin (PCT) concentrations. There was also association between intensive care unit (ICU) admission and age above 50 years old, quick sepsis related organ failure assessment (qSOFA) score above 0, smoking, higher C-reactive protein (CRP) concentrations and elevated procalcitonin (PCT) levels. Interestingly, being a smoker and elevated procalcitonin (PCT) concentrations were only factors found to be correlated with both pass away and intensive care unit (ICU) admission. Both factors have also been associated with unfavorable outcomes by other searches and systematic reviews. In addition, the fact that an elevated procalcitonin (PCT) associates with bacterial, and not viral, sepsis supposes that ill persons with serious illness might additionally have an element of bacterial pneumonia. Comparably, several searches have found correlation between older age and elevated C-reactive protein (CRP) concentrations and bad outcomes. High quick sepsis related organ failure assessment (qSOFA) score and sequential organ failure assessment (SOFA) score were found to be correlated with decease by Zhou *et al.* (2020). Almazeedi *et al.* (2020) findings did not find an

association between quick sepsis related organ failure assessment (qSOFA) score and decease, but they did find a correlation with intensive care unit (ICU) admission. This may be due to small number of deceases in study sample.

Age, male sex, obesity, and underlying illness have emerged as risk factors for severe and fatal cases of coronavirus disease 2019 (COVID-19) in United Kingdom, according to large cohort study published by The BMJ. Besides increasing age, and underlying heart, lung, liver and kidney illnesse, factors already known to cause poor outcomes, the researchers found that obesity and gender were key factors associated with need for higher levels of care and higher risk of decease in hospital.

A study found notable relationship between sex, obesity and poor outcomes for coronavirus disease 2019 (COVID-19) affected persons. As an emerging contagious illness, population of all races and ages is generally susceptible. In mainland China, ages range from 30 to 65year old persons account for 71.45% and children under age 10 years old account for 0.35%. Elderly people and persons with underlying basic disturbances such as asthma, diabetes mellitus (DM), cardiovascular diseases (CVD), and cancer may be more susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion. Smoking and obesity are also susceptible factors. Persons who are in close contact with symptomatic or subclinically symptomatic infected persons are part of high-risk population. High contagion risk is also considered in healthcare workers and family members of infected persons.

Susceptibility of certain viral contagions has been linked to antigenic determinants of ABO blood groups. To describe antigenic determinant it is an epitope and it is part of antigen (Ag) that is recognized by immune system, particularly by antibodies (Abs) and B and T cells and other immune cells like antigen presenting cells (APCs) cannot recognize epitopes [only pathogen-associated molecular pattern molecules (PAMPS) and damage-associated molecular patterns (DAMPs)]. Data from Wuhan, China, first epicenter of coronavirus disease 2019 (COVID-19) pandemic, shows ABO blood group linkage with coronavirus disease 2019 (COVID-19) contagions. Zhao *et al.* (2020) compared ABO blood groups of controls from general population with 2173 coronavirus disease 2019 (COVID-19) contracted persons from three hospitals in Wuhan region. Across all three hospitals, blood group A was associated with a higher risk for coronavirus disease 2019 (COVID-19) in comparison with non-A blood groups, whereas blood group O was related to significantly lower risk for conntagiiion compared with

non-O blood groups. Another observational study on data from New York Presbyterian hospital system, on 1559 persons examined for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with known blood group type, also administered comparable results. In severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) positive cases, there was high proportion of blood group A, with a low proportion of blood group O.

low levels of serum testosterone (T), which may be associated with aging and obesity and other chronic diseases, lead to systemic inflammation, endothelial dysfunction (EtD) and increased platelet activity, predisposing to thrombosis and thromboembolism (TE) and promoting atherosclerosis and cardiovascular diseases (CVD). In men with obstructive sleep apnea syndrome (OSAS) or in those affected by chronic obstructive pulmonary disease (COPD) or other background pulmonary disease, a higher prevalence of hypogonadism has been found. In these clinical settings, men with lower level of testosterone (T) are more prone to develop pulmonary and systemic inflammation and worse respiratory and general parameters. Moreover, testosterone (T) predisposes men to less effective immune response (IR) against contagious agents and male hypogonadism may trigger detrimental cytokine dysfunction, including high circulating levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-1 beta (IL-1 β), responsible for poor prognosis in coronavirus disease 2019 (COVID-19). Additionally, androgens enhance transmembrane protease, serine 2 (TMPRSS2) expression, thus, leading to a baseline predisposition to wider severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spread into man body than that occurring in women. This mechanism could explain greater male susceptibility to more serious clinical course in coronavirus disease 2019 (COVID-19). Of note, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could infect testicle, potentially affecting testosterone (T) secretion also in young men and directly inducing (primary hypogonadism) or aggravating a preexistent condition of hypogonadism in already predisposed men. The magnitude of this phenomenon as well as the importance of gonadotropins' levels, which varies among the different forms of hypogonadisms in affected patients (primary versus secondary or tertiary hypogonadism or mixed forms), remains still debated and potential implications on prognosis in course of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion require further investigation for both diagnostic and therapeutic purposes.

13.Prevention

In states where community transport is widespread, preventive strategies for all persons in a health care setting are warranted to decrease possible exposures. Additional measures are warranted for individuals with suspected or affirmed coronavirus disease 2019 (COVID-19).

If community transfer of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is found, residents should be encouraged to practice social distancing by avoiding crowds and maintaining a distance of six feet (two meters) from others when in public. Individuals should avoid close contact with coronavirus disease 2019 (COVID-19) contracted individuals. Individuals are also encouraged to wear masks when out in public.

The following general measures are recommended to decrease transport of coronavirus disease 2019 (COVID-19) contagion:

- 1-Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60 percent alcohol is adequate alternative if hands are not visibly dirty.
- 2-Respiratory hygiene (e.g., covering cough or sneeze).
- 3-Avoiding touching face (particularly eyes, nose, and mouth).American Academy of Ophthalmology proposes that individuals not wear contact lenses, because contact lenses make individuals touch their eyes more often.
- 4-Cleaning and disinfecting objects and surfaces that are often touched.
- 5-Ensure suitable ventilation of indoor spaces.

These measures should be followed by all persons, but should be emphasized for older persons and people with chronic medical conditions, in particular.

It is presumed that clinicians advise coronavirus disease 2019 (COVID-19) infected people to wear non-medical masks when in public spaces where social/physical distancing is not suitable. World Health Organization (WHO) recommends mask-wearing as part of comprehensive approach to decreasing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transference in settings where there is diffused transference and social distancing is hard (e.g., in public settings, in congregate living settings, on public transportation). In such settings, World Health Organization (WHO) advises that most people in community wear non-medical mask

(e.g., a cloth or fabric mask), although it specifies that persons who are greater than 60 years old or have underlying medical comorbidities should wear medical mask, as should those who have symptoms consistent with coronavirus disease 2019 (COVID-19). In United States, Centers for Disease Control and Prevention (CDC) also recommends that persons wear cloth face covering (e.g., a cloth mask or cloth face covering made from household items) when in public settings where social distancing is hard to achieve, particularly in areas with actual community transference. Centers for Disease Control and Prevention (CDC) specifies that face covering recommendation does not involve medical masks, which should be reserved for health care workers. World Health Organization (WHO) has also issued standards for ideal composition of cloth mask to optimize fluid resistance and filtration efficacy. Cloth face coverings should ideally be made with several layers of fabric.

When advising ill individuals on use of masks or other face coverings, clinicians should counsel them to avoid touching eyes, nose, and mouth when putting on or removing mask, to practice hand hygiene before and after handling mask, and to launder cloth masks routinely. Clinicians should also assert that mask or face covering does not diminish importance of other preventive measures, such as social distancing and hand hygiene.

Reasons for all persons (regardless of symptoms) to wear mask or face covering in community is principally to contain secretions of and prevent transfer from infected individuals, involving those who have asymptomatic or presymptomatic contagion. People who develop acute respiratory disease (e.g., with fever and/or respiratory symptoms) or other symptoms consistent with coronavirus disease 2019 (COVID-19) should be encouraged to self-isolate at home (away from other persons and pets in household) for duration of illness and wear mask or face covering if they have to be around other individuals. Some may warrant evaluation for coronavirus disease 2019 (COVID-19). People who are caring for suspected or documented infected persons with coronavirus disease 2019 (COVID-19) at home should also wear face cover when in same room with contracted person.

Use of masks or face coverings to provide source control and decrease transference in community is boosted by indirect proof. In a retrospective study of 124 contracted persons with affirmed coronavirus disease 2019 (COVID-19) and their families in Beijing, China, secondary transmission occurred in 41 families; use of masks by family members (including index patient)

prior to disease start in index patient was independently combined with decreased risk of contagion. Type of mask used (medical or cloth) was not specified. In a case report of two hair stylists with coronavirus disease 2019 (COVID-19) who worked while symptomatic prior to diagnosis but wore face coverings, there were no subsequent coronavirus disease 2019 (COVID-19) diagnoses among 139 mates with vicine contact, all of whom were also wearing face coverings; both medical masks and cloth face coverings were used. In another study that included 17 infected individuals with common cold coronavirus contagions, use of medical mask eliminated detectable viral ribonucleic acid (vRNA) in droplet and aerosol particles collected from exhaled breath [although viral ribonucleic acid (vRNA) was only detected in 30 and 40 percent of such specimens when infected persons were not wearing masks]. Although limited by assumptions and estimates, modeling studies have also supposed that high adoption of mask-wearing by general public can decrease transport, even if masks are only moderately efficient in containing contagious respiratory secretions. Studies on filtration efficacy of fabrics presume that certain fabrics [e.g., tea towel fabric (termed dish towel fabric in United States)], particularly when double-layered, can approach filtration efficacy of medical masks. For some fabrics (e.g., cotton T-shirt material), more than two layers may be necessary for suitable filtration.

Mask-wearing in community may also be correlated with protection for wearer. In a report of 382 service members who were surveyed about personal preventive strategies in setting of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) breaking out in United States Navy aircraft carrier, self-report of wearing face cover was independently related to lower probability of contagion [odds ratio (OR) 0.3], as were avoiding common areas (OR 0.6) and observing social distancing (OR 0.5).

On January 30, 2020, World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) breaking out public health emergency of international interest and, in March 2020, began to characterize it as pandemic in order to assert gravity of situation and urge all countries to take action in detecting contagion and preventing spread. Throughout world, countries have employed differed nonpharmaceutical interventions to decrease transport. In addition to personal preventive measures (e.g., hand hygiene, respiratory etiquette and face covers, environmental disinfection), transmission reduction strategies comprise:

1-Social/physical distancing orders

- 2-Stay-at-home orders
- 3-School, venue, and nonessential business closure
- 4-Bans on public gatherings
- 5-Travel restriction with exit and/or entry screening
- 6-Aggressive case identification and isolation (separating infected individuals from others)
- 7-Contact tracing and quarantine (separating people who have been exposed from others).

These measures have been associated with reductions in incidence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) contagion over time, although relative contribution of each is hard to evaluate, as most countries have employed combination of interventions. As an example, in pestilence study in Wuhan, number of these interventions (implementation of travel restrictions in and around Wuhan with home quarantine and compulsory mask-wearing in public, followed by centralized quarantine for all cases and contacts, followed by proactive symptom checking for all residents) were associated with progressive reductions in incidence of assirted cases in Wuhan and decrease in effective reproduction number from more than 3 prior to interventions to 0.3 after them. However, effective reproduction number can be referred to as average number of secondary cases for each case in a population made up of both susceptible and nonsusceptible persons. In another study from China, cities in which combined control measures were preemptively implemented prior to identification of coronavirus disease 2019 (COVID-19) cases recorded 33 percent fewer laboratory-assirted cases during first week of breaking out compared with cities that implemented control measures later. In a study from United States estimating incident cases in bordering counties in Illinois, which issued stay-at-home order, and Iowa, which did not, counties in Iowa experienced more quick increase in infected persons following implementation of order in Illinois, estimated to result in 217 excess contracted persons after one month.

Physical distancing is probably independently correlated with decreased gravity of transference. In a meta-analysis of observational studies assessing relationship between physical distance and transport of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV), vicinity and hazard of contagion were closely associated, and contagion rate was higher with contact within three feet (one meter) compared with contact

beyond that distance (12.8 versus 2.6 percent). A distance more than six feet (two meters) was bound to further decrease in transport.

For cities where incidence has fallen and relaxation of transmission reduction measures is being considered, World Health Organization (WHO) has issued interim guidance on implementation, which involves step-wise approach that is adjusted according to local circumstances and prioritizes protecting vulnerable populations; it recommends that personal preventive measures be maintained and that public health efforts to detect infected individuals for isolation and to identify contacts for quarantine be strengthened.

In United States, Centers for Disease Control and Prevention (CDC) recommends that persons avoid all nonessential international travel and nonessential travel from some domestic places . Because gravity of travel changes hastily, travelers should check government websites for restrictions.

In areas where severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is widespread, all residents should be encouraged to stay alert for symptoms and practice social distancing by staying home as much as possible and maintaining six feet (two meters) distance from others when they have to leave home.

In United States, Centers for Disease Control and Prevention (CDC) supposes this way for all residents. For those returning from international travel (including cruise ship travel) and those who have had close contact with ill individual with suspected or confirmed coronavirus disease 2019 (COVID-19) (including during 48 hours prior to that contracted person developing symptoms), Centers for Disease Control and Prevention (CDC) also supposes:

1-Self-quarantine at home for 14 days following last exposure, with maintenance of at least six feet (two meters) from others at all times.

2-Avoiding contact with persons at high risk for severe illness (unless they are household members with same exposure).

3-Twice-daily temperature checks with monitoring for fever, cough, or dyspnea. If they develop such clinical manifestations, they should continue to stay at home away from other household members and contact their medical providers.

For asymptomatic persons who are critical infrastructure workers, Centers for Disease Control and Prevention (CDC) has provided guidance on returning to work during 14-day post-exposure period with symptom and temperature checking, mask use, social distancing, and workspace disinfection.

Numerous vaccine candidates are being evaluated for prevention of coronavirus disease 2019 (COVID-19). These include differed types of vaccines, comprising nucleic acid-based [messenger ribonucleic acid (mRNA) and deoxyribonucleic acid (DNA)] vaccines, viral-vector vaccines, and inactivated or recombinant protein vaccines. The different vaccine schemes differ in their possible safety and immunogenicity, speed and cost of manufacturing, and other characteristics crucial for meeting global demand. Several of these vaccines have induced binding antibodies (Abs), neutralizing activity, and T cell responses in healthy adults during early trials. Studies of vaccine candidates in nonhuman primates have also reported lower concentrations or more haste clearance of viral ribonucleic acid (vRNA) in respiratory tract specimens following viral challenge in vaccinated animals compared with unvaccinated controls.

There is also concern in Bacille-Calmette-Guerin (BCG) immunization for prevention of coronavirus disease 2019 (COVID-19), and clinical trials are underway to evaluate its use among health care workers. Studies have presumed that, although its primary purpose is prevention of tuberculosis, Bacille-Calmette-Guerin (BCG) immunization induces innate or nonspecific immune response that may have protective effects against non-mycobacterial, including viral contagions. Any impact of Bacille-Calmette-Guerin (BCG) immunization on coronavirus disease 2019 (COVID-19) is not known. World Health Organization (WHO) recommends Bacille-Calmette-Guerin (BCG) vaccination not be used for prevention or lessening seriousness of coronavirus disease 2019 (COVID-19), pending further data.

Clinical trials are also being conducted in United States and elsewhere to estimate safety and efficiency of post-exposure drug prophylaxis against coronavirus disease 2019 (COVID-19). No agent is known to be efficient in preventing contagion; it is recommended that post-exposure prophylaxis not be attempted outside clinical trial.

Hydroxychloroquine (HCQ) was one candidate medication for post-exposure prophylaxis, but available data propose it is not effective in preventing contagion. In double-blind trial, 821

individuals were randomly assigned to hydroxychloroquine (HCQ) or placebo folate tablets within four days of a household or occupational exposure to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which was described as contact within six feet for more than 10 minutes without eye shield; most were also not wearing medical mask. Hydroxychloroquine (HCQ) did not decrease percent of combined outcome of polymerase chain reaction (PCR)-assisted coronavirus disease 2019 (COVID-19) or consistent symptoms within 14 days (11.8 versus 14.3 percent with placebo, difference -2.4 percentage points, 95% CI -7.0 to 2.2); there were also no differences in separate rates of polymerase chain reaction (PCR)-confirmed or presumed cases. Side effects were reported in 40.1 percent of hydroxychloroquine (HCQ)-treated versus 16.8 percent of placebo-treated subjects. Loss to follow-up in about 11 percent, a greater rate of management discontinuation in the hydroxychloroquine (HCQ) group, and use of self-reported symptoms as proxy for incident coronavirus disease 2019 (COVID-19) reduce confidence in findings; nevertheless, the study did not demonstrate role for hydroxychloroquine (HCQ) for prevention of coronavirus disease 2019 (COVID-19).

CHAPTER THREE

COMPLICATIONS and THERAPY

1.Hypokalemia

Potassium (K^+) ions are predominant intracellular cations. Potassium (K^+) ions homeostasis depends on external balance [dietary intake (usually 100 mmol per day) versus excretion (95% via kidney; 5% via the colon) and internal balance (distribution of potassium (K^+)) ions between intracellular and extracellular fluid compartments]. Uneven distribution of potassium (K^+) ions across cell membranes indicates that mere 1% shift in its distribution can lead to 50% change in plasma potassium (K^+) ions level. Hormonal mechanisms [including insulin, β -adrenergic agonists (BAA), and aldosterone] modulate potassium (K^+) ions distribution by inducing quick transfer of potassium (K^+) ions across plasma membrane. Under normal circumstances, kidney's distal nephron secretes potassium (K^+) ions and defines final urinary excretion.

Hypokalemia is one of commonest electrolyte disturbances observed in clinical practice and, although more predominant than hyperkalemia, most suffering individuals are mild. Although thresholds for definition of hypokalemia differ a bit, excessively quoted lower limit for normal serum potassium (K^+) ion level is 3.5 mmol/l. Serum potassium (K^+) ion level of 2.5–3.0mmol/l is regarded moderate hypokalemia and a level <2.5 mmol/l is indicated severe hypokalemia.

Hypokalemia is a consequence of renal or non-renal loss of potassium (K^+) ions . Extrarenal potassium (K^+) ions losses from body are usually small, but can be notable in persons with chronic diarrhea, severe burns or prolonged sweating. Intracellular potassium (K^+) ions shift will develop to transient hypokalemia, while inadequate dietary intake is seldom cause of hypokalemia. Hypokalaemia can be either resulted from decreased intake of potassium (K), or by excessive losses of potassium (K) in urine or through gastrointestinal tract (GIT). The latter is more recognizable. Excessive excretion of potassium (K) in urine (kaliuresis) may come from use of diuretics medications, endocrine illnesses such as primary hyperaldosteronism (PA), kidney anomalies, and genetic syndromes effecting renal function. Gastrointestinal (GI) losses of potassium (K) are due to prolonged diarrhea or vomiting, intestinal obstruction or infections, and chronic laxative abuse. An intracellular shift of potassium (K) can also progress to severe hypokalemia. Insulin administration, stimulation of sympathetic nervous system (SNS),

thyrotoxicosis (also known as hyperthyroidism or overactive thyroid) and familiar periodic paralysis (PP) are some of the reasons for this phenomenon. Congenital adrenal hyperplasia (CAH) due to enzymatic defects, is genetic syndrome strongly associated with hypertension (HTN) and hypokalemia, resulting from excessive mineralocorticoid effects. Drugs, such as diuretics and penicillin (P, PCN or PEN) can be frequently underlying cause of hypokalemia. Hypomagnesemia is very important since more than 50% of clinically recognized hypokalemia has concomitant magnesium deficiency and is clinically most frequently seen in persons taking loop or thiazide diuretic medication. Concomitant magnesium deficiency has been estimated to aggravate hypokalemia. Hypokalemia correlated with magnesium deficiency is frequently refractory to therapy with potassium (K^+).

Low potassium also increases the gravity of abnormal heart rhythm (also called arrhythmia), which is often too slow and can cause cardiac arrest (the abrupt loss of heart function). Regarding seriousness of hypokalemia, symptoms can differ from absent to lethal heart arrhythmias. It is worthy to refer to arrhythmia, arrhythmia also known as cardiac arrhythmia or heart arrhythmia, it is group of conditions in which heartbeat is irregular, too fast, or too slow. Arrhythmias occur in the atria (the top chambers of heart) are named supraventricular (above the ventricles) in origin, whereas ventricular arrhythmias start in ventricles (the lower chambers of heart), and majority of potentially lethal arrhythmias are ventricular in origin. Symptoms of arrhythmias usually resolve with correction of hypokalemia. Manifestations can be grouped according to affected system. Effects of hypokalemia concerning renal function can be metabolic acidosis, rhabdomyolysis (a breakdown of muscle fibers syndrome), and, rarely, impairment of tubular transport, chronic tubulointerstitial disease (TID) and cyst formation. Nervous system is also affected, the patient can experience leg cramps, weakness, paresis or ascending paralysis. Constipation or intestinal paralysis and respiratory failure frequently occur as signs of severe hypokalemia. Hypokalaemia can result in detrimental effects on the cardiovascular (CVD) system, causing electrocardiographic (ECG) changes which include flattening and inversion of T waves in mild hypokalemia, followed by Q-T interval prolongation, visible U wave and mild ST depression in more severe hypokalemia. Severe hypokalemia can also result in arrhythmias such as Torsades de points (TdP) and ventricular tachycardia (VT), and heart failure (HF).

Cases with serum potassium (K^+) ions in the range of 3.0-3.5 mmol/l are usually treated with oral potassium (K^+) salts as long as they can take oral therapy. Cases with serum potassium (K^+) < 3 mmol/l may require intravenous (IV) potassium (K^+) ions particularly in emergencies such as arrhythmias, rhabdomyolysis and respiratory failure (RF). In many conditions both by mouth (PO) and intravenous (IV), potassium (K^+) salts are administered. Intravenous (IV) replacement of potassium (K^+) is proper for cases with electrocardiogram (ECG) changes, and in hypokalemia correlated with diabetic ketoacidosis (DKA) or taking digitalis. Potassium (K^+) ions deficit is about 200-400 mmol/l for every 1 mmol/l drop in potassium (K^+), but effective quantity differs among persons. Most patients are managed with potassium chloride (KCl). Potassium chloride (KCl) is to large degree available in multiple forms [extended release (ER) tablets, capsules, liquid, and intravenous (IV)]. Potassium chloride (KCl) functions hastily and is the preferred agent particularly in cases with concomitant metabolic alkalosis. In those patients, replenishment of chloride (Cl^-) ion is essential. Chloride (Cl^-) remains especially in extracellular compartment (ECC). If potassium (K) bicarbonate is administered, bicarbonate (HCO_3^-) hugely enters cell and potassium (K^+) follows, this lets potassium bicarbonate ($KHCO_3$) (and citrate/acetate, which are precursors of bicarbonate) less effective. Intravenous potassium chloride (IV KCl) must be administered at a rate that does not surpass 10 mmol/h. A higher rate up to 20 mmol/h is a status in emergency conditions such as cardiac arrhythmias (heart rhythm disorders), telemetry screening is required. Administration of intravenous potassium chloride (IV KCl) must be performed if available via central venous catheter (CVC), which is also called central line, central venous line, or central venous access catheter, it is a catheter located into a large vein. Intravenous potassium chloride (IV KCl) can develop phlebitis (or venitis, the inflammation of a vein), and many patients suffer from painful infusion. It is better to administer intravenous potassium chloride (IV KCl) in 0.9 normal saline (NS). Administration of intravenous potassium chloride (IV KCl) in a dextrose solution may induce insulin secretion and probably aggravate hypokalemia. Potassium chloride (KCl) salt substitutes are well source of oral potassium (K^+) and they contain about 13.6 mmol/g. Potassium (K^+) ions containing foods are suitable for chronic treatment of mild hypokalemia. These are not effective for emergency management because the amount necessary for correction is large, and potassium (K) in food is potassium (K) citrate or phosphate which is less effective in comparison with potassium chloride (KCl) as illustrated. Bananas are good source of potassium (K^+) ions. Bananas have about 1

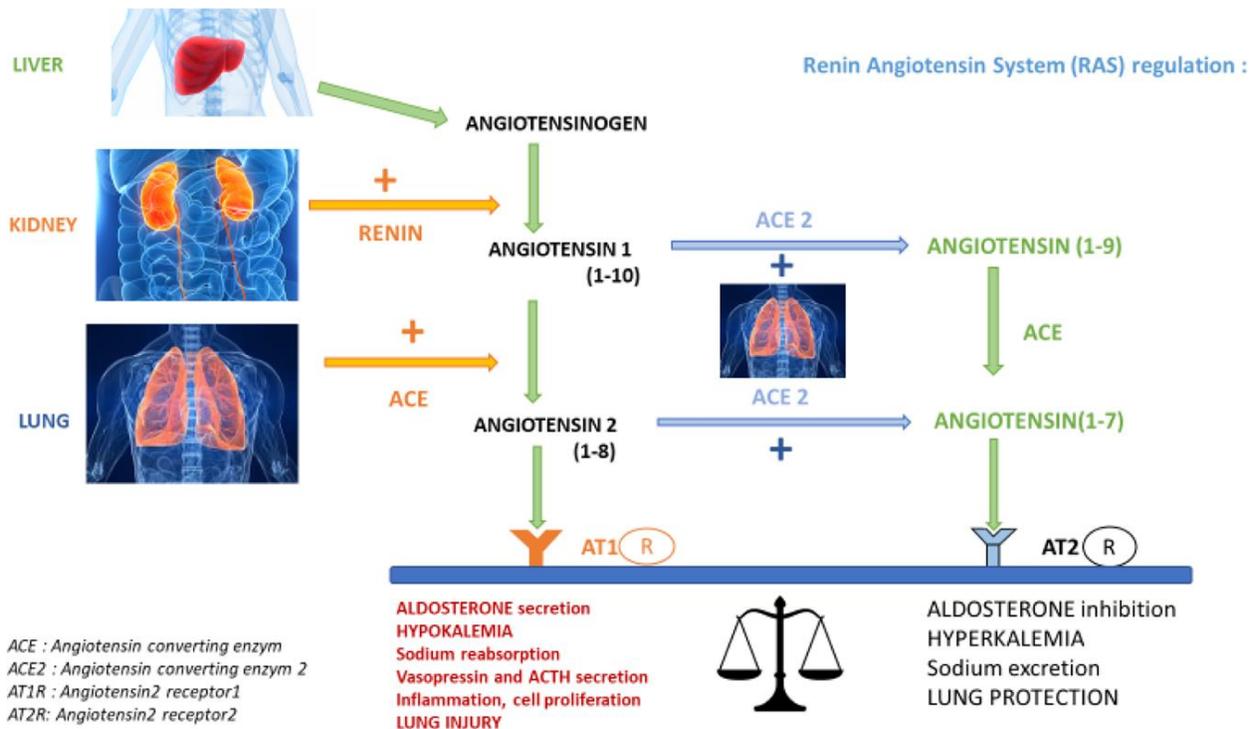
mmol/cm. Therefore, eating 2 large bananas result in getting 40 mmol of potassium (K^+) ions. Examples of foods that are rich in potassium (K^+) ions involve: dried fruits (dates, figs, prunes), spinach, broccoli, kiwis, mangos, oranges, tomatoes, avocados, bananas, milk, raisins, and lima beans. Potassium (K) sparing diuretics can be adequate for chronic treatment of hypokalemia particularly in patients who are already on a thiazide or a loop diuretic. Aldosterone receptor antagonists (spironolactone and eplerenone) can assist in treatment of patients with advanced heart failure (or advanced HF) and in patients with resistant hypertension (RHTN, defined as uncontrolled blood pressure despite use of ≥ 3 antihypertensive agents of different classes). Amiloride is better endured, it blocks epithelial sodium channel (ENaC) in the collecting duct (CD). Triamterene (a potassium-sparing diuretic) is scarcely correlated with kidney stones, and administration of amiloride [called a water pill (diuretic)], eplerenone (a potassium-sparing diuretic), or spironolactone [a potassium-sparing diuretic (water pill)] is preferable. Laxatives and diuretics must be stopped if hypokalemia is a result of their abuse. Symptomatic management of diarrhea and vomiting is beneficial. If there is a need to administer to the patient both bicarbonate (HCO_3^-) and potassium (K) intravenously (IV), potassium (K) have to be administered first because bicarbonate (HCO_3^-) leads to intracellular potassium (K^+) ions shift.

1.1 Renin-Angiotensin Aldosterone System, Hypokalemia, and COVID-19 Infection

Renin-angiotensin system (RAS), or renin-angiotensin aldosterone system (RAAS) is hemodynamic and biological system that regulates blood pressure, plasma potassium (K), and stability of pulmonary epithelial membranes. In renin-angiotensin system (RAS), two antagonistic pathways are balanced. The first is angiotensinogen (AGT) pathway that transforms angiotensinogen (AGT) into angiotensin I (AngI) (by renin), and then converts it into angiotensin II (AngII) by angiotensin converting enzyme (ACE). Angiotensin II (AngII) attaches to angiotensin II type 1 receptor (AT1R) and activates the system to trigger vasoconstriction, aldosterone secretion stimulation, hypokalemia, and pulmonary epithelia degradation. The second pathway in which the angiotensin system is balanced includes angiotensin-converting enzyme2 (ACE2). This pathway transforms part of angiotensin I (AngI) and angiotensin II (AngII) before it attaches to its angiotensin II type 1 receptor (AT1R). Angiotensin I (AngI) and angiotensin II (AngII) phosphorylation products are angiotensin 1-9 (Ang1-9) and angiotensin

1–7 (Ang1-7). They attach to angiotensin II type 2 receptor(AT2R) receiver, triggering antagonist effects compared with angiotensin II type 1 receptor (AT1R).

In the infection phase, coronavirus disease 2019 (COVID-19) virus uses the receptor of angiotensin-converting enzyme2 (ACE2) to penetrate host cell. Coronavirus (CoV) attachment to angiotensin converting enzyme2 (ACE2) is observed to cause a downregulation of angiotensin-converting enzyme2 (ACE2), leading to an increase in angiotensin II (AngII) via angiotensin-converting enzyme (ACE), as the decrease in angiotensin-converting enzyme2 (ACE2) leads to a lower conversion of angiotensin (Ang) to angiotensin 1–7 (Ang1-7) vasodilator. The lower level of angiotensin-converting enzyme2 (ACE2), the lesser angiotensin I (AngI) and angiotensin II (AngII) will be degraded; thus, their plasmatic concentration progressively elevates. A United States intensive care unit (US ICU) team showed that an increase in angiotensin 1–10 (Ang1-10) and a decrease in angiotensin 1–9 (Ang1-9) which is the angiotensin-converting enzyme2 (ACE2) processing product, were associated with poor prognosis in acute respiratory distress syndrome (ARDS). Therefore, increases in angiotensin II (AngII) levels and induction of angiotensin II type 1 receptor (AT1R) result in a decrease in the stability of the pulmonary endothelium and an aggravation of respiratory distress. The other impacts are elevated release of aldosterone, hypokalemia stimulated by kaliuresis, and elevated sodium reabsorption and inflammation. Hypokalemia is often present in patients with coronavirus disease 2019 (COVID-19). A Chinese team reported that hypokalemia was correlated with a poor outcome (Wuhan's experience). Conversely, renin-angiotensin system (RAS) inhibitors can increase angiotensin-converting enzyme2 (ACE2) and potentially induce virus loading into the cell. It is thought that prime imbalance in renin-angiotensin system (RAS) stimulated by downregulation of angiotensin-converting enzyme2 (ACE2) is crucial element of undesirable evolution in patients with coronavirus disease 2019 (COVID-19). The biological marker of this imbalance seems be hypokalemia.



Figure(31):Renin-angiotensin system in COVID-19 infection and incidence of hypokalemia [Silhol F.; Sarlon G.; Deharo JC.; Vaisse B. (2020). Downregulation of ACE2 induces overstimulation of the renin-angiotensin system in COVID-19; should we block the renin-angiotensin system?. *Hypertens Res.* <https://doi.org/10.1038/s41440-020-0476-3>]

1.2Hypokalemia in COVID-19 Infection

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) invades human cells via binding angiotensin I converting enzyme 2 (ACE2) on cell membrane. Angiotensin-converting enzyme2 (ACE2) is broadly distributed in many human tissues, particularly in vital organs, such as heart, liver, kidney, and lungs. Angiotensin-converting enzyme2 (ACE2) is the primary counter-regulatory mechanism for the main axis of renin–angiotensin system (RAS) that is a crucial player in the control of blood pressure and electrolyte balance. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) attaches angiotensin-converting enzyme2 (ACE2) and enhances the degradation of angiotensin-converting enzyme2 (ACE2), and therefore lowers the counter-act of angiotensin-converting enzyme2 (ACE2) on renin-angiotensin system (RAS). The final impact is to elevate reabsorption of sodium (Na) and water, and thereafter elevate blood

pressure and excretion of potassium (K^+) ions. Further, patients with coronavirus disease 2019 (COVID-19) frequently suffer from gastrointestinal (GI) symptoms such as diarrhea and vomiting. Collectively, the effects on renin-angiotensin system (RAS) and gastrointestinal (GI) system by coronavirus disease 2019 (COVID-19) may result in disruptions of homeostasis of electrolytes and pH. One of the disruptions that may reflect progression of coronavirus disease 2019 (COVID-19) and must be closely monitored is hypokalemia. Potassium (K^+) ions are prevalent intracellular cations and affect membrane polarization of cells. Hypokalemia causes cellular hyperpolarity, elevates resting potential (RP), and hastens depolarization in cardiac cells and lung cells. Potassium is predominant intracellular cation. Normal serum potassium levels are between 3.5 and 5.5 mEq/L. This is much less than intracellular levels that range between 140 and 150 mEq/L. The distribution of potassium levels across cellular membranes helps determine the resting membrane potential (RMP) as well as the timing of membrane depolarization as membrane depolarization induces sodium channels through conformation changes from closed, nonconducting states to an open, current-conducting state. Sodium (Na^+) and potassium (K^+) currents are produced responding to sustained membrane depolarization. Inward sodium (Na^+) current is traditionally described as downward and the outward potassium (K^+) current is shown as upward. Sodium (Na^+) current elevates due to sodium (Na^+) channel opening and then declines due to sodium (Na^+) channel inactivation. Potassium (K^+) current, resulted by delayed rectifier type of potassium (K^+) channels, is delayed in regard to sodium (Na^+) current because potassium (K^+) channels open more slowly. Potassium (K^+) current declines little with sustained depolarization because inactivation is less obvious in potassium (K^+) channels compared with sodium (Na^+) channels. Therefore, organ systems broadly dependent on membrane depolarization for function are mostly affected by changes in serum potassium (K^+) levels. In hypokalemia, resting membrane potential (RMP) is increased. Both action potentials and refractory periods are prolonged. Symptoms do not generally develop unless potassium (K^+) levels are less than 3.0 mEq/L. The following signs and symptoms should raise the concern for hypokalemia: first, cardiac manifestations involve T wave flattening, ST depression, appearance of U wave, and arrhythmias; second, skeletal and smooth muscle manifestations involve hypotonia and muscle weakness, respiratory depression, muscle cramps, constipation and/or ileus, and rhabdomyolysis and myoglobinuria. Severe hypokalemia of under 3 mmol/l plasma potassium (K^+) ions can

trigger ventricular arrhythmia and respiratory muscle dysfunction, both issues being life-threatening in patients in severe coronavirus disease 2019 (COVID-19) situation.

A study found that patients with serious hypokalemia had a statistically higher prevalence of dyspnea or tachypnea, no relation was seen between gravity of hypokalemia and prevalence of common respiratory symptoms, such as cough and running nose. As to the gastrointestinal (GI) symptoms that might develop hypokalemia, 34 (19%) patients had diarrhea with an average of 6 onset times per day and frequently ended within 1–4 days, dominantly in the patients with hypokalemia ($P < 0.05$). Few patients had vomiting and abdominal pain. Patients with severe hypokalemia had statistically higher body temperature than patients with hypokalemia and patients with normokalemia. Comparable difference was also recognized in the highest patient's temperature during hospital stay. Patients with severe hypokalemia also had a significant higher heart rate and respiratory rate than the remaining patients. Laboratory exams showed that creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and erythrocyte sedimentation rate (ESR) were noticeably associated with the seriousness of hypokalemia. Collectively, these attributes with highly increased levels were associated with myocardial injury. A total of 108 patients with hypokalemia showed moderate decreases in sodium (Na), white blood cells (WBCs), and lymphocytes (LYM) than the 67 patients with normokalemia. Severe and critically ill patients had higher incidence of severe hypokalemia, hypokalemia, abnormal electrocardiogram (ECG) results, as well as notable high levels of creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), and C-reactive protein (CRP). Among these abnormal indices, hypokalemia was most common as 93% of severe and critically ill patients had hypokalemia. In contrast, elevated levels of blood urea nitrogen (BUN) and creatinine (Cr) were scarce. Abnormal electrocardiogram (ECG) findings were usually representative of hypokalemia and improved with potassium (K^+) ions supplement management. Elevated levels of creatine kinase (CK), creatine kinase MB (CK-MB), and lactate dehydrogenase (LDH) frequently return normal within 3–6 days. Elevated levels of alanine aminotransferase (ALT) and aspartate transaminase (AST) were mild and return normal after liver support treatment. Most patients with intermittent abnormal oxygen saturation were improved after oxygen inhalation except for three critically ill patients who were given invasive mechanical ventilation (IMV). The most considerable adverse effect of hypokalemia is myocardial injury that can be well reflected by electrocardiogram (ECG), creatine kinase (CK),

and creatine kinase MB (CK-MB). A careful check showed a recognizable jump of increase in the predominance of abnormal electrocardiogram (ECG) results and elevated creatine kinase (CK) levels and in particular increased creatine kinase MB (CK-MB) levels in patients with severe hypokalemia. This study reported high prevalence of hypokalemia in patients with coronavirus disease 2019 (COVID-19) and positive association between degree of hypokalemia and severity of coronavirus disease 2019 (COVID-19). The study also came to proof that hypokalemia was more attributable to renal loss of potassium (K^+) ions than gastrointestinal (GI) wasting. Previous research has proved that sufficient and appropriate concentrations of plasma potassium (K^+) ions have a protective role in inhibiting myocardial failure through weakening cellular hyperpolarity and depolarization. It is crucial to patients with coronavirus disease 2019 (COVID-19) that plasma potassium (K^+) ions concentrations be checked and kept between 4.0 and 5.5 mmol/l or 4.5 and 5.5 mmol/l for serum potassium (K^+) as serum in general has more potassium (K^+) ions than plasma. Several laboratory indices, such as elevated creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate transaminase (AST) returned to normal level or substantially improved after relevant management. Superficial mildness contradicted with sudden progression of disease in some patients. This contradiction might result from the fact that biomarkers were not sensitive to reflect whole progression of this illness. Therefore, a more sensitive biomarker to monitor the ongoing condition is urgently needed for progression patients.

A study conducted by researchers from Wenzhou Medical University in Zhejiang province led by Chen *et al.* (2020) demonstrated that almost all coronavirus disease 2019 (Covid-19) patients suffered from hypokalemia and that supplementation with potassium (K^+) ions was one of the many ways that participated in their healing. They concluded that as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus attacks human cells via angiotensin-converting enzyme-2 (ACE2), it also attacks renin-angiotensin system (RAS), leading to decreased electrolyte concentrations particularly potassium (K^+) ions. This study included 175 patients in collaboration with Wenzhou Hospital revealed that almost all patients experienced hypokalemia and for those who already had hypokalemia, the situation even drastically worsened as illness progressed. It was shown from this study that patients responded well to potassium ions (K^+) supplements and were with a better opportunity to heal. In addition, in this study, patients with coronavirus disease 2019 (COVID-19) were divided into three groups and as following: severe

hypokalemia, hypokalemia, and normokalemia groups. The target of the study was to investigate the relationship between hypokalemia and clinical features, the underlying causes and clinical implications of hypokalemia. The 175 patients with coronavirus disease 2019 (COVID-19) (92 women and 83 men; median age, 46 years) were admitted to hospital in Wenzhou, China, consisting 39 severe hypokalemia, 69 hypokalemia, and 67 normokalemia patients. Gastrointestinal (GI) symptoms were not correlated with hypokalemia among 108 hypokalemia patients ($P>0.05$). Body temperature, creatine kinase (CK), creatine kinase MB, lactate dehydrogenase (LDH), and C-reactive protein (CRP) were considerably correlated with seriousness of hypokalemia ($P<0.01$). It was found that 93% of severe and critically ill patients and hypokalemia was most common among increased creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels. Urine potassium ions (K^+) loss was the main cause of hypokalemia. Severe hypokalemia patients was given 3g/day, adding 34 (SD=4) g potassium (K) during hospital stay. There was astonishing result which was that patients responded well to potassium ions (K^+) supplements when they were inclined to heal. The authors concluded that hypokalemia was predominant in patients with coronavirus disease 2019 (COVID-19). The correction of hypokalemia is challenging because of continuous renal potassium ions (K^+) loss caused by the degradation of angiotensin-converting enzyme 2 (ACE2). The end of urine potassium ions (K^+) loss refers to a good prognosis and can be a reliable, in time, and sensitive biomarker directly reflecting the end of adverse impact on renin-angiotensin system (RAS).

Urine potassium (K) loss leads to hypokalemia, and it has been mentioned that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus attaches angiotensin-converting enzyme 2 (ACE2) on the cell membrane and stimulates degradation of angiotensin-converting enzyme 2 (ACE2), and thus lessens the counter-act of angiotensin-converting enzyme 2 (ACE2) on renin-angiotensin system (RAS). This mechanism elevates reabsorption of sodium (Na) and water, and elevates the excretion of potassium (K). The authors revealed that correction of hypokalemia was challenging as a result of continuous loss of potassium (K), and for cardiovascular (CV) effects and neurohormonal activation, and other vital organs by hypokalemia.

It was found that electrolyte imbalance could occur in any critical systemic illness and precipitated arrhythmias, especially in cases with underlying cardiac disorders. There is a special concern about hypokalemia in coronavirus disease 2019 (COVID-19), attributed to the interaction of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus with renin-angiotensin-aldosterone system (RAAS). Hypokalemia increases to various tachyarrhythmias which are arrhythmias characterized by a quick irregular heartbeat.

A study suggested that loss of potassium (K) through kidney may be attributed to elevated angiotensin II (Ang II) concentrations resulted from binding of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus to angiotensin-converting enzyme 2 (ACE2) receptors. This could inhibit the action of angiotensin-converting enzyme 2 (ACE2) in maintaining the balance between angiotensin-converting enzyme 2 (ACE2) and angiotensin II (Ang II) levels.

A recognizable research showed that severe and critically ill patients with coronavirus disease 2019 (COVID-19) had a higher predominance of hypokalemia that resulted from renal potassium (K) loss. This finding can be explained by downregulation of angiotensin-converting enzyme 2 (ACE2) following viral intrusion causing decreased degradation of angiotensin-II (AngII), elevated aldosterone release and consequently elevated urinary potassium (K) wasting. Early normalization of serum potassium (K) has been supposed to predict a good prognosis in coronavirus disease 2019 (COVID-19). Therefore, angiotensin-converting enzyme 2 (ACE2) overexpression, while facilitating entry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus to cell, is not capable of protecting against lung injury as enzymes get degraded by the virus.

It is implied that hypokalemia may have a recognizable impact on management outcome of patients with coronavirus disease 2019 (COVID-19) and must be seriously tackled as these patients have a high prevalence of dysfunction in heart, lungs, and other vital organs.

2. Antiphospholipid Syndrome

Antiphospholipid syndrome, or antiphospholipid antibody syndrome (APS or APLS), is an autoimmune, hypercoagulable state caused by antiphospholipid (aPL) antibodies. Antiphospholipid (aPL) antibodies are autoantibodies (AAB) directed toward molecular

complexes of phospholipids (PL) and proteins. Antiphospholipid syndrome (APS) triggers blood clots (thrombosis) in both arteries and veins as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, and severe preeclampsia. Antiphospholipid syndrome (APS) leading to multiple, and recurrent fetal losses, is often accompanied by a moderate thrombocytopenia, in the presence of antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), or anti-beta2 glycoprotein-I (β 2GPI) antibodies. It is worthy to refer to the following antiphospholipid antibodies: lupus anticoagulants (LA) are autoantibodies (AAB) produced by the immune system that mistakenly attack certain components of the body's own cells. They specifically target phospholipids (PL) as well as proteins associated with phospholipids (PL) that are found in the outer-most layer of cells (cell membranes). These autoantibodies (AAB) interfere with the blood clotting process in a way that is not fully understood and elevate a person's risk of developing a blood clot; in addition, Cardiolipin antibodies are autoantibodies (AAB) produced by the immune system that mistakenly target the body's own cardiolipins (CLs), substances found in the outermost layer of cells (cell membranes) and platelets. These autoantibodies (AAB) can affect body's ability to regulate blood clotting in a way that is not well understood; further, Anti-cardiolipin antibodies (aCL) and anti- β -2-glycoprotein I antibodies (anti-2GPI) represent two out of three laboratory criteria for detection of antiphospholipid syndrome (APS). The domain I (DI) in anti- β -2-glycoprotein I is a new target for better identification of antibodies (Ab) and may be associated with thrombotic risk in antiphospholipid syndrome (APS). Anti- β -2-glycoprotein I antibodies (anti-2GPI) antibodies specifically reacting with domain I (DI) have a notable clinical importance being more commonly detected amongst patients with antiphospholipid syndrome (APS) and other autoimmune diseases (AID).

The antiphospholipid syndrome (APS) can be found in patients having neither clinical nor laboratory confirm of another definable condition [primary antiphospholipid syndrome (APS)] or it may be associated with other diseases, mainly systemic lupus erythematosus (SLE), but occasionally with other autoimmune conditions, infections, drugs, and malignancies. Primary antiphospholipid syndrome (APS) patients rarely develop systemic lupus erythematosus (SLE). Only 8% of 128 patients, who were followed up for about 9 years, developed lupus, and a positive Coombs' test [also known as antiglobulin test (AGT)] was a clinically considerable predictor of progression. Antiphospholipid antibodies (aPL) can appear in different scenarios,

such as asymptomatic carrier patients for antiphospholipid antibodies (aPL), classical antiphospholipid syndrome (APS) with recurrent venous and/or arterial thrombosis, antiphospholipid syndrome (APS) affecting otherwise healthy women with recurrent pregnancy loss (RPL, also called recurrent miscarriage or habitual abortion), patients with antiphospholipid antibodies (aPL) positivity with non-thrombotic antiphospholipid antibodies (aPL) manifestations [i.e., thrombocytopenia, hemolytic anemia (HA), or livedo reticularis(LR)] or, in a small subset of patients, as a life-threatening form characterized by a rapid progression of microthrombosis (A very small thrombosis) that led to rapid multiorgan failure (MOF), which is termed catastrophic antiphospholipid syndrome (CAPS).

Despite the strong association between antiphospholipid antibodies (aPL) and thrombosis, the pathogenic role of antiphospholipid antibodies (aPL) in the development of thrombosis has not been fully elucidated. Available data indicate that many of the autoantibodies (AAB) associated with antiphospholipid syndrome (APS) are directed against a number of plasma proteins and proteins expressed on, or bound to, the surface of vascular endothelial cells (VEC) or platelets. The involvement of antiphospholipid antibodies (aPL) in clinically important normal procoagulant and anticoagulant reactions and on certain cells altering the expression and secretion of various molecules may offer a basis for definitive investigations of possible mechanisms by which antiphospholipid antibodies (aPL) may develop thrombotic events in patients with antiphospholipid syndrome (APS). The clinical picture of the antiphospholipid syndrome (APS) is characterized by venous and arterial thromboses, fetal losses and thrombocytopenia. Single vessel involvement or multiple vascular occlusions may give rise to a wide variety of presentations. Antiphospholipid syndrome (APS) manifestations include thrombocytopenia (3.7%), livedo reticularis (LR) (2.6%), stroke (2.4%), transient ischemic attacks (TIAs) (2.3%), deep vein thrombosis (DVT) (2.1%), pulmonary embolism (PE) (2.1%), epilepsy (1.7%), valve vegetations (or vegetative endocarditis), (1.4%), and myocardial infarction (MI) (1%), among others.

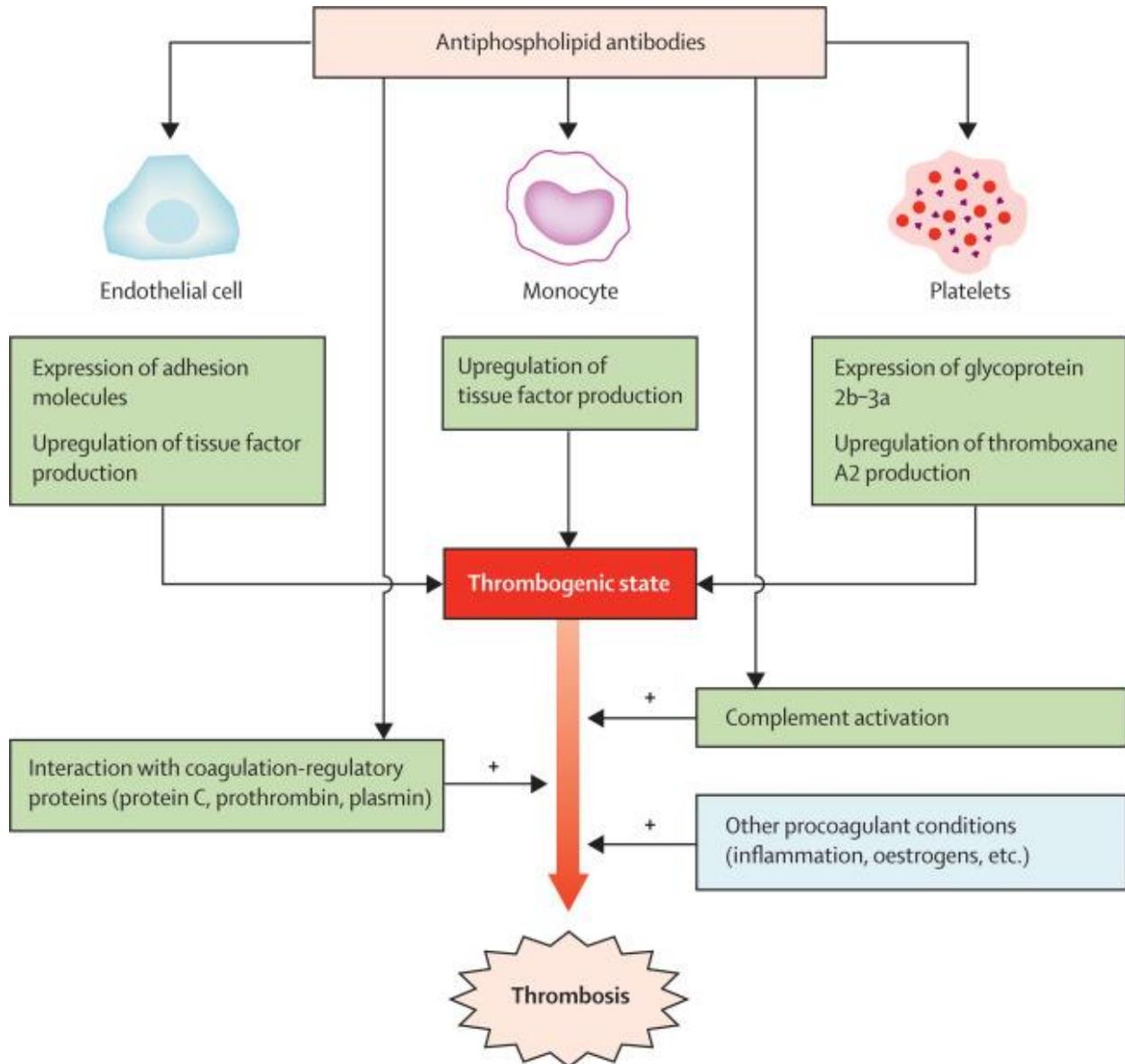
Elimination of antiphospholipid antibodies (aPL) may be accomplished by several therapeutic regimens, including high dose steroid administration, immunosuppression (e.g. cyclophosphamide) or plasma exchange. The decrease or elimination is, however, temporary and antibodies (Abs) rapidly return (within 1e3 weeks) on cessation of therapy. Therefore, therapy

should not primarily be directed at effectively reducing the antiphospholipid antibodies (aPL) levels and the use of immunotherapy is generally not indicated, unless required for the treatment of the underlying condition, e.g. systemic lupus erythematosus (SLE), or in acute life-threatening situations, such as the catastrophic antiphospholipid syndrome (CAPS). The risk of recurrence of thrombosis is markedly increased in the first 6 months after discontinuation medication, suggesting a rebound phenomenon. Therefore, for patients who have already experienced thrombotic events, life-long treatment with anticoagulants is crucial. In cases of first venous event, low-risk antiphospholipid antibodies (aPL) profile or a known transient precipitating factor [e.g. oral contraceptives, OCs, also known as birth control pills], anticoagulation could be limited to 3e6 months and antiaggregants (antiplatelet drugs, also called platelet agglutination inhibitors or platelet aggregation inhibitors) , as well as avoidance of the triggering factors, may indeed be sufficiently effective for future thromboprophylaxis. Patients with definite antiphospholipid syndrome (APS) with a first venous thrombosis event should receive oral anticoagulant therapy to a target international normalised ratio (INR) 2.0-3.0. Patients with definite antiphospholipid syndrome (APS) and arterial thrombosis should receive oral anticoagulant therapy to a target around 3.0 or receive a combined therapy with antiaggregant plus anticoagulation with an international normalized ratio (INR) target between 2.0 and 3.0. Long-term anticoagulation with oral vitamin K antagonists such as warfarin is the cornerstone treatment in antiphospholipid syndrome (APS). However, novel oral anticoagulation therapies have been developed during the last years; these therapies are direct anti-Xa inhibitors and included rivaroxaban, apixaban and edoxaban as well as a direct thrombin inhibitor named dabigatran etexilate. It is worthy to talk briefly about factor Xa inhibitors which are a type of anticoagulants that work by selectively and reversibly blocking the activity of clotting factor Xa, preventing clot formation. They affect both factor Xa within the blood and within a preexisting clot. They do not affect platelet aggregation. They are used for the treatment and prevention of deep vein thrombosis (DVT) and acute pulmonary embolism (PE), and to reduce the risk of stroke and embolism in people with nonvalvular atrial fibrillation (NVAf). Factor Xa is generated by both extrinsic and intrinsic coagulation pathways and is responsible for activating prothrombin (factor II, a vitamin K–dependent plasma protein) to thrombin (factor IIa, a Na⁺-activated, allosteric serine protease). Factor Xa inhibitors have predictable anticoagulant effects and do not require routine checking, unlike some other anticoagulants. Direct thrombin

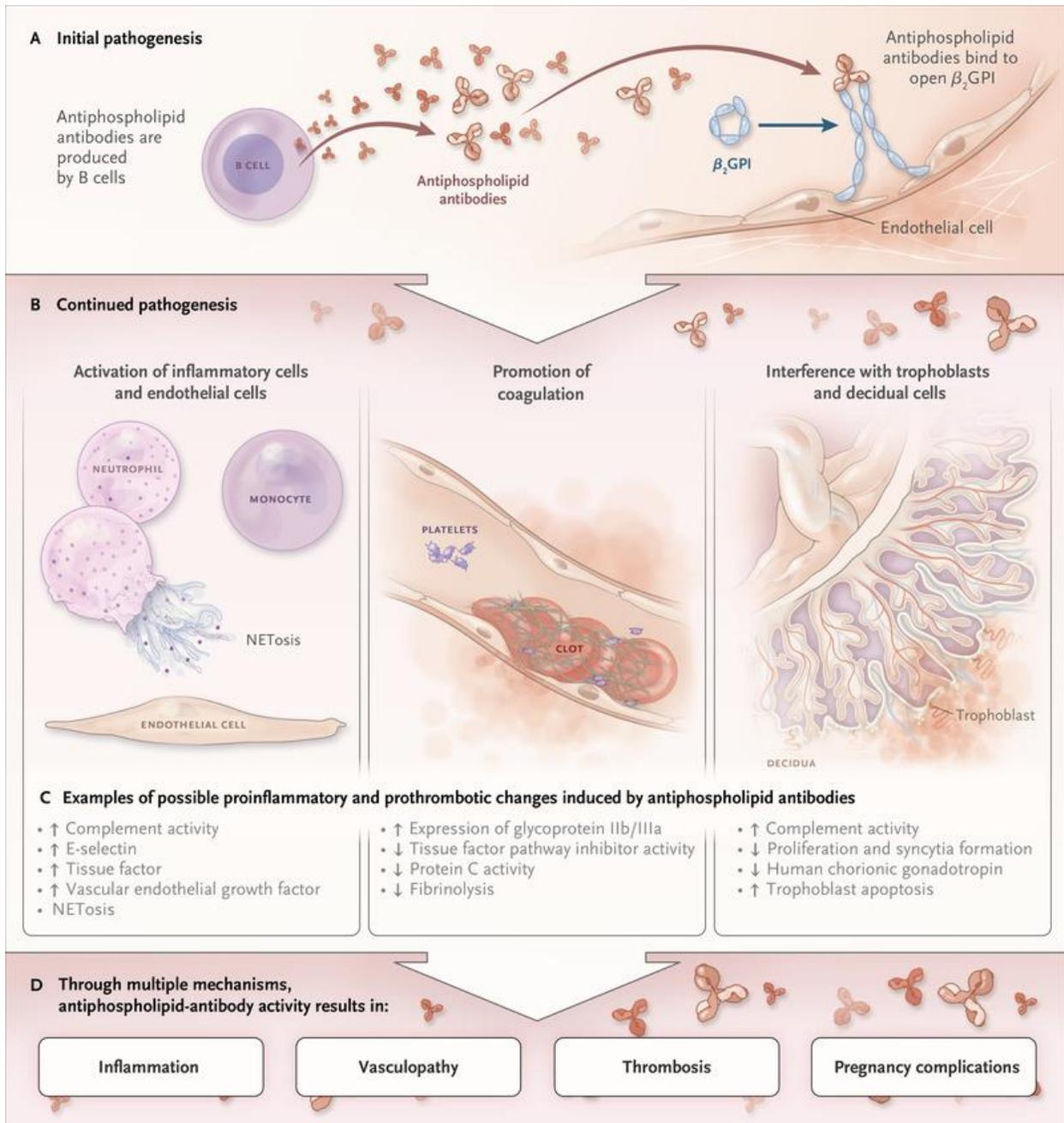
inhibitors (DTIs) are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin (factor IIa).

Although direct anti-Xa inhibitors and direct thrombin inhibitors are therapies for patients with arterial or venous thrombosis, data in antiphospholipid syndrome (APS) is scarce and prospective clinical trials usually do not include patients with antiphospholipid syndrome (APS). The thrombocytopenia occurring during the course of the antiphospholipid syndrome (APS) is usually mild and does not require any active intervention. However, in a minority of cases it can be severe and refractory to prednisone (a corticosteroid drug) treatment. In these cases, immunosuppressive therapy (e.g. azathioprine), intravenous immunoglobulins (IVIG) or rituximab which is a chimeric monoclonal antibody against the protein CD20 mainly found on the surface of immune system B cells, may be effective. A published non-randomized prospective pilot study has shown the efficacy and safety of rituximab for the management of non-criteria antiphospholipid antibodies (aPL) manifestations in patients with classic antiphospholipid syndrome (classic APS). According to the results, rituximab may be effective in controlling some non-criteria antiphospholipid antibodies (aPL) manifestations, such as thrombocytopenia and skin ulcers. It is important to consider that presence of moderate to severe thrombocytopenia in patients with on-going thrombosis is not contraindication for anticoagulation. Management of catastrophic antiphospholipid syndrome (CAPS) includes an aggressive approach with a combined treatment that includes anticoagulation with heparin, high dose steroids, plasma exchange and/or intravenous immunoglobulins (IVIG). For patients with refractory catastrophic antiphospholipid syndrome (CAPS), rituximab and eculizumab (a long-acting humanized monoclonal antibody (mAb) targeted against complement C5) are good alternatives. A notable publication demonstrated that 75% of patients with refractory catastrophic antiphospholipid syndrome (CAPS) healed from the acute catastrophic antiphospholipid syndrome (CAPS) episode; however, 20% of them deceased at the time of the event. Eculizumab is currently approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and is a promising medication in catastrophic antiphospholipid syndrome (CAPS). Eculizumab treatment benefits patients with microangiopathies (or microvascular disease, or small vessel disease), reducing intravascular hemolysis and blocking complement-mediated pathogenic effects. Eculizumab is also a promising therapy for patients with

antiphospholipid syndrome (APS) with renal posttransplant thrombotic microangiopathy (renal post-transplant TMA). It is valuable to say that thrombotic microangiopathy (TMA) is a severe complication of kidney transplantation that often causes graft failure (GF). Thrombotic microangiopathy (TMA) may occur de novo, often triggered by immunosuppressive drugs and acute antibody-mediated rejection, or recur in patients with previous history of hemolytic uremic syndrome (HUS).



Figure(32):Antiphospholipid syndrome [Ruiz-Irastorza G.; Crowther P.; Branch W.; Khamashta M. (2010). Antiphospholipid syndrome. The Lancet, 376(9751):1498-1509]



Figure(33):Proposed mechanisms by which antiphospholipid antibodies cause clinical symptoms [Garcia D.; Erkan D. (2018). Diagnosis and management of the antiphospholipid syndrome. N Engl J Med, 378:2010-2021. DOI:10.1056/NEJMra11705454]

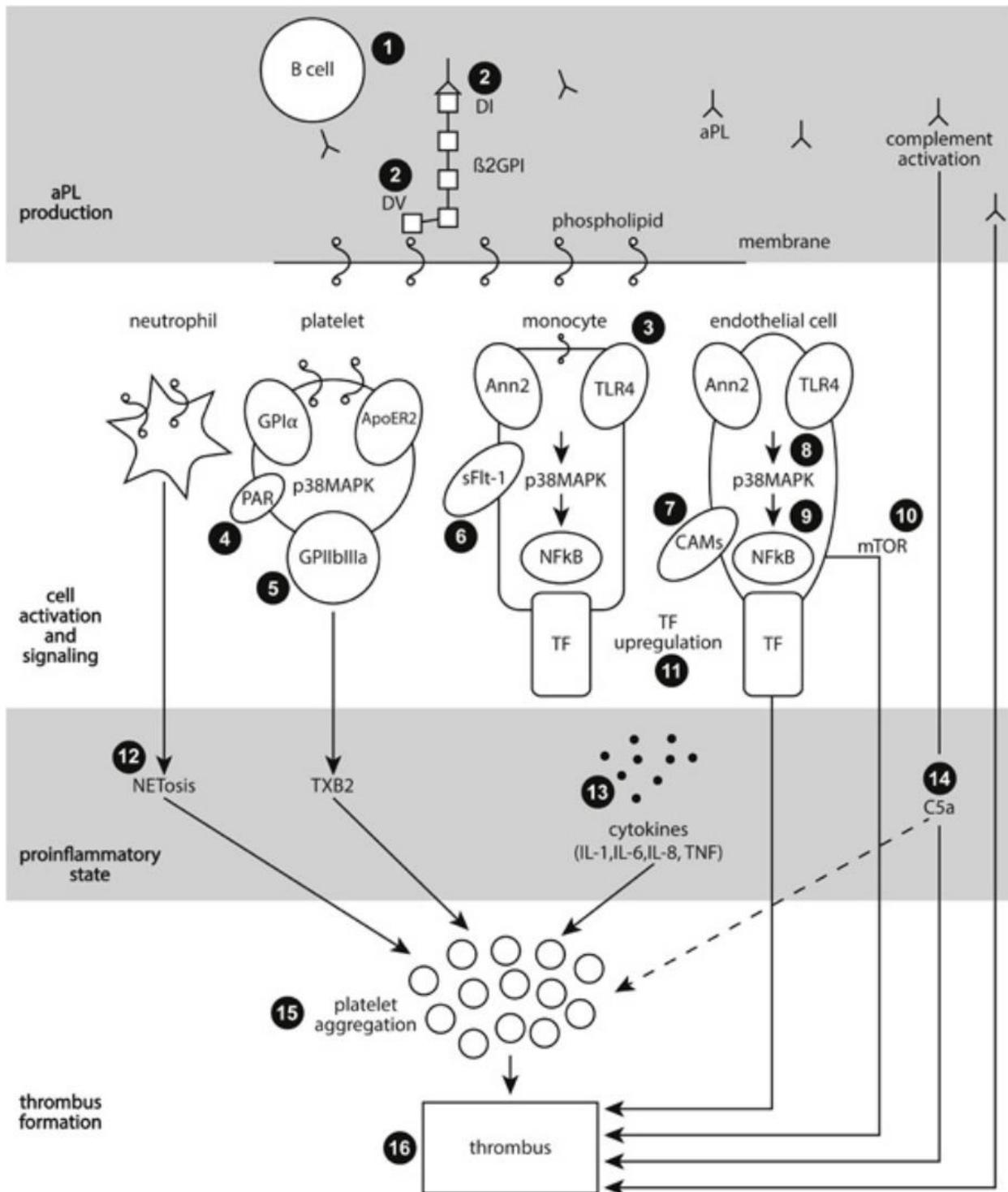
2.1 Antiphospholipid Antibodies in COVID-19 Infection

A patient admitted to Peking Union Medical College Hospital in the Sino-French New City Branch of Tongji Hospital in Wuhan, China was with coronavirus disease 2019 (COVID-19) and clinically significant coagulopathy, antiphospholipid antibodies (aPL), and multiple infarcts. He was one of three patients with these findings in an intensive care unit (ICU) designated for patients with coronavirus disease 2019 (COVID-19) in that hospital. This unit was set up on an emergency basis to accept the most critically ill patients during the outbreak of coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) infection was confirmed in all the cases by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay or serologic testing. A 69 year old man with a history of hypertension (HTN), diabetes mellitus (DM), and stroke presented with fever, cough, dyspnea, diarrhea, and headache. Coronavirus disease 2019 (COVID-19) was diagnosed in the patient on January 25, 2020, on the basis of reverse transcriptase polymerase chain reaction (RT-PCR) testing that detected severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The initial management was supportive; however, the illness subsequently developed to hypoxemic respiratory failure warranting the initiation of invasive mechanical ventilation. It is important to add that invasive mechanical ventilation is a lifesaving intervention for patients with respiratory failure. The most commonly used modes of mechanical ventilation are assist-control, synchronized intermittent mandatory ventilation, and pressure support ventilation. When employed as a diagnostic tool, the ventilator offers data on the static compliance of the respiratory system and airway resistance. The clinical scenario and the data got from the ventilator let the clinician to offer effective and safe invasive mechanical ventilation through manipulation of the ventilator settings. While life-sustaining in many circumstances, mechanical ventilation may also be toxic and should be withdrawn when clinically appropriate. On examination, the study showed that the patient had evidence of ischemia in the lower limbs bilaterally as well as in digits two and three of the left hand. Computed tomography (CT) imaging of the brain revealed bilateral cerebral infarcts in multiple vascular territories. Pertinent laboratory results involved leukocytosis, thrombocytopenia, an elevated prothrombin time (PT), and partial thromboplastin time (PTT), and elevated concentrations of fibrinogen and D-dimer. Subsequent serologic testing showed the presence of anticardiolipin IgA antibodies as well as anti- β 2glycoprotein I IgA and IgG antibodies. Two other patients with similar findings were observed at the specialized intensive

care unit (ICU) for patients with coronavirus disease 2019 (COVID-19) at Tongji Hospital. Serologic tests in these patients were positive for anticardiolipin IgA antibodies as well as anti- β 2-glycoprotein I IgA and IgG antibodies. Lupus anticoagulant was not detected in any of the patients, although testing was done while the patients were acutely ill. Antiphospholipid (aPL) antibodies abnormally target phospholipid proteins, and the presence of these antibodies (Abs) is essential to the diagnosis of the antiphospholipid syndrome (APS). However, these antibodies (Abs) can also arise transiently in patients with critical illness and various infections. The presence of these antibodies (Abs) may scarcely develop to thrombotic events that are difficult to differentiate from other causes of multifocal thrombosis in critically patients, such as disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), and thrombotic microangiopathy (TMA).

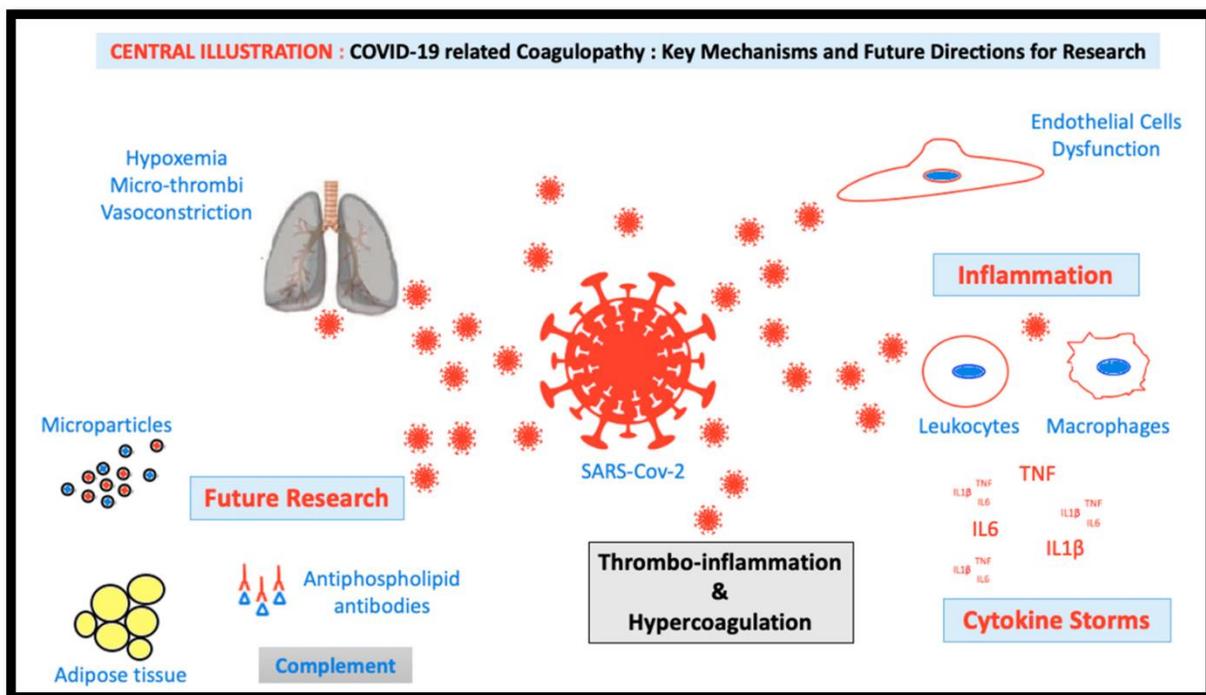
Hossri *et al.* (2020) described two cases of patients with coronavirus disease 2019 (COVID-19) presenting with thrombotic events potentially caused by this infection. The mechanism by which coronavirus disease 2019 (COVID-19) may cause thrombotic events is theorized to be associated with immobilization, hypoxia, or disseminated coagulopathy (also known as consumption coagulopathy). Both patients were found to have elevated concentrations of anticardiolipin antibodies (ACA), which may be regarded as a key association between this novel virus and an acquired coagulopathy. While major critically ill patients with coronavirus disease 2019 (COVID-19) initially present with respiratory failure, a sizeable portion progress to multi-organ failure with the development of coagulopathy considered as crucial pertinent prognostic factor. A study reported coagulopathy presented by considerably elevated D-dimer, fibrin degradation products, and longer prothrombin time (PT) and activated partial thromboplastin time [aPTT, also known partial thromboplastin time, PTT] tests was described in non-survivors versus survivors. Moreover, 71.4% of non-survivors met the criteria for disseminated intravascular coagulation (DIC) during their hospital stay vs 0.6% of survivors. As guidelines continue to develop concerning coagulopathies in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) patients, some current recommendations propose starting prophylactic anticoagulation in all cases requiring hospitalization in the absence of any contraindication. Antiphospholipid syndrome (APS) describes venous and/or arterial thrombosis with the presence of antiphospholipid antibodies (aPLs). Catastrophic antiphospholipid

syndrome (CAPS) represents the most severe form of the disease, and is associated with multiorgan failure resulting from microvascular thrombosis. While anticoagulation continues to be the mainstay of therapy, there is still elevated risk of recurrent thrombosis and bleeding complications. Only three cases of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) patients also progressing to clinically highly recognizable antiphospholipid syndrome (APS). These patients were found in Tongji Hospital in Wuhan, China and demonstrated multiple cerebral infarcts discovered on brain imaging. The cases demonstrated clinically significant antiphospholipid syndrome (APS) manifesting as multiple cerebral and splenic infarcts in case 1, and peripheral arterial disease in case 2. There have been many different proposed etiologies to progressing coagulopathy with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). According to an important literature there is also a high incidence of lupus anticoagulant in patients that were positive for coronavirus disease 2019 (COVID-19), however none of them had any reported thrombotic events. It is worth noting there is an evidence of association between highly increased antiphospholipid (aPL) antibodies and sepsis secondary to viral illness, most commonly in hepatitis C, Epstein Barr virus (EBV), Human immunodeficiency virus (HIV), Human cytomegalovirus (HCMV), and Leprosy. Despite the positive titers of anti- β 2-glycoprotein and anti-cardiolipin (aCL) antibodies, these are typically not associated with clinical manifestations such as thrombosis. These cases in this study represent a new form of coagulopathy in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) patients. While it remains unclear if the development of anticardiolipin (aCL) antibodies represents a response to the septic phase of the disease or a true manifestation of antiphospholipid syndrome (APS), the thrombotic events presented in these patients are concerning for the latter.



Figure(34):Thrombosis in antiphospholipid syndrome [Signorelli F.; Balbi G.; Domingues V.; Levy R. (2018). New and upcoming treatments in antiphospholipid syndrome: a comprehensive review. Pharmacological Research, 133:108-120. <https://doi.org/10.1016/j.phrs.2018.04.012>]

The importance of antiphospholipid (aPLs) antibodies in the development of coronavirus disease 2019 (COVID-19) coagulopathy was seen in description of multi-cerebral infarctions in 3 patients with antiphospholipid (aPL) antibodies that were characterized as anticardiolipin IgA, anti B2 glycoprotein I IgA, and IgG. Mechanisms of thrombosis in antiphospholipid syndrome (APS) comprise endothelial cell dysfunction, platelet activation, complement system activation, inflammatory cell-mediated mechanisms, alteration of anticoagulant properties (tissue factor pathway inhibition, inhibition of the protein C pathway, interference with the action of antithrombin), and reduced fibrinolysis (elevated PAI-1 levels, inhibition of plasminogen binding, and plasma activity).



Figure(35): Antiphospholipid antibodies in COVID-19 related coagulopathy [Marchandot B.; Sattler L.; Jesel L.; Matsushita K.; Schini-Kerth V.; Grunebaum L.; Morel O. (2020). COVID-19 related coagulopathy: a distinct entity?. J. Clin. Med., 9(6), 1651. <https://doi.org/10.3390/jcm9061651>]

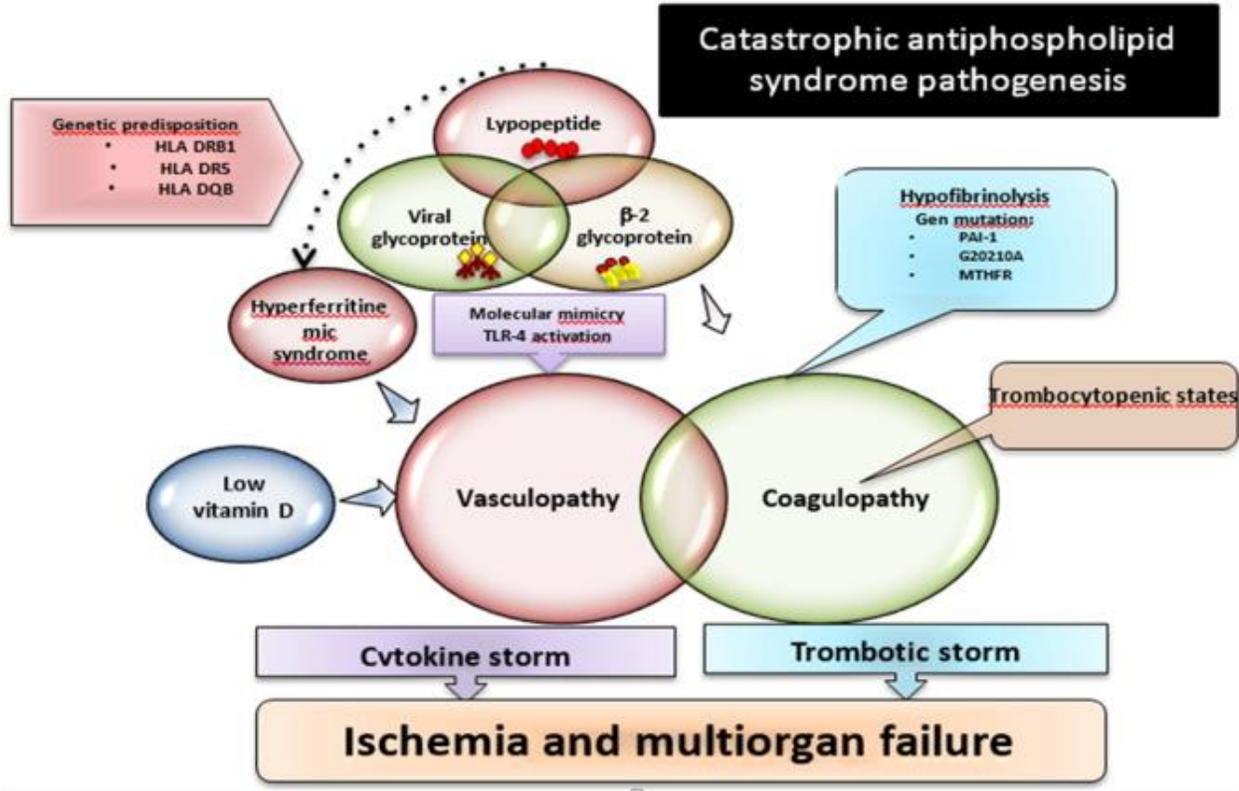
Catastrophic antiphospholipid syndrome (CAPS), also called Asherson syndrome, is a variant of the antiphospholipid syndrome (APS) that is incident in less than 1% of antiphospholipid syndrome (APS) patients. The etiology of catastrophic antiphospholipid syndrome (CAPS) is uncertain; however, several triggering factors have been recognized. The most common of these are infectious diseases, especially those of the respiratory tract. Catastrophic antiphospholipid

syndrome (CAPS) pathogenesis is incompletely understood, but several theories have been proposed, such as the molecular mimicry theory, which describes the production of anti- β 2-glycoprotein I (GP1) antibody in response to infection. The process is complex and includes the activation of Toll-like receptor 4 (TLR-4), which induces a cytokine storm, followed by endothelial alterations that stimulate a procoagulant state.

The catastrophic antiphospholipid syndrome (CAPS) is a scarce, life-threatening situation characterized by multiple thrombosis, impacting mainly small vessels and involving three or more organs, developing in less than a week and associated with persistent antiphospholipid antibodies (aPL) positivity. Catastrophic antiphospholipid syndrome (CAPS) is induced by precipitating factors and infections, mainly in respiratory tract, are the most frequent events. The underlying pathogenetic mechanism is not completely understood, but could be precipitated by a cytokine storm, with diffuse vasculitis and direct or indirect damage on endothelium. The clinical course and the autopsy findings in patients died for coronavirus disease 2019 (COVID-19) in Bergamo [the epicenter city of coronavirus disease 2019 (COVID-19) outbreak in Italy] suppose that some patients may have progressed catastrophic antiphospholipid syndrome (CAPS).

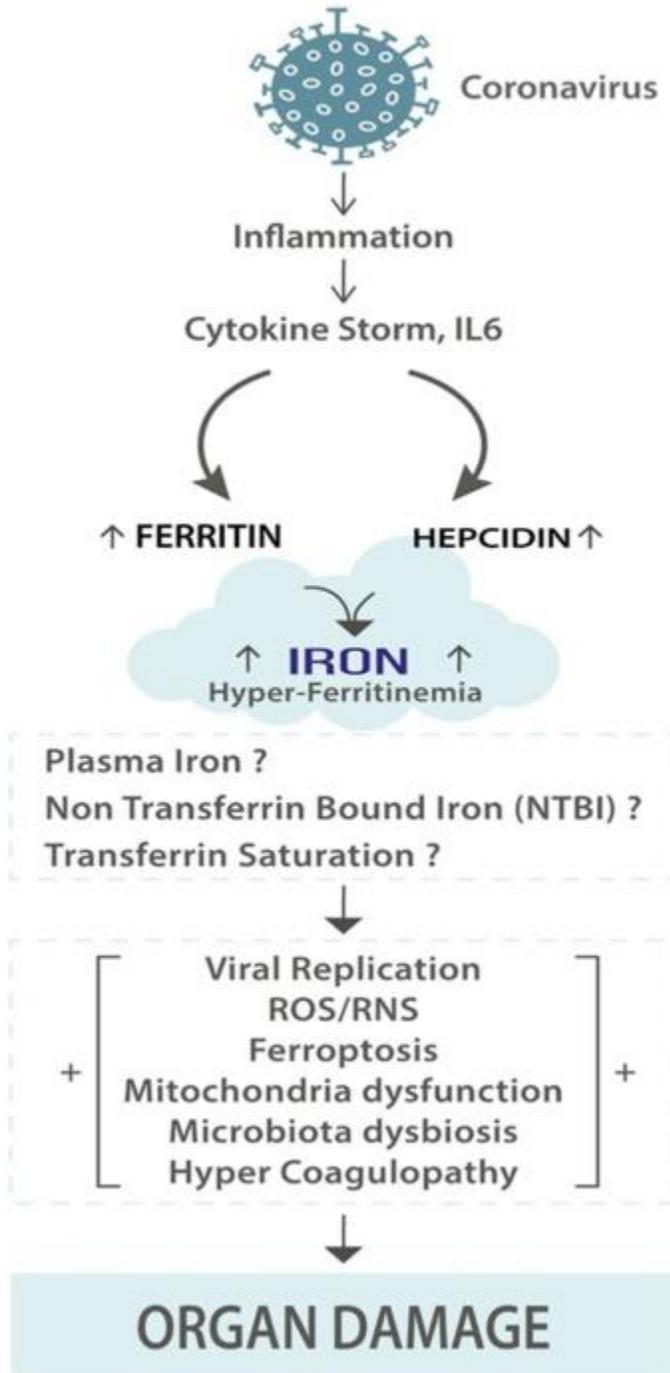
Venous and arterial thromboembolic phenomena are well described in an elevated rate of coronavirus disease 2019 (COVID-19) cases, indicating high concentrations of D-dimer (DD) and, in some patients, prolonged coagulation tests, especially prothrombin time-international normalized ratio (PT-INR); in those patients, the antithrombotic prophylaxis with low-molecular-weight heparin (LMWH, a class of anticoagulant medications) or unfractionated heparin (UFH) is recommended since it is associated with reduced mortality. The thromboembolic disease in coronavirus disease 2019 (COVID-19) could have a multifactorial pathogenesis. Hypoxia and prolonged immobilization are important factors, but the diffuse inflammatory state and the resulting cytokine storm looks to be the principal inducers. The autopsies that have been conducted at the Pathology Department of the Papa Giovanni XXIII Hospital in Bergamo during the recent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak, showed a thrombotic damage in several organs that was clinically underestimated during the hospital stay. Several diseases such as disseminated intravascular coagulation (DIC), sepsis, macrophage activated syndrome (MAS) and catastrophic

antiphospholipid syndrome (CAPS) could be the underlying causes of such damages. Some authors proved that the most coronavirus disease 2019 (COVID-19) patients meet the diagnostic criteria for disseminated intravascular coagulation (DIC).



Figure(36):Catastrophic antiphospholipid syndrome pathogenesis [Garcia-Carrasco M.; Mendoza-Pinto C.; Macias-Diaz S.; de Lara F.; Etchegaray-Morales I.; Galvez-Romero J.; Mendez-Martinez S.; Cervera R. (2015). The role of infectious diseases in the catastrophic antiphospholipid syndrome. *Autoimmunity Reviews*, 14(11):1066-1071. <https://doi.org/10.1016/j.autrev.2015.07.009>]

3. Hyperferritinemic Syndromes and Systemic Inflammation in COVID-19 Infection



Figure(37):Hyperferritinemia in COVID-19 infection [Edeas M.; Saleh J.; Peyssonnaud C. (2020). Iron: innocent bystander or vicious culprit in COVID-19 pathogenesis?. International Journal of Infectious Diseases, 97:303-305. DOI: <https://doi.org/10.1016/j.ijid.2020.05.110>]

The umbrella term hyperferritinemic syndromes encompasses four clinical conditions, including macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS), and septic shock, all characterized by high serum ferritin and a life-threatening hyperinflammation sustained by a cytokines storm which ultimately causes multiorgan failure. The severe form of coronavirus disease 2019 (COVID-19) share several clinical and laboratory characteristics with four entities gathered under the term hyperferritinemic syndromes and involving macrophage activation syndrome (MAS), adult-onset Still's disease (AOSD), catastrophic anti-phospholipid syndrome (CAPS) and septic shock. Coronavirus disease 2019 (COVID-19) systemic inflammatory reaction and hyperferritinemic syndromes are all defined by high serum ferritin and a life-threatening hyperinflammation sustained by a cytokines storm which eventually results in multiorgan failure. The idea of a third later stage of coronavirus disease 2019 (COVID-19) as the dramatic result of an overwhelming cytokine storm is boosted by the recognition of the elevated concentration of different molecules including interleukin-1beta (IL-1 β), interleukin-1 receptor antagonist (IL-1RA), interleukin-7 (IL-7), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-10 (IL-10), fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN γ), granulocyte-colony stimulating factor (G-CSF), interferon- γ -inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF- α) and vascular endothelial growth factor (VEGF). Particularly in severe conditions, interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-10 (IL-10), granulocyte-colony stimulating factor (G-CSF), interferon- γ -inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A), and tumor necrosis factor-alpha (TNF- α) look to be extremely high and noticeable elevation of interleukin-6 (IL-6) in non-survival patients has been observed. In addition to cytokine profile, other features make coronavirus disease 2019 (COVID-19) similar to the members of the hyperferritinemic syndromes, at least in some of their stages: lymphopenia, decreased natural killer (NK) cells number and activity, abnormal liver function tests, coagulopathy and of course hyperferritinemia.

Hyperferritinemia is the notable mark of the hyperferritinemic syndromes and increasing evidence supports the notion that high circulating ferritin may not only reflect an acute phase response but also play a critical role in inflammation. Ferritin is a main intracellular iron storage

protein and the ratio between its two subunits, H and L, may differ depending on tissue type and physiologic status of the cell. H-ferritin looks to display not only an immunomodulatory function but also a proinflammatory activity culminating with the stimulation of the expression of different inflammatory mediators, including interleukin-1beta (IL-1 β). Hyperferritinaemia characterizes several autoimmune diseases where it may play a pathogenetic role on the ground of its immunomodulatory features. The origin of circulating serum ferritin during inflammatory statuses is still debated. In vitro experiments demonstrated that ferritin might be actively produced by hepatocytes as well as by macrophages (M Φ) through a non-classical pathway. Thus, it is possible that in hyperferritinemic syndromes macrophage (M Φ) activation could actively contribute to ferritin production. In line with this hypothesis, in a worthy study, it was demonstrated that in adult-onset Still's disease (AOSD) ferritin serum levels were not only correlated with disease activity, but also with macrophage (M Φ) activation. Interestingly, in a valuable study describing a cohort of 39 hospitalized patients with coronavirus disease 2019 (COVID-19), ferritin serum concentrations were found recognizably associated with disease severity. Besides an active release, during the inflammatory reaction, a main component of serum ferritin derives by cellular death and, in particular, by hepatic cells death. Once secreted, ferritin loses part of the inner iron content giving rise to extremely high serum concentrations of free iron. It seems that the excess of circulating free iron detectable during severe inflammatory environments, can deteriorate the inflammatory reaction with the specialr ability to stimulate a notable pro-coagulant state. This capacity is related to changes in the morphology of red blood cells (RBCs) and fibrin induced by free iron able itself to favor the production of hydroxyl radical. Oxidative stress (OS) on red blood cells (RBCs) and fibrin can promote the production of dense clots responsible for stroke development. Due to the capacity of iron chelation to taper the inflammatory response through a reduction of reactive oxygen species (ROS) production and to induce an antiviral activity, the utility of this therapeutic approach in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has been addressed. A clinical trial on the use of Desferal (Deferoxamine, a medication able to bind iron in case of iron overdose) is currently ongoing in IRAN in patients with mild to severe coronavirus disease 2019 (COVID-19) infection (NCT04333550).

Coagulopathy is one of the main complications occurring in hospitalized patients with severe coronavirus disease 2019 (COVID-19). Despite prophylaxis with low molecular weight heparin

(LMWH), the occurrence of cardiovascular (CV) stroke is considerably high, in some cases in the form of a diffused intravascular coagulopathy (DIC). In a Chinese cohort from Wuhan, disseminated intravascular coagulation (DIC) occurred in about 6.4% of patients who died for severe coronavirus disease 2019 (COVID-19). Acro-ischemia is one of the most frequent presentations of this complication being associated with a considerable rate of death. It is valuable to demonstrate that acro-ischemia lesions reported to be occurring broadly in asymptomatic children and adolescents with coronavirus disease 2019 (COVID-19); they majorly affect the feet and sometimes the hands; the toes and fingers are typically affected, but in some cases also the plantar region; the lesions affect not all toes and fingers, on average 3, usually separated by unaffected toes and fingers; the lesions are sometimes rounded, a few millimeters in size and multiple or affect the entire finger usually with a clear demarcation at the metatarsophalangeal level; initially they have a reddish-purple or bluish color; they can become bullous or present blackish crusts in the subsequent evolution; they are usually painful and evolve within 2 weeks with restitutio ad integrum. Interestingly, disseminated intravascular coagulation (DIC) is also a major complication the other hyperferritinemic syndromes including adult-onset Still's disease (AOSD), macrophage activation syndrome (MAS), sepsis, and catastrophic antiphospholipid syndrome (CAPS). Inflammation promotes increased coagulation by two different effects: by activating the cascade coagulation system and by downregulating the anticoagulant mechanisms. The endothelial cell and platelet activation occurring in catastrophic anti-phospholipid syndrome (CAPS) is a key contributor to the genesis of a thrombotic storm and in this setting, it is significant the role of infections as triggers of the disease. It is of note that three Chinese coronavirus disease 2019 (COVID-19) patients admitted to intensive care unit (ICU) and presenting thrombotic events tested positive for anticardiolipin IgA antibodies as well as anti- β 2 glycoprotein I IgA and IgG antibodies.

However, it is noted that the increased vascular coagulation occurring in coronavirus disease 2019 (COVID-19) patients is more close to a lung centric pulmonary intravascular coagulopathy (PIC) rather than a classical disseminated intravascular coagulation (DIC). However, it is considered to refer that the lung pathology seen in patients with coronavirus disease 2019 (COVID-19) shows notable microvascular thrombosis and haemorrhage linked to extensive alveolar and interstitial inflammation that shares features with macrophage activation syndrome (MAS). It has been termed the lung-restricted vascular immunopathology associated with

coronavirus disease 2019 (COVID-19) as diffuse pulmonary intravascular coagulopathy, which in its early stages is distinct from disseminated intravascular coagulation (DIC). Increased circulating D-dimer (DD) concentrations (reflecting pulmonary vascular bed thrombosis with fibrinolysis) and elevated cardiac enzyme concentrations (reflecting emergent ventricular stress induced by pulmonary hypertension) in the face of normal fibrinogen and platelet levels are key early characteristics of severe pulmonary intravascular coagulopathy related to coronavirus disease 2019 (COVID-19). Extensive immunothrombosis over a large pulmonary vascular territory without confirmation of coronavirus disease 2019 (COVID-19) viraemia in early disease best interprets the adverse impact of male sex, hypertension (HTN), obesity, and diabetes mellitus (DM) on the prognosis of patients with coronavirus disease 2019 (COVID-19). The immune mechanism underlying diffuse alveolar and pulmonary interstitial inflammation in coronavirus disease 2019 (COVID-19) includes a macrophage activation syndrome (MAS)-like state that provokes extensive immunothrombosis, which might unmask subclinical cardiovascular disease (CVD) and is distinct from the macrophage activation syndrome (MAS) and disseminated intravascular coagulation (DIC) that is more familiar to rheumatologists.

This peculiar presentation seems related to a macrophage activation syndrome (MAS)-like intrapulmonary inflammation. Really, although severe coronavirus disease 2019 (COVID-19) has several abnormal laboratory parameters similar to macrophage activation syndrome (MAS), the lack of other features, such as the classical organomegaly, is considerable, leading to suppose a hyperactivation of the immune system primarily confined to the lung parenchyma.

Further similarities between hyperferritinemic syndromes and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) severe infection are revealed from the few autopsies on coronavirus disease 2019 (COVID-19) patients reported so far. Macroscopic features in autopsies comprise pleurisy, pericarditis, lung consolidation, pulmonary edema; microscopic findings include diffuse alveolar damage with inflammatory infiltrates composed mainly by monocytes and macrophages (MΦ), but minimal lymphocytes infiltration, and multinucleated giant cells alongside large atypical pneumocytes. Cardiac involvement in the form of myocarditis has been also described. Similarly, pleurisy, pericarditis and myocarditis have been largely described in patients with adult-onset Still's disease (AOSD) and macrophage activation syndrome (MAS). Some recommendations and guidelines to safely perform autopsies in

coronavirus disease 2019 (COVID-19) patients have been published but the literature on this aspect is still poor even if pathological aspects are of utmost importance to better understand the extent and type of damage associated with this infection and its possible pathogenesis.

Why some patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection evolve to a hyperinflammation condition with such a dramatic course while others seem to respond to treatment, is still unknown. The severity of its evolution does not seem exclusively ascribable to viral factors, but probably to host features including different epidemiologic and molecular factors. Among them, the presence of an age and sex preference is evident with a higher occurrence of severe inflammation especially in elderly and men. The different lung expression of the angiotensin-converting enzyme2 (ACE2) molecule, the receptor used by coronavirus disease 2019 (COVID-19) to enter cells, could be one of the reasons responsible for a higher prevalence of the severe disease in this specific subset of patients. Accordingly, specific medications modulating the expression of this receptor such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers could be considered an additional external factor providing a major risk for patients. Co-morbidities represent an ulterior risk factor for the development of severe coronavirus disease 2019 (COVID-19) systemic inflammation and among them, type 2 diabetes mellitus (T2DM) is one of the mostly described. To this regard, the increased expression of another receptor named human dipeptidyl peptidase 4 (DPP4), highly expressed in patients with type 2 diabetes mellitus (T2DM), might be implicated in the worst disease outcome due to the possible ability of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to infect cells through dipeptidyl peptidase 4 (DPP4) binding, as already described in Middle East coronavirus (MERS-CoV) infection. Ethnicity might also have some impact on virus infection outcome. At birth, differences in innate immune response between Caucasian and Asian people have been identified. Macrophages (MΦ) derived from healthy Filipinos and challenged with *Mycobacterium tuberculosis*, demonstrate a lower production of interleukin-1 (IL-1) and interleukin-6 (IL-6) as well as higher production of interleukin-8 (IL-8), compared to Chinese and non-Hispanic white people. Additionally, studies on peripheral blood mononuclear cell (PBMC) from children vaccinated for measles showed race-related variation in the amount of cytokine produced following stimulation.

Another fascinating hypothesis supporting the differences in coronavirus disease 2019 (COVID-19) infection outcome is an antibody-dependent enhancement of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to previous exposure to other coronavirus. Indeed, previous contact with other coronaviruses responsible for a boost in immune response before coronavirus disease 2019 (COVID-19) infection could be accountable for the differences in disease severity observed among people.

What is sure right now is that for reasons that still need to be clarified, in some coronavirus disease 2019 (COVID-19) patients there is an over-inflammatory reaction, which strictly reminds the one observed in other inflammatory conditions, such as adult-onset Still's disease (AOSD), which is a prototype of idiopathic autoinflammatory disorder frequently triggered by infections. Due to similarities with this condition, a genetic predisposition cannot be excluded as well. In adult-onset Still's disease (AOSD), the presence of rare coding variants in interleukin-1 (IL-1) related pathways and gene polymorphism associated with interleukin-18 (IL-18) have been identified. At the same extent, heterozygous mutations related to PRF1 and UNC13D genes, have been linked to a specific subset of macrophage activation syndrome (MAS) patients.

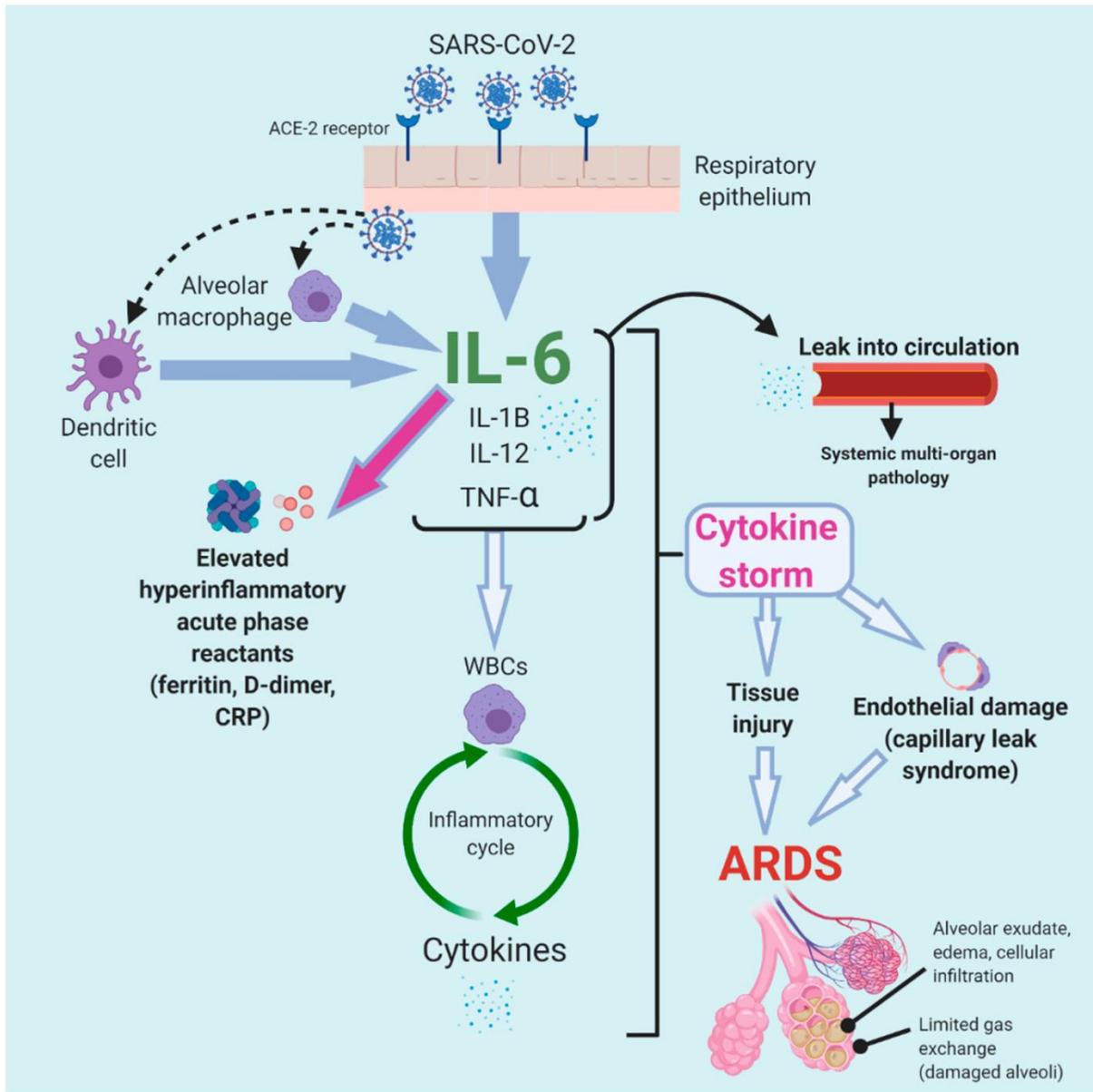
Besides genetic factors, the modulation of the expression of different cytokines both by lung epithelial cells and by innate and adaptive immune cells needs to be taken into account. Regarding interleukin-1beta (IL-1 β), it is notable to remind that previous studies on severe acute respiratory syndrome coronavirus (SARS-CoV) presented the ability of the virus to up-regulate inflammasome activity with consequent capacity to actively increase the production of interleukin-1beta (IL-1 β). Due to the similarities between severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (82% nucleotide sequence homology), it is probably that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) displays the same capacity to induce an exaggerated interleukin-1beta (IL-1 β) mediated response. Thus, the link between coronavirus disease 2019 (COVID-19) induced inflammatory reaction and hyperferritinemic syndromes, such as adult-onset Still's disease (AOSD) or macrophage activation syndrome (MAS), is immediately evident being both related to a massive interleukin-1beta (IL-1 β) systemic release. During macrophage activation syndrome (MAS), it is also important to remind the role of type II interferon (IFN), which is a crucial mediator of the inflammatory response and whose neutralization looks promising. In this

regard, although it is known that type I interferon (IFN) represents the main antiviral pathway, studies on severe acute respiratory syndrome coronavirus (SARS-CoV) revealed that both type I and type II interferon (IFN) (alpha-beta and gamma) synergize to inhibit virus replication with a concomitant active virus attempt to reduce such interferon (IFN) production. Preliminary data from coronavirus disease 2019 (COVID-19) patients suppose how a suppressed interferon-gamma (IFN- γ) production by CD4+ T cells is associated with more severe illness. Nonetheless, in the advanced stages of the disease, an over-expression of this molecule may occur, due to a second wave of systemic inflammatory reaction similar to macrophage activation syndrome (MAS). For this reason, a clinical trial evaluating the efficacy of concomitant inhibition of interleukin-1 (IL-1) (Anakinra) and interferon-gamma (IFN- γ) (emapalumab) in severe coronavirus disease 2019 (COVID-19) patients has started (NCT04324021). However, in patients with coronavirus disease 2019 (COVID-19), a clear distinction between acute respiratory distress syndrome (ARDS) and macrophage activation syndrome (MAS) is challenging, especially in the first phases of the disease where acute respiratory distress syndrome (ARDS) represents the main source of interleukin-6 (IL-6) and interleukin-1 (IL-1). Results from Anakinra/Emapalumab trial will surely provide interesting insights on coronavirus disease 2019 (COVID-19) associated macrophage activation syndrome (MAS) like-syndrome.

Besides interleukin-1beta (IL-1 β), the majority of studies published up to now presumes a predominant role of interleukin-6 (IL-6) in severe coronavirus disease 2019 (COVID-19) inflammatory reaction. In patients with acute respiratory distress syndrome (ARDS), the lung epithelium and immune cell hyperexpression of interleukin-6 (IL-6) is associated with a poor disease outcome, as confirmed by a notable study on coronavirus disease 2019 (COVID-19) patients. However, interleukin-6 (IL-6) is also an essential regulator of the balance among fibroblasts, macrophages (M Φ), and epithelial lung cells and is able to participate in the resolution of inflammation. Thus, a prolonged therapeutic blockade of this cytokine and the exact timing to do that needs to be carefully considered.

Finally, regarding other epidemiological factors possibly able to influence disease outcome, the use of concomitant immune modulating/immune-suppressive therapies is certainly critical. Interestingly, preliminary observations point out that immunosuppressed heart-transplanted patients present a milder form of coronavirus disease 2019 (COVID-19) during the later stages

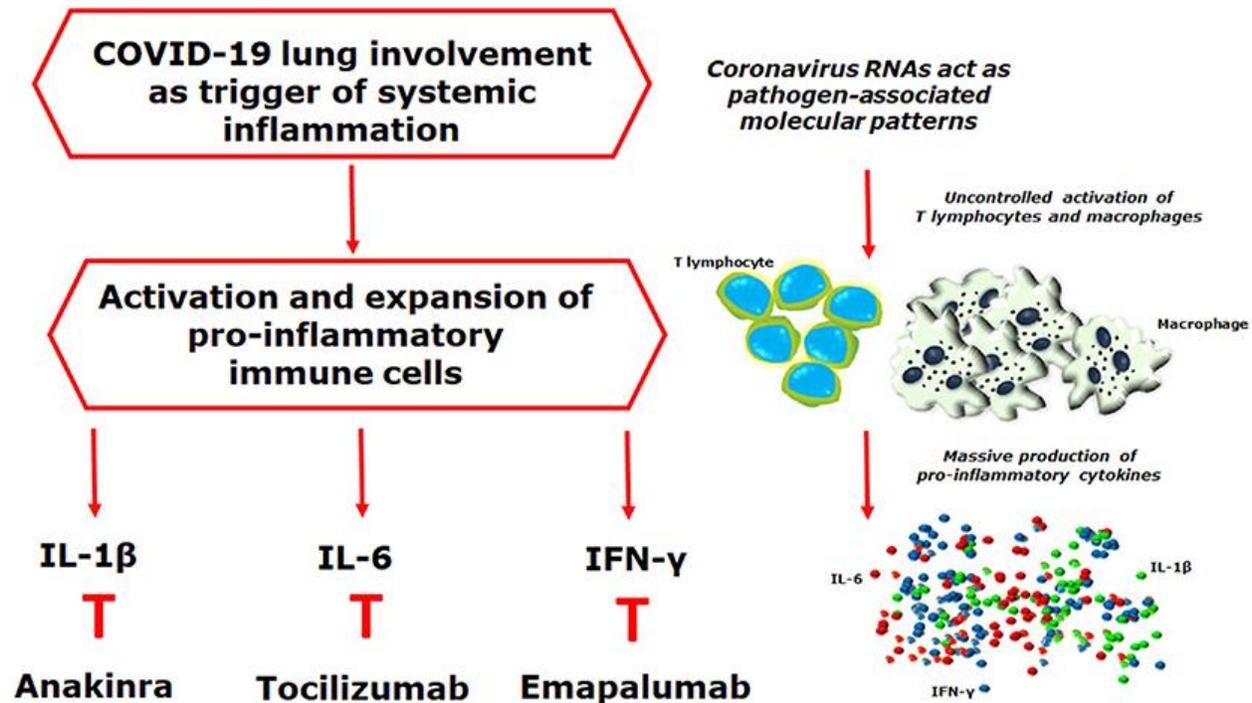
when the clinical evolution is mediated by the host inflammatory response. At the moment, the Italian Society of Rheumatology has organized a national registry to gather information regarding patients with immune-rheumatologic disease infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the European League Against Rheumatism (EULAR) has proposed a similar registry too. Very preliminary results on a large cohort of Italian patients with chronic arthritis managed with immunosuppressive agents (biologic and targeted synthetic DMARDs), showed no increased risk of respiratory or life-threatening complication from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.



Figure(38):Proposed model of the cytokine storm in severe COVID-19[Farooqi F.; Dhawan N.; Morgan R.; Dinh J.; Nedd K.; Yatzkan G. (2020). Treatment of severe COVID-19 with Tocilizumab mitigates cytokine storm and averts mechanical ventilation during acute respiratory distress: a case report and literature review. Tropical Medicine and Infectious Disease, 5(3),112. <https://doi.org/10.3390/tropicalmed5030112>]

Figure (38) shows a proposed model of the cytokine storm in severe coronavirus disease 2019 (COVID-19), revealing the mechanistic complexity of the cytokine cascade and subsequent pathology. The model is primarily based on current knowledge of cytokine storm, as seen in macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH), and

chimeric antigen receptor (CAR) T-cell therapy. Notably, cytokine storm in both macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) displays increased levels of cytokines interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-18 (IL-18), macrophage colony stimulating factor (M-CSF), interferon-gamma (IFN- γ), and tumor necrosis factor-alpha (TNF- α), in addition to interleukin-6 (IL-6), although definitive causality due to all these cytokines has not been determined.



Figure(39):Clinical inhibition of IL-1 β , IL-6, and IFN- γ in hyperinflammation in COVID-19 infection [Ruscitti P.; Berardicurti O.; Benedetto P.; Cipriani P.; Lagnocco A.; Shoanfeld Y.; Giacomelli R. (2020). Severe COVID-19, another piece in the puzzle of the hyperferritinemic syndrome. An immunomodulatory perspective to alleviate the storm. Front Immunol. <https://doi.org/10.3389/fimmu.2020.01130>]

4.Coagulopathy

Coagulopathy, also known as a bleeding disorder, is a condition in which the blood's ability to coagulate is impaired. This condition can lead to prolonged or excessive bleeding (bleeding diathesis), which may happen spontaneously or following an injury or medical and dental procedures. Coagulopathy may progress to uncontrolled internal or external bleeding. Uncontrolled bleeding if left untreated can cause damage to joints, muscles, or internal organs and may be life-threatening. Patients should be subjected to immediate medical care for serious

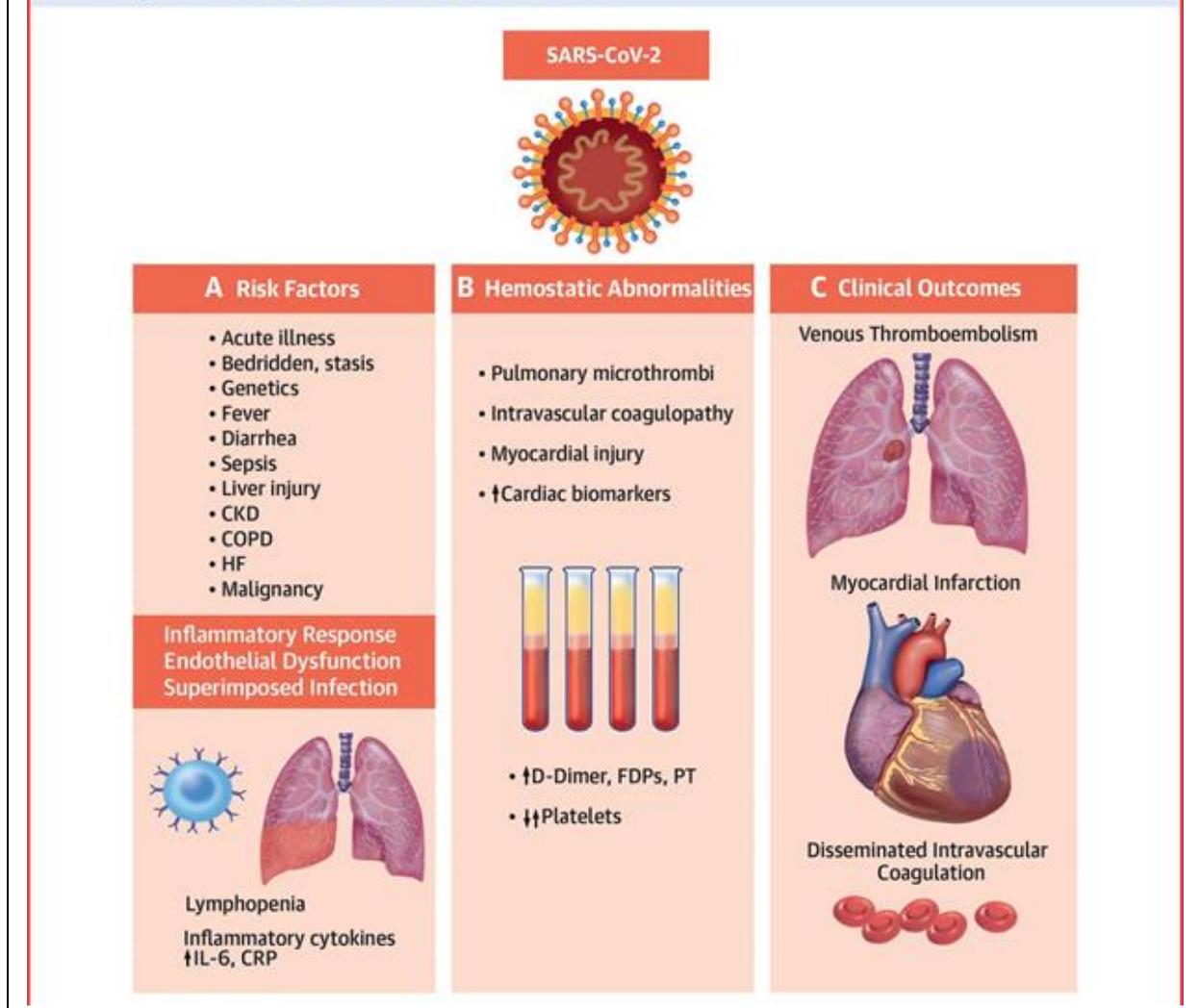
symptoms, involving heavy external bleeding, blood in the urine or stool, double vision, severe head or neck pain, repeated vomiting, difficulty walking, convulsions, or seizures. Patients must follow prompt medical care if they suffer from mild but unstoppable external bleeding or joint swelling and stiffness.

The normal clotting process depends on the interplay of various proteins in the blood. Coagulopathy can result from reduced concentrations or absence of blood-clotting proteins, called clotting factors or coagulation factors. Coagulopathy can be incident as a result of dysfunction or decreased concentrations of platelets.

It is supposed that moderate and severe coronavirus disease 2019 (COVID-19) patients present prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and elevated D-dimer (DD) concentrations with consequent poorer results.

In coronavirus disease 2019 (COVID-19), elevated plasma concentrations of pro-inflammatory cytokines [interleukin-2 (IL-2), interleukin-7 (IL-7), granulocyte colony-stimulating factor (G-CSF), interferon-inducible protein 10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1alpha (MIP-1 α), and tumor necrosis factor-alpha (TNF- α)] have been seen in patients admitted to intensive care units (ICUs), indicating development of cytokine storm in patients with severe disease with a secondary hemophagocytic lymphohistiocytosis (sHLH). While many pro-inflammatory cytokines trigger the coagulation system, it was shown that the increase in interleukin-6 (IL-6) was different with the elevations in D-dimer (DD); interleukin-6 (IL-6) concentrations appeared to increase only 13 days after disease onset, whereas D-dimer (DD) levels were already 10-fold increased by that time. This recognition presumes that the very high D-dimer (DD) concentrations seen in coronavirus disease 2019 (COVID-19) patients are not only secondary to systemic inflammation, but also reflect true thrombotic disease, probably induced by local, cellular activation, induced by virus infiltration. Although the decreased platelet count and longer prothrombin times (PT) seen in patients with severe coronavirus disease 2019 (COVID-19) suggest that disseminated intravascular coagulation (DIC) might be present, at the same time (pulmonary) venous thrombosis, deep vein thrombosis (DVT), and/or pulmonary embolism (PE) may be present.

CENTRAL ILLUSTRATION: Postulated Mechanisms of Coagulopathy and Pathogenesis of Thrombosis in COVID-19

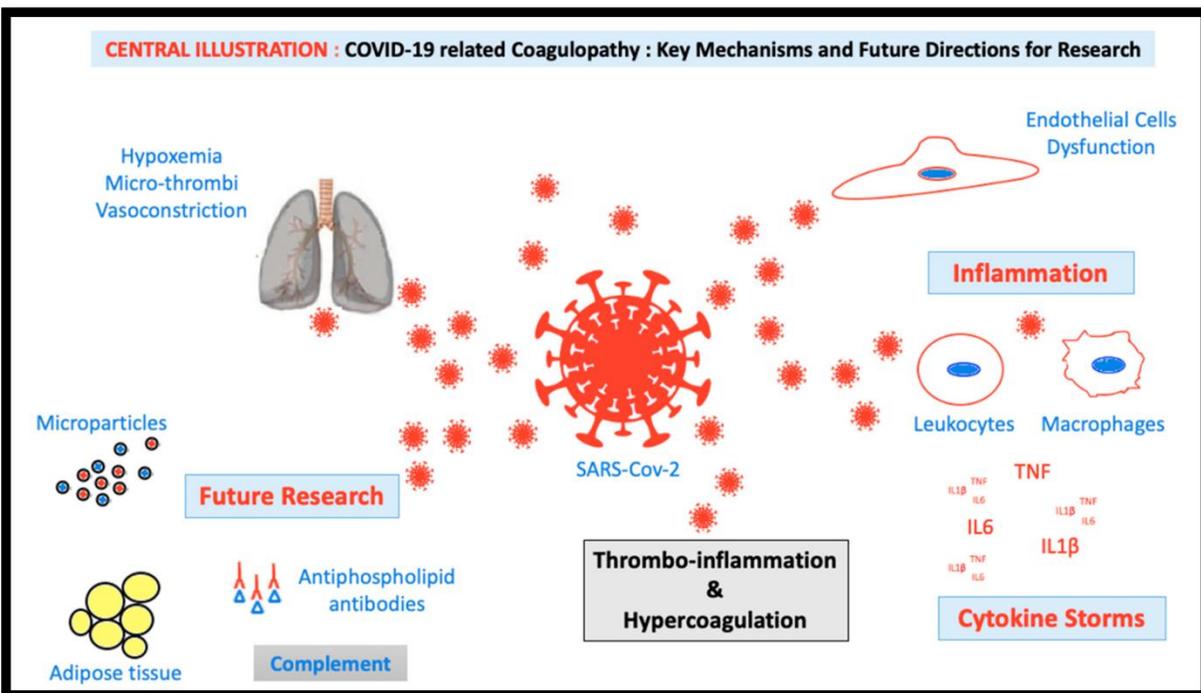


Figure(40):Coagulopathy and thrombosis in COVID-19 infection [Bikdeli B.; Madhavan M.; Jimenez D.; Chuich T.; Dreyfus I.; Driggin E.; Nigoghossian C.; Ageno W.; Madjid M.; Guo Y.; Tang L.; Hu Y.; Giri J.; Cushman M.; Quere I.; Dimakakos E.; Gibson C.; Lippi G.; Falavaro E.; Fareed J.; Caprini J.; Tafur A.; Burton J.; Francese D.; Wang E.; Falanga A.; McLintock C.; Hunt B.; Spyropoulos A.; Barnes G.; Eikelboom J.; Weinberg I.; Schulman S.; Carrier M.; Piazza G.; Beckman J.; Steg P.; Stone G.; Rosenkranz S.; Goldhaber S.; Parikh S.; Monreal M.; Krumholz H.; Konstantinides S.; Weitz J.; Lip G. (2020). COVID-19 and thrombotic or thromboembolic disease:implications for prevention, antithrombotic therapy, and follow-up. Journal of the American College of Cardiology, 75(23)DOI: 10.1016/j.jacc.2020.04.031]

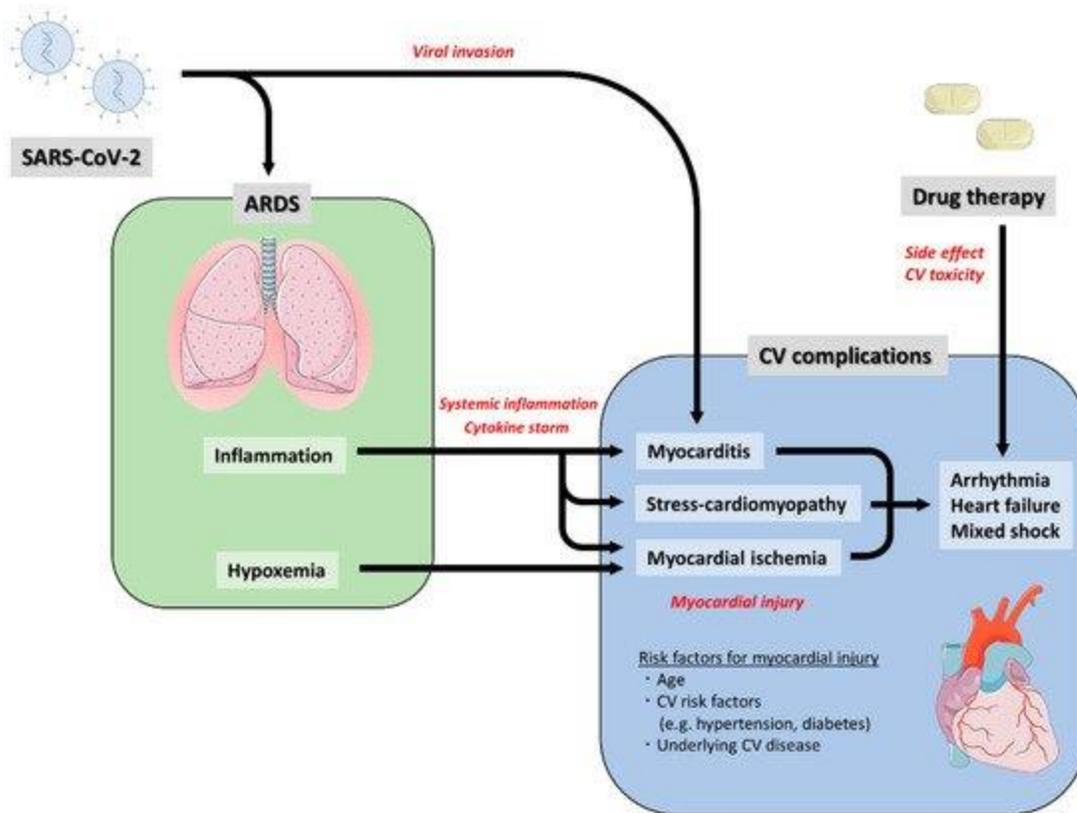
4.1 Thrombotic Burden in COVID-19 Infection

Higher thrombotic burden in the acute phase of coronavirus disease 2019 (COVID-19) bases on a complex interplay between pro-inflammatory cytokine/chemokine secretion, elevated endothelial dysfunction/damage, and possible sepsis-induced coagulopathy progress in severe cases, all developing coagulation activation. The striking highly pro-thrombotic features of coronavirus disease 2019 (COVID-19) look to come from:

- 1-Severe and prolonged hypoxemia known to induce thrombosis;
- 2-High incidence of cytokine storms in critically ill patients; and finally
- 3-A presumptive role of local pulmonary thrombotic phenomena.



Figure(41): COVID-19 related coagulopathy [Marchandot B.; Sattler L.; Jesel L.; Matsushita K.; Schini-Kerth V.; Grunebaum L. (2020). COVID-19 related coagulopathy: a distinct entity?. Journal of Clinical Medicine, 9(6):1651. <https://doi.org/10.3390/jcm9061651>]



Figure(42):Potential mechanisms of cardiovascular complication caused by COVID-19[Matsushita K.; Marchandot B.; Jesel L.; Ohlmann P.; Morel O. (2020). Impact of COVID-19 on the cardiovascular system: a review. Journal of Clinical Medicine, 9(5):1407. <https://doi.org/10.3390/jcm9051407>]

4.1.1 Inflammation

Inflammation has been accepted as a common pathway through which various risk factors stimulate thrombogenesis. Cytokines and chemokines have been correlated with crucial role in immunity and immunopathology during viral infections. The immune response to acute severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and the accompanying surge of cytokines and inflammatory mediators [interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-22 (IL-22), C-x-C motif chemokine 10 (CXCL10, also known as Interferon gamma-induced protein 10 (IP-10) or small-inducible cytokine B10), etc.] can cause activating pro-coagulant pathways. Inflammatory cytokines, together with endothelial injury, can up-regulate tissue factor expression and further lead to a pro-thrombotic state. In coronary arteries, circulating cytokines can induce macrophages (MΦ) within the plaque to elevate local cytokine synthesis and secretion, and also trigger tissue factor overexpression that makes lesions more thrombogenic.

This mechanism of a local, intraplaque response to systemic stimuli was regarded as an echo phenomenon by Libby. Systemic cytokines can induce leukocyte adhesion molecule expression on the endothelial cells overlying established atheroma, supporting local recruitment of these inflammatory cells. It is worthy to refer that the leukocyte adhesion molecules are members of larger superfamilies of cell surface receptors that play critical roles in immunosurveillance, inflammation, hemostasis, wound healing, morphogenesis, maintenance of tissue architecture, atherogenesis, and tumor metastasis.

Early reports from China illustrated severely elevated concentrations of inflammatory biomarkers and cytokines such as interleukin-6 (IL-6), interleukin-1beta (IL-1 β), C-reactive protein (CRP), Tumor necrosis factor-alpha (TNF- α), granulocyte-colony stimulating factor (G-CSF), and ferritin. Advanced stages of coronavirus disease 2019 (COVID-19) have been bound to cytokine storm syndromes and identified patients at higher risk of developing severe diseases involving disseminated intravascular coagulation (DIC), acute myocardial injury due to myocarditis or stress-cardiomyopathy, and death. Siddiqi *et al.* (2020) have presumed a schema to estimate the severity of systemic hyperinflammation in coronavirus disease 2019 (COVID-19). Depending on this paradigm, the host response to coronavirus disease 2019 (COVID-19) is first localized in the lung parenchyma, but a systemic surge in pro-inflammatory cytokines can happen, defined as a cytokine storm, which play a significant role in coronavirus disease 2019 (COVID-19) etiologies and manifestations.

4.1.2 Endothelial Activation

Clinical and pre-clinical proof boosts the hypothesis that the endothelium is a key target organ of coronavirus disease 2019 (COVID-19). The importance of the endothelium in the pathogenesis of coronavirus disease 2019 (COVID-19) infection was confirmed by data showing direct endothelial cell infection and endotheliitis in the time course of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. In humans, the angiotensin-converting enzyme 2 (ACE2) receptor has been found in the lung epithelium (in particular the type II pneumocyte) and the myocardium, and is highly expressed in arterial and venous endothelial cells. Endothelial cell activation/damage due to the virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor provoking acute inflammation and hypercoagulation may be of fundamental importance to interpret the high thrombotic burden seen.

Under physiological conditions, pulsatile shear stress elevated angiotensin-converting enzyme 2 (ACE2) expression, triggering nitric oxide production, and decreasing inflammation and proliferation in vascular endothelial cells. The description of higher angiotensin-converting enzyme 2 (ACE2) expression as defined by ribonucleic acid (RNA) sequencing and affirmed by proteomic profiling in heart muscle disease patients might interpret why heart failure (HF) patients could be more prone to heart infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Pericytes, which spread outside the endothelial cell of capillaries and parts of venules, were also presumed to be a key target in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and might interpret the importance of capillary endothelial cell dysfunction and microcirculation disorder in that status. General mechanisms of endothelial activation following a cytokine burst involve calcium mobilization, oxidative stress (OS), down-regulation of the endothelial nitric oxide synthase-derived nitric oxide formation, plasma membrane remodeling, exposure of procoagulant phospholipid (PL) such as phosphatidylserine (PS), procoagulant microparticles (MPs) shedding, tissue factor expression, disruption of the natural anticoagulant shield represented by annexin 5 (or annexin V, a cellular protein in the annexin group), expression of selectins and cytoadhesins [vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1)], and cytokines release [monocyte chemoattractant protein-1 (MCP-1/CCL2)]. Within pulmonary microvascular endothelial cells, exposure to various inflammatory stimulus [tumor necrosis factor-alpha (TNF- α), lipopolysaccharide (LPS)] stimulated the secretion of endothelial-derived microparticles (EMPs), harbouring angiotensin-converting enzyme (ACE) and a simultaneous decrease of endothelial cell-surface angiotensin-converting enzyme (ACE) expression. In a mouse model of lung injury, ACE⁺-EMPs/EMPs were evidenced to be a marker of wet-to-dry lung injury as a possible witness of alveolar capillary barrier alterations. In sepsis, the importance of these results was assured by the definition of increased levels of ACE⁺-EMPs and ACE⁺-EMPs/EMPs in the blood of patients who progressed acute respiratory distress syndrome (ARDS). Endothelial cell activation/damage due to the virus binding to the angiotensin-converting enzyme 2 (ACE2) receptor triggering acute inflammatory and hypercoagulable may be of primary importance to interpret the high thrombotic burden recognized.

4.1.3 Severe Hypoxemia

Hypoxemia indicates low level of oxygen in blood, and the more general term hypoxia is an abnormally low oxygen content in any tissue or organ, or the body as a whole. Hypoxemia can lead to hypoxia (hypoxemic hypoxia), but hypoxia can also be incident through other mechanisms, such as anemia. Hypoxemia is usually defined in terms of reduced partial pressure of oxygen (mm Hg) in arterial blood, but also in terms of reduced content of oxygen (ml oxygen per dl blood) or percentage saturation of hemoglobin with oxygen, which is either found singly or in combination. Hypoxemia can lead to symptoms such as those in respiratory distress. These involve breathlessness, an increased rate of breathing, use of the chest and abdominal muscles to breathe, and lip pursing.

Chronic hypoxemia may be compensated or uncompensated. The compensation may cause symptoms to be overlooked initially, however, further disease or a stress such as any increase in oxygen demand may finally unmask the existing hypoxemia. In a compensated state, blood vessels supplying less-ventilated areas of the lung may selectively contract, to redirect the blood to areas of the lungs which are better ventilated. However, in a chronic context, and if the lungs are not well ventilated generally, this mechanism can result in pulmonary hypertension (PH), overloading the right ventricle of the heart and causing cor pulmonale and right sided heart failure. Polycythemia can also happen. It is important to refer to polycythemia as an abnormally increased concentration of haemoglobin in the blood, either through reduction of plasma volume or increase in red cell numbers. It may be a primary disease of unknown cause, or a secondary condition linked to respiratory or circulatory disorder or cancer. In children, chronic hypoxemia may manifest as delayed growth, neurological development and motor development and decreased sleep quality with frequent sleep arousals. Other symptoms of hypoxemia may involve cyanosis, digital clubbing, and symptoms that may relate to the cause of the hypoxemia, including cough and hemoptysis.

Serious hypoxemia typically occurs when the partial pressure of oxygen in blood is less than 60 mm Hg, the beginning of the steep portion of the oxygen–hemoglobin dissociation curve, where a small decrease in the partial pressure of oxygen leads to a large decrease in the oxygen content of the blood. Severe hypoxia can progress to respiratory failure.

Acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemia from altered permeability pulmonary edema causing decreased functional residual capacity (FRC), which in turn leads to hypoxemia from intrapulmonary shunting, and areas of low alveolar ventilation to perfusion. Pulmonary hypertension (PH) is also a common feature of acute respiratory distress syndrome (ARDS) arising from pulmonary vascular endothelial injury as well as from the effects of hypoxemia, hypercapnia, and acidosis that, if remained, develops to cor pulmonale and increased mortality risk.

Because lung injury in acute respiratory distress syndrome (ARDS) is non-homogeneous, portions of the lungs may remain functionally normal, so that tidal ventilation is preferentially distributed to these alveoli. Inhaled vasodilators, such as nitric oxide (NO) and aerosolized prostaglandin I₂, use this pathophysiology by stimulating local pulmonary vasodilation, thereby increasing alveolar ventilation/perfusion matching. These agents also reduce pulmonary arterial pressure in acute respiratory distress syndrome (ARDS). Furthermore, aerosolized prostaglandin I₂ possesses both anti-inflammatory properties and anticoagulant properties. In theory, these characteristics may lessen the impact of pulmonary vascular endothelial injury and abnormal pro-coagulation that are prominent features of acute respiratory distress syndrome (ARDS).

Silent hypoxemia has been mentioned in many coronavirus disease 2019 (COVID-19) patients. Patients were hypoxemic as they may have had an oxygen saturation of about 80% room air, but clinically looked comfortable, and not dyspneic or tachypneic. Complementary reports reinforce the high frequency and noxious impact of severe hypoxemia. Acute respiratory distress syndrome (ARDS) occurred in approximately 40% of 201 patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The coronavirus disease 2019 (COVID-19) pneumonia has been addressed as a specific disease with particular phenotypes. Its main characteristic is the separation between the severity of the hypoxemia and the maintenance of relatively good respiratory mechanics.

Severe lung inflammation and impaired pulmonary gas exchange in coronavirus disease 2019 (COVID-19) can induce thrombosis through a hypoxia-inducible transcription factor-dependent signaling pathway. It is important to indicate that the heterodimeric transcription factor hypoxia-inducible factor-1 (HIF-1) is activated under hypoxic conditions, resulting in the upregulation of its target genes plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor (VEGF). Plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor

(VEGF) are also stimulated in response to vascular injury, which is characterized by the activation of platelets and the coagulation cascade as well as the generation of reactive oxygen species (ROS). However, it is not known whether hypoxia-inducible factor-1 (HIF-1) is also induced by thrombotic factors. It is investigated the role of thrombin, platelet-associated growth factors, and reactive oxygen species (ROS) derived from the p22^{phox}-containing reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the activation of hypoxia-inducible factor-1 (HIF-1) and the induction of its target genes plasminogen activator inhibitor-1 (PAI-1) and vascular endothelial growth factor (VEGF) in human vascular smooth muscle cells (VSMCs). Thrombin, platelet-derived growth factor-AB (PDGF-AB), and transforming growth factor- β 1 (TGF- β 1) upregulated hypoxia-inducible factor-1alpha (HIF-1 α) protein in cultured and native vascular smooth muscle cells (VSMCs). This response was accompanied by nuclear accumulation of hypoxia-inducible factor-1alpha (HIF-1 α) as well as by increased hypoxia-inducible factor-1 (HIF-1) deoxyribonucleic acid (DNA)-binding and reporter gene activity. The thrombin-induced expression of hypoxia-inducible factor-1alpha (HIF-1 α), plasminogen activator inhibitor-1 (PAI-1), and vascular endothelial growth factor (VEGF) was attenuated by antioxidant treatment as well as by transfection of p22^{phox} antisense oligonucleotides. Inhibition of p38 mitogen-activated protein kinase and phosphatidylinositol-3-kinase significantly decreased thrombin-induced hypoxia-inducible factor-1alpha (HIF-1 α), plasminogen activator inhibitor-1 (PAI-1), and vascular endothelial growth factor (VEGF) expression. These findings demonstrate that the hypoxia-inducible factor-1 (HIF-1) signaling pathway can be stimulated by thrombin and platelet-associated growth factors and that a redox-sensitive cascade activated by reactive oxygen species (ROS) derived from the p22^{phox}-containing NADPH oxidase is crucially involved in this response.

In addition, hypoxia, and acute respiratory distress syndrome (ARDS) particularly, is observed to stimulate hypoxic pulmonary vasoconstriction and pulmonary hypertension, increase right ventricular afterload, and favor blood viscosity.

4.1.4 Pulmonary Microvascular Thrombosis

Pulmonary embolism (PE) is an acute, serious condition that can be directly life threatening. Pulmonary embolism (PE) occurs when an artery in the lungs is blocked by a substance that has traveled from elsewhere in the body through the bloodstream. This substance usually results from a blood clot in the legs or pelvis. The blockage of an artery that supplies the lungs, leads to

severe damage, interrupts their smooth operation and may, depending on the importance of the blocked artery, directly result in death. The most common form of emboli that causes pulmonary embolism is the blood clot described above. But there are also other situations that may occur, such as amniotic emboli during childbirth, scatter tumor emboli from a malignant disease or even traumatic fat emboli originating from the bone or bone marrow in patients with sustained blunt trauma and multiple fractures. It is important to mention that nonthrombotic pulmonary embolism is embolization of the pulmonary arteries by microscopic fragments of tissue, organisms, foreign material, chemical agents, or gas and excludes bland thrombus embolization and formation in situ.

If the venous clot is dislodged from the position in which it was formed, then its embolism to a vessel of pulmonary circulation or arterial systemic circulation follows. Paradoxical embolism is recognized in cases of open foramen ovale. It has been experimentally proved that when 60% of the pulmonary artery's vascular network is blocked, then a severe drop in blood pressure and acute bend of the right ventricular (acute cor pulmonale) is caused. In cases where the blockage reaches 80% of the vascular network, sudden death occurs. Cardiac hemodynamic effects on pulmonary embolism depend on the occlusion rate of the pulmonary vasculature, the distance of this network and the release of vasomotor substances that lead to bronchospasm followed by further reduction of pulmonary perfusion and an increase of dead space ventilation (VD). Acute pulmonary heart is caused by the sudden increase in the average pressure of the pulmonary artery, in concentrations greater than 40 mmHg due to increased pulmonary vascular resistance. The effects of pulmonary embolism by the cardiovascular (CV) system may be acute pulmonary heart disease, myocardial ischemia, acute circulatory failure, and the left-sided failure and from the lungs, hypoxia and atelectasis. In acute deficiency, the pressure in the right ventricle increases, resulting in septum's displacement to the left, lowering end-diastolic volume of the left ventricular, dysfunction of both ventricles, decrease in cardiac output and a drop of blood pressure. Coronary insufficiency due to pulmonary embolism is attributed to the significant reduction of cardiac output, the drop in aorta's pressure, hypoxia, and possibly to the existence of a reflex through vagal which reduces the width of the coronary vessels. Pulmonary infarction appears as thickening hemorrhagic lung area when average size pulmonary arteries are unclogged due to left heart failure and drop of pressure in the systemic circulation. Pulmonary infarction or lung infarction, is death of one or more sections of lung tissue due to deprivation of

an adequate blood supply. The section of dead tissue is called an infarct. The cessation or lessening of blood flow results ordinarily from an obstruction in a blood vessel that serves the lung. Pulmonary infarction occurs only in 10% of cases of pulmonary embolism because the pulmonary parenchyma is satisfactorily oxygenated through the bronchial. The fate of thromboembolism in the lung will specify the further course of the disease. Several mechanisms restore the circulation of the pulmonary artery, unless the episodes are repeated. When an oversized embolous plugs in the pulmonary circulation, it can lead to transient syncope, but then it can be destroyed and dissolved within a few 24-hour, otherwise when it remains, it is organized, shrink and coalesced with the vessel wall.

Focal microvascular thrombosis and pulmonary emboli in a small autopsy series have recently been reported in coronavirus disease 2019 (COVID-19) cases. Microvascular thrombosis has recently been demonstrated in patients with coronavirus disease 2019 (COVID-19), and has been proposed to mediate the pathogenesis of organ injury in this disease. In many of these conditions, microvascular thrombosis is accompanied by inflammation, an association referred to as thromboinflammation. However, focal thrombotic lung injury paved the way for the concept of a focal pulmonary thrombosis phenomenon in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The entry receptor utilized by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is angiotensin-converting enzyme2 (ACE2), which is highly expressed in lung alveolar cells, principally type II alveolar cells. High pulmonary viral loads in the alveoli of coronavirus disease 2019 (COVID-19)-infected patients have been reported. The main infection initiates alveolar injury, leading to a local inflammatory response, and these microvascular thrombi have been described in an environment of marked inflammatory changes involving mononuclear cell infiltrates, virally infected cells, and diffuse alveolar damage (DAD). Diffuse alveolar damage (DAD) represents a global injury to the gas-exchange surfaces due to disruption of the blood-air barrier leading to exudative edema and fibrosis, resulting in severely impaired blood and tissue oxygenation. The key question relies upon whether acute respiratory distress syndrome (ARDS) and/or disseminated intravascular coagulation (DIC) develop pulmonary microvascular thrombi on one hand, and, on the other hand, whether focal pulmonary microthrombi can cause further hypoxemic respiratory failure, enhanced thrombo-inflammation, and hypercoagulability with acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC) as final consequences: Both options are probable. It may be

hypothesized that lung injury causes microthrombus formation further enhanced in the case of a hypercoagulable state like disseminated intravascular coagulation (DIC).

The view of a pulmonary thrombosis in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease was developed. The view of a prothrombotic pulmonary endothelial dysfunction, causing a severe acute inflammation via complement and cytokine secretion, and a blood coagulation activation with vascular microthrombosis that further triggers a local consumption coagulopathy, i.e., a disseminated intravascular coagulation (DIC), leading to acute respiratory distress syndrome (ARDS) was emphasized. It was suggested that anticoagulant treatment might be helpful by limiting the vicious circle of inflammation-blood coagulation activation-inflammation, thus improving the severely impaired gas exchange in these patients. A study showed that the use of an increased dose of low-molecular-weight heparin (LMWH) appeared to reduce the downstream thrombotic effects of the marked inflammatory response to coronavirus disease 2019 (COVID-19) as it looks to decrease the contribution of microvascular thrombosis in severely hypoxemic coronavirus disease 2019 (COVID-19) patients.

4.2 D-Dimer Generation in COVID-19 Infection

High level of D-dimer (DD) is one of the abnormal laboratory parameters in patients with coronavirus disease 2019 (COVID-19) infection. D-dimer (DD) is the fibrin degradation products released upon cleavage of cross-linked fibrin by plasmin. Historically, the role of D-dimer (DD) is limited due to its non-specificity, with high concentrations are frequently observed with advanced age, African American race, female sex, active malignancy, surgery, pregnancy, immobility, cocaine use, connective tissue disorders, end-stage renal disease, and prior thromboembolic disease. The D-dimer (DD) is routinely used clinically in diagnosing disseminated intravascular coagulation (DIC) and those with low pretest likelihood for deep vein thrombosis (DVT) and pulmonary embolism (PE). D-dimer (DD) has been researched to identify patients believed to progress to severe coronavirus disease 2019 (COVID-19) infection earlier in their course of disease. High D-dimer (DD) level was discovered in about 36%-47% of hospitalized patients with coronavirus disease 2019 (COVID-19) infection, the majority of whom are those with severe coronavirus disease 2019 (COVID-19) infection. A prior meta-analysis comprising of 4 studies revealed a higher D-dimer (DD) concentration in patients with severe coronavirus disease 2019 (COVID-19) infection in comparison with those with the non-severe

disease. A meta-analysis study comprising of 18 studies estimated the prognostic role of D-dimer (DD) in coronavirus disease 2019 (COVID-19) and the key findings of this pooled analysis are:

1-The D-dimer (DD) concentrations were elevated in patients with severe coronavirus disease 2019 (COVID-19) infection and those who passed away in comparison with non-severe disease and those who survived, respectively after adjusting for age, comorbid condition, and C-reactive protein (CRP) concentrations;

2-Patients with high D-dimer (DD) concentrations were at elevated risk of progressing severe coronavirus disease 2019 (COVID-19) infection and elevated all-cause mortality compared to those with normal D-dimer concentrations.

Zhou *et al.* (2020) reported that D-dimer (DD) level >1 mg/L on admission was independently correlated with elevated odds of mortality. Also, it was found that patients with advanced age, higher Sequential Organ Failure Assessment (SOFA) score, elevated troponin (Tn), and B-type natriuretic peptide (BNP) had been correlated with poor outcomes and mortality in coronavirus disease 2019 (COVID-19) infection. Studies have shown that rising D-dimer (DD) levels during the course of hospitalization are associated with worst long term outcomes. In addition, coronavirus disease 2019 (COVID-19) patients with one or more comorbidities [hypertension (HTN), diabetes mellitus (DM), and cardiovascular diseases (CVD)] are associated with adverse consequences [i.e. severe coronavirus disease 2019 (COVID-19) and/or mortality]. In a pooled analysis study, patients with severe coronavirus disease 2019 (COVID-19) infection had significantly high D-dimer (DD) concentrations, with an increasing prevalence of hypertension (HTN), diabetes mellitus (DM), and coronary artery disease (CAD). There has been upcoming proof concerning an elevated incidence of venous thromboembolic events (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with severe coronavirus disease 2019 (COVID-19) infection. Further, disseminated intravascular coagulation (DIC) has been increasingly reported in these patients. Tang *et al.* (2020) documented a 3.5-fold increase in D-dimer (DD) concentrations in those who passed away and 71% of them met the International Society on Thrombosis and Hemostasis (ISTH) criteria for disseminated intravascular coagulation (DIC) in comparison with 0.6% only among those who survived. Similarly, another study supposed that D-dimer (DD) level >1.5 mg/L may help detect venous thromboembolic (VTE) events with a sensitivity of 85.0% and specificity of 88.5%, however, findings should be explained with caution due to small sample size and lack of external validation. The risk of

venous thromboembolic events (VTE) is higher in patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Due to several causes for D-dimer (DD) increase in these patients, imaging studies to diagnose deep vein thrombosis (DVT) or pulmonary embolism (PE) should only be pursued if clinically ensured. High clinical suspicion for deep vein thrombosis (DVT) or pulmonary embolism (PE) is registered in patients with elevated D-Dimer (DD) (more so in $> 2\text{mg/dl}$), as failure to manage may lead to adverse clinical results. Possibly is that patients who remained untreated for this catastrophe condition, explained adverse clinical results.

Hemostatic changes and high D-dimer (DD) levels in coronavirus disease 2019 (COVID-19) patients have been interpreted by:

- (a)-Excess thrombin generation and early fibrinolysis shutdown secondary to endothelial activation induced by the infectious trigger;
- (b)-Severe hypoxemia known to induce thrombosis through both increased blood viscosity and hypoxia-inducible transcription factors; and finally
- (c)-local pulmonary thrombotic phenomena with a high frequency of pulmonary microthrombosis in small autopsy series. Such focal thrombotic lung injury paved the way for the concept of a focal pulmonary thrombosis phenomenon in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

Perhaps, empirically managing all coronavirus disease 2019 (COVID-19) patients with intermediate or full (therapeutic) doses of anticoagulation to inhibit microvascular thrombosis (MVT) might be of benefit (provided a thorough risk-benefit assessment given these patients are also at risk of spontaneous bleeding). Moreover, it remains unclear at this time regarding the optimal dosing and duration in these patients and hence needs to be investigated further. Although, extended deep vein thrombosis (DVT) prophylaxis with oral anticoagulation at discharge (for up to 45 days) may be adequate in patients at higher risk for the thromboembolic event [i.e. active malignancy, immobility and elevated D-dimer (DD) level $>$ two times the upper limits of normal] and lower bleeding risk. Thus, using D-dimer (DD) levels as a replaced sign for disease severity and underlying thromboembolic disease, especially, in coronavirus disease 2019 (COVID-19) patients who cannot get dedicated imaging might be valuable.

4.3 Role of Microparticles in COVID-19-Induced Coagulopathy

Microparticles (MPs) are submicron (<1 μ m diameter) membrane-derived exocytic vesicles that are released into the circulation *in vivo* and generated in stored blood products *ex vivo*. Platelets, endothelial cells, erythrocytes, polymorphonuclear leukocytes (PMNL), lymphocytes, and monocytes all produce microparticles (MPs) in a tightly controlled process induced by stimuli such as shear stress, complement activation, proapoptotic stimulation, or cellular damage. Physiologic and pathologic processes are accountable for microvesicle formation in both healthy and diseased persons and the presence of these vesicles has affirmed detrimental for recipients of blood transfusions. Microparticles (MPs) usually express antigens, and contain cell surface proteins, cytoplasmic contents, and nuclear components from their cell of origin. These biomolecules define their composition, characterization, and transfer of biologic information. Microparticles (MPs) have been correlated with thorough pro-inflammatory and procoagulant influences and have been implied as a crucial part of both normal and abnormal coagulation. They also contribute to systemic inflammation and cardiovascular (CV), hematologic, and oncologic disease events. Microparticles (MPs) are generated from their cell of origin by a budding of the cell membrane secondary to disruption of the normal phospholipid (PL) asymmetry, as the distribution of phospholipids (PL) across the membrane bilayer of eukaryotic cells is highly organized and asymmetric.

In the time course of coronavirus disease 2019 (COVID-19) infection, it is possible that the cytokine storm stimulates a strong activation of circulating blood cells including platelets and leukocytes, and also of endothelial cells lining the luminal surface of the vasculature. This activation process causes cell blebbing with the shedding of microparticles (MPs) into the circulation. These microparticles (MPs) accommodate a mixture of membrane proteins similar to those of the cell membrane of origin, and carry proteins and micro ribonucleic acid (miRNA) to transmit the activator signal to distant cells following cell-cell interaction, thereby contributing to the spread of the disease. The target cell activation and the circulating microparticles (MPs) stimulate pro-coagulant responses due to the exposure of tissue factor, and the physiological activator of the coagulation cascade and of negatively-charged phospholipids (PL) such as phosphatidylserine (PS), needed for the establishment of the tenase and prothrombinase coagulation complexes eventually causing thrombin generation. In the context of cardiovascular disease (CVD) patients, vulnerable people in the time course of coronavirus disease 2019

(COVID-19) infection, high concentrations of procoagulant microparticles (MPs) were described in a variety of conditions involving arterial hypertension (HTN), diabetes mellitus (DM), dyslipidemia, obesity, pulmonary embolism (PE), acute coronary syndromes (ACS), heart failure (HF), etc. In a large community-based Framingham Heart study, circulating endothelial microparticles (MPs) concentrations were related to the presence of cardiometabolic risk factors including hypertension (HTN) and metabolic factors, known predisposing factors to severe coronavirus disease 2019 (COVID-19) infections. It has been indicated that circulating microparticles (MPs) of patients with acute coronary syndrome (ACS-MPs), dominantly of activated endothelial cell and platelet origin, induce pro-oxidant, prothrombotic, and pro-inflammatory responses in endothelial cells developing to endothelial senescence and dysfunction. The stimulatory influence of microparticles (MPs) includes the up-regulation of angiotensin-converting enzyme (ACE), which in turn induces a pro-oxidant response in endothelial cells. In addition, the circulating microparticles (MPs) of patients with acute coronary syndrome (ACS-MPs) were observed to carry angiotensin-converting enzyme (ACE) activity, presuming that they originate predominantly from activated endothelial cells. Another report done in microvascular lung endothelial cells and in acute respiratory distress syndrome (ARDS) patients has assured the importance of ACE⁺- endothelial-derived microparticles (MPs) as a probable marker of disease severity. Although the presence of angiotensin-converting enzyme2 (ACE2) was not specifically characterized in those studies, these data propose that circulating microparticles (MPs) are key modulators of various angiotensin-converting enzyme (ACE) activities within the vascular compartment and could therefore function as an important mediator of coronavirus disease 2019 (COVID-19) pathogenicity. In the context of human immunodeficiency virus (HIV) infection, the transfer of the chemokine receptor between cells by membrane-derived microparticles (MPs) was also identified to be a strong mechanism for cellular human immunodeficient virus infection. In line with this paradigm, Data have shed light that exosome, a subtype of extracellular microvesicles shed by endothelial progenitor cells, stimulates survival and function of endothelial cells through angiotensin-converting enzyme2 (ACE2) delivery. Preliminary results in coronavirus disease 2019 (COVID-19) patients requiring hospitalization relate a 2-fold generation of procoagulant microparticles (MPs) with respect to values measured in non-coronavirus disease 2019 (COVID-19) patients.

recognition molecules of the classic, lectin, and alternative pathways. Activated complement generates three major types of effectors:

1-Anaphylatoxins (C3a and C5a), which are vigorous pro-inflammatory molecules that attract and activate leukocytes through interaction with their cognate G-protein–coupled receptors, C3a receptor (C3aR) and C5a receptor (C5aR);

2-Opsonins (C3b, iC3b, and C3d), which decorate target surfaces through covalent bonding to facilitate transport and favor removal of target cells or immune complexes; and

3-The terminal membrane attack complex (MAC, C5b-9) that directly lyses targeted (opsonized) pathogenic agents or damaged self-cells.

These effectors let the complement system have an important role in host defense against bacteria, and in the removal of immune complexes and apoptotic cells, as suggested by the result that persons with inherited and acquired complement deficiencies are susceptible to bacterial infections and immune complex diseases. However, other important functions of complement have been revealed, involving regulation of the adaptive immune response, stimulation of tissue regeneration and angiogenesis, mobilization of stem cells, proper development of the central nervous system (CNS), and control of embryo implantation. Regrettably, the effector function of the system is not focused solely on the targets to be neutralized, but also may include bystander cells. The end results depend on the extent and the persistence of the activation process. The undesired effects of complement activation are controlled by several complement regulators acting at different steps of the cascade and these are found in the fluid phase as well as on the surface of tissue and circulating cells. Unrestricted complement activation easily can overcome the protection of the complement regulators and may lead to extensive host tissue injury. This situation often is encountered in acute pathologic states, such as sepsis or ischemia-reperfusion, or in chronic diseases sustained and amplified by complement, activated by immune complexes, an ongoing inflammatory process, and/or by apoptotic/necrotic cells.

Thrombotic microangiopathies (TMAs) represent a heterogeneous group of syndromes with the same phenotype: a clinical triad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia and organ damage. This heterogeneous group of syndromes with significant clinical overlap comprises two principal existences with distinguished pathophysiology: thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). Besides these two well-defined clinical conditions, the thrombotic microangiopathies (TMA) spectrum

also involves pathologies correlated with underlying conditions, such as drugs, malignancy, scleroderma-associated renal crisis (SRC), systemic lupus erythematosus (SLE), malignant hypertension, transplantation, HELLP syndrome, and disseminated intravascular coagulation (DIC).

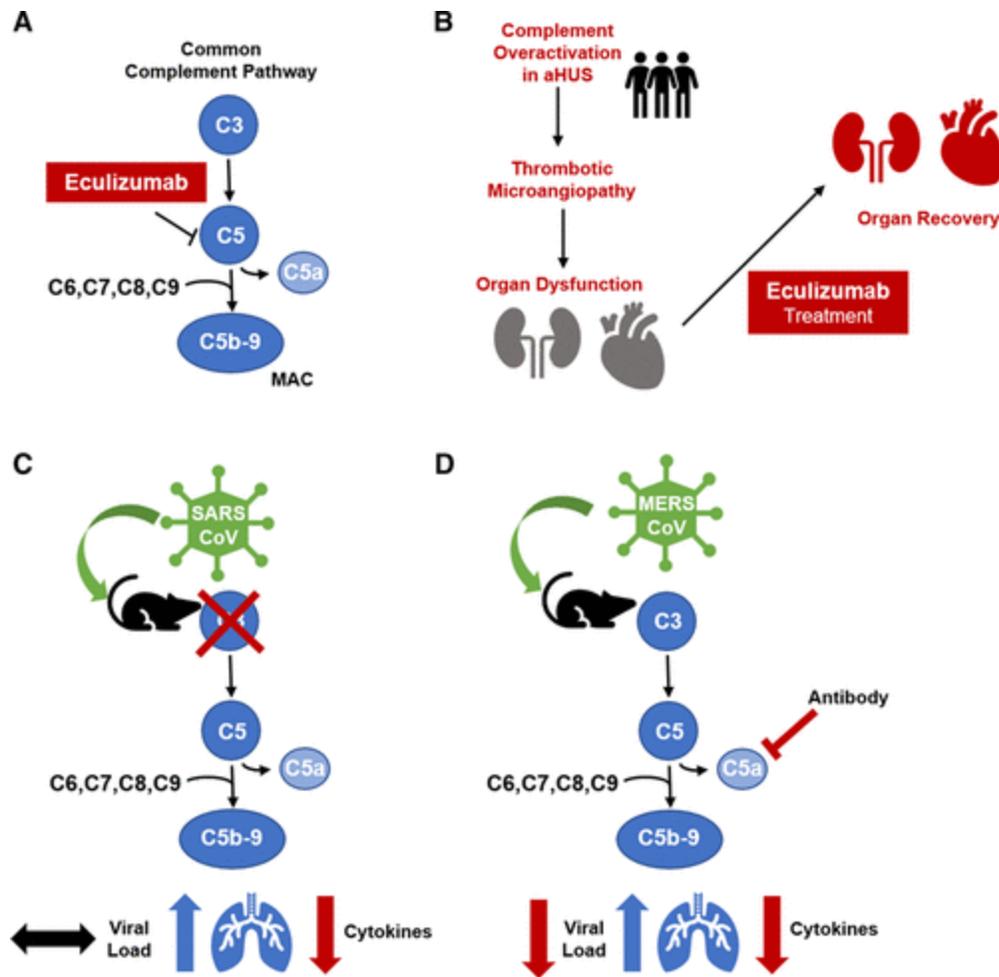
The thrombotic microangiopathies (TMA) are a group of disorders determined by the presence of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. The most common of these is thrombotic thrombocytopenic purpura (TTP), which is a systemic disorder of microvascular thromboses due to deficiency of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). A less common thrombotic microangiopathy (TMA) is the atypical hemolytic uremic syndrome (aHUS), which is a renal vascular thrombotic microangiopathy (TMA) resulted from complement dysregulation. Despite overlapping clinical and pathologic manifestations, thrombotic thrombocytopenic purpura (TTP) and atypical hemolytic uremic syndrome (aHUS) have distinguished etiologies. Thrombotic thrombocytopenic purpura (TTP) is frequently developed from a deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) that is the result of gene mutations or acquired autoantibodies. Atypical hemolytic uremic syndrome (aHUS) is resulted from defects of regulation and/or excessive activation of the alternative complement pathway. The mechanism by which complement dysregulation contributes to atypical hemolytic uremic syndrome (aHUS) is not strictly determined, although complement-mediated glomerular endothelial injury and enhanced complement-mediated platelet activation are likely included. Atypical hemolytic uremic syndrome (aHUS) is a rare form of thrombotic microangiopathy (TMA). Approximately 5%-10% of hemolytic uremic syndrome (HUS) cases are classified as atypical hemolytic uremic syndrome (aHUS) because they are not caused by Shiga toxin producing bacteria or streptococci; these cases comprise a heterogeneous group of patients. The clinical outcome is unfavorable in this group, with death rates as high as 25% during the acute phase and up to 50% of cases progressing to end-stage renal failure (ESRF). Uncontrolled complement activation through the alternative pathway is thought to be the main underlying pathophysiology of atypical hemolytic uremic syndrome (aHUS) and corresponds to all the deleterious findings of the disease. The onset of atypical hemolytic uremic syndrome (aHUS) is generally sudden. Most patients have the complete triad of hemolytic uremic syndrome with anemia, thrombocytopenia, and renal failure, with or without anuria or reduced

urine volume, and proteinuria if diuresis is maintained. Microangiopathic hemolysis is confirmed by the presence of schistocytes, low haptoglobin, and high lactate dehydrogenase (LDH) levels. Patients usually complain of fatigue and general illness. Extrarenal manifestations are observed in 20% of patients and most of them (10%) are related to central nervous system (CNS) involvement. Central nervous system (CNS) involvement is usually manifested by irritability, drowsiness, seizures, diplopia, cortical blindness, hemiparesis/hemiplegia, stupor, or coma. If diagnosis is delayed, life-threatening hyperkalemia, acidosis, and volume overload with arterial hypertension and hyponatremia may be observed. Arterial hypertension is frequent and often severe, due both to volume overload in the case of oliguria/anuria and to hyperreninemia secondary to renal thrombotic microangiopathy (TMA). Cardiac failure or neurological complications (seizures) due to hypertension (HTN) are possible. Myocardial infarction (MI) due to cardiac microangiopathy has been reported in 3% of patients. Distal ischemic gangrene can also occur. Half of children and the majority of adults need dialysis at admission. Multiorgan failure due to diffuse thrombotic microangiopathy (TMA) is present in 5% of patients. Today empiric plasma therapy still is recommended by expert opinion to be used as early as possible in any patient with symptoms of atypical hemolytic uremic syndrome (aHUS). The overall treatment goal remains restoration of a physiological balance between activation and control of the alternative complement pathway. So it is a reasonable approach to block the terminal complement complex with eculizumab in order to prevent further organ injury and increase the likelihood organ recovery. Persistence of hemolysis or lack of improvement of renal function after 3-5 daily plasmaphereses have to be regarded as the major criteria for uncontrolled thrombotic microangiopathy (TMA) even if platelet count has normalized and as an indication to switch the treatment to eculizumab. Eculizumab has changed the future perspectives of patients with atypical hemolytic uremic syndrome (aHUS) and both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved it as life-long treatment. However, there are still some unresolved issues about the follow-up such as the optimal duration of eculizumab treatment and whether it can be stopped or how to stop the therapy. Thrombotic thrombocytopenic purpura (TTP) is a clearly defined entity of the thrombotic microangiopathies (TMA), a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia with red cell fragmentation, thrombocytopenia and organ dysfunction due to disturbed microcirculation. Thrombotic thrombocytopenic purpura (TTP) is characterized by a severe

deficiency of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), an enzyme responsible for physiological cleavage of von Willebrand factor (VWF). Thrombotic thrombocytopenic purpura (TTP) was originally defined pathologically as a systemic disease with widespread von Willebrand factor (VWF)-platelet thrombi in the arterioles and capillaries of multiple organs. Advances in recent years have demonstrated that von Willebrand factor (VWF)-platelet thrombi result from a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency. Autoimmune inhibitors against a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) account for most of the cases, known as acquired thrombotic thrombocytopenic purpura (TTP). Genetic mutations are also found in a small number of patients with a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) deficiency. Triggers and co-factors directing systemic platelet deposition in thrombotic thrombocytopenic purpura (TTP) are not completely understood. Proof that complement activation might play a role in thrombotic thrombocytopenic purpura (TTP) raises the possibility of a cross-talk between a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13)/ultra-large von Willebrand factor (ULVWF) and the complement system. Data presume that the complement system may be an important co-factor included in the pathogenesis of thrombotic microangiopathy (TMA). Excessive alternative pathway activity happened in a considerable number of thrombotic thrombocytopenic purpura (TTP) patients regarding that concurrent defects in a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13) and complement regulation may happen more often than previously mentioned. Further, results demonstrate that excessive alternative pathway activity can be correlated with a thrombocytopenic purpura (TTP)-like thrombotic microangiopathy (TMA) in some patients who do not have severe deficiencies of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13). Organ dysfunction can be severe and life-threatening, and immediate start of appropriate therapy for thrombotic thrombocytopenic purpura (TTP) is necessary to avoid permanent damage or death. Until recently, therapeutic options were limited to symptomatic measures, which were not standardized or based on high scientific evidence. In recent years, not only considerable progress has been made in better diagnosis of thrombotic thrombocytopenic purpura (TTP), but also new therapeutic strategies have been established. Initial treatment is still based on plasma exchange

and symptomatic measures to protect organ function, but new concepts (immunosuppression, targeted anti-VWF or anti-complement therapy, replacement with recombinant enzymes) have recently demonstrated impressive advantages.

Coronavirus disease 2019 (COVID-19) insights have proposed that thrombotic microangiopathy (TMA) could involve pathogenic complement activation. Antibody-antigens complexes could trigger the classical pathway, stimulating the production of C3a and C5a inflammatory markers. Data from murine models have revealed that in the case of the C3 defect, coronavirus disease 2019 (COVID-19) infection was decreased, as witnessed by the decrease of respiratory dysfunction and cytokines levels, in spite of equal virus loads. Along this line, complement inhibition was indicated to be a promising management for severe coronavirus disease 2019 (COVID-19) by decreasing the innate immune-mediated consequences of severe drastic acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections.



Figure(44): Complement inhibition in COVID-19 treatment [Campbell C.; Kahwash R. (2020). Will complement inhibition be the new target in treating COVID-19-related systemic thrombosis?. *Circulation*, 141(22):1739-1741. <https://doi.org/10.1161/CIRCULATIONAHA.120.047419>]

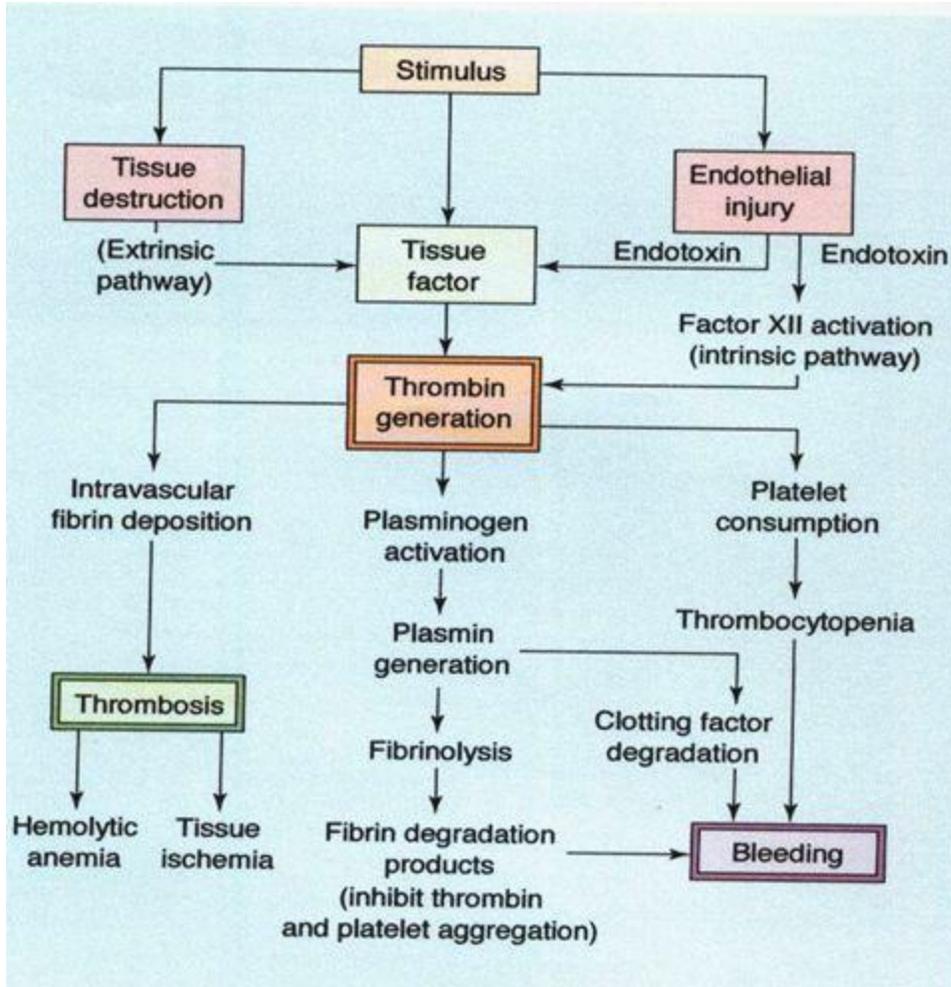
In figure(44): simplified diagram of the common complement pathway. A, Eculizumab blocks C5, inhibiting breakdown into C5a and C5b, which is an integral component of the membrane attack complex (MAC). B, In humans, overactivation of the complement pathway can cause thrombotic microangiopathy, leading to renal and cardiac dysfunction. In atypical hemolytic-uremic syndrome (aHUS), early management with eculizumab reverses organ dysfunction. C, On the basis of the mouse model of severe acute respiratory syndrome coronavirus (SARS-CoV) infection described in a study, lack of the C3 protein causes improved lung function, less cytokine release, and no change in viral load in comparison with mice with an intact complement system. D, On the basis of the mouse model of Middle East respiratory syndrome coronavirus (MERS-CoV) infection described in another study, antibody blockade of C5 leads to improved lung function, less cytokine release, and less viral load compared with untreated mice.

4.5 Disseminated Intravascular Coagulation

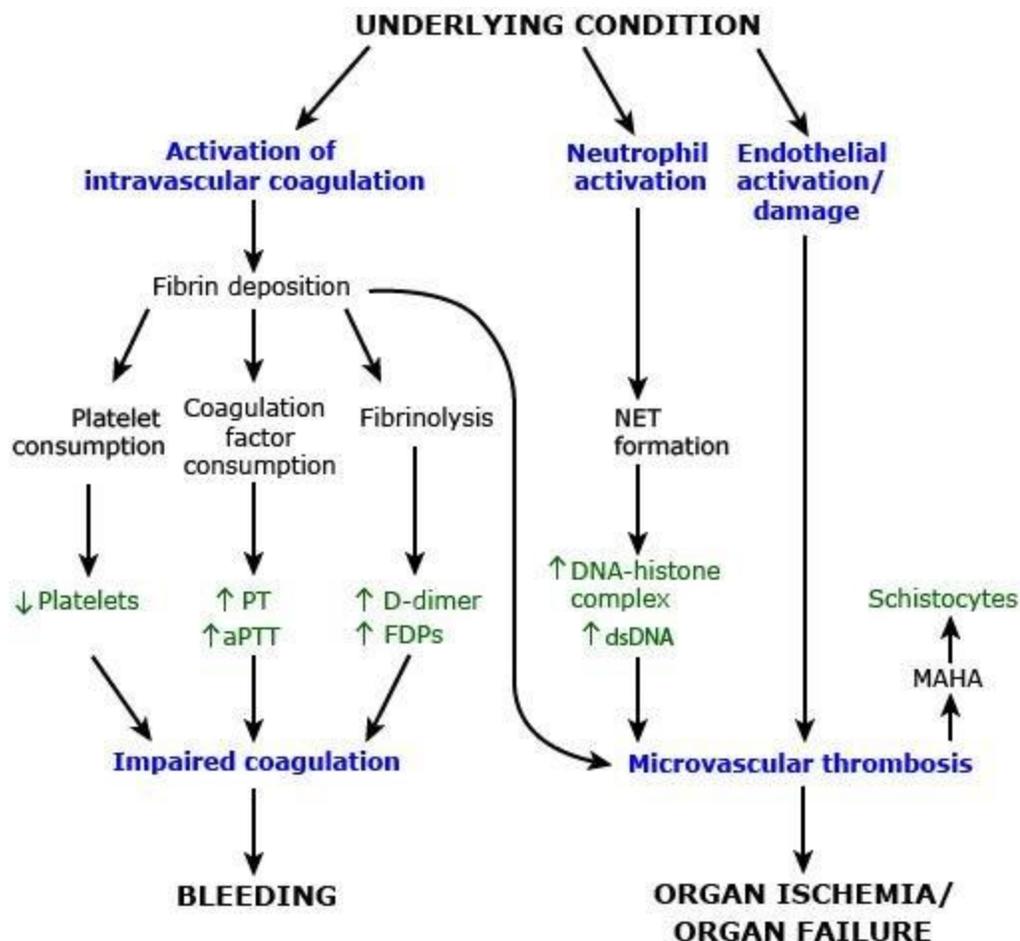
Disseminated intravascular coagulation (DIC) is a serious, life-threatening complication, previously known as consumptive coagulopathy or defibrination syndrome. Disseminated Intravascular Coagulation (DIC) is a disorder that is characterized by the systemic intravascular activation of the coagulation system, simultaneously causing intravascular thrombi, compromising an adequate blood supply to the organs, and to bleeding as consequence of exhaustion of the platelets and coagulation factors. The clinical features of disseminated intravascular coagulation (DIC) involve spontaneous or induced bleeding complications and thrombotic complications, whereas multiple organ failure may be in part a result of intravascular fibrin formation. Further, the generation of multiple proteolytically active enzymes of the clotting cascade may enhance inflammatory activity, which may worsen the systemic inflammatory syndrome. Three factors, commonly termed Virchow's triad, predispose patients to thrombosis: stasis, hypercoagulability (synonym thrombophilia) and blood vessel wall injury. Therefore, any disease process that results in capillary stasis, loss of vascular integrity, or hypercoagulability can result in disruption of the balance between hemostasis and fibrinolysis and subsequently induce disseminated intravascular coagulation (DIC). The conditions that result in disseminated intravascular coagulation (DIC) are the same as those correlated with systemic inflammatory response syndrome and are characterized by activation of cytokine production. The primary mediators are interleukin-1 (IL-1) and interleukin-6 (IL-6) and tumor necrosis factor (TNF), which are secreted from the monocyte-macrophage system. These cytokines induce macrophages (M Φ) to express several procoagulant moieties (mainly tissue factor) on their outer surface. The reactions included in coagulation initiation and amplification require a membrane surface that contains negatively charged phospholipids (PL). Normally, these negatively charged phospholipids (PL) are not expressed on cell surfaces in sufficient concentrations for initiation and propagation of the coagulation cascade to occur. To express the optimal procoagulant lipid surface, potent cell agonists, such as a combination of collagen and thrombin, are required. In addition, increased interleukin-1 (IL-1) concentrations have been seen to elevate platelet reactivity and thrombogenic potential. Actually, disseminated intravascular coagulation (DIC) is both a bleeding and thrombotic disorder. A variety of disorders, involving infections or inflammatory conditions and malignant disease, can cause activation of coagulation. In many cases this activation of coagulation may not result in clinical complications and may not even be

detected by routine laboratory tests. However, if activation of coagulation is sufficiently strong, a lowering platelet count and prolongation of global clotting time may become manifest. The treatment of disseminated intravascular coagulation (DIC) is mainly directed at managing the underlying disease, but supportive care may be necessary. This care may consist of supplementing the depleted coagulation factors and endogenous coagulations inhibitors, and of inhibiting coagulation by various anticoagulant strategies, or by manipulating the fibrinolytic system.

The premier phase of disseminated intravascular coagulation (DIC) consists of formation of microvascular thrombosis in kidneys and lungs with several degree of acute renal failure (ARF) and adult acute respiratory distress syndrome (ARDS). In the second phase, which may follow rapidly, wide-spread activation of fibrinolysis microthrombi but destructs coagulation factors and platelets, all of which are rapidly consumed and depleted. This severe consumption coagulopathy causes uncontrolled bleeding from wounds and spontaneous haemorrhage into tissue, gut and brain. Organ failure due to hypercoagulopathy is considered an important aspect of the pathology of disseminated intravascular coagulation (DIC). Studies have exhibited that several factors such as leukocyte activation, vascular endothelial cell injury and release of chemical mediators are involved in organ failure. Tissue factor can induce the extrinsic pathway of coagulation (the pathway of blood coagulation activated by tissue factor, a protein extrinsic to blood). Its activity in peripheral blood is notably increased upon tissue injury and activation of monocytes. The high tissue factor activity leads to the transformation of prothrombin to form fibrin thrombus. Elevated tissue factor synthesis is regarded the most essential for the onset of disseminated intravascular coagulation (DIC). Tissue factor is considerably elevated in leukemic cells of patients with disseminated intravascular coagulation (DIC) presuming that disseminated intravascular coagulation (DIC) in leukemia is caused by highly increased tissue factor in leukemic cells. Tissue factor is also significantly high in disseminated intravascular coagulation (DIC) patients with solid tumors such as gastric cancer.



Figure(45): Disseminated intravascular coagulopathy (www.google.com)



Figure(46): Disseminated intravascular coagulation pathogenesis [Anadure R.; Jha V. (2019). Handbook of medical emergencies. Department of Medicine Command Hospital (AF) Bangalore. AK Enterprises]

It is acceptable that the cornerstone for the management of patients with disseminated intravascular coagulation (DIC) is the treatment of the underlying disorder. The consumption of coagulation factors and platelets in disseminated intravascular coagulation (DIC) patients elevates the risk of bleeding. Management with plasma or platelet concentrates is evident by the clinical status of the patients and should not be constructed only on the basis of laboratory result. The efficiency of management with plasma and platelets has been observed in patients with low laboratory concentrations who necessitate an invasive step. There is no proof to boost the prophylactic administration of platelets or plasma to patients who are not bleeding and who are not at high risk of bleeding. To adequately correct the coagulation defect, large volumes of plasma may be required, up to 6 units per 24 hours. The administration of coagulation factors concentrates may control this need; however, they may be contaminated with traces of activated

coagulation factors and may therefore be especially mischievous for patients with disseminated intravascular coagulation (DIC). Cryoprecipitate, which contains fibrinogen as well as factor VIII, von Willebrand factor, factor XIII, and fibronectin, is also administered as replacement remedy, without however any support from controlled trials. In theory, interruption of coagulation should be of benefit in patients with disseminated intravascular coagulation (DIC). Really, experimental studies have demonstrated that heparin can partially block the activation of coagulation in cases that are in relation with sepsis or other causes. Appropriate prophylaxis is also required to exclude the risk of venous thromboembolism (VTE). Heparin has been administered for the management of disseminated intravascular coagulation (DIC) since 1959. Animal researches have revealed that this therapy can block the activation of coagulation in experimental septicemia but does not impact mortality. Although the safety of heparin in patients with disseminated intravascular coagulation (DIC) who are vulnerable to bleeding has been disputed, clinical researches have not indicated that management with heparin considerably increased bleeding incidence. Taken together, there is no check of proof in favor of the use of heparin as routine reedy in patients with disseminated intravascular coagulation (DIC), but it is likely useful, especially in those with clinically overt thromboembolism or extensive deposition of fibrin as occurs with purpura fulminans or acral ischemia. Low molecular weight heparin (LMWH) has a decreased risk of bleeding while having at least the same antithrombotic potential as unfractionated heparin. Moreover, the impacts of dalteparine sodium in the therapy of disseminated intravascular coagulation (DIC) have been studied in a multicenter, double-blind, randomized trial. This study showed that dalteparin sodium had greater efficiency than unfractionated heparin in ameliorating bleeding symptoms and in mending subjective organic symptoms score. From this study it may be assumptioned that low molecular weight heparin (LMWH) present the benefit of decreased bleeding complications in comparison with unfractionated heparin in the management of disseminated intravascular coagulation (DIC). Hirudin seemed to be efficient in managing disseminated intravascular coagulation (DIC) in animal studies. The elevated risk of bleeding may probably restrict its use in patients with disseminated intravascular coagulation (DIC). Antithrombin III is a substantial inhibitor of coagulation, and low concentrations in plasma are correlated with increased mortality. The use of this inhibitor in supraphysiologic levela decreased sepsis-related mortality in animals. Several controlled trials, largely in patients with sepsis, have demonstrated advantageous influences in

conditions of improvement of disseminated intravascular coagulation (DIC) and sometimes organ function. The conclusion from the studies is that antithrombin III is capable of improving disseminated intravascular coagulation (DIC), but that interest in conditions of clinical outcome is less assured. The drooping of the protein C system may considerably contribute to the pathophysiology of disseminated intravascular coagulation (DIC). Therefore, supplementation of activated protein C might probably be beneficial. However, activated protein C looks to be more efficient in higher disease severity groups , and a prospective trial in septic patients with relatively low disease severity did not exhibit any benefit of activated protein C. Since tissue factor functions a key role in the initiation of coagulation during disseminated intravascular coagulation (DIC), blocking its action could be valuable in the management of disseminated intravascular coagulation (DIC). In an animal study, the infusion of recombinant tissue factor pathway inhibitor immediately after endotoxin administration considerably prevented the consumption of coagulation factors and platelets. Phase II clinical trials of recombinant tissue factor pathway inhibitor in patients with sepsis exhibited promising findings, but a phase III trial did not exhibit an overall survival benefit in patients who were managed with tissue factor pathway inhibitor.

4.5.1 Disseminated Intravascular Coagulation in COVID-19 Infection

Tang *et al.* (2020) reported that 71.4% of non-survivors and 0.6% of survivors showed proof of disseminated intravascular coagulation (DIC), presumptive of a recurrent manifestation with severe coronavirus disease 2019 (COVID-19). The pathophysiology of disseminated intravascular coagulation (DIC) in the case of sepsis and acute respiratory distress syndrome (ARDS) is multifactorial and includes a complex interplay between cellular and plasmatic elements of the hemostatic system with immune-mediated exhaustion of the coagulation and fibrinolytic systems triggering bleeding and thrombosis in the same suffering individual. Severe infections and sepsis are a leading cause of disseminated intravascular coagulation (DIC), and the pro-inflammatory and immune activation recognized in severe coronavirus disease 2019 (COVID-19) is probably enough to induce disseminated intravascular coagulation (DIC). Such involvement of the hemostatic system in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) astonished the intensive care and hemostasis community due to the elevated probability to progress to disseminated intravascular coagulation (DIC).

4.6 Venous Thromboembolism

Venous thromboembolism (VTE) is the result of a venous blood clot formation which may manifest itself as deep vein thrombosis (DVT) or pulmonary embolism (PE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) are part of the same syndrome. However, important distinguishing factors in terms of epidemiology, diagnosis and management found between the two. Deep vein thrombosis (DVT) is a condition in which the clotting of venous blood happens in a deep vein of an extremity, particularly one of the legs (such as the femoral or saphenous vein) or the pelvis (in the ileofemoral position). There is a considerable increase in the occurrence of deep vein thrombosis (DVT) after the age of 40 years, with an annual incidence in the region of 108 in 100 000 people, making it the third most common cardiovascular disease (CVD). Moreover, pulmonary embolism (PE) is the third most common cause of cardiovascular (CV) mortality, after myocardial infarction (also called heart attack) and strokes. This number is expected to elevate since elderly and obese people are increasing. Local damage to the tunica intima, venous stasis (also called venostasis) and hypercoagulability are major predisposing factors. As a result, events that impair venous return develop to endothelial injury or dysfunction, or develop to hypercoagulability, might lead to deep vein thrombosis (DVT). Deep vein thrombosis (DVT) is the main cause of pulmonary embolism (PE). A venous thrombus usually progresses in one of the lower extremities, likely as a result of the higher incidence of a clot formation in the legs, from where it also extends more proximally. If a portion of the clot ultimately break free (i.e. an embolus), it will firmly reach the inferior vena cava (IVC) and the right-sided cardiac chambers, and thereafter become settled in the pulmonary arterial circulation, resulting in either partial or complete obstruction of pulmonary blood flow [in 4–13% of deep vein thrombosis (DVT) patients]. It is mentioned that approximately half of all patients with deep vein thrombosis (DVT) also have occult pulmonary embolism (PE), and at least 30% of patients with pulmonary embolism (PE) have verifiable deep vein thrombosis (DVT). The consecutive stages of venous thromboembolism (VTE) [namely deep vein thrombosis (DVT) in a calf vein, proximal deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE)] may or may not be symptomatic. The degree or of the thrombosis or embolism defines the progression and extent of the symptoms suffered by the patient. The capacity of the patient to endure such a thrombosis is an additional factor which affects the development of the symptomatology. For example, a moderately sized pulmonary embolism (PE) may found with no

symptoms in a patient who is in good health otherwise, while it may cause severe symptoms, or even death, in a patient who already experiences advanced cardiopulmonary disease.

Virchow offered the notion in 1856 that three different pathophysiological events boost the formation of deep vein thrombosis (DVT). These three events, thereafter termed Virchow's triad, are:

- 1-Damage to the vessel wall;
- 2-Alterations to the venous blood flow;
- 3-Hypercoagulability of the blood.

These are still indicated to be the main causes of thrombus formation. However, more complex pathophysiological events may be included as well. It must also be admitted while taking these complexities into account that early recognition and effective intervention are essential to achieving satisfactory outcomes in the preponderance of patients, and that venous thromboembolism (VTE) is a highly blocking status. Once formed, a thrombus may cause, or undergo, any of the following:

- 1-Remain as an asymptomatic phenomenon.
- 2-Undergo spontaneous lysis.
- 3-Cause an obstruction in the venous circulation.
- 4-Spread to more proximal veins.
- 5-Form an embolus, or
- 6-Act in any combination of the aforementioned ways.

Postthrombotic syndrome (PTS) is a frequent finding following venous thromboembolism (VTE), with an incidence as high as one half of all patients with ileofemoral deep vein thrombosis (DVT) who only received anticoagulation therapy. It progresses as an outcome of thrombus-related damage to the venous valves, which cause subsequent incompetency and retrograde blood flow, i.e. venous reflux. The combination of reflux, combined with the possibility of residual thrombotic obstruction, leads to venous hypertension (HTN) of the limb. This subsequently leads to the symptoms of postthrombotic syndrome (PTS). Risk factors for the development of postthrombotic syndrome (PTS) include the involvement of a proximal vein, the extent of the thrombus, advancing age, obesity, a history of ipsilateral thrombosis and being of the female gender. Possible complications of deep vein thrombosis (DVT) involve pulmonary embolism (PE), indicated to be the most common complication, chronic venous insufficiency

(CVI) and postphlebotic syndrome. The condition may even have a fatal outcome. Moreover, there is an increased risk of recurrent episodes in patients who have suffered a first episode of venous thromboembolism (VTE).

4.6.1 Venous Thromboembolism in COVID-19 Infection

High dimerized plasmin fragment D (D-dimer) concentrations and procoagulant changes in coagulation pathways were observed among cases with severe coronavirus disease 2019 (COVID-19). An increased rate of venous and arterial thrombotic conditions correlated with coronavirus disease 2019 (COVID-19) infection has also been mentioned.

Data from 1026 patients with coronavirus disease 2019 (COVID-19) in China presumed that 40% of patients at the time of hospital admission were indicated at elevated venous thromboembolic (VTE) risk on the basis of a Padua Prediction Score (PPS) ≥ 4 .

A total of 34 consecutive patients were included in a study performed by Nahum *et al.* (2020). Coronavirus disease 2019 (COVID-19) diagnosis was confirmed with polymerase chain reaction on nasopharyngeal swabs of 26 patients (76%); 8 patients (24%) had a negative result on polymerase chain reaction but had a typical pattern of coronavirus disease 2019 (COVID-19) pneumonia on chest computed tomography scan. Mean age was 62.2 years, and 25 patients (78%) were men. Major comorbidities were diabetes mellitus (DM) [15 (44%)], hypertension (HTN) [13 (38%)], and obesity body mass index was 31.4kg/m². Overall, 26 patients (76%) required norepinephrine at admission, 16 (47%) required prone positioning, and 4 (12%) required venous extracorporeal membrane oxygenation. Only 1 patient (3%) received anticoagulant therapy before hospitalization. Deep vein thrombosis (DVT) was found in 22 patients (65%) at admission and in 27 patients (79%) when the venous ultrasonograms performed 48 hours after intensive care unit (ICU) admission were included. Eighteen patients (53%) had bilateral thrombosis, and 9 patients (26%) had proximal thrombosis. The patients had high concentrations of D-dimer (DD), fibrinogen, and C-reactive protein (CRP). Mortality of patients with coronavirus disease 2019 (COVID-19) admitted to intensive care units (ICUs) has been seen to be elevated, at 50%. Frequent venous and arterial thrombotic conditions have been recorded, with rates from 27% to 69% of peripheral venous thromboembolism (VTE) and up to 23% of pulmonary embolism (PE). The occurrence of pulmonary embolism (PE) might be favored by deep vein thrombosis (DVT). In view of the elevated percent (i.e, 79%) of deep vein thrombosis (DVT) mentioned in this study, prognosis might be ameliorated with early detection

and a prompt start of anticoagulant therapy. Despite anticoagulant prophylaxis, 15% of patients suffered deep vein thrombosis (DVT) only 2 days after intensive care unit (ICU) admission.

While a number of literature have shown that coagulation dysfunction is predominant in patients with severe novel coronavirus pneumonia, only a few studies have concentrated on the predominance of venous thromboembolism (VTE) in coronavirus disease 2019 (COVID-19) patients. The first retrospective registry cohort of 25 acute pulmonary embolism (APE)-suspected coronavirus disease 2019 (COVID-19) patients in China with computed tomography (CT) pulmonary angiography revealed that those with affirmed acute pulmonary embolism (APE) (n = 10) had D-Dimer (DD) concentrations higher than 7000 ng/mL. In 91 hospitalized patients with severe coronavirus disease 2019 (COVID-19), venous thromboembolism (VTE) patients accounted for 25%, were older, and exhibited elevated coagulopathy abnormalities and thrombotic susceptibility [lower lymphocytes count, longer activated partial thromboplastin time (aPTT), and higher D-Dimer concentrations]. A study reported a 31% occurrence of thrombotic complications in spite of systematic thrombosis prophylaxis and no disseminated intravascular coagulation (DIC) development among a cohort of 184 intensive care unit (ICU) patients.

Helms *et al.* (2020) reported occurrence of 42.6% of thrombotic complications, mainly acute pulmonary embolism (APE) (16.7%) in 150 activated partial thromboplastin time (aPTT) patients admitted in intensive care unit (ICU) for hypoxemic acute respiratory failure. Twenty-eight out of twenty-nine patients (96.6%) receiving continuous renal replacement therapy experienced circuit clotting, and three thrombotic occlusions of centrifugal pump occurred in 12 patients supported by extracorporeal membrane oxygenation. Most patients (>95%) had high D-dimer (DD) concentrations and fibrinogen, while no patient suffered disseminated intravascular coagulation (DIC). Most importantly, despite anticoagulation, patients with acute respiratory distress syndrome (ARDS) secondary to coronavirus disease 2019 (COVID-19) experienced notably more thrombotic complications in comparison with non- coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) patients (11.7% vs. 2.1%, $p < 0.008$). The authors supposed in their discussion appealing mechanisms of coagulopathy and pathogenesis of thrombosis in severe hypoxemic coronavirus disease 2019 (COVID-19) patients. They underlined the primary importance of:

(a)- Obvious endothelial inflammation with very high concentrations of Von Willebrand factor antigen (a protein helping blood clotting) and factor VIII [a blood protein (a beta globulin) involved in clotting];

(b)- Hypotheses considering profound hypoxemia in the pulmonary capillaries that may cause vasoconstriction decreasing blood flow and stimulating vascular occlusion; and finally

(c)- The intriguing high frequency of positive lupus anticoagulant that was detected in 50 patients out of the 57 tested (87.7%). Lupus anticoagulant is an immunoglobulin that binds to phospholipids (PL) and proteins associated with the cell membrane. Lupus anticoagulant is a misnomer, as it is actually a prothrombotic antibody. Lupus anticoagulant in living systems leads to an increase in inappropriate blood clotting.

Altogether, the increased presence of venous thromboembolism (VTE) holds true for coronavirus disease 2019 (COVID-19) patients, most recognizable among those with severe disease.

4.7 Antithrombotic Therapy and COVID-19-Related Coagulopathy

Regarding antithrombotic options, the International Society of Thrombosis and Haemostasis (ISTH) consensus statement recommended prophylactic dose low-molecular weight heparin (LMWH) in all patients (including non-critically ill) who required hospital admission for coronavirus disease 2019 (COVID-19) infection, in the absence of any contraindications (active bleeding and/or platelet count less than $25 \times 10^9/L$). Heparin represents the typical thromboprophylactic and antithrombotic regimen endorsed by contemporary guidelines for patients hospitalized with coronavirus disease 2019 (COVID-19) related diseases. Tang *et al.* (2020) described that anticoagulant therapy mainly with low-molecular weight heparin (LMWH) seemed to be correlated with a better prognosis in 449 severe coronavirus disease 2019 (COVID-19) patients meeting sepsis induced coagulopathy (SIC) criteria ≥ 4 or with markedly elevated D-dimer (DD) levels (greater than six-fold at the upper limit of normal). In this study, however, only 99 patients (22%) had received prophylactic heparin. Heparin therapy has several advantages:

1-It represents, in the time of a pandemic, an easily available anticoagulant therapy, given the initial concerns regarding drug shortages;

2-Incremental anti-inflammatory effects have been reported and it may mitigate cytokine storms in severe coronavirus disease 2019 (COVID-19) patients;

3-Experimental models reported a potential antiviral role of heparin still to be confirmed in clinical practice and in the setting of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection; and finally

4-There is currently no evidence from randomized clinical trials that any potential therapy improves outcomes in patients with either suspected or confirmed coronavirus disease 2019 (COVID-19).

Given the high prevalence of lupus anticoagulant and changes of standard hemostasis parameters in this certain pathology, monitoring of heparin should not rely on activated partial thromboplastin time (aPTT), but solely on anti-Xa activity, which is an assay designed to measure plasma heparin (unfractionated heparin (UH) and low molecular weight heparin (LMWH)) concentrations and to monitor anticoagulant therapy. A fundamental body of evidence proposes how heparin can be necessary in selected high-risk coronavirus disease 2019 (COVID-19) patients.

5.COVID Toes

The term COVID toes is recognized when patients who have the coronavirus disease 2019 (COVID-19) virus present with extremity symptoms. These patients may or may not carry an official diagnosis of coronavirus disease 2019 (COVID-19). These patients may present with a digital ischemic appearance of purplish or red lesions on their toe(s) that are frequently painful. However, one could easily confuse the presentation of such symptoms for frostbite, Raynaud's disease or chilblains. Most reports of such a phenomenon are noticed mostly in younger people with or without other symptoms.

The precise cause of these symptoms is not known. One prominent theory includes a probably underrecognized vascular component to the disease. The coronavirus disease 2019 (COVID-19) virus is known to attack cells in the lung via the angiotensin-converting enzyme 2 (ACE2) receptor. The angiotensin-converting enzyme 2 (ACE2) receptor is not restricted to just the lungs. It is also present in other organs involving the heart, kidney, and intestinal tract. The angiotensin-converting enzyme 2 (ACE2) receptor is also present on endothelial cells that line vessels throughout the whole circulatory system, comprising the very small vessels in the toes. Researchers out of the Pathology and Cardiology Departments from University Hospital Zurich,

in Zurich, Switzerland consider that the virus attaching in these small vessels causes the vascular symptoms now known as COVID toes.

In a report out of China, Zhang and colleagues discussed seven critical patients with the coronavirus disease 2019 (COVID-19) virus, who had an average age of 59 years and clinical symptoms involving finger/toe cyanosis, skin bullae, and dry gangrene to the digits. These patients also reportedly had prolonged prothrombin time (PT), an elevated D-dimer (DD) concentration and diagnosed disseminated intravascular coagulation (DIC). Five of the seven patients ended up dying from the coronavirus disease 2019 (COVID-19) virus.

However, most reports on COVID toes come from various news media and look to be in younger age groups with many of these patients not having any respiratory symptoms. A press release from the French National Union of Dermatologists and Venereologists warns of skin manifestations of coronavirus disease 2019 (COVID-19) that the group classifies as acrosyndromes (i.e., associated with vasomotor disorders). This group determines symptoms as the appearance of pseudo-frostbite, a sudden appearance of persistent and sometimes painful redness, and transient hive lesions on the fingers and/or toes.

In a case study out of Italy from the International Federation of Podiatrists, Mazzotta and Troccoli mention self-healing lesions in children and adolescents, and think the etiology is vascular in nature. It is stated that the presentation is similar to chilblains but the etiology is vascular, not thermal, in nature. It is attributed to small vessel blockages as emerging proof refers to the coronavirus disease 2019 (COVID-19) virus contributing to a hypercoagulable state.

Physicians in France and Spain also report lower extremity symptoms in various younger populations. As the aforementioned report out of China shows, COVID toe is not limited to the young but may possibly be the only symptom present in a patient with the coronavirus disease 2019 (COVID-19) virus.



Images (1,2) (www.google.com)

On April 6, 2020, a 13-year-old female presented to the office complaining of severely painful reddish and purple lesions to her toes bilaterally [see images (1, 2)]. Her symptoms began several weeks earlier and a specialist physician originally treated this as cellulitis with an antibiotic. The condition eventually spread to multiple toes with blisters developing on some of the lesions [see images (3,4)]. The pain was so severe the patient could not tolerate shoes.



Images (3,4) (www.google.com)

The initial presentation was consistent with Raynaud's disease as it was almost certainly some type of vasculopathy. The patient denied trauma and did not exhibit any signs or symptoms of infection. The patient had palpable dorsalis pedis and posterior tibial pulses, a sluggish capillary refill time and toes cool to the touch consistent with Raynaud's disease. The family shared this suspicion as they noted a family history of Raynaud's disease. At this time, this seemed to be the most likely diagnosis. It was dispensed a prescription for nitroglycerin paste for the patient's pain and symptoms.



Images (5,6) (www.google.com)

Ten days later, the patient reported an improvement in her symptoms and clinical presentation, which was confirmed with pictures sent by the patient's mother [see images (5,6)].

At this point in time, similar symptoms began to appear in reports of children around the world connected to coronavirus disease 2019 (COVID-19). Further questioning of the patient and her mother confirmed that the patient had a serious flu-like condition the previous month. There were also siblings in the household who had exhibited a fever, sore throat and cough approximately two weeks in duration. These siblings also tested negative for influenza and strep. When the patient began experiencing exhaustion and shortness of breath, she never had testing for influenza due to her siblings' negative status. She did, however, test negative for mononucleosis. Her pediatrician prescribed an antibiotic and an inhaler. She did not receive a coronavirus disease 2019 (COVID-19) test.

Anecdotally, it was learned through social media of a 13-year-old male from the same school of the first patient who exhibited similar symptoms and painful complaints about his toes. His symptoms had a six-week duration and consisted of erythema and pain to his toes [see images (7,8)]. The erythema eventually progressed to purpuric-appearing lesions on all of the toes very similar in nature to the previous patient.



Images (7,8) (www.google.com)

His pediatrician prescribed oral steroids three weeks after the initial presentation of symptoms and this treatment eventually allowed the patient to tolerate shoe gear. This patient displayed no clinical symptoms of the coronavirus disease 2019 (COVID-19) virus and had no other pertinent findings such as fever or dermatological lesions elsewhere. Accordingly, the patient was not tested for coronavirus disease 2019 (COVID-19) at that time.

The aforementioned cases provide anecdotal evidence of two patients in the same geographic area who presented with symptoms that are possibly consistent with COVID toes albeit without a confirmed diagnosis of the coronavirus disease 2019 (COVID-19) virus. Both patients were in their early teens and early reports have proposed that COVID toes seem to be most prevalent in

this age group. Both patients described color changes and a painful presentation with four to six weeks of symptoms before noting improvement. Only one of the patients exhibited crusted lesions as noted in an aforementioned report out of France. One patient had other symptoms suggestive of the coronavirus disease 2019 (COVID-19) virus and the other patient did not. This is consistent with similar findings in another recent report out of Spain that noted COVID toe in both symptomatic and asymptomatic patients. While these authors recommended topical corticosteroid treatment for patients with these lesions, other cautions exist regarding the use of systemic steroids in patients with the COVID-10 virus so practitioners should exercise caution in this population.

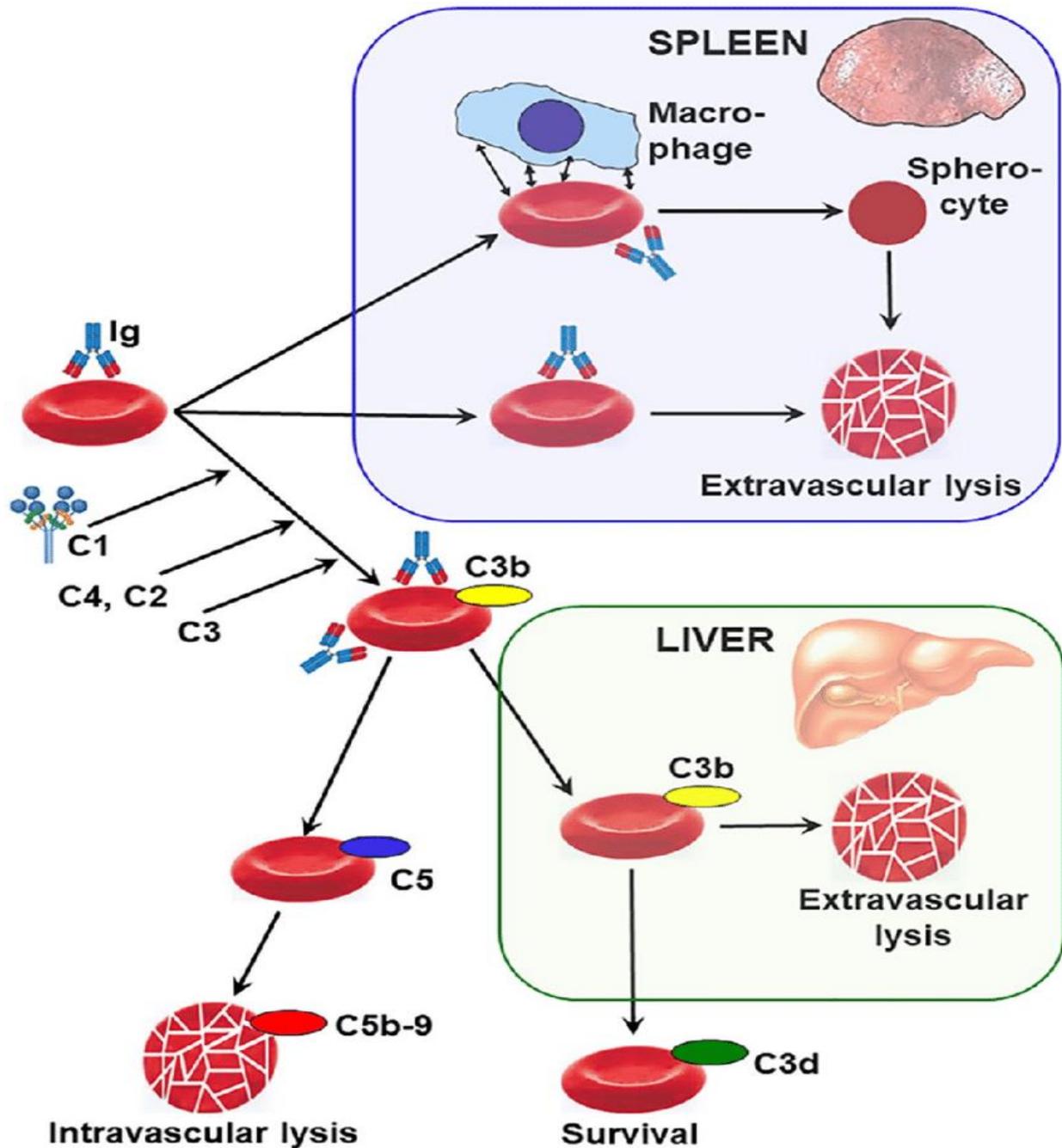
For the presented patients above, improvement occurred with nitroglycerin paste and topical steroids respectively. It may also suggest that similar patients exercise caution and self-quarantine due to the possible association with the coronavirus disease 2019 (COVID-19) virus.

There is evidence to propose that the two aforementioned patients who presented with pain, red-to-blue colored lesions and vasculitis to their toes could possibly have had COVID toes. The symptom timeline along with the presence of the virus in the United States supports this. In fact, more research is necessary to specifically correlate known coronavirus disease 2019 (COVID-19) status and COVID toe presentation before it can be confirmed the true etiology and association of COVID toes.

6.Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia (AIHA) is characterised by an increased breakdown of red blood cells (RBCs) due to autoantibodies (auto-Ab's) with or without complement activation. The diagnostic characteristics of autoimmune hemolytic anemia (AIHA) comprise the combination of clinical and laboratory signs of red blood cells (RBCs) hemolysis together with the detection of autoantibodies (auto-Ab's) and/or complement deposition on red blood cells (RBCs) as particularly appeared by a positive direct antiglobulin test (DAT) also called direct Coombs test. A negative direct Coombs test using standard techniques does not exclude the diagnosis of autoimmune hemolytic anemia (AIHA). In more than 50% of the patients the development of autoimmune hemolytic anemia (AIHA) is combined with an underlying disease [secondary autoimmune hemolytic anemia (AIHA)], but can happen without any proof of an underlying disorder [idiopathic or primary autoimmune hemolytic anemia (AIHA)]. Dependent on the

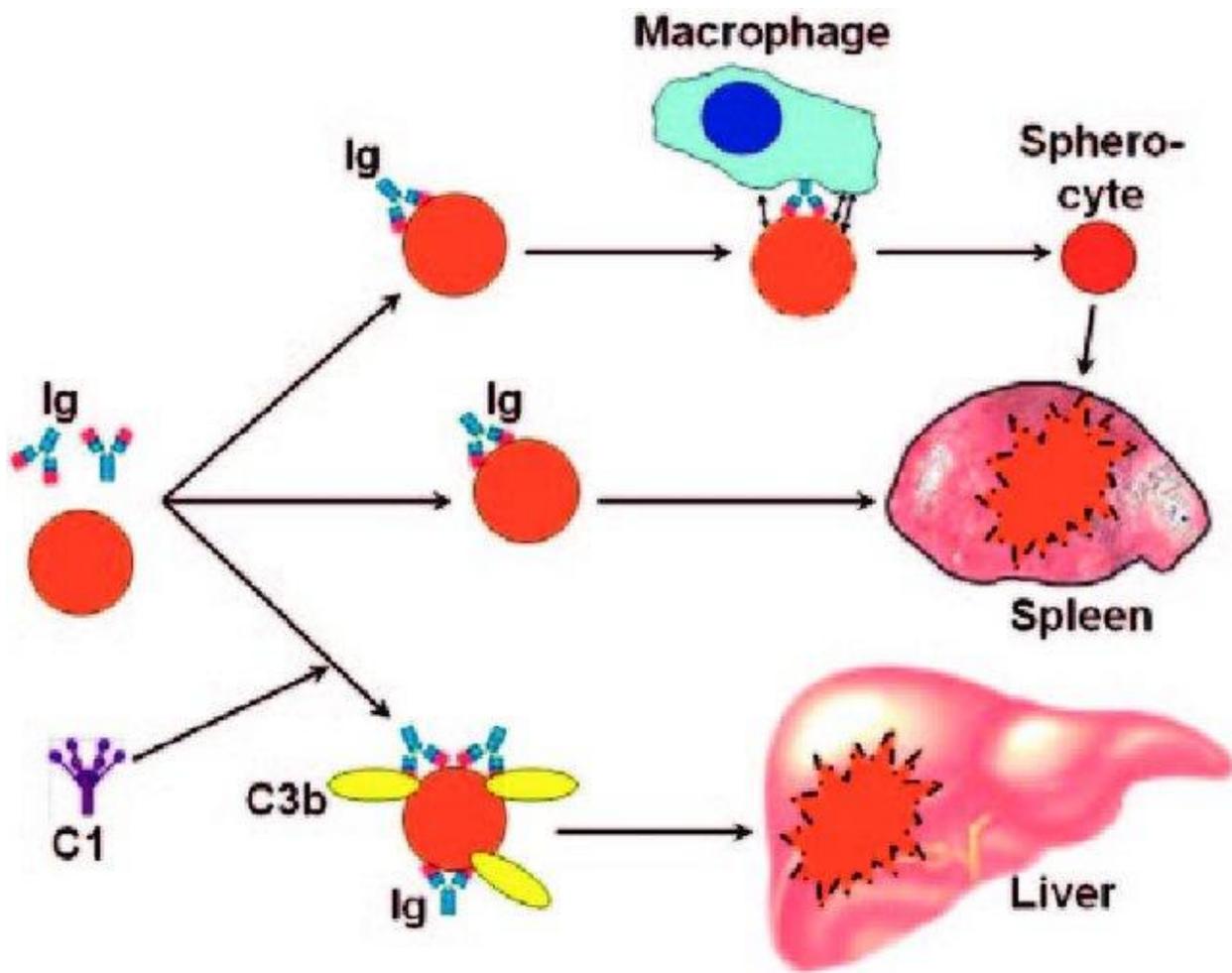
optimal temperature for autoantibody (auto-AB) binding to red blood cells (RBCs), autoimmune hemolytic anemia (AIHA) is divided into a warm antibody autoimmune hemolytic anemia (WA-AIHA), cold antibody autoimmune hemolytic anemia (CA-AIHA) or autoimmune hemolytic anemia (AIHA) due to biphasic autoantibody (paroxysmal cold haemoglobinuria, PCH). With an incidence of 1:100,000 warm antibody autoimmune hemolytic anemia (WA-AIHA) is a scarce disease, the incidence of cold antibody autoimmune hemolytic anemia (CA-AIHA) is even lower (1:1,000,000). In contrast, 10% of patients experiencing lupus erythematosus progress to an autoimmune hemolytic anemia (AIHA). On occasion, lymphoma is complicated by autoimmune hemolytic anemia (AIHA), but it can also be a herald of a lymphoma that has not yet been diagnosed. This is proved by certainty that 18% of patients with primary autoimmune hemolytic anemia (AIHA) progress to overt lymphoma at a subsequent time. Lymphoma is cancer beginning in infection-fighting cells of the immune system, called lymphocytes; lymphocytes are found in the lymph nodes, spleen, thymus, bone marrow, and other parts of the body; when experiencing lymphoma, lymphocytes change and grow out of control.



Figure(47):Mechanism of hemolysis in warm antibody autoimmune haemolytic anaemia [Berentsen S.; Hill A.; Hill Q.; Tvedt T.; Michel M. (2019). Novel insights into the treatment of complement-mediated hemolytic anemias. *Therapeutic Advances in Hematology*, 10:1-20. DOI: [10.1177/2040620719873321](https://doi.org/10.1177/2040620719873321). CC BY-NC 4.0]

In figure (47): complement-mediated hemolytic anemias can either be resulted from deficiencies in regulatory complement components or by autoimmune pathogenesis that arouses inadequate complement activation. In paroxysmal nocturnal hemoglobinuria [PNH, a rare acquired, life-threatening disease of the blood; characterized by destruction of red blood cells (RBCs)

(hemolytic anemia), blood clots (thrombosis), and impaired bone marrow function (not making enough of the three blood components)]hemolysis is completely complement-driven. Hemolysis is also considered to be complement-dependent in cold agglutinin disease (CAD) and in paroxysmal cold hemoglobinuria (PCH, a rare blood disorder where body's immune system producing antibodies that destroy red blood cells (RBCs); occurring when the person exposed to cold temperatures), whereas warm antibody autoimmune hemolytic anemia (WA-AIHA) is a partially complement-mediated disorder, relying on the subtype of warm antibody autoimmune hemolytic anemia (WA-AIHA) and the range of complement activation. Therapeutic terminal complement inhibition using eculizumab has revolutionized the remedy and prognosis in paroxysmal nocturnal hemoglobinuria (PNH) but has evidenced less efficient in cold agglutinin disease (CAD). Upstream complement modulation seems to be a highly promising remedy, and two such agents have entered phase II and III trials. Of these, the anti-C1s monoclonal antibody sutimlimab has exhibited favorable activity in cold agglutinin disease (CAD), while the anti-C3 cyclic peptide pegcetacoplan seems to be promising in paroxysmal nocturnal hemoglobinuria (PNH) as well as cold agglutinin disease (CAD), and may also have a therapeutic possibility in warm antibody autoimmune hemolytic anemia (WA-AIHA).



Figure(48):Erythrocyte destruction in warm-antibody mediated autoimmune hemolytic anemia [Berentsen S. (2015). Role of complement in autoimmune hemolytic anemia. *Transfusion Medicine and Hemotherapy*, 42:303-310. DOI:[10.1159/000438964](https://doi.org/10.1159/000438964)]

In figure(48): erythrocyte destruction in warm-antibody mediated autoimmune hemolytic anemia. Ig = Immunoglobulin; C = complement.

In warm antibody autoimmune hemolytic anemia (WA-AIHA), polyclonal autoantibodies with a temperature optimum at 37°C bind to the red blood cell (RBC) surface. The included antibody class is most frequently immunoglobulin G (IgG) (mostly IgG1 or IgG3) but can be immunoglobulin A (IgA) or warm-reactive immunoglobulin M (IgM) combined with immunoglobulin G (IgG), or, rarely, immunoglobulin M (IgM) or immunoglobulin A (IgA) alone. Almost 50% of warm antibody autoimmune hemolytic anemia (WA-AIHA) cases are secondary to (i.e. associated with or caused by) other diseases, involving lymphoproliferative disorders (LPDs), autoimmune diseases, or other immune dysregulation involving common

variable immunodeficiency (CVID). The remaining 50% are designated as primary. Chronic lymphocytic leukemia (CLL) is the most commonly associated lymphoproliferative disorder (LPD).

The immune-initiated red blood cell (RBC) breakdown in warm antibody autoimmune hemolytic anemia (WA-AIHA) is not totally complement-mediated. Depending on the direct antiglobulin test (DAT) pattern, complement is included in 28–65% of warm antibody autoimmune hemolytic anemia (WA-AIHA). Main noncomplement mechanisms are macrophage-inflicted membrane damage with subsequent formation of spherocytes, which are vulnerable to destruction in the red pulp of the spleen and, concomitantly or alternatively, phagocytosis of immunoglobulin (Ig)-opsonized red blood cells (RBCs) by the mononuclear phagocytic system, which at most happens in the spleen. On red blood cells (RBCs) opsonized with immunoglobulin M (IgM) or heavily coated with immunoglobulin G (IgG), the antigen-antibody (Ag-Ab) complex will initiate the complement control proteins (CCP, proteins interact with components of the complement system). Immunoglobulin G (IgG) is a weaker complement activator than immunoglobulin M (IgM). Of the immunoglobulin G (IgG) subclasses, it is mainly immunoglobulin G3 (IgG3), and to a lesser extent immunoglobulin G1 (IgG1), that is capable of activating complement, while immunoglobulin G2 (IgG2) is an even weaker activator. Immunoglobulin G4 (IgG4) and immunoglobulin A (IgA) do not elicit the complement system. However, immunoglobulin A (IgA)-mediated warm antibody autoimmune hemolytic anemia (WA-AIHA) can be fulminant, probably as a result of concomitant immunoglobulin M (IgM) participation. Complement control proteins (CCP) activation will leave the red blood cells (RBCs) opsonized with C3b and, therefore, susceptible to extravascular hemolysis by the mononuclear phagocytic system (MPS), primarily by Kupffer cells (KCs) in the liver, while intravascular hemolysis mediated by the terminal pathway is prominent only in severe cases. The explanation is possibly the protective effect of the CD55 and CD59 which, unlike in nocturnal hemoglobinuria (PNH), are intact in autoimmune hemolytic anemia (AIHA).

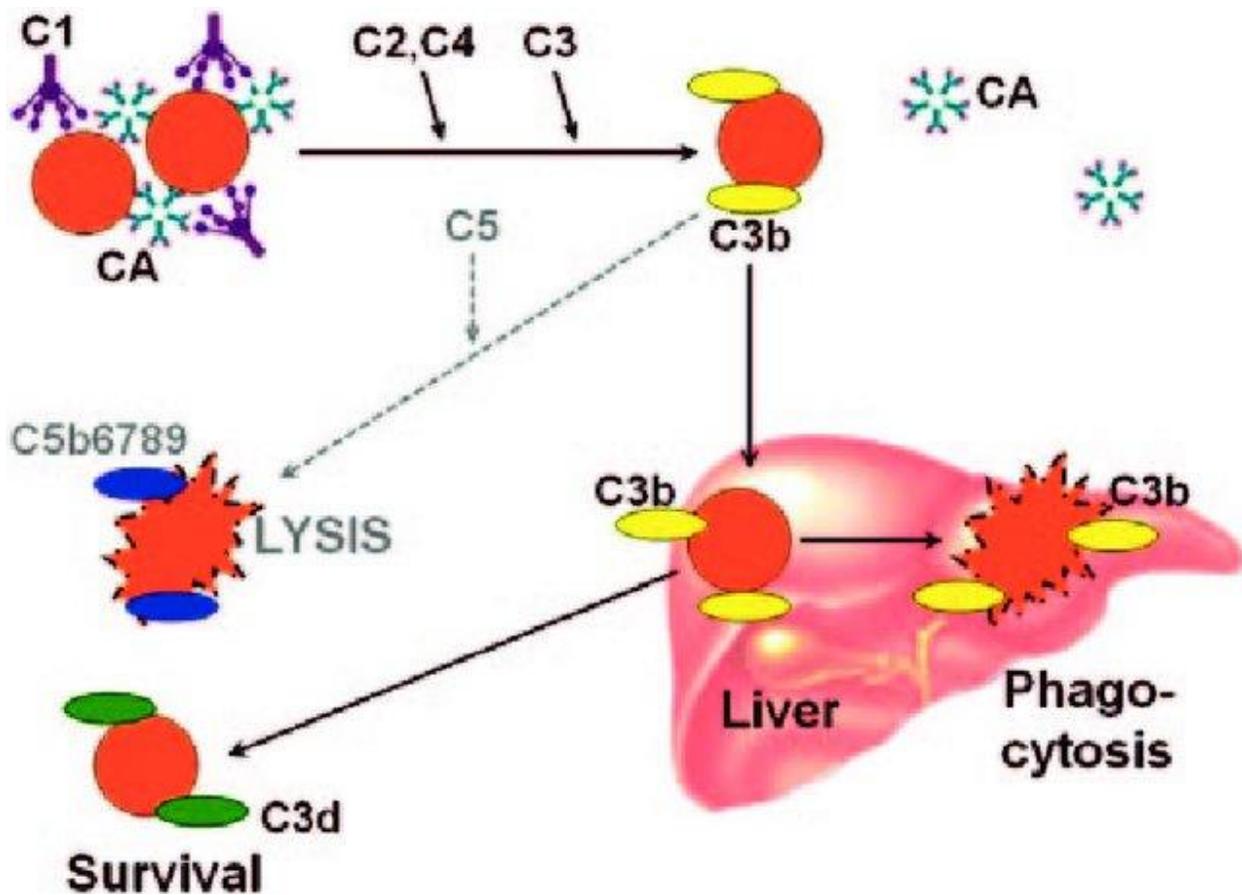
Cold agglutinins (CAs) are autoantibodies, in most cases of the immunoglobulin M (IgM) class, that agglutinate red blood cells (RBCs) upon binding to the cell surface at an optimum temperature of 3–4°C. Most cold agglutinins (CAs) in cold agglutinin disease (CAD) are specific for the surface carbohydrate antigen termed I. Rare specificities include anti-Pr or anti-i.

Primary cold agglutinin disease (CAD) is determined by chronic hemolysis, a considerable cold agglutinin (CA) titer (usually defined as ≥ 64) at 4°C, typical findings by the direct antiglobulin test (DAT), and the absence of an underlying specific infection or overt (i.e. clinically or radiologically detectable) malignancy.

Anemia in cold agglutinin disease (CAD) is frequently mild to moderate, and in some cases fully compensated hemolysis happens. A large number of patients, however, experience severe anemia. In a descriptive study of 86 unselected patients, the median hemoglobin level was 8.9g/dl (range, 4.5–15.6g/dl; lower tertile, 8.0g/dl). Up to 90% of the patients according to a Norwegian study (possibly less in warmer climates) experience cold-induced circulatory symptoms affecting acral parts of the body (i.e., belonging to the extremities of peripheral body). Acrocyanosis is the most common circulatory symptom, but Raynaud-like phenomena can also occur and in some patients, this can be disabling. The presence and severity of acrocyanosis does not relate to the severity of anemia. Estimates on transfusion requirements exhibit large variations, likely due to patient selection and variable transfusion criteria. In unselected cohorts, approximately half of the patients received transfusions.

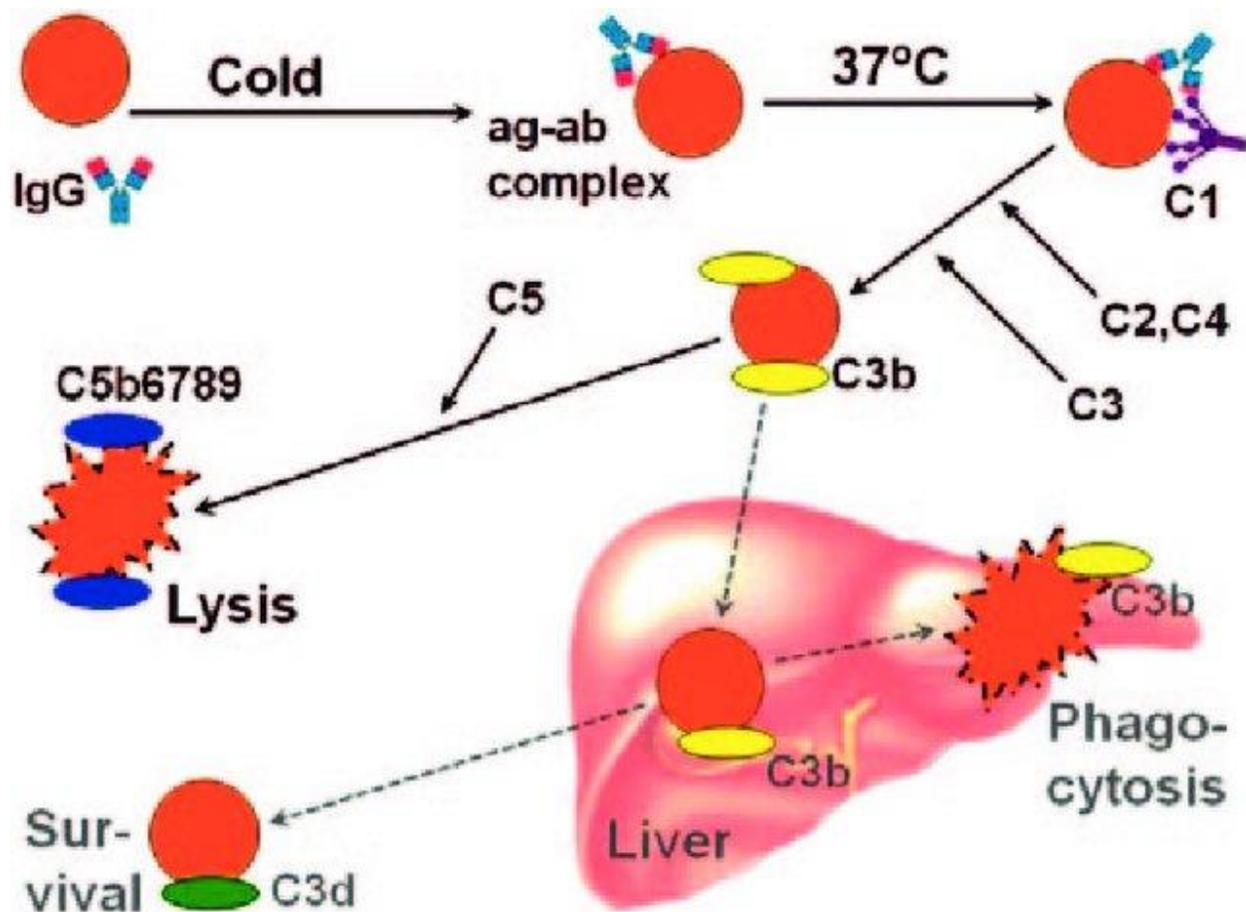
Cold agglutinins (CAs) bind to the red blood cell (RBC) surface at temperatures below the central body temperature. These temperatures are normally found in acral parts of the body. This leads to red blood cell (RBC) agglutination and, more often, ischemic symptoms from the capillary circulation. These symptoms are not complement-mediated. In more than 90% of patients with cold agglutinin disease (CAD), the cold agglutinins (CA) is an immunoglobulin M kappa (IgM κ) and therefore a potent activator of the complement control proteins (CCP). Cold agglutinins (CAs) of the immunoglobulin G (IgG) class are scarce but descriptions that they lead to hemolytic anemia have been persuasive. Some differences from typical, immunoglobulin M (IgM)-mediated cold agglutinin disease (CAD) may refer to a different mechanism of hemolysis in the immunoglobulin G (IgG)-mediated cases, for example, some of the cases have been mentioned to respond to splenectomy (a surgical operation involving removal of the spleen), which is not efficient in cold agglutinin disease (CAD) of the immunoglobulin M (IgM) type. Infrequently, cold agglutinins (CAs) of the immunoglobulin A (IgA) class have also been recognized, although immunoglobulin A (IgA) is not expected to activate complement. A study shows that some patients reported as having monoclonal immunoglobulin A (IgA) with cold agglutinin (CA) activity did not have hemolysis. Another patient had clinical cold agglutinin

disease (CAD) together with monoclonal immunoglobulin A (IgA) but turned out to have two independent clonal disorders, indicating that the cold agglutinin (CA) was not identical to the clonal immunoglobulin A (IgA). This means that immunoglobulin A (IgA)-mediated cold agglutinin disease (CAD) does not occur. Upon the binding of immunoglobulin M-cold agglutinin (IgM-CA) to its antigen, activation of the complement control proteins (CCP) leaves the red blood cells (RBCs) opsonized with C3b and, therefore, susceptible to extravascular hemolysis by the mononuclear phagocytic system; this dominantly happens in the liver. On the surviving red blood cells (RBCs), C3b is metabolized to C3d, which most probably saves the cell against further phagocytic attack. The terminal pathway is likely not considerably activated in mild and steady-state cold agglutinin disease (CAD), but has been shown to be active in severe disease and acute exacerbations. Part of the interpretation for the restricted role of the terminal pathway is maybe the protective impact of the membrane-bound physiologic inhibitors CD55 and CD59, which are intact in cold agglutinin disease (CAD). A unique phenomenon in cold agglutinin disease (CAD) is an exacerbation of hemolytic anemia during febrile infections [medical term for elevated body temperature (or a fever)] and other conditions with acute-phase reaction, originally described as paradoxical hemolysis and later found to occur in at least 70% of the patients. Acute-phase proteins (APPs) are a class of proteins whose plasma concentrations increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation. This response is called the acute-phase reaction (also called acute-phase response). The acute-phase reaction characteristically involves fever, acceleration of peripheral leukocytes, circulating neutrophils and their precursors. The constant complement consumption during steady-state disease leads to low serum levels of C3 and, particularly C4, which looks to be rate-limiting for complement control proteins (CCP)-dependent hemolysis. Acute-phase reaction has been shown to increase the production of these components. The serum concentrations are full, complement control proteins (CCP) activity is boosted, and exacerbation of hemolysis succeeds. Thus, cold agglutinin disease (CAD) patients should likely not receive transfusion with complement-rich blood products, for example, plasma, even though this has not been systematically tested.



Figure(49):Complement-mediated hemolysis in cold agglutinin disease and cold agglutinin syndrome[Berentsen S. (2015). Role of complement in autoimmune hemolytic anemia. Transfusion Medicine and Hemotherapy, 42:303-310. DOI:10.1159/000438964]

In figure(49): Complement-mediated hemolysis in cold agglutinin disease (CAD) and cold agglutinin syndrome (CAS). CA = Cold agglutinin; C = complement.



Figure(50):Biphasic, complement-mediated hemolysis in paroxysmal cold hemoglobinuria [Berentsen S. (2015). Role of complement in autoimmune hemolytic anemia. *Transfusion Medicine and Hemotherapy*, 42:303-310. DOI:10.1159/000438964]

In figure(50): biphasic, complement-mediated hemolysis in paroxysmal cold hemoglobinuria. Ig = Immunoglobulin; ag = antigen; ab = antibody; C = complement.

In warm antibody autoimmune hemolytic anemia (WA-AIHA), complement-mediated cell lysis is clinically pertinent in a rate of the patients but is barely crucial for hemolysis in most patients. Cold antibody-mediated autoimmune hemolytic anemias [primary cold agglutinin disease (CAD), secondary cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH)] are completely complement-mediated disorders. In cold agglutinin disease (CAD), effective remedies have been developed in order to target the pathogenic B-cell clone, but complement modulation is still hopeful in some clinical conditions. No determined therapy exists for secondary cold agglutinin syndrome (CAS) and paroxysmal cold hemoglobinuria (PCH), and

the potency of therapeutic complement inhibition is interesting. Currently, complement modulation is not clinically documented in any autoimmune hemolytic anemia (AIHA).

The clinical manifestation of autoimmune hemolytic anemia (AIHA) is not different from other forms of acute hemolytic anemia [a reduction in red blood cell (RBC) survival] or acute crisis of a chronic haemolytic anaemia. Considerably, patients are icteric (affected with jaundice) and undergo clinical signs of anemia, such as pallor (an unhealthy pale appearance), fatigue, shortness of breath and palpitations. In contrast, haemoglobinuria as a sign of intravascular haemolysis is scarce, but the patient must explicitly be asked for that symptom. In case of cold agglutinins, cold exposure may cause agglutination of red blood cells (RBCs) in the circulation as reflected by cyanotic discolouring of the acra, such as toes, fingers, ears and nose. After warming up, the cyanotic discolouring disappears quickly and in contrast to a Raynaud phenomenon, no reactive hyperaemia happens. The presence of a disease often reported to be correlated with autoimmune hemolytic anemia (AIHA) boosts the suspected diagnosis. Since many of these diseases are accompanied by anemia, the diagnosis of a mild autoimmune hemolytic anemia (AIHA) can easily be missed.

-For management of warm antibody autoimmune hemolytic anemia (WA-AIHA):

(a)-Transfusion: the blood product must be compatible with respect to complement-activating alloantibodies present in patient's serum. Alloantibody is an antibody formed in response to pregnancy, transfusion, or transplantation targeted against a blood group antigen that is not present on the person's red blood cells. If possible the selected product must be negative for the antigens, to which alloantibodies have been determined in the antibody screening. Moreover, the development of new or additional alloantibodies must be prevented. Therefore, a blood product as compatible as possible with the recipient antigens will be selected. The minimal requirement is that the selected product must be compatible to Rhesus and Kell antigens. In case of severe haemolysis blood product selection may also consider the specificity of autoantibodies (auto-Ab's). When there is a conflict making the right choice to select red blood cell (RBC) it is important to keep in mind that in case of transfusion alloantibodies are more important than autoantibodies (auto-Ab's). If there is no time to wait for the result of the serological examinations, it must be taken into account to prevent alloantibody formation by matching patient and donor for the most important red blood cell (RBC) antigens: Rhesus (Rh), Kell, Kidd,

Duffy, and Ss. Blood group antigens are either sugars or proteins, and they are attached to various components in the red blood cell (RBC) membrane. The Rh blood group system consists of 49 defined blood group antigens, among which the five antigens D, C, c, E, and e are the most important. There is no d antigen. Rh(D) status of an individual is normally described with a positive or negative suffix after the ABO type. The Kell antigen system (also known as Kell–Cellano system) is a group of antigens on the human red blood cell (RBC) surface which are important determinants of blood type and are targets for autoimmune or alloimmune diseases which destroy red blood cells (RBCs). Kidd blood group system, classification of human blood based on the presence of glycoproteins known as Kidd (Jk) antigens on the surfaces of red blood cells (RBCs). The Kidd glycoprotein functions to maintain the osmotic stability of red blood cells by acting as a transporter of urea. Duffy blood group system, classification of human blood based on the presence of glycoproteins known as Fy antigens on the surface of red blood cells (RBCs), endothelial cells (cells lining the inner surface of blood vessels), and epithelial cells in the alveoli of the lungs and in the collecting tubules of the kidneys. SS and AC are the abnormal genotypes or the sickle cells. All people have a specific pair of these hemoglobin in their blood which are inherited from both parents.

(b)-Steroids: steroids are efficient in the management of autoimmune hemolytic anemia (AIHA). Steroids decrease the production of autoantibodies (auto-Ab's) by B-cells. Further, steroids decrease the density of Fc-gamma receptors on phagocytes in the spleen. Commonly, prednisolone, 1 mg/kg/day is started, and depending on the clinical response is tapered slowly. After stabilization of the hemoglobin a scheme often used at a department is to taper prednisolone to a dosage to 20 mg/day in two weeks. If the hemoglobin concentration keeps stable, dosage can further be reduced to 10 mg/day after a month. Thereafter, the steroid dosage can further be tapered and be stopped after two weeks. In order to diagnose steroid-induced diabetes mellitus early, blood glucose levels must be monitored regularly. Moreover, osteoporosis prophylaxis must be started since the patients suffering from autoimmune hemolytic anemia (AIHA) receive steroids over a long period of time. The psychological side effects of steroid management are often underestimated (e.g. agitation, lack of self-control, psychosis) and might become an incriminatory trouble for the patient and social environment. Therefore steroid doses have to be reduced frequently or the therapy has even to be stopped.

(c)-Cytotoxic drugs: Azathioprine and cyclophosphamide are both immune suppressors causing a decrease of autoantibody production. The addition of these therapies can be considered if steroid therapy does not achieve a sufficient result, when a steroid maintenance dose of more than 20 mg/ day is needed or steroid doses must be tapered due to side effects. Cyclophosphamide (100 mg/d) or azathioprine (100-150 mg/d) can be given as monotherapy or in combination with steroids. Due to their myelosuppressive effects peripheral blood cell counts must be controlled regularly and if needed dosage must be adapted. In refractory autoimmune hemolytic anemia (AIHA) pulse therapy with cyclophosphamide (50 mg/kg over 4 days) in combination with mesna (a sulfhydryl compound used to reduce the incidence of hemorrhagic cystitis associated with certain chemotherapeutic agents) and granulocyte colony-stimulating factor (G-CSF) might be successful. In desperate cases vincristine might be a valuable alternative bearing the advantage of being less myelotoxic than cyclophosphamide. Immunosuppressive drugs, such as cyclosporine or mycophenolate-mofetil seem to be effective in some cases.

(d)-Splenectomy: by means of splenectomy red blood cell (RBC) destruction is abated and the production of autoantibodies (auto-Ab's) is decreased. Two weeks after splenectomy anemia has stabilized in more than 50% of the patients. Approximately 20% of the patients reach long-time remissions or are even cured from the disease. In half of the patients steroids can further be tapered. However, one-third of the patients do not reach a substantial remission. The mortality of splenectomy by laparotomy is around 1%, in laparoscopic splenectomy it is about 0.5%. Patients after splenectomy have a notable risk for infections as compared with the normal population. Vaccination against *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, if possible prior to splenectomy, significantly decreases the risk for infection in these patients.

(e)-Anti-CD20 antibody: rituximab is a chimeric, monoclonal antibody targeting CD20 expressed on all B-cells except plasma cells. Taking rituximab decreases autoantibody production by targeted destruction of B cells. Retrospective studies mention a complete remission in 20 to 70% of the patients. In prospective studies, >60% of the patients achieve a complete remission, but most patients will relapse sooner or later (>24 months). Rituximab is well tolerated, occasionally allergic reactions with hives, chills and hypotension occur. As a very rare but fatal complication, progressive multifocal leucoencephalopathy (PML) after rituximab therapy in patients suffering from systemic lupus erythematosus (SLE) has been observed. In spite of the lack of controlled

prospective studies rituximab has to be indicated to replace splenectomy as therapy of choice in steroid-resistant warm antibody autoimmune hemolytic anemia (WA-AIHA). If splenectomy is reconsidered after failure of rituximab therapy, it must be taken into account that vaccination to encapsulated bacteria might be ineffective after rituximab therapy.

(f)- Immunoglobulins: in approximately 40% of patients, administration of immunoglobulins improves anemia temporarily. This is primarily attributed to a reduction of red blood cell (RBC) destruction in the spleen. Moreover, immunomodulatory impacts of gammaglobulins might contribute to the beneficial effect as well. Treatment with immunoglobulins might be considered in acute life-threatening conditions in order to reduce breakdown of patients or donor erythrocytes.

-Treatment of cold antibody autoimmune hemolytic anemia (CA-AIHA):

Luckily, anemia in cold antibody autoimmune hemolytic anemia (CA-AIHA) is usually mild and there is no need for correction. The basic management in that state is quite simple: keep it warm. Patients must protect themselves properly against the cold by wearing gloves, a hat and warm shoes. If necessary, transfusion must be done under controlled conditions at 37 °C by means of a controlled heating system. During surgery, body temperature must be kept at 37 °C. The criteria to choose a blood product are similar to those in warm antibody autoimmune hemolytic anemia (WA-AIHA). However, the treatment of cold antibody autoimmune hemolytic anemia (CA-AIHA) remains a frustrating issue. Steroids are clearly less efficient than in warm antibody autoimmune hemolytic anemia (WA-AIHA). The same holds for cyclophosphamide and azathioprine. In cold antibody autoimmune hemolytic anemia (CA-AIHA) there is no role for splenectomy. A couple of studies recorded some beneficial effects of gammaglobulins. In two controlled trials, rituximab was demonstrated to trigger a response in 40 to 50%, but again achievement of complete remission is rare and relapses are common. Since immunoglobulin M (IgM) are mainly located intravascularly, plasmapheresis induces a quick reduction of immunoglobulin M (IgM) concentrations and may therefore contribute to a short-term stabilization of an autoimmune hemolytic anemia (AIHA). It is worthy to add that plasmapheresis is a method of removing blood plasma from the body by withdrawing blood, separating it into plasma and cells, and transfusing the cells back into the bloodstream. It is

performed especially to remove antibodies in treating autoimmune conditions. Since plasmapheresis has to be performed at 37 °C, the technical procedure remains a challenge.

The treatment options in case of fulminant intravascular haemolysis are limited. Therapy focuses on supportive care with a close monitoring of vital functions, renal function and haemolysis parameters. In the literature, gammaglobulins and plasmapheresis have been mentioned as management choices. In selected cases an inhibitor of the activation of complement component C5 (eculizumab) has been administered thereby attenuating the formation of the membrane attack complex.

6.1 Autoimmune Hemolytic Anemia in COVID-19 Infection

Lopez *et al.* (2020) reported a patient suffering from simultaneous presentation of coronavirus disease 2019 (COVID-19) disease and warm autoimmune hemolytic anemia (AIHA). A 46-year-old woman with a medical history of congenital thrombocytopenia not on therapy presented with dyspnea and cough to the Emergency Department (ED). She was found to have pneumonia after chest computed tomography (CT) showed a dense left upper lobe consolidation with minimal surrounding ground glass opacities and no evidence of pulmonary embolism (PE). She had normal vital signs and pulse oximetry on ambient air. She was initiated on azithromycin 500 mg on day 1 then 250 mg daily and discharged home. Her symptoms worsened over three days with progressive cough and dyspnea. Her vital signs were a temperature of 40°C, pulse 130 bpm, respiratory rate 20 breaths per min, blood pressure 123/83 mm Hg and SpO₂ 99% on ambient air. Her exam was only notable for diminished left-sided breath sounds. Laboratory investigations showed hemoglobin 97 g/l, white blood cells (WBCs) 985 9 10³ /l with lymphopenia (068 9 10³ /l), and platelets 43 9 10³ /l. Lactate dehydrogenase (LDH) was 296 U/l. She was admitted to the hospital. Her Coombs test was positive, with direct antibody testing positive for immunoglobulin G (IgG) and C3. A test for antinuclear antibody (ANA) was negative. On hospital day 3, she exhibited to be positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) and started on hydroxychloroquine (HCQ) 400 mg bid on day 1, then 200 mg bid for four days because of its theoretical antiviral activity. Influenza, respiratory syncytial virus (RSV), viral respiratory polymerase chain reaction (PCR) assay, blood cultures and urine antigens for *Streptococcus pneumoniae* and *legionella sp.* were negative. Given her active coronavirus disease 2019 (COVID-19) disease she was started initially on intravenous

immunoglobulin (IVIG) at 1 g/kg/day rather than prednisone. Despite this, she required transfusion of three units of packed red blood cells, and after three days was started on prednisone 60 mg/day. This caused stabilization of her blood counts. She completed a five-day course of hydroxychloroquine (HCQ). During her hospital stay, her lactate dehydrogenase (LDH) rose from 296 to 553 U/l, falling to 355 U/l at discharge, and haptoglobin remained low. Her reticulocyte count was normal (954 9 103 /l) on admission and rose to 206 9 103 /l at discharge. Her pneumonia improved and she was discharged on a prednisone taper on hospital day 8. At follow-up after one week, her hemoglobin was 11 g/l and lactate dehydrogenase (LDH) was normal. Autoimmune hemolytic anemia (AIHA) is the destruction of red cells by autoantibodies. Upon presentation, the patient had a warm antibody (immunoglobulin G, IgG) hemolytic anemia along with coronavirus disease 2019 (COVID-19) disease. Because of concerns for causing immunosuppression and worsening viral shedding, she was first started on intravenous immunoglobulin (IVIG), but did not have a response, which is consistent with the literature showing a poor response to intravenous immunoglobulin (IVIG) in autoimmune hemolytic anemia (AIHA). Her blood count stabilized with prednisone, which will be tapered. Authors suspected that as her infection cleared this would also resolve the autoimmune hemolytic anemia (AIHA). While many haematological complications of coronavirus disease 2019 (COVID-19) infections have been reported, the finding of autoimmune hemolytic anemia (AIHA) is novel.

Another study concerning coronavirus disease 2019 (COVID-19) and autoimmune hemolytic anemia (AIHA) was conducted. Median age of patients was 62 years (range, 61-89 years), and all patients presented with risk factors for developing a severe form of coronavirus disease 2019 (COVID-19) such as hypertension (HTN), diabetes mellitus (DM) and chronic renal failure (CRF). All patients had both positive oropharyngeal swab for severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) and typical images of coronavirus disease 2019 (COVID-19) infection on chest computed tomography (CT)-scans (25% to 75% extension). Three patients were admitted in intensive care unit (ICU) but only one required invasive ventilation. Invasive mechanical ventilation can become a lifesaving intervention for patients with respiratory and breathing difficulties. The term invasive is used if it includes any instrument penetrating via the mouth (such as an endotracheal tube), nose, or the skin (such as a tracheostomy tube through a stoma, a surgically-created hole in the windpipe) to serve as an artificial airway. Management of

coronavirus disease 2019 (COVID-19) infection differed according to the standards of each center. Thus, three patients received hydroxychloroquine (HCQ), in association with azithromycin for two of them, and one patient received lopinavir and ritonavir. The median time between the first coronavirus disease 2019 (COVID-19) symptoms and autoimmune hemolytic anemia (AIHA) onset was 9 days (range 4 to 13 days), and hemoglobin concentration decreased by more than 30 g/L in all patients. Median hemoglobin concentration at the time of autoimmune hemolytic anemia (AIHA) diagnosis was 70 g/L (range 3.8-10.8), and all patients presented with marked hemolysis signs. Direct antiglobulin test (DAT) was positive in all cases either for immunoglobulin G (IgG) (n=2), for C3d (n= 2), or for both immunoglobulin G (IgG) and C3d (n=3). Anti-erythrocyte antibodies were warm antibodies in 4 cases [2 of immunoglobulin G (IgG) specificity and 2 IgG+C3d] and cold agglutinins in 3 cases (2 of C3d specificity and 1 IgG+C3d). At the time of autoimmune hemolytic anemia (AIHA) onset, all patients had higher markers of inflammation [i.e. fibrinogen, D-dimers (DD) and C reactive protein (CRP)]. Interestingly, among the patients with warm antibodies, 2 patients were known for stable untreated Binet stage A chronic lymphocytic leukemia (CLL) and an immunoglobulin G (IgG) kappa monoclonal gammopathy of undetermined significance was evidenced in a third one. In 2/3 patients with cold agglutinin, systematic lymphocyte immunophenotyping demonstrated the presence of a monotypic B lymphoid population with a phenotype compatible with marginal zone lymphoma (MZL). The third one was diagnosed with prostate cancer. Autoimmune hemolytic anemia (AIHA) treatment involved corticosteroids (CS) for five patients, and red blood cells (RBCs) infusions for two. Even if the follow-up is still short, 3 patients receiving corticosteroids (CS) were evaluable for response of autoimmune hemolytic anemia (AIHA). Two patients reached partial response determined by hemoglobin concentration greater than 100 g/L along with an increase of 20 g/L at least 7 days after a red blood cells infusion. Corticosteroid (CS) failure caused rituximab injection in the third case (patient#6), and one responding patient is scheduled to receive rituximab because of the marginal zone lymphoma (MZL) clone (patient#3). At the time of last follow-up, all patients were alive and had at least partly recovered from coronavirus disease 2019 (COVID-19). To conclude, authors report 7 patients of warm and cold autoimmune hemolytic anemia (AIHA) associated with coronavirus disease 2019 (COVID-19) infection, all of them occurring after the beginning of the symptoms of the infection and within a timeframe compatible with that of the cytokine storm. Four out of the seven patients had

indolent B lymphoid malignancy either already known or discovered because of the hemolytic episode. Autoimmune hemolytic anemia (AIHA) is a classical complication of both chronic lymphocytic leukemia (CLL) and marginal zone lymphoma (MZL) , and viral infections are known to provoke autoimmune cytopenias. Autoimmune cytopenias are a group of heterogeneous but closely related conditions defined by immune-mediated destruction of hematologic cell lineages, including white blood cells (neutrophils), red blood cells, and platelets. This destruction can be primary or secondary to other illnesses. Whether the presence of an underlying malignant B lymphoid clone facilitated the onset of autoimmune hemolytic anemia (AIHA) or not is unknown in the study. Nonetheless, these recognitions argue for systematically investigating for the presence of a lymphoid clone in patients presenting with coronavirus disease 2019 (COVID-19) infections and autoimmune cytopenias.

Onset of autoimmune hemolytic anemia (AIHA) needs to be considered in coronavirus disease 2019 (COVID-19) patients who present with severe anemia.

7.Acute Porphyria

Acute porphyrias are scarce inherited disorders due to deficiencies of hem synthesis enzymes. The acute porphyrias belong to a wider group of porphyrias, each of which is a cause of deficiency of a specific enzyme of the hem synthesis pathway, apart from X-linked erythropoietic protoporphyria, which is due to gain of function mutations. Clinical characteristics depend on where the block in this pathway happens, and the resulting accumulation of hem precursors or porphyrins, which are dominantly from the bone marrow (BM) and liver. Porphyrias may be counted in two groups: acute porphyrias, presenting with acute neurovisceral attacks, and cutaneous porphyrias, characterized by photosensitive skin lesions, although there is interfere. The acute hepatic porphyrias (AHPs) are a group of four inherited diseases of hem biosynthesis that display with episodic, acute neurovisceral symptoms. The four types are 5-aminolevulinic acid (ALA) dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). The 4 acute porphyrias of which the recessive delta aminolevulinic acid (ALA) dehydratase deficiency porphyria (ADP) is extremely scarce, with only a spot of case reports in the research. Acute intermittent porphyria (AIP) is the most common acute porphyria in European people and usually most severe. Variegate porphyria (VP) and hereditary coproporphyria (HCP) are rarer

and may exhibit with acute attacks or photosensitive skin lesions or both. Their diagnoses are frequently missed or delayed because the clinical symptoms echo other more common disorders. Recent results demonstrate that acute intermittent porphyria (AIP), the most severe of the more common types of acute hepatic porphyria (AHP), is more predominant than previously believed, happening in about 1 in 1600 Caucasians, but with low clinical penetrance (approximately 2%-3%). Symptomatic attacks occur primarily in females aged between 14 and 45 years. Acute hepatic porphyrias (AHP) manifest in attacks and are characterized by overproduction of porphyrin precursors, developing often serious abdominal, psychiatric, neurologic, or cardiovascular (CV) symptoms. Patients with variegate porphyria (VP) and hereditary coproporphyria (HCP) can exhibit with skin photosensitivity. Acute hepatic porphyria (AHP) is diagnosed by finding considerably raised concentrations of porphyrin precursors are 5-aminolevulinic acid (ALA) and porphobilinogen in urine. Acute attacks in each patient are deemed to result from overproduction of a neurotoxic hem precursor from the liver, although the exact pathophysiology is not fully understood. Their first-degree relatives should undergo targeted gene testing. Diagnosis bases on measurement of elevated urinary 5-aminolevulinic acid (in patients with aminolevulinic acid dehydratase deficient porphyria) or increased 5-aminolevulinic acid and porphobilinogen (in patients with other acute porphyrias). Treatment of attacks demands intensive care, strict avoidance of porphyrinogenic therapies and other precipitating factors, caloric support, and often hem remedy.

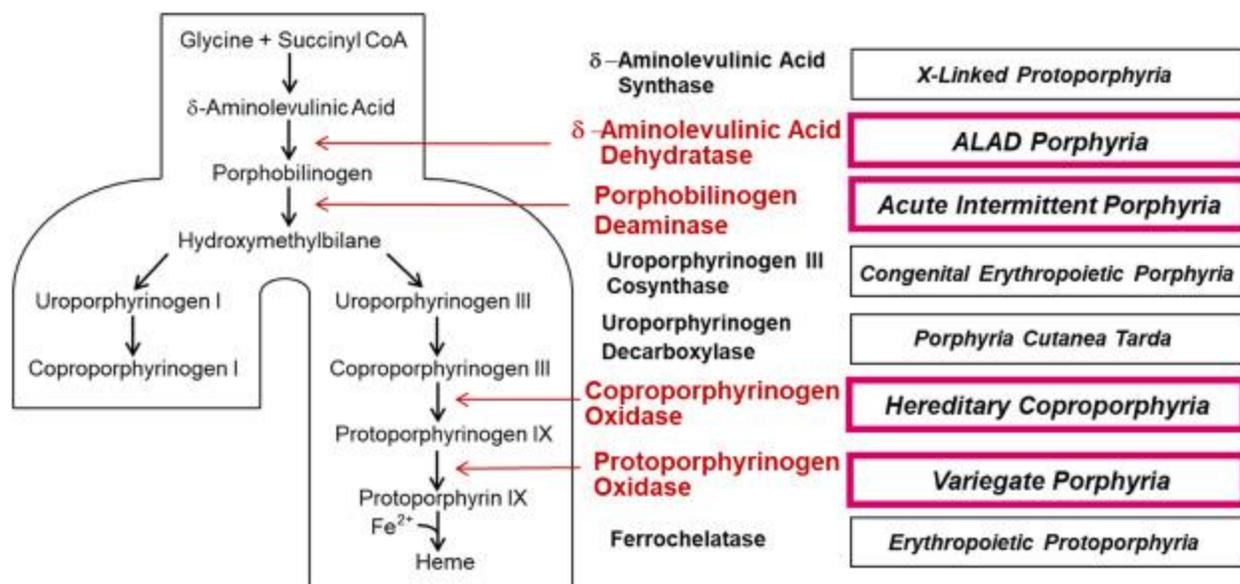
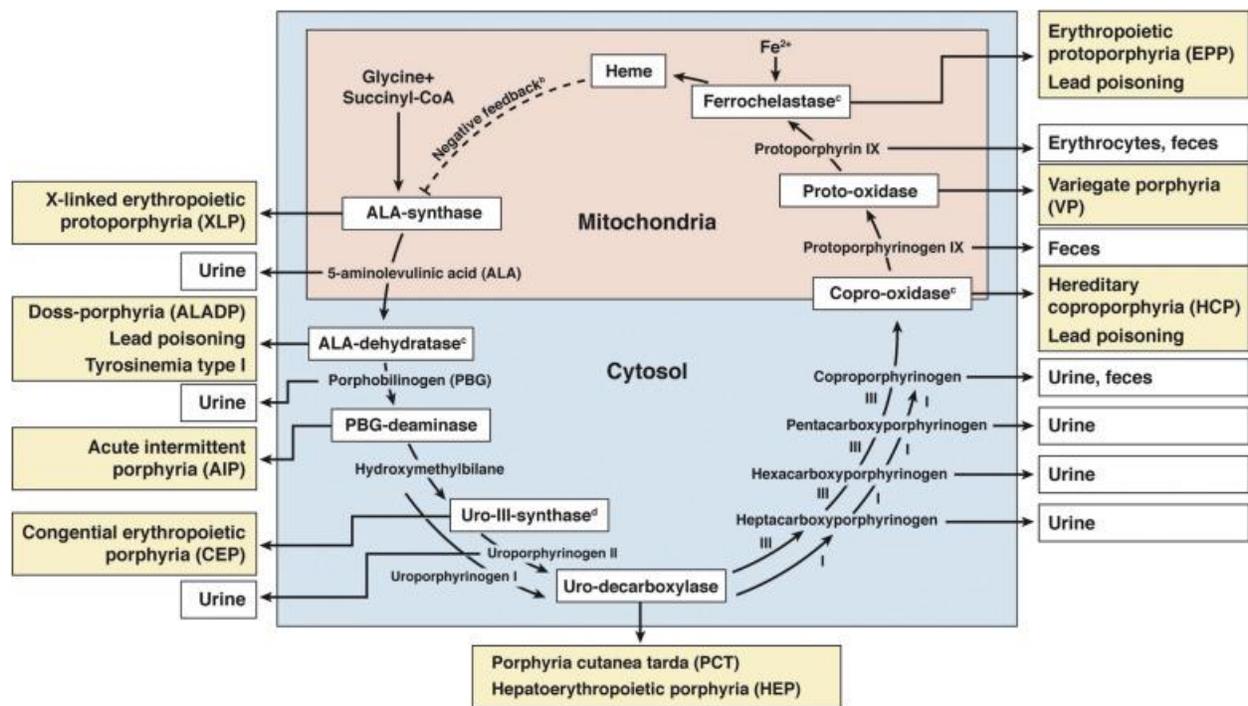


Figure (51): Acute hepatic porphyria [Anderson K. (2019). Acute hepatic porphyrias: current diagnosis and management. *Molecular Genetics and Metabolism*, 128(3):219-227]

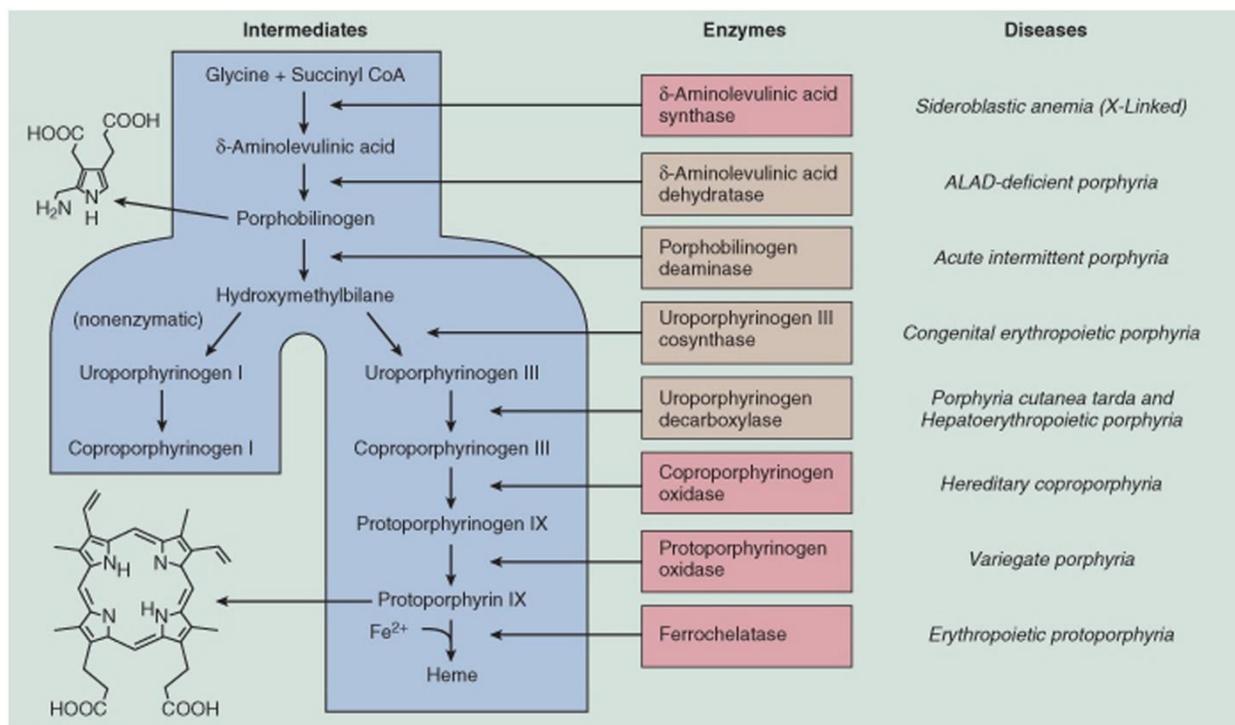
The non-acute porphyrias are porphyria cutanea tarda, erythropoietic protoporphyria, X-linked protoporphyria, and the rare congenital erythropoietic porphyria. They lead to the accumulation of porphyrins that cause skin photosensitivity and occasionally severe liver damage. Secondary high urinary or blood porphyrins can happen in patients without porphyria, for example, in liver diseases, or iron deficiency. Patients with porphyria cutanea tarda benefit from iron depletion, hydroxychloroquine (HCQ) therapy, and, if applicable, elimination of the hepatitis C virus. An α -melanocyte-stimulating hormone analogue can reduce sunlight sensitivity in patients with erythropoietic protoporphyria or X-linked protoporphyria. Strategies to address dysregulated or dysfunctional steps within the hem biosynthetic pathway are in progress.

Hem-containing proteins have crucial and diverse biological functions involving oxygen transport, electron transfer and catalysis. Hem synthesis occurs in all nucleated cells, but 80–90% of hem is synthesized in developing red blood cells (RBCs) in the bone marrow (BM) where it is used for haemoglobin, with most of the remainder produced in hepatocytes for various hem-containing proteins, especially the microsomal cytochrome P450 enzymes. Regulatory mechanisms differ at these two sites: erythroid hem synthesis depends mainly on the availability of iron, while hepatic hem synthesis is regulated by the free hem pool. The first step in hem synthesis is the formation of 5-aminolevulinic acid (ALA) within the mitochondria catalyzed by

5-aminolevulinic acid synthase (ALAS). This enzyme presents as 2 isoforms, ubiquitously expressed 5-aminolevulinic synthase 1 (ALAS1) and erythroid 5-aminolevulinic synthase 2 (ALAS2). 5-Aminolevulinic synthase 1 (ALAS1) is rate limiting in hepatic hem synthesis and strictly regulated by intracellular hem, which is the basis for the therapeutic effect of haemin (an iron-containing porphyrin with chlorine that can be formed from a haem group, such as haem b found in the haemoglobin of human blood) in acute porphyria attacks, and the target for a new ribonucleic acid (RNA) silencing therapy undergoing clinical trials. 5-Aminolevulinic synthase 1 (ALAS1) transcription may also be stimulated directly through activation of nuclear receptors responding to xenobiotic and steroid challenge and to transcription factors activated by fasting.



Figure(52):Synthesis of haem and defects leading to porphyrias [Stolzel U.; Doss M.; Schuppan D. (2019). Clinical guide and update on porphyrias. Gastroenterology, 157(2):365-381.e4. <https://doi.org/10.1053/j.gastro.2019.04.050>]



Figure(53):Haem synthetic pathways and enzymatic defects associated with porphyria [Wang B.; Rudnick S.; Cengia B.; Bonknvsky H. (2018). Acute hepatic porphyrias: review and recent progress. *Hepatology Communications*, 3(2):193-206. <https://doi.org/10.1002/hep4.1297>]

In figure(53): summary of the heme synthetic pathway, highlighting the enzymatic defects associated with the porphyrias. The hem synthetic pathway includes eight enzymes, four of which are functional in the mitochondria and four of which are functional in the cytoplasm. The pathway is started and completed in the mitochondria. Intermediate steps in the cytoplasm begin with the activity of aminolevulinate dehydratase (ALA dehydratase), also called porphobilinogen synthase (PBG synthase). Open arrows indicate progression through the pathway. Deficiency (indicated by blocked red arrows) in any of the eight enzymes included in the pathway may contribute to the progress of acute or chronic hepatic porphyrias or erythropoietic porphyrias, as revealed in red. Abbreviations: Ac, acetate; CoA, coenzyme A; Copro'gen, coproporphyrinogen; Pr, propionate; proto'gen, protoporphyrinogen; Uro'gen, uroporphyrinogen; and Vi, vinyl.

In the dominant acute porphyrias, a functional gene is inherited from the unaffected parent, so residual enzyme activity is typically 50% and sufficient for hem homeostasis. However, the partial enzyme deficiency becomes rate limiting when there is upregulation of 5-aminolevulinate synthase 1 (ALAS1), leading to increased metabolic flux through the pathway with collection and release of porphyrins and their precursors from the liver. Raised concentrations of 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) are correlated with inherited deficiency of hydroxymethylbilane synthase (HMBS) in acute intermittent porphyria (AIP), while in

variegate porphyria (VP) and hereditary coproporphyria (HCP) this is believed to come from allosteric inhibition of hydroxymethylbilane synthase (HMBS) by gathering coproporphyrinogen and or protoporphyrinogen. A complex network of transcriptional pathways regulates hepatic 5-aminolevulinate synthase 1 (ALAS1), and may interpret the broad variation in susceptibility to attacks in acute porphyria gene carriers. The pathogenesis of attacks remains uncertain but it is thought that 5-aminolevulinic acid (ALA) exhibits toxic effects on nerves, either directly, or by interacting with receptors for the structurally similar neurotransmitter γ -aminobutyric acid (GABA), or by forming free radicals and reactive oxygen species (ROS). The efficiency of liver transplantation as a management for severe acute porphyria, and the onset of acute attacks in a patient who received a liver transplant from a symptomatic acute intermittent porphyria (AIP) donor affirm the focal role of the liver in the pathological process.

Acute neurovisceral attacks may happen in all the acute porphyrias and are clinically indiscernible. Recognition of an attack in a patient without a known diagnosis of acute porphyria is difficult and frequently delayed, as symptoms and signs are non-specific, especially in the early stages of the disease, and because porphyrias are so scarce. The diagnosis should be investigated in patients with recurrent or prolonged episodes of unexplained abdominal pain, especially when this is correlated with neurological complications, psychiatric characteristics or hyponatraemia (occurring when the concentration of sodium in blood is abnormally low; sodium an electrolyte, and helps regulate the amount of water that's in and around body cells). Most of the clinical characteristics of an attack emerge from influences on the central, peripheral and autonomic nervous systems. The major symptom is severe, poorly localized abdominal pain (present in more than 90% of cases), sometimes with pain at other sites, particularly the back and legs, and frequently accompanied by nausea, vomiting and constipation. Raised blood pressure and tachycardia are nearly always exist, but checking is frequently otherwise normal. Mental changes involving agitation, depression, insomnia and confusion are incident often in correlation with acute pain, and can also be found in the prodromal stages of an attack. Scarcely these are more severe with psychosis, delusions and hallucinations. Mental changes solve completely on remission. Severe attacks, particularly when diagnosis is delayed and exposure to porphyrinogenic factors is prolonged, may be complicated by neurological characteristics comprising an axonal neuropathy, seizures and posterior reversible encephalopathy syndrome (PRES). A symmetrical motor neuropathy with weakness beginning proximally in the upper

limbs is representative and may scarcely develop quickly to give complete paralysis, incontinence or urinary retention, swallowing difficulties and respiratory failure. Paralysis is usually reversible with adequate sustenance management but needs many months of rehabilitation. Sensory disturbance may manifest as neuropathic pain, paraesthesiae or numbness (the state of being numb). Focal neuropathy is unusual. Rare complications of attacks involve cardiac arrhythmias, which may consider for incidental studies of sudden death, and rhabdomyolysis (i.e., the destruction of striated muscle cells). Routine biochemical and hematological studies are frequently normal, apart from hyponatraemia which happens in up to 40% of attacks. In many cases this is attributed to the syndrome of inadequate antidiuretic hormone (SIADH), but renal or gastrointestinal (GI) sodium loss and over hydration may contribute. Severe hyponatraemia may cause seizures. Altered urine color, darkening to red particularly on exposure to light, is frequently noticeable and is attributed to oxidation of porphobilinogen (PBG) to uroporphyrin and porphobilin. Although non-specific, this is a well-known characteristic of acute porphyria.

Patients with variegate porphyria (VP) and hereditary coproporphyria (HCP) may exhibit photosensitive skin lesions influencing exposed sites especially the face and the back of the hands. This is attributed to deposition of porphyrins in the skin, which are activated by visible violet light with a wavelength peak at 400–410 nm leading to a local phototoxic reaction. Affected skin is exceedingly fragile, resulting in blisters, milia, and scarring. Skin symptoms in variegate porphyria (VP) and hereditary coproporphyria (HCP) may accompany an acute attack, or may be the only clinical manifestation of porphyria, particularly in variegate porphyria (VP). Skin lesions do not occur in acute intermittent porphyria (AIP) except when there is end stage renal disease (ESRD). Patients should be advised to keep exposed skin protected from light with suitable clothing and wear a wide-brimmed hat and gloves. Opaque sun creams blocking visible light are efficient, but conventional sun creams blocking ultraviolet A (UVA) and ultraviolet B (UVB) rays are rarely helpful. It is important to refer that ultraviolet A (UVA) ray has a longer wavelength and is associated with skin aging, while ultraviolet B ray has a shorter wavelength and is associated with skin burning.

The majority of patients with moderate or severe attacks demand hospital admission for estimation, management and monitoring. Other causes of symptoms should be excluded,

especially manageable situations demanding urgent management, such as appendicitis, complications of pregnancy or pancreatitis. Inducing factors should be determined and removed if conceivable, involving examining therapy for porphyrinogenicity. Porphyrinogenicity is the quality or degree of being porphyrinogenic; the porphyrinogens are the functional intermediates in the biosynthesis of hem and if oxidized to their corresponding porphyrins, such as occurs in porphyrias, are irreversibly removed from the biosynthetic pathway and accumulate in tissues. Symptomatic and supportive management with therapies that are known to be safe in acute porphyria should be initiated soon. Pain is representatively severe and opiates are usually prescribed, frequently in large quantities. Administration of opiates at regular intervals, or via a Patient Controlled Analgesia pump is prioritized. It is helpful to look for advice from a specialist pain management team. Intravenous fluids are suggested if there is vomiting, dehydration or electrolyte imbalance; normal saline or glucose mixed with normal saline are the suggested options. Hyponatraemia is common and can progress quickly; this should be estimated through paired urine and serum measurements of sodium and osmolality, and estimation of extracellular fluid volume condition, with adequate management relying on the underlying reason. Carbohydrate loading was the standard management for an acute attack of porphyria prior to availability of haemin, and the rationale is relied on the inhibitory influence of glucose (Glc) on 5-aminolevulinate synthase 1 (ALAS1). Carbohydrate loading also called carbo-loading is an eating routine used by some athletes that involves downing large amounts of carbohydrates several days before a potentially exhausting endurance event. Carbo-loading has no known potential benefits for anyone except athletes under these special circumstances. Oral carbohydrate is often beneficial in mild attacks, but the role of intravenous carbohydrate loading is debatable as a result of the probable risk of hyponatraemia causing cerebral edema and osmotic demyelination. Experts in the United States and Sweden advise intravenous glucose (Glc) offering at least 300 g carbohydrate daily together with monitoring for hyponatraemia, while guidelines from the United Kingdom and South Africa advice avoiding all intravenous solutions of glucose (Glc) in water. Human haemin was supposed as a management for acute attacks relied on its likelihood to suppress 5-aminolevulinic acid synthase (ALAS) activity and decrease synthesis of hem precursors. It has become the treatment of choice for all severe or prolonged attacks, particularly when there is hyponatraemia, convulsions, psychosis or neuropathy. Two forms of human haemin are currently ready, haem arginate, a stable form of

human haemin in a complex with arginine, is used in Europe and many other countries, while a lyophilised form of human haemin is used in the United States of America, where haem arginate does not have Food and Drug Administration consent. The only placebo-controlled exam of human haemin including 12 patients did not exhibit a statistically significant impact, but clinical experience gathered in many different countries over the past 25 years proposes that patients managed with haemin at an early stage in their attack have faster mitigation of symptoms, shorter hospital stays and a lower incidence of complications involving neuropathy and seizures, than those who did not receive haemin. Haemin will not reverse an established neuropathy, but may prevent onset or development of nerve damage. The recommended dose of haemin varies between 1 and 4 mg/kg body weight, with doses above 6 mg/kg/day regarded as toxic. The recommended dose of haem arginate is 3 mg/kg (up to a maximum of 250 mg) daily for 4 consecutive days, although longer courses are sometimes used in severe attacks with neuropathy. Haem arginate should be reconstituted in 100 ml normal saline, although many clinicians prefer to use 100 ml 20% human serum albumin (alb), which recorded decreases the risk of local vascular complications. The solution is stable for 1 h and should be infused through an online filter over 30–60 min, after which the vein should be flushed immediately with saline. Haemin is an irritant and thrombophlebitis (inflammation of the wall of a vein with associated thrombosis) is the most common side effect. Infusions should therefore be given through a large peripheral vein or a central line to reduce the risk of damage to the superficial venous system. The National Acute Porphyrria Service is a highly specialized service providing clinical advice and haem arginate where adequate for patients in mainland Britain with either one-off acute attacks or recurrent attacks of porphyria.

A minority of patients with acute porphyria progress recurrent attacks, usually defined as 4 or more attacks requiring admission to hospital in 1 year. Severe recurrent acute attacks affect 3–5% of newly diagnosed symptomatic patients, and are more common in acute intermittent porphyria (AIP) and in women. In women with acute intermittent porphyria (AIP), attacks sometimes happens regularly in the luteal phase of the menstrual cycle, although in many patients there is no recognizable style or trigger. There is no convention on what level of pain or combination of symptoms and signs is needed to ascertain a new attack in this group, so the diagnosis bases heavily on clinical resolution. Urine porphobilinogen (PBG) excretion is continually elevated in patients with recurrent attacks of acute intermittent porphyria (AIP), but

Careful urine porphobilinogen (PBG) monitoring may be beneficial by permitting values when symptomatic to be compared with a novel baseline. Treatment of patients with recurrent attacks is confronting and results are changing. A considerable percent of these patients, who are almost entirely young women, suffer a prolonged period of chronic pain, depression, neuropathy and disability. All patients with recurrent attacks should be advised for a specialist porphyria service for consultation on treatment and long term monitoring. The most straightforward treatment approach is to manage each attack individually following medical evaluation to exclude other reasons, surpassing through direct admission to an acute medical unit with expertise of treating that patient. This should involve monitoring urine porphobilinogen (PBG) at the start of each episode prior to the administration of haemin. This approach must be balanced against the risk of complications with each attack and the impact of repeated attacks and hospital admissions on quality of life. Most porphyria specialists would begin interpreting choices to prevent repeated attacks if there is no improvement in the clinical state after 6–12 months. Gonadotropin releasing hormone (GnRH) analogues preventing ovulation may be helpful in women with recurrent premenstrual attacks of porphyria. The benefits require to be weighed against the risks of estrogen deficiency. Menopausal side-effects may be decreased by addition of a low dose estrogen patch, although this may elevate the risk of acute attacks together with the high risk of uterine carcinoma correlated with unopposed estrogens. Gonadotropin releasing hormone (GnRH) treatment should be initiated within the first few days of menstruation to decrease the risk of an attack induced by transitory ovarian stimulation. Regular monitoring of bone mineral density, and additional gynecology monitoring for patients on estrogen replacement, should be arranged during the management period, and the resolution to continue management should be checked every 1–2 years. Prophylactic haemin, although an unlicensed drug, is broadly used to decrease the frequency of recurrent attacks in severely affected patients. Prophylactic haemin should be administered via a central line if possible. Liver transplantation has been commenced in at least 10 acute intermittent porphyria (AIP) patients in the United Kingdom and Ireland and is considered as a curative management for patients with severe recurrent attacks where medical treatment has been unsuccessful or where complications, such as loss of vascular access, make this unattainable. The probable side effects of medical treatment require to be balanced against the short- and long-term risks of liver transplantation and prolonged immunosuppression.

7.1 Acute Porphyria in COVID-19 Infection

It is argued that coronavirus disease 2019 (COVID-19) has elevated probability of being more than a disease of pneumonia, and that critical coronavirus disease 2019 (COVID-19) patients may be suffering from a form of acquired acute porphyria. Readily available interventions exist to manage acute porphyria and the position is advanced that urinalysis of critical coronavirus disease 2019 (COVID-19) patients would diagnose this pathology.

Erythrocytes are robustly included in the pathophysiology of coronavirus disease 2019 (COVID-19). Wuhan University researchers discuss that the role of erythrocytes in the pathophysiology of coronavirus disease 2019 (COVID-19) is under-estimated; the co-efficient of variation of red blood cell distribution width (RDW) is predictive of severity of disease status. Increased red blood cell distribution width (RDW) is associated with decreased erythrocyte turnover; red blood cells (RBCs) become smaller as they age and the delay in clearance expands the low-volume tail of the volume distribution. Suppressed erythrocyte turnover may refer to erythropoietic distress and act as a compensative mechanism to maintain circulating red blood cells (RBCs) concentrations. Excess porphyrins in red blood cells (RBCs) can result cell lysis and progress of hemolytic anemia. Macaques infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) also have reduced red blood cells (RBCs) numbers and susceptibility to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) seems to be defined by blood group; blood group A is most affected whereas blood group O appears to be protected. This finding is concurrent with previous researches indicating that susceptibility to the 2003 strain of severe acute respiratory syndrome coronavirus (SARS-CoV) was defined by blood group. Precursory proof proposes that CD147, the determinant of the Ok blood group system, binds the spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is valuable here to mention that the only antigen of the OK blood group system Ok^a is a very high incidence blood group character. The Ok(a-) phenotype has thus far been found only in eight Japanese families. The Ok^a antigen is not restricted to erythrocytes but is expressed on all haematopoietic cells. It is also found on many tissue cells (epithelial cells in particular) and various malignant cell lines. The gene encoding the Ok^a protein maps to chromosome 19 at position p13.2-pter. Indiscriminately, CD147 works as an essential receptor for erythrocyte invasion by *Plasmodium falciparum*. Blockade of CD147 abolishes the normal recirculation of erythrocytes, from the

spleen into the general circulation, resulting in selective trapping of red blood cells (RBCs) in the spleen as development of a form of anemia. Autopsy of deceased coronavirus disease 2019 (COVID-19) patients shows that the spleen is significantly decreased in size. Decrease in spleen size would be expected in the event that the spleen has emptied its reserve of erythrocytes into the circulation as part of a normal physiological response to anemia.

Primate models of coronavirus disease 2019 (COVID-19) and human coronavirus disease 2019 (COVID-19) patients have subnormal hemoglobin concentrations. Clinical estimation of almost 100 Wuhan patients shows hemoglobin concentrations below the normal range in most patients as well as high total bilirubin and increased serum ferritin. Hyperbilirubinemia is recognized in acute porphyria and would be consistent with ineffective erythropoiesis and rapid hemoglobin turnover. High serum ferritin concentrations are representative of acute porphyria and would be anticipated upon dissociation of iron from hem. A mechanism by which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) might attack the 1beta chain of hemoglobin has been presumed; the product of open reading frame 8 (ORF8) binds to the porphyrin of hem and displaces iron (Fe), according to bioinformatics prediction analyses. The oxygen-carrying capacity of erythrocytes would therefore be compromised by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that way exacerbating the difficulties perhaps experienced by the patient, in terms of preserving partial pressure of oxygen in the alveoli (PaO₂). It is important to add that the partial pressure of oxygen in alveolar air is about 104 mm Hg, whereas the partial pressure of the oxygenated pulmonary venous blood is about 100 mm Hg. When ventilation is sufficient, oxygen enters the alveoli at a high rate, and the partial pressure of oxygen in the alveoli remains high. In contrast, when ventilation is insufficient, the partial pressure of oxygen in the alveoli drops. Without the large difference in partial pressure between the alveoli and the blood, oxygen does not diffuse efficiently across the respiratory membrane.

While the impact of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) targeting of hemoglobin on oxygen content of the blood would therefore be significant, it is supposed that probably of greater interest, are possible divergences upon homeostatic regulation of hem anabolism. Hem biosynthesis is fabulously controlled by seven enzyme-controlled reactions launching from the first intermediate, aminolevulinic acid (ALA), to hem as the final output. Hem negatively regulates the first step in the pathway by repressing expression of

aminolevulinic acid synthase (ALAS). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is foreseen to directly interfere with hem synthesis, and this prediction is boosted by experimental proof of decreased hemoglobin concentrations in coronavirus disease 2019 (COVID-19) patients and in animal models of the disease. Reduced hem synthesis dampens repression of aminolevulinic acid synthase (ALAS), and that way elevates the synthesis of hem precursors, resulting in accumulation of porphyrin intermediate metabolites. All of the hem pathway intermediates are possibly toxic. During an attack of acute porphyria, aminolevulinic acid synthase (ALAS) is stimulated and this disturbance continues until sufficient hem synthesis is returned.

Overproduction of haem precursors - aminolevulinic acid (ALA) and porphobilinogen (PBG) in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, manifests life-threatening attacks with neurovisceral symptoms, comprising: abdominal pain (85-95% cases), vomiting (43-88%), constipation (48-84%), muscle weakness (42-60%), mental symptoms (40-58%), pain of the limbs, head, neck and chest (50-52%), hypertension (HTN) (36-54%), tachycardia (28-80%), convulsion (10-20%), sensory loss (9-38%), fever (9-37%), respiratory paralysis (5-12%) and diarrhoea (5-12%). Neurotoxicity of aminolevulinic acid (ALA) interprets the plethora of neurovisceral symptoms and, interestingly, there is significant interference between neurovisceral complaints of aminolevulinic acid (ALA) surplus and extra-pulmonary symptoms of critical coronavirus disease 2019 (COVID-19) patients. Extra-pulmonary symptoms of coronavirus disease 2019 (COVID-19) are considerable but under-estimated, involving gastrointestinal symptoms, which is suggested to affect in the region of 50% coronavirus disease 2019 (COVID-19) patients. Neurological problems also seem to be looked out by the hyper-focus on respiratory symptoms. Of 214 coronavirus disease 2019 (COVID-19) patients, 36.4% suffered from neurological manifestations involving: headache, dizziness, acute cerebrovascular incidents and impaired consciousness. Loss of autonomic control of breathing has also been mentioned and autonomic neuropathy is a clinical characteristic of acute porphyria. Neuropsychiatric symptoms of coronavirus disease 2019 (COVID-19) may be downstream of irregularities in hem metabolism.

In brief, critical coronavirus disease 2019 (COVID-19) patients are experiencing a form of acquired acute porphyria; the second part is that managing critical coronavirus disease 2019

(COVID-19) patients with aminolevulinic acid (ALA) synthase inhibitors may recover extra-pulmonary symptoms of the disease. Aminolevulinic acid (ALA) urinary excretion of 25-100 mg/d or porphobilinogen (PBG, a pyrrole-containing intermediate in the biosynthesis of porphyrins) urinary excretion of 50-200 mg/d is representative of acute porphyria. Current therapeutic interventions licensed for management of porphyria involve:

1-Blood transfusion (erythropoietic porphyria);

2-Glucose (Glc);

3-Intravenous haematin; and,

4-Chloroquine. Chloroquine stimulates the release of tissue-bound porphyrins; the initial event following chloroquine administration to porphyria cutanea tarda (PCT) patients is a release of bound hepatic porphyrin and its rapid elimination. Chloroquine is also a known zinc ionophore and aids zinc uptake; chloroquine may indirectly facilitate zinc insertion, catalysed by ferrochelatase, into excess protoporphyrin. Zinc protoporphyrin is less toxic than free protoporphyrin. Protoporphyrin is a purple porphyrin acid obtained from hemin or hem by removal of bound iron.

Finally, if haemoglobin-targeting is an important component of the coronavirus disease 2019 (COVID-19) pathophysiology, susceptibility to the disease may differentiate according to ethnicity-dependence upon the particularities of hemoglobin-targeting. South East Asian ethnicities have higher prevalence of hemoglobin E; epidemiologically, this would be analogous to maintenance of sickle cell heterozygosity in West African ethnicities as a selective advantage in protecting against malaria.

8.Kawasaki Disease

Kawasaki disease (KD) is an acute systemic vasculitis which develops to cause coronary artery abnormalities in 25% of unmanaged patients. The term vasculitis indicates inflammation of a blood vessel, which is characterized by the presence of an inflammatory infiltrate and destruction of the vessel wall. Commonly, vasculitis points to the systemic vasculitides, which are autoimmune disorders characterized by inflammation of blood vessels. The systemic vasculitides are a diverse group of disorders that indicate a broad range of organ involvement and clinical

severity. Though considerable differences in epidemiological distribution of Kawasaki disease (KD) have been recognized worldwide, a number of factors seem relatively constant. These comprise a male predominance, with a male-to-female ratio of between 1.5:1 and 2:1; remarkable seasonality, with elevated incidence in winter and early spring in moderate climates and summer tops in some Asian countries about 75% of cases occurring in children aged under 5 years; and an increased incidence in individuals of Asian descent, both inside and outside Asia.

A genetic inclination is boosted by the elevated relative risk of Kawasaki disease (KD) within families, whereby siblings of a Kawasaki disease (KD) patient are at a 10-fold higher risk of Kawasaki disease (KD) in comparison with the general people. Linkage analysis and genome-wide association studies have determined several single nucleotide polymorphisms (SNPs) that exhibit correlation with genetic susceptibility to Kawasaki disease (KD). A single-nucleotide polymorphism (SNP) is a substitution of a single nucleotide at a specific position in the genome. Remember that the deoxyribonucleic acid (DNA) sequence is formed from a chain of four nucleotide bases: adenine (A), cytosine (C), guanine (G), and thymine (T). If more than 1% of a population does not carry the same nucleotide at a specific position in the deoxyribonucleic acid (DNA) sequence, then this variation can be classified as a single nucleotide polymorphism (SNP). If a single nucleotide polymorphism (SNP) happens within a gene, then the gene is regarded as having more than one allele. In these situations, single nucleotide polymorphisms (SNPs) may cause variations in the amino acid (AA) sequence. Single nucleotide polymorphisms (SNPs), however, are not just correlated with genes; they can also be incident in noncoding regions of deoxyribonucleic acid (DNA). Two distinguished discoveries involve functional polymorphisms of the FC gamma RIIa locus and the ITPKC gene, which have been seen to predispose persons in Japan and North America to Kawasaki disease (KD) and the later progress of coronary artery aneurysms. It is noticeable to add that coronary artery aneurysms (CAAs) are uncommon and exhibit a localized dilatation of a coronary artery segment more than 1.5-fold the normal size of adjacent normal segments. The ITPKC gene is a T-cell activity modulator, and its identification as a susceptibility gene proposes that T-cell activity regulation may be an underlying mechanism in identifying predisposition to and severity of the disease course.

It is broadly presumed that, following exposure to one or multiple environmental triggers in childhood, the immune response in a small, genetically susceptible patient subset manifests as

systemic vasculitis. This hypothesis is upheld by the sudden symptomatic onset of Kawasaki disease (KD), the seasonal and temporal clustering of cases, the spontaneous degeneration of the disease even without management in the majority of patients, and the domination of immunoglobulin A (IgA) plasma cells at mucosal surfaces in the immune response, common features of the infectious diseases of childhood. In addition, Kawasaki disease (KD) is incident primarily between the ages of three months and five years, when susceptibility to ubiquitous infectious microbes is at its highest. This epidemiological clustering proposes that most adults have immunity to the causative microbe following exposure, and transplacental antibodies protect newborn infants. It is probable that bacterial or viral infections, super antigens, humoral factors, or a combined super antigen conventional peptide antigen response may underlie the onset of the illness, though to date, no etiological agents have been asserted in literature. Authors have isolated intracytoplasmic inclusion bodies in the ciliated bronchial epithelium of acute-stage Kawasaki disease (KD) sufferers, presuming that an intracellular viral microbe is probably to be at work. Inclusion bodies, sometimes called elementary bodies, are nuclear or cytoplasmic aggregates of stable substances, usually proteins. They typically represent sites of viral multiplication in a bacterium or a eukaryotic cell and usually consist of viral capsid proteins. Inclusion bodies can also be notes of genetic illnesses. Inclusion bodies contain very little host protein, ribosomal components or deoxyribonucleic acid/ribonucleic acid (DNA/RNA) fragments. An intrinsic autoimmune cause looks improbable relied on current proof, given patients' lack of autoantibodies and the spontaneous resolution and absence of recurrence observed in the condition.

The clinical course of Kawasaki disease (KD) consists of four phases:

1-Acute, the period lasting 1-2 weeks if unmanaged, when the child has an established, often remittent 40° Celsius fever and major symptomatic characteristics and may exhibit cardiac manifestations involving valvitis, pericarditis, and myocarditis;

2-Subacute, the approximately 2 week period following the subsidence of fever when the child is at the greatest risk of abrupt death due to myocardial infarction. Myocardial infarction is the medical name for a heart attack, a life-threatening condition happens when blood flow to the heart muscle is suddenly cut off, leading to tissue damage. This is usually the result of a blockage in one or more of the coronary arteries;

3-Convalescent, the clinically invisible period following the cessation of symptoms and continuing until acute-phase reactants return to normal serum levels. It is important to interpret that acute phase reactants (APR) are inflammation markers that exhibit considerable changes in serum level during inflammation. These are also important mediators synthesized in the liver during acute and chronic inflammatory conditions. Interleukin-6 (IL-6) is the principal cytokine responsible for stimulating the synthesis in the liver. Interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ) can also trigger the synthesis of acute-phase reactants (APR). Acute phase reactants (APR) result in several adverse effects. These comprise fever, anemia of chronic disease, anorexia, somnolence, lethargy, amyloidosis, and cachexia; and

4-Chronic, which refers patients who require follow-up treatment due to coronary artery involvement.

Diagnosis should occur in the acute stages of that immediate management can be administered to recede inflammation and decrease the risk of coronary artery involvement in the later disease phases.

Kawasaki disease (KD) is illness correlated with considerable morbidity and possible mortality, yet no certain diagnostic test is ready. Increased physician awareness of the main characteristics of Kawasaki disease (KD) and adequate use of echocardiography have together ameliorated patient outcomes through facilitating appropriate management, but in complete presentations complicate diagnosis and are correlated with considerably worse coronary outcomes. Given the severe consequences of late diagnosis, the prompt benefits presented by available remedies involving intravenous immunoglobulin (IVIG), and the elevated incidence of Kawasaki disease (KD) worldwide, it is notable that neonatal and pediatric clinicians regard Kawasaki disease (KD) as a diagnosis in cases of prolonged pediatric fever.

8.1 Kawasaki Disease in COVID-19 Infection

Increasing evidence proposes that tissue damage in coronavirus disease 2019 (COVID-19) is mostly mediated by the host innate immunity. Kawasaki disease (KD) is an acute and usually self-limiting vasculitis of the medium calibre vessels, which almost exclusively affects children. In the acute phase of the disease, patients with Kawasaki disease (KD) might have haemo dynamic instability, a situation known as Kawasaki disease shock syndrome (KDSS). Kawasaki

disease shock syndrome (KDSS) indicate Kawasaki disease (KD) patients who exhibit more than 20% decrease in systolic blood pressure in comparison with healthy persons of the same age, or to those patients who exhibit peripheral blood circulation perfusion disorder. Peripheral vascular disease (PVD) is a blood circulation disorder that causes the blood vessels outside of the heart and brain to narrow, block, or spasm. Clinical manifestations of Kawasaki disease shock syndrome (KDSS) are atypical. It has been summarized the following features for Kawasaki disease shock syndrome (KDSS):

1-It is more common in males;

2-Symptoms involve lymphadenectasis, hypoalbuminemia, hyponatremia, hepatic insufficiency, anemia, and electrocardiogram abnormalities; the incidence of coronary artery dilatation is high, and some children may have severe gastrointestinal symptoms;

3-Inflammatory indicators are significantly increased;

4-Patients frequently exhibit intravenous immunoglobulin (IVIG) resistance;

5-50% of patients require hormone management; and

6-Shock appears at an early stage. It can rapidly develop into shock, and often with strong inflammatory responses which could develop to coronary artery disease and multiple organ dysfunctions.

Other patients with Kawasaki disease (KD) might attain the criteria of macrophage activation syndrome (MAS), like secondary haemophagocytic lymphohistiocytosis (sHLH). Macrophage activation syndrome (MAS), which is currently grouped under secondary or acquired haemophagocytic lymphohistiocytosis (sHLH), is a scarce and fatal disorder that emerges from excess activation of T-cells and macrophages ($M\Phi$). Though the pathogenesis of macrophage activation syndrome (MAS) is poorly understood, various pro-inflammatory cytokines like interleukins [interleukin-1 (IL-1), interleukin-6 (IL-6)], tumor necrosis factor-alpha (TNF- α), and interferons (IFN) are believed to play considerable functions. Macrophage activation syndrome (MAS) is correlated with various clinical characteristics such as non-remitting fever, bleeding, cytopenias, splenomegaly, hepatic dysfunctions, elevated concentrations of triglyceride (TG), ferritin and reduced concentrations of albumin (alb) and fibrinogen. Early diagnosis and

interventions are essential to decrease mortality risk but diagnosis is not frequently easy due to persistence of broad range of characteristics that interfere with other rheumatic diseases, most commonly systemic juvenile idiopathic arthritis (sJIA). Corticosteroids (CSs) and cyclosporins are commonly administered for macrophage activation syndrome (MAS) management. Intravenous immunoglobulins (IVIG), biologic agents like interleukin-1 (IL-1) blockers (anakinra, canakinumab), interleukin-6 (IL-6) blockers (tocilizumab) are also often administered. The cause of Kawasaki disease (KD) keeps unknown; however, earlier evidence presumes that an infectious pathogen stimulates a cascade that causes the disease.

A study concerning Kawasaki disease (KD) as a complication of coronavirus disease 2019 (COVID-19) was performed. Patients with Kawasaki-like presentations were determined according to the 2017 criteria of the American Heart Association, comprising both the classic type and incomplete types. The classic type characterized by fever for ≥ 5 days plus four or more clinical criteria, including bilateral bulbar non-exudative conjunctivitis, changes of the lips or oral cavity, non-suppurative laterocervical lymphadenopathy (a disease affecting the lymph nodes), polymorphic rash, erythema of the palms and soles, and firm induration. Incomplete types characterized by fever for ≥ 5 days plus two or three of the aforementioned clinical criteria, the values of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), or both, were taken as an additional diagnostic criterion in association with the presence of anemia, thrombocytosis after 7 days of fever, hypoalbuminaemia, hypertransaminasaemia, leukocytosis, sterile pyuria, or an echo cardiogram showing coronary aneurysms or cardiac dysfunction. Kawasaki disease shock syndrome (KDSS) was defined as Kawasaki disease accompanied by systolic arterial hypotension, a decrease from basal systolic blood pressure of at least 20%, or the appearance of signs of peripheral hypoperfusion. Ejection fraction (EF), and concentrations of troponin I (a cardiac and skeletal muscle protein family) and pro-B-type natriuretic peptide (proBNP) were measured and indicated as indirect signs of myocarditis and heart failure (HF). Macrophage activation syndrome (MAS) was determined using the Paediatric Rheumatology International Trials Organisation criteria for the classification of macrophage activation syndrome (MAS) in systemic juvenile idiopathic arthritis (SJIA). The macrophage activation syndrome (MAS) criteria are validated for systemic juvenile idiopathic arthritis, but they are commonly used for other systemic autoinflammatory diseases such as Kawasaki disease (KD) and pediatric systemic lupus erythematosus (SLE).

Authors in this study reported that the most reasonable hypothesis boosts an aberrant response of the immune system to one or more unidentified microbes in genetically predisposed patients. This study showed a high number of Kawasaki-like disease patients in the Bergamo province following the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic, with a monthly incidence that is at least 30 times greater than the monthly incidence of the previous 5 years, and has a clear starting point after the first case of coronavirus disease 2019 (COVID-19) was diagnosed in that area. Given the pathogenesis of the disease, serology testing looks a more credible tool than real-time polymerase chain reaction (RT-PCR) assay in detecting the cause of infection. This proposes that the coronavirus family might act one of the inducers of Kawasaki disease (KD), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) being a specially virulent strain capable of eliciting a powerful immune response in the host. In this study, the clinical and biochemical characteristics of patients with Kawasaki disease (KD) diagnosed during the coronavirus disease 2019 (COVID-19) pandemic looked to be different from the historical cohort of patients; therefore, the authors have classified these patients as Kawasaki-like disease. From a clinical view, they were older, had respiratory and gastrointestinal involvement, meningeal signs, and signs of cardiovascular (CV) involvement. From a biochemical view, they had leucopenia with marked lymphopenia, thrombocytopenia, and increased ferritin, as well as markers of myocarditis. Similar clinical characteristics are shared by patients with coronavirus disease 2019 (COVID-19). Additionally, these patients had a more severe disease course, with resistance to intravenous immunoglobulin (IVIG) and need of adjunctive steroids, biochemical evidence of macrophage activation syndrome (MAS), and clinical signs in keeping with Kawasaki disease shock syndrome (KDSS). The pro-inflammatory effect of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been reported in adults with the most severe respiratory complications of coronavirus disease 2019 (COVID-19). Many of these patients have a constellation of characteristics classified under the term cytokine storm, such as fever, lymphopenia, elevated transaminases, lactate dehydrogenase (LDH), D-dimer (DD), and ferritin, in keeping with macrophage activation syndrome (MAS). Likewise, macrophage activation syndrome (MAS) is a form of cytokine storm, and might affect patients with Kawasaki disease (KD). All these elements upheld the requirement to start adjunctive steroids. In authors' experience, this management is efficient and safe, and should be indicated by physicians managing patients with Kawasaki-like presentations in the context of the coronavirus disease

2019 (COVID-19) pandemic. Evidence of contact with the virus was assured by the presence of antibodies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The immune response to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is accountable for a Kawasaki-like disease in susceptible patients. The association between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and Kawasaki-like disease should be considered when it comes to determining social reintegration policies for the pediatric population. However, the Kawasaki-like disease described here remains a scarce situation, likely affecting no more than one in 1000 children exposed to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This evaluate is relied on the limited data from the case series in the region of the study. In brief this study reported a strong association between an outbreak of Kawasaki-like disease and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic in the Bergamo province of Italy. Patients diagnosed with Kawasaki-like disease after the viral spreading exhibited a severe course, including Kawasaki disease shock syndrome (KDSS) and macrophage activation syndrome (MAS), and required adjunctive steroid management.

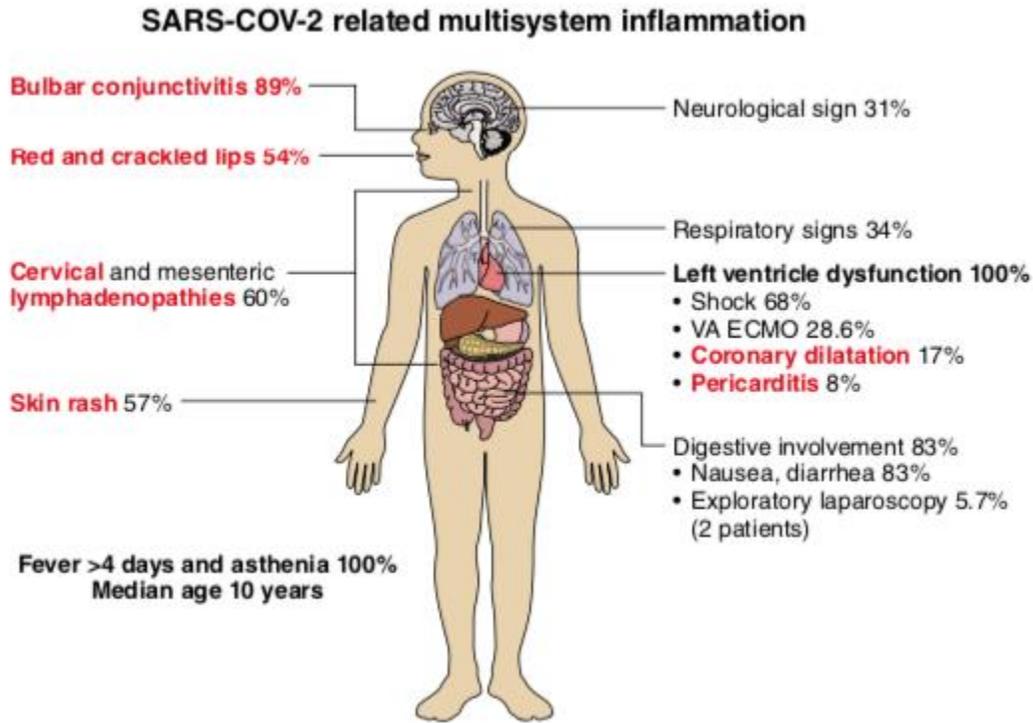
Another study conducted in 2020 argues that in comparison with the two previous years, authors found a 13-fold increased incidence in Kawasaki disease (KD) in children hospitalized in the general pediatrics department of a large university hospital center in Paris. The temporal association with the onset of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic in France and the results of real-time polymerase chain reaction (RT-PCR) assay and immunoglobulin G (IgG) testing in the patients included in this study suppose an accidental link. Moreover, all but one of the patients had no presumed symptoms of acute coronavirus disease 2019 (COVID-19) and most had positive serum immunoglobulin G (IgG) responses, proposing that the development of Kawasaki disease (KD) in these patients is more probably to be the result of a post-viral immunological reaction. Association between Kawasaki disease (KD) and viral respiratory infections has been previously suspicioned, particularly rhinovirus (RH)/enterovirus (EV) and various viral microbes involving human coronaviruses (CoVs). However, no difference in clinical exhibition between infected and non-infected Kawasaki disease (KD) patients was previously mentioned. This study recorded an over-representation of incomplete Kawasaki disease (IKD) (53%), which might be interpreted by a high proportion of severe Kawasaki disease (KD) with myocarditis and Kawasaki disease shock syndrome (KDSS), consistent with previous findings. The incomplete Kawasaki disease (IKD) patients share

Kawasaki disease (KD)-specific laboratory marker profiles in terms of complete blood cell counts and acute phase reactant levels with complete Kawasaki disease (CKD) patients. However, the factors predicting coronary dilation differ according to the phenotype; lower acute and subacute age-adjusted hemoglobin levels predict coronary dilation only in incomplete Kawasaki disease (IKD) patients. Mild myocarditis is very common in the early phase of Kawasaki disease (KD) as shown by cardiac biopsies and scintigraphy, and generally ameliorates rapidly as inflammation dissipates. However, more severe myocarditis with decreased left ventricular contractility can sometimes happen, particularly in the condition of Kawasaki disease shock syndrome (KDSS). Kawasaki disease shock syndrome (KDSS) is a scarce complication affecting 1.5 to 7% of Kawasaki disease (KD) patients with a increased incidence in Western countries than in Asia. It seems to result from both myocardial dysfunction and decreased peripheral vascular resistance, usually requiring intravenous (IV) fluid recovery together with inotropic and vasoactive agent infusion in intensive care unit (ICU). Kawasaki disease shock syndrome (KDSS) pathophysiology is still unclear. An increased concentration of circulating pro-inflammatory cytokines may contribute to the distributive component of shock. In fact, Kawasaki disease shock syndrome (KDSS) was previously observed associated with increased concentrations of interleukin-6 (IL-6), C-reactive protein (CRP) and procalcitonin (PCT). The authors of this study recognized very high concentrations of procalcitonin (PCT). C-reactive protein (CRP) and interleukin-6 (IL-6) concentrations were also elevated. This main pro-inflammatory condition may reflect a mostly strong post-viral immunological reaction to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in comparison with other viral microbes. A cytokine storm syndrome with elevated inflammatory markers such as interleukin-6 (IL-6) was mentioned in adult coronavirus disease 2019 (COVID-19) patients, and has been correlated with fatality. Besides inflammatory markers, clinical and biological characteristics of study patients were frequently symmetric with the diagnosis of Kawasaki disease shock syndrome (KDSS). Really, older age, higher D-dimer (DD), lower hemoglobin (Hb) and albumin (alb) concentrations and more severe hyponatremia were previously found associated with Kawasaki disease shock syndrome (KDSS). This study found only 18% of patients were above the 75th percentile for weight, which does not boost the hypothesis of overweight as a risk factor for Kawasaki disease (KD) after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Intravenous immunoglobulin (IVIG) resistance and coronary artery abnormalities

were less frequent in this study series than in previous ones. However, these findings should be taken with caution as coronary artery abnormalities may appear later during follow-up. Gastrointestinal (GI) symptoms were also unusually common, affecting 100% of the patients. A research reported intestinal pseudo-obstruction in only 2% of 310 patients. As previously described, other Kawasaki disease (KD) symptoms appeared in all cases after the intestinal ones, which may have led to diagnostic and therapeutic delays in some children. Suspected mechanisms include intestinal ischemia, secondary to bowel vessel vasculitis. Rapid degeneration of symptoms in all patients after intravenous immunoglobulin (IVIG) boosts this hypothesis. Pancreatitis, detected by higher lipase level in 7 patients, may also reflect vasculitis. Hypoalbuminemia was severe and may partially be attributed to exudative enteropathy. The recognition of an increased rate of patients originating from sub-Saharan Africa and the Caribbean islands is agreeable with findings reported by a valuable study, proposing either adverse social and living situations or genetic susceptibility. Kawasaki disease (KD) is scarcely reported in sub-Saharan Africa, but it may be more common than previously thought. In the United States of America, a 2.5-fold higher incidence was reported in children of Asian than of European ancestry with an intermediary 1.5-fold risk for children of African ancestry. Besides, African Americans have been disproportionately hit by the coronavirus disease 2019 (COVID-19) pandemic, also presuming higher susceptibility to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Therefore, African countries where severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic has spread may encounter a possibly large number of Kawasaki disease (KD) in children, and intravenous immunoglobulin (IVIG) supply shortages should be expected in such settings. The absence of reported cases of Kawasaki disease (KD) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in Asian countries where the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) epidemic started, and where the incidence of Kawasaki disease (KD) is the highest, is quite recognizable. Ethnic differences in the development of Kawasaki disease shock syndrome (KDSS) were previously reported, with a lower incidence rate in Asia than in Western countries. In conclusion this study documents an outbreak of Kawasaki disease (KD) in the Paris area and its association with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Kawasaki disease (KD) patients reported in this study have features that differ from classic Kawasaki disease (KD): this form looks to be much more often among children of

African ancestry, with dominant acute gastrointestinal (GI) manifestations, hemodynamic instability and myocarditis.

9. Multisystem Inflammatory Syndrome in Children



Figure(54): Multiinflammatory syndrome in children [Bonnet D. (2020). Immunotherapy, steroids had positive outcomes in children with COVID-related multi-system inflammatory syndrome. Circulation Journal Report]

In children, coronavirus disease 2019 (COVID-19) is usually mild. However, in scarce cases, children can be severely affected, and clinical manifestations can be different from adults. In April of 2020, reports arose from the United Kingdom of a presentation in children similar to incomplete Kawasaki disease (IKD) or toxic shock syndrome (TSS). It is important here to define toxic shock syndrome (TSS) as a condition caused by bacterial toxins. Symptoms may involve fever, rash, skin peeling, and low blood pressure. There may also be symptoms connected to the specific underlying infection such as mastitis, osteomyelitis, necrotising fasciitis, or pneumonia. Since then, there have been increasing reports of similarly affected

children in other parts of the world. The syndrome has been termed multisystem inflammatory syndrome in children [MIS-C; also referred to as pediatric multisystem inflammatory syndrome (PMIS), pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (PIMS-TS), pediatric hyperinflammatory syndrome, or pediatric hyperinflammatory shock].

While the occurrence of multisystem inflammatory syndrome in children (MIS-C) is obscure, it seems to be a scarce complication of coronavirus disease 2019 (COVID-19) in children. The first reports of multisystem inflammatory syndrome in children (MIS-C) arose from the United Kingdom in April, 2020. Since then, there have been reports of similarly affected children in other parts of the world, involving Europe, Canada, and the United States. Many children with multisystem inflammatory syndrome in children (MIS-C) subtend criteria for complete or incomplete Kawasaki disease (KD). However, the epidemiology is different from that of classic Kawasaki disease (KD). Most multisystem inflammatory syndrome in children (MIS-C) cases have incident in older children and adolescents who were previously healthy. Black and Hispanic children may be disproportionately influenced. By contrast, classic Kawasaki disease (KD) primarily affects infants and young children and has an increased occurrence in East Asia and in children of Asian descent. The epidemiology of multisystem inflammatory syndrome in children (MIS-C) also differs from that of acute coronavirus disease 2019 (COVID-19) illness in children, which tends to be most severe in infants <1 year of age and in children with underlying health issues. The first report of multisystem inflammatory syndrome in children (MIS-C) was a series of eight children checked at a tertiary center in South East England. In three subsequent case series from the United Kingdom (n = 58), France and Switzerland (n = 35), and New York (n = 33), the preponderance of children were previously healthy (88 percent in the United Kingdom series, 89 percent in the French series, and 79 percent in the New York series). The most common comorbidities were obesity and asthma. The average age was 9 to 11 years (range 1 to 17 years). It is unclear if the risk of developing multisystem inflammatory syndrome in children (MIS-C) varies by race, though black and Hispanic children account for a disproportionately elevated number of cases and Asian children account for only a small number of cases in the initial reports. In the United Kingdom series, 38 percent of patients were black, 19 percent white, 11 percent Asian, and 5 percent biracial. In the New York series, 24 percent were black, 27 percent Hispanic, 9 percent white, and 9 percent Asian. In a series of 21 patients from a single

center in France, 57 percent had at least one parent with African ancestry and 14 percent had at least one parent of Asian ancestry. Based on the patterns seen in the United Kingdom, New York, and Italy, there seems to be a lag of several weeks between the peak of coronavirus disease 2019 (COVID-19) cases within communities to the peak of multisystem inflammatory syndrome in children (MIS-C) cases. For example, in London, the peak of coronavirus disease 2019 (COVID-19) cases occurred in the first to second weeks of April, while the peak of multisystem inflammatory syndrome in children (MIS-C) cases occurred in the first to second week of May. This three- to four-week lag coincides with the timing of acquired immunity and supposes that multisystem inflammatory syndrome in children (MIS-C) may characterize a postinfectious complication of the virus rather than acute infection, at least in some children.

It has been proposed that the syndrome results from an abnormal immune response to the virus, with some similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome (CRS).

Many affected children have negative polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) but have positive serology, a finding that further upholds the hypothesis that multisystem inflammatory syndrome in children (MIS-C) is connected to immune dysregulation happening after acute infection has passed. However, some children do have positive polymerase chain reaction (PCR) testing. In case series from the United Kingdom, New York, Italy, and France there were 142 children in whom both polymerase chain reaction (PCR) and serology were done. Of these, 63 percent had positive serology with negative polymerase chain reaction (PCR), 30 percent were positive on both tests, and 8 percent were negative on both tests.

In the available case reports, clinical presentations were similar, involving: persistent fevers (median duration four days) (100%), gastrointestinal (GI) symptoms (abdominal pain, vomiting, diarrhea) (60 to 100%), rash (52 to 76%), conjunctivitis (45 to 81%), mucous membrane involvement (29 to 76%), neurocognitive symptoms (headache, lethargy, confusion) (29 to 58%), respiratory symptoms (21 to 65%), swollen hands/feet (16%), sore throat (10%). Gastrointestinal (GI) symptoms (abdominal pain, vomiting, diarrhea) were especially common and notable, with some children mimicking appendicitis. Some children have been noted to have terminal ileitis on abdominal imaging and/or colitis on colonoscopy. It is important to determine

terminal ileitis as a chronic inflammatory disease of the intestine including only the end of the small intestine (the terminal ileum). In addition colitis is identified as a chronic digestive disease characterized by inflammation of the inner lining of the colon. Infection, loss of blood supply in the colon, inflammatory bowel disease (IBD) and invasion of the colon wall with collagen or lymphocytic white blood cells are all possible causes of an inflamed colon. Many patients exhibited three to five days of fever, then continued to progress to vasodilatory/distributive shock. Distributive shock results from excessive vasodilation and the impaired distribution of blood flow. Septic shock is the most common form of distributive shock and is described by significant mortality (treated, around 30%; untreated, probably >80%). Patients exhibiting fewer days of fever have been mentioned. Shock is frequently refractory to volume resuscitation, requiring vasopressors and, in scarce conditions, mechanical hemodynamic boost. Pulmonary involvement was not a distinguished character in most cases, though many children required supplemental oxygen or positive pressure ventilation for cardiovascular (CV) stabilization. Respiratory symptoms (tachypnea, labored breathing), when found, were most often due to severe shock. Cough was uncommon.

In the obtainable case reports, common clinical results involve: shock (50 to 80%), criteria met for complete Kawasaki disease (KD) (22 to 64 %), myocardial dysfunction [by echocardiogram or elevated troponin/brain natriuretic peptide (BNP)] (51 to 100%), acute respiratory failure (ARF), requiring noninvasive or invasive ventilation (43 to 52%), acute kidney injury (AKI) (most cases were mild) (22 to 70%), serositis (24 to 57%), and acute (fulminant) hepatic failure (AHF) (21%).

It is increasingly becoming clear that there is a wide spectrum of disease severity in multisystem inflammatory syndrome in children (MIS-C). The initial case series largely reported the most severe end of the spectrum, developing to an increased reported incidence of shock, myocardial involvement, and respiratory failure. It is probably that as presumption of milder forms of multisystem inflammatory syndrome in children (MIS-C) heightens, the incidence of shock, left ventricular (LV) dysfunction, respiratory failure, and acute kidney injury will be lower.

Evaluation should involve measurement of sequential inflammatory markers, including complete blood count (CBC)/differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR);

coagulation parameters including Ddimer (DD) and ferritin; liver function markers; and a cytokine panel. Children should have antibody (Ab) testing in addition to polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), since many children are antibody (Ab)-positive even when polymerase chain reaction (PCR)-negative.

Laboratory abnormalities recognized in the obtained case series involve: first, abnormal blood cell counts [lymphocytopenia (80 to 95%), neutrophilia (80 to 90%), mild anemia (70%), and thrombocytopenia (31 to 80%)] ; second, elevated inflammatory markers, including: C-reactive protein (CRP) (90 to 100%), erythrocyte sedimentation rate (ESR) (80%), D dimer (DD) (80 to 100%), fibrinogen (90 to 100%), ferritin (55 to 76%), procalcitonin (PCT) (80 to 95%), and interleukin-6 (IL-6) (80 to 100%); third, elevated cardiac markers including: troponin (Tn) (68 to 95%), brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) (78 to 100%); fourth, hypoalbuminemia (73 to 95%); fifth, mildly elevated liver enzymes (62 to 70%); sixth, elevated lactate dehydrogenase (LDH) (56 to 60%); seventh, hypertriglyceridemia (HTG) (70%). Laboratory markers of inflammation seem to associate with severity of disease. For example, in one series, children who suffered from shock had higher C-reactive protein (CRP) levels (mean 32.1 versus 17.6 mg/dL), higher neutrophil counts (16 versus 10.8 x10⁹/L), lower lymphocyte counts (0.7 versus 1.3 x10⁹/L), and lower serum albumin (alb) levels (2.2 versus 2.7 g/dL) in comparison with children without shock. In addition, children with shock more commonly had higher cardiac markers.

Findings on diagnostic imaging may involve:

1-Echocardiography: children with this syndrome should have serial echocardiograms comprising particular evaluation of the coronary arteries (CAs). Many to date have been found to have low heart function, and some have enlargement of the coronary arteries (CAs). Children with serious cardiac complications should be followed longer-term. Echocardiographic findings may involve depressed left ventricular (LV) function and coronary artery (CA) abnormalities (including dilation or aneurysm), mitral valve regurgitation, and pericardial effusion. The frequency of cardiac involvement in multisystem inflammatory syndrome in children (MIS-C) is uncertain. In the initial reports, approximately 50 to 60 percent of patients had depressed left ventricular (LV) function and approximately 20 to 50 percent had coronary artery (CA)

abnormalities. However, most of the children in the early reports were severely affected, and these evaluations may not reflect the risk in the wide population. In subsequent reports that involved children with milder cases of multisystem inflammatory syndrome in children (MIS-C), the risk of cardiac involvement looks to be recognizably lower than the initial reports. In one series of 58 hospitalized children, of whom only a subset required intensive care, depressed left ventricular (LV) function was seen in 31 percent of cases and coronary artery (CA) abnormalities were detected in only 14 percent.

2-Chest radiograph: many patients had normal chest radiographs. Abnormal findings involved small pleural effusions, patchy consolidations, focal consolidation, and atelectasis. It is important to mention small pleural effusions refer to the build-up of excess fluid between the layers of the pleura outside the lungs. The pleura are thin membranes that line the lungs and the inside of the chest cavity and act to lubricate and facilitate breathing. In addition, a pulmonary consolidation is a region of normally compressible lung tissue that has filled with liquid instead of air. The condition is marked by induration (swelling or hardening of normally soft tissue) of a normally aerated lung. It is considered a radiologic sign. Further, atelectasis refers to partial collapse or incomplete inflation of the lung.

3-Computed tomography (CT) of chest : chest computed tomography (CT) (when obtained) generally had findings similar to those on chest radiograph. A few patients had nodular ground-glass opacification. Ground-glass opacification/opacity (GGO) is a descriptive term referring to an area of increased attenuation in the lung on computed tomography (CT) with preserved bronchial and vascular markings.

4-Abdominal imaging: findings on abdominal ultrasound or computed tomography (CT) included free fluid, ascites (i.e.,the accumulation of fluid in the peritoneal cavity, causing abdominal swelling), and bowel and mesenteric inflammation including terminal ileitis, mesenteric adenopathy/adenitis (inflammation and swelling in the lymph nodes inside the abdomen), and pericholecystic edema.

Patients with multisystem inflammatory syndrome in children (MIS-C) are at risk of undergoing thrombotic complications. For example, patients with severe left ventricular (LV) systolic dysfunction are at risk for apical left ventricular (LV) thrombus, and those with Kawasaki disease (KD) who have large or giant coronary artery (CA) aneurysms are at risk for myocardial

infarction. In addition, patients may be at risk for venous thromboembolism (VTE), involving pulmonary embolus, due to hypercoagulability related to coronavirus disease 2019 (COVID-19).

As more is learned about coronavirus disease 2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C), it is becoming apparent that the spectrum of disease ranges from mild to severe. The understanding of the full spectrum, including subphenotypes, is evolving:

1-Coronavirus disease 2019 (COVID-19) without an exaggerated immune response: in most children, coronavirus disease 2019 (COVID-19) causes no or only mild symptoms.

2-Coronavirus disease 2019 (COVID-19)-associated febrile inflammatory state: some children may exhibit persistent fevers and mild symptoms (e.g., headache, fatigue). Inflammatory markers (especially ferritin) may be elevated, but signs of multisystem involvement are lacking.

3-Coronavirus disease 2019 (COVID-19)-associated Kawasaki disease (KD): some children meet criteria for complete or incomplete Kawasaki disease (KD) and do not develop shock and multisystem involvement. It is unclear if the incidence of coronary artery (CA) aneurysms is elevated in coronavirus disease 2019 (COVID-19)-associated Kawasaki disease (KD) in comparison with classic Kawasaki disease (KD). Coronary aneurysms are abnormal dilations of the coronary arteries. This can occur as post-stenotic dilation during atherosclerotic coronary disease or can occur as a part of a vasculitis. Kawasaki's disease during childhood can lead to coronary aneurysms in adulthood causing ischemic heart disease and angina.

4-coronavirus disease 2019 (COVID-19)-associated multisystem inflammatory syndrome in children (MIS-C): children with multisystem inflammatory syndrome in children (MIS-C) have a more severe presentation, with markedly elevated inflammatory markers and multisystem involvement. Cardiac involvement and shock are common.

All patients with suspected multisystem inflammatory syndrome in children (MIS-C) should be examined for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), comprising both serology and reverse transcription polymerase chain reaction (RT-PCR) on a nasopharyngeal swab. Most affected children have positive serology with negative polymerase chain reaction (PCR), though some have positive polymerase chain reactions (PCRs).

In addition to troponin (Tn) and brain natriuretic peptide/ N-terminal (NT)-pro hormone brain natriuretic peptide (BNP/NT-pro-BNP) levels, the cardiac evaluation of a patient with suspected multisystem inflammatory syndrome in children (MIS-C) includes a 12-lead electrocardiogram

(ECG) and echocardiography. Echocardiography is also recommended for children with documented severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) who do not meet all criteria for multisystem inflammatory syndrome in children (MIS-C) but who have either shock or features consistent with incomplete or complete Kawasaki disease (KD).

Children and adolescents with mild coronavirus disease 2019 (COVID-19) without signs of systemic inflammation are unlikely to have coronary artery (CA) changes or myocarditis. In such children, echocardiography is generally not necessary but may be taken into account if there are particular clinical interests.

In children with multisystem inflammatory syndrome in children (MIS-C), baseline electrocardiograms (ECGs) may be nonspecific, though arrhythmia and heart block have been illustrated. Findings on initial echocardiography may involve coronary artery (CA) dilation, left ventricular (LV) systolic dysfunction, and pericardial effusion. The coronary artery (CA) abnormalities can develop to aneurysm, involving giant coronary aneurysms.

A study performed by Whittaker *et al.* (2020) showed that fifty-eight children (median age, 9 years) were identified who met the criteria for multisystem inflammatory syndrome in children (MIS-C) infection. In total, 45 of 58 patients (78%) had evidence of current or prior severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) illness. All children exhibited fever and nonspecific symptoms, involving vomiting [26/58 (45%)], abdominal pain [31/58 (53%)], and diarrhea [30/58 (52%)]. Rash existed in 30 of 58 (52%), and conjunctival injection in 26 of 58 (45%) cases. Laboratory evaluation was consistent with notable inflammation. Of the 58 children, 29 developed shock (with biochemical evidence of myocardial dysfunction) and required inotropic support and fluid resuscitation [including 23/29 (79%) who received mechanical ventilation]; 13 met the American Heart Association definition of Kawasaki disease (KD), and 23 had fever and inflammation without characteristics of shock or Kawasaki disease (KD). Eight patients (14%) experienced coronary artery (CA) dilatation or aneurysm. Comparison of multisystem inflammatory syndrome in children (MIS-C) with Kawasaki disease (KD) and with Kawasaki disease shock syndrome (KDSS) showed differences in clinical and laboratory features, including older age (median age, 9 years vs 2.7 years and 3.8 years, respectively), and greater elevation of inflammatory markers such as C-reactive protein (CRP) (median, 229 mg/L vs 67 mg/L and 193 mg/L, respectively).

From March through May 2020, during the coronavirus disease 2019 (COVID-19) pandemic, pediatricians in the United Kingdom and elsewhere noted hospitalizations of children who developed fever and multisystem inflammation. Some of these children were critically ill with shock and multiorgan failure and required intensive care, and some had characteristics that were similar to Kawasaki disease (KD) or Kawasaki disease shock syndrome (KDSS). The clinical evidence presumed the development of multisystem inflammatory syndrome in children (MIS-C). In this case series of 58 hospitalized children who met wide definitions for childhood multisystem inflammatory disorders recently proposed in the United Kingdom, United States, or by the World Health Organization (WHO), there was a wide spectrum of presenting signs and symptoms, including fever, gastrointestinal symptoms, and rash, as well as disease severity, including myocardial injury, shock, and development of coronary artery (CA) aneurysms. Comparison with patients from cohorts with Kawasaki disease (KD), Kawasaki disease shock syndrome (KDSS), and toxic shock syndrome (TSS) provides additional insights into this syndrome, and suggests that multisystem inflammatory syndrome in children (MIS-C) differs from these pediatric inflammatory entities. In addition, there provisionally appears to be 3 patterns of disease among children hospitalized with multisystem inflammatory syndrome in children (MIS-C). One group of children had persistent fever and higher concentrations of inflammatory markers, but without characteristics of Kawasaki disease (KD), shock, or organ failure. A second group achieved the diagnostic criteria for Kawasaki disease (KD). A third group had shock and clinical, echocardiographic, and laboratory evidence of myocardial injury. Cases of multisystem inflammatory syndrome in children (MIS-C) generally occurred in children older than those with Kawasaki disease (KD) and Kawasaki disease shock syndrome (KDSS), and with different laboratory characteristics. When multisystem inflammatory syndrome in children (MIS-C) cases with coronary artery (CA) aneurysms were compared with pre-coronavirus disease 2019 (COVID-19) Kawasaki disease (KD) cases that progressed coronary artery (CA) aneurysms, children with multisystem inflammatory syndrome in children (MIS-C) tended to be older, have more intense inflammation, and have elevated concentrations of markers of cardiac injury, supposing that these are 2 separate entities and that management for multisystem inflammatory syndrome in children (MIS-C) may need to be different than that for Kawasaki disease (KD). Various biomarkers, including C-reactive protein (CRP), ferritin, troponin (Tn), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations may

be beneficial in assuming development of disease. However, comparison of children with multisystem inflammatory syndrome in children (MIS-C) who underwent coronary artery dilatation or aneurysms with those who did not failed to identify any differences in clinical or laboratory markers. Of particular interest was the finding that coronary artery (CA) aneurysms were found in a subset of all 3 groups of multisystem inflammatory syndrome in children (MIS-C). The lack of association either between the concentrations of inflammation in these groups or markers of cardiac injury and progress of coronary artery (CA) aneurysms supposes that the coronary changes are not solely a consequence of severity of inflammation. Children with Kawasaki disease (KD) require coronary echocardiography to detect coronary artery (CA) aneurysms, and the echocardiographic changes may either worsen or resolve, leading to recommendations for both acute echocardiographic studies, as well as sequential follow-up at 2 and 6 weeks. The elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin (Tn) concentrations raise interest as to myocardial cell injury, and follow-up of cardiac function as well echocardiographic studies to detect coronary artery (CA) aneurysms are warranted across the spectrum of multisystem inflammatory syndrome in children (MIS-C) in both the acute and convalescent phases. Patients were managed with a range of immunomodulatory medications, according to local practice. This study also cannot address the mechanisms underlying multisystem inflammatory syndrome in children (MIS-C). However, the timing of the disorder emerging in relation to the epidemic, and the finding that most patients were negative for detection of the virus but positive for antibody against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), raises the possibility that the disorder may involve an aberrant development of acquired immunity. There is evidence from severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) that antibodies (Abs) place disease either through antibody enhancement of viral entry or replication as has been seen in dengue¹¹ or through promoting of a host inflammatory response either through formation of immune complexes or direct antitissue or cellular activation. Antispikes antibodies against severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) have been observed to set inflammation in primates and in human macrophages (MΦ) and it is therefore possible that as antibodies develop against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) they may induce an inflammatory process through a similar mechanism. Although this study has shown that multisystem inflammatory syndrome in children (MIS-C) has differences from pre-coronavirus disease 2019 (COVID-19)

Kawasaki disease (KD), the similarity in clinical characteristics in some cases and progression of coronary artery (CA) aneurysms in both disorders may offer clues to the underlying mechanisms of both. Immune complexes have been well documented in Kawasaki disease (KD) and may also mediate vascular injury, through activation of inflammatory responses through the Fc gamma receptor or neutrophil activation. In this study, most patients with multisystem inflammatory syndrome in children (MIS-C) were managed with intravenous immunoglobulin (IVIG) and/or corticosteroids (CSs), and fewer patients received a range of other immunomodulating agents. In view of the excessively elevated C-reactive protein (CRP) concentrations, interleukin-6 (IL-6) may be included in the myocardial depression. Finally, authors concluded that in this case series of hospitalized children who met criteria for multisystem inflammatory syndrome in children (MIS-C), there was a broad spectrum of presenting signs and symptoms and disease severity, ranging from fever and inflammation to myocardial injury, shock, and progression of coronary artery (CA) aneurysms. The comparison with patients with Kawasaki disease (KD) and Kawasaki disease shock syndrome (KDSS) offers views into this syndrome, and proposes this disorder differs from other pediatric inflammatory entities.

Multisystem inflammatory syndrome in children (MIS-C) can present with signs and symptoms that mimic those of septic shock and toxic shock syndrome (TSS). Thus, patients exhibiting severe multisystem involvement, especially those with shock, should receive prompt empiric broad-spectrum antibiotic therapy pending culture results. An adequate empiric regimen consists of ceftriaxone (CE) plus vancomycin (VA). Ceftaroline (CFT) plus piperacillin-tazobactam (PIP-TAZ) is an alternative regimen, especially for children with acute kidney injury (AKI). Clindamycin (CL) is added if there are characteristics consistent with toxin-mediated illness (e.g., erythroderma). Antibiotics should be discontinued once bacterial infection has been excluded if the child's clinical condition has stabilized.

The role of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antiviral therapies (e.g., remdesivir) in the management of multisystem inflammatory syndrome in children (MIS-C) is obscure. Many patients are polymerase chain reaction (PCR)-negative for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and multisystem inflammatory syndrome in children (MIS-C) likely represents a postinfectious complication rather than active infection. However, some children do have positive polymerase chain reaction (PCR) testing and may have

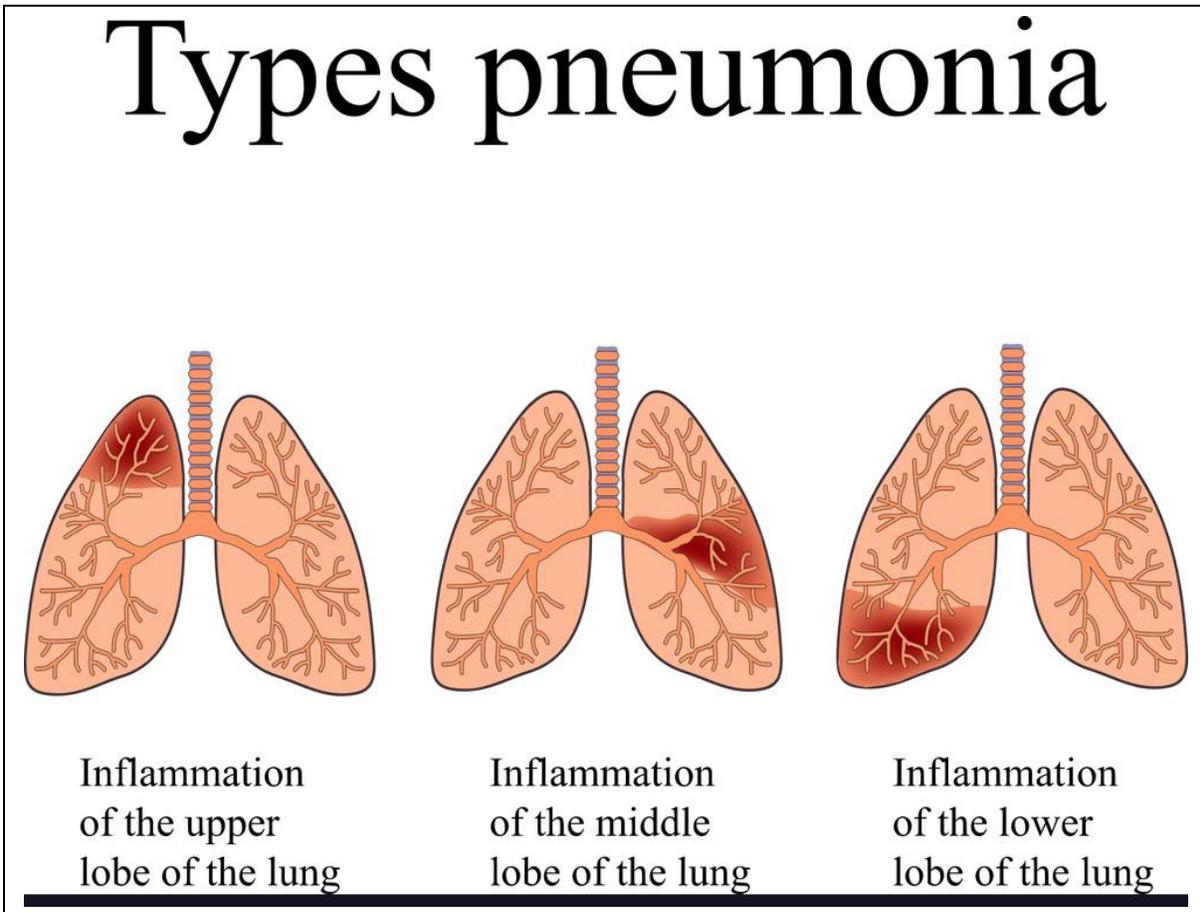
active infection. Thus, antiviral remedy may have probably to impact the disease process in some, but not all, patients. Use of antiviral agents is generally restricted to children with severe multisystem inflammatory syndrome in children (MIS-C) manifestations. Additional therapy depends on the clinical presentation. These presentations can intervene, and it may be suitable to offer interventions from more than one category. For example, patients presenting with Kawasaki disease (KD) with associated distributive shock should receive management for Kawasaki disease (KD) [i.e., intravenous immunoglobulin (IVIG) and aspirin (or acetylsalicylic acid (ASA))] and appropriate hemodynamic support [i.e., volume expansion and epinephrine(EP)]. Children presenting with shock should be recovered according to standard protocols. In the available case series, most children with multisystem inflammatory syndrome in children (MIS-C) experienced vasodilatory shock that was refractory to volume expansion. Epinephrine (EP) or norepinephrine (NE) are the preferred vasoactive agents for the treatment of fluid-refractory shock in children; epinephrine (EP) is favored when there is evidence of ventricular dysfunction. In children presenting with severe ventricular dysfunction, the addition of milrinone (MIL) may be helpful. Patients who meet criteria for incomplete or complete Kawasaki disease (KD) should be administered standard remedies for Kawasaki disease (KD), involving intravenous immunoglobulin (IVIG), aspirin, and, if there are persistent signs of inflammation or coronary artery (CA) dilation/aneurysm, glucocorticoids (GCs). During the acute inflammatory phase (beginning within seconds to minutes following injury to tissues, characterized by redness, heat, swelling, and pain) of disease, children with myocardial dysfunction may experience arrhythmias and hemodynamic compromise. Serial echocardiographic assessment of cardiac function and monitoring of brain natriuretic peptide (BNP) and troponin (Tn) levels can help guide therapy. Management focuses on supportive care to maintain hemodynamic stability and ensure adequate systemic perfusion. Intravenous immunoglobulin (IVIG) is frequently administered in severe cases when the clinical picture is consistent with myocarditis, though conclusive evidence of benefit is lacking. Continuous cardiac monitoring is crucial so that arrhythmias are immediately detected and managed. Patients with considerable ventricular dysfunction are managed with intravenous (IV) diuretics and inotropic agents, such as milrinone (MIL), dopamine (DA), and dobutamine (DOB). In cases of fulminant disease, mechanical hemodynamic boost may be beneficial in the form of extracorporeal membrane oxygenation (ECMO) or a ventricular assist device. All patients who

meet criteria for complete or incomplete Kawasaki disease should receive antithrombotic therapy, which, at a minimum, includes low-dose aspirin. Additional antiplatelet and/or anticoagulant therapy may be warranted in select patients, depending on the degree of coronary artery (CA) dilation. Systemic anticoagulation may be adequate for patients with moderate to severe left ventricular (LV) dysfunction. In patients without Kawasaki disease (KD) or considerable left ventricular (LV) dysfunction, the decision to initiate therapy for prevention of venous thromboembolism (VTE) is individualized. The diagnosis of coronavirus disease 2019 (COVID-19)-related multisystem inflammatory syndrome in children (MIS-C) itself should be regarded a major risk factor for venous thromboembolism (VTE). Venous thromboembolism (VTE) prophylaxis is generally adequate for older children and adolescents hospitalized with moderate to severe multisystem inflammatory syndrome in children (MIS-C), provided that bleeding risk is low. In infants and young children, the decision is made on a case-by-case basis, weighing other venous thromboembolism (VTE) risk factors and the patient's bleeding risk. When venous thromboembolism (VTE) prophylaxis is used, low molecular weight heparin (LMWH) is generally the favored agent. Nonpharmacologic strategies for venous thromboembolism (VTE) prophylaxis [e.g., intermittent pneumatic compression devices (size permitting) and early mobilization] are encouraged, but multisystem inflammatory syndrome in children (MIS-C)-related coagulopathy may warrant a higher level of intervention. The benefits and risks of adjunctive therapies [glucocorticoids (GCs), interleukin-1 (IL-1) inhibitors (e.g., anakinra, canakinumab), interleukin-6 (IL-6) inhibitors (e.g., tocilizumab), convalescent plasma from recovered coronavirus disease 2019 (COVID-19) patients] are obscure. Consultation with pediatric infectious disease and rheumatology specialists is advised. Decisions about the use of adjunctive therapies depend on a case-by-case basis, according to disease severity and markers of inflammation or active severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Glucocorticoids (GCs) are adequate for patients with characteristics of Kawasaki disease (KD) who have persistent fever after intravenous immunoglobulin (IVIG) or coronary artery (CA) dilation/aneurysm. In addition, glucocorticoids (GCs) can be described for patients with cytokine release syndrome (CRS). Cytokine release syndrome (CRS), also called cytokine storm, is characterized by persistent fever, markedly elevated inflammatory markers (e.g., C-reactive protein (CRP), D-dimer (DD), ferritin) and elevated proinflammatory cytokines [e.g., interleukin-6 (IL-6)]. Anakinra (ANA), canakinumab (INN), and tocilizumab (TOC) are

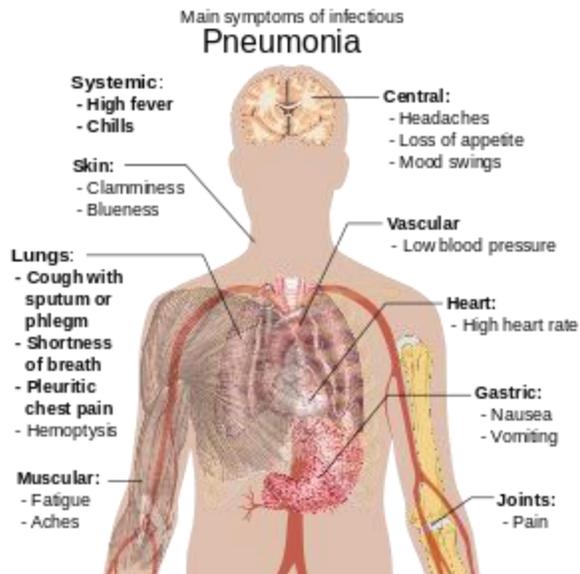
alternative options for management of cytokine release syndrome (CRS) in patients who cannot receive glucocorticoids (GCs) and those who are refractory to glucocorticoids (GCs). Such decisions should be made under the direction of a pediatric rheumatologist and should occur in the context of a clinical trial whenever possible.

10. Respiratory Manifestations

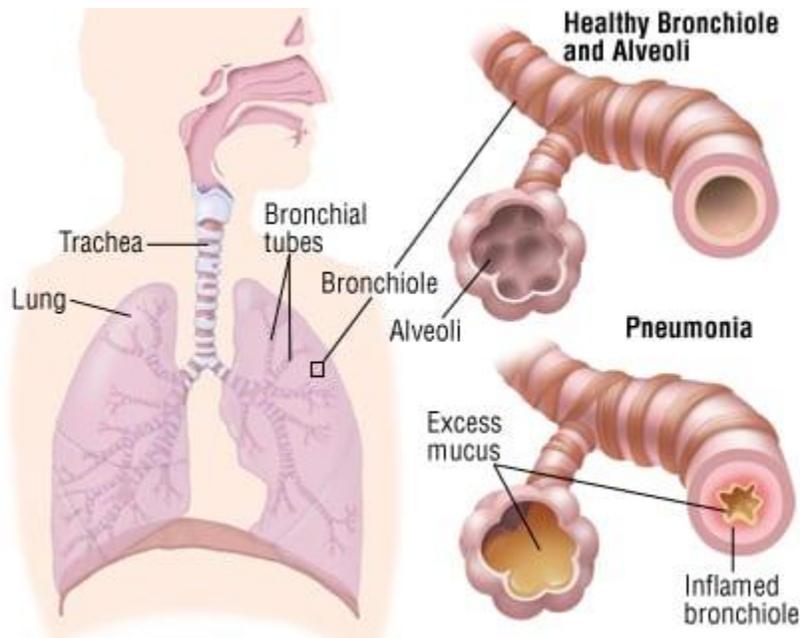
10.1 Pneumonia



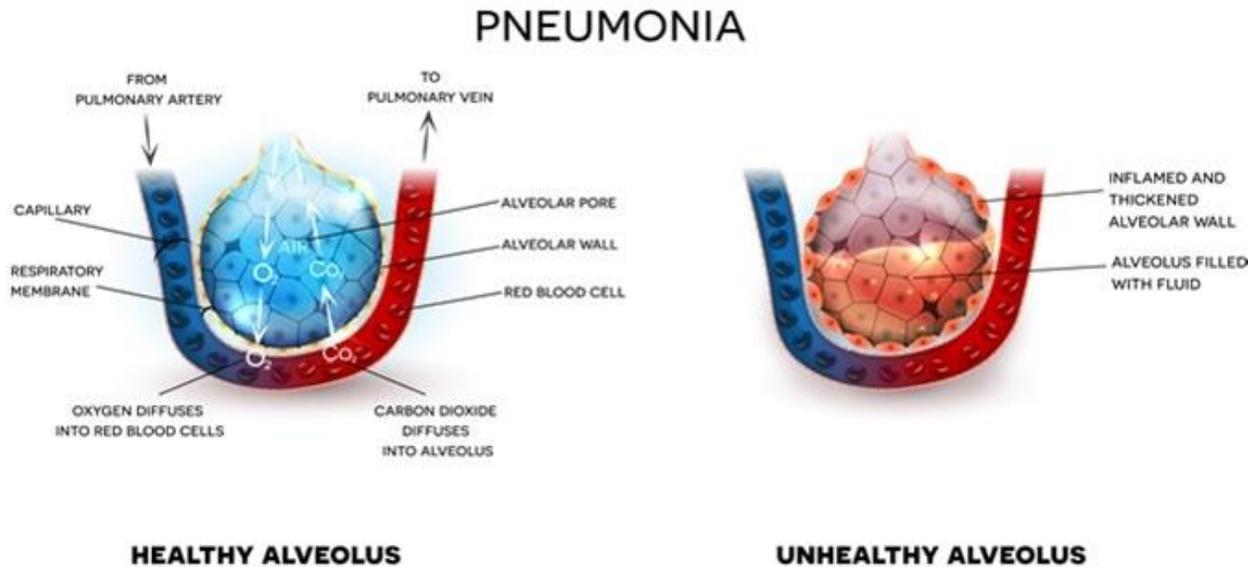
Figure(55): Pneumonia types (www.google.com)



Figure(56): Pneumonia symptoms (www.google.com)



Figure(57):Pneumonia (www.google.com)



Figure(58): Healthy alveolus versus Unhealthy alveolus in pneumonia [Lashkari C.; Thomas L. (2019). Is walking pneumonia contagious?. News. Medical Life Sciences]

Pneumonia has been defined as an infection of the lung parenchyma. Rather than looking at it as a single disease, health care professionals must mind that pneumonia is an umbrella term for a group of syndromes resulted from a variety of organisms leading to varied manifestations and sequelae. There have been many endeavors to classify pneumonia depended on the etiology, clinical setting in which the apparent acquired the infection, and the type of involvement of lung parenchyma, among other classifications. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (also called bronchopneumonia) affects patches throughout both lungs. Community-acquired Pneumonia (CAP) is any pneumonia acquired outside of a hospital in a community environment. Hospital-acquired pneumonia (HAP) is any pneumonia acquired 48 hours after being admitted in an inpatient status such as a hospital and not incubating at the time of admission is considered as hospital-acquired pneumonia (HAP). Now all pneumonia acquired in the status of assisted-living facilities, rehabilitation facilities, and other healthcare facilities have been involved under community-acquired pneumonia, and a hospital environment is requisite for classifying pneumonia as hospital-acquired pneumonia (HAP). Ventilator associated pneumonia (VAP) is any pneumonia acquired 48 hours after endotracheal intubation is described as ventilator associated pneumonia (VAP). These categories have aided confirm the common organisms responsible for each type of pneumonia and assisted to

formulate treatment guidelines for the effective treatment in both in-patient and out-patient setting.

-Based on the type of involvement, pneumonia has historically also been studied as:

1-Focal non-segmental or lobar pneumonia: involvement of a single lobe of the lung. Lobar pneumonia, also known as non-segmental pneumonia or focal non-segmental pneumonia, is a radiological pattern associated with homogeneous and fibrinosuppurative consolidation of one or more lobes of a lung in response to pathogenic microbial pneumonia.

2-Multifocal bronchopneumonia or lobular pneumonia. Bronchopneumonia, also known as multifocal or lobular pneumonia, is radiographically identified by its patchy appearance with peribronchial thickening and poorly defined air-space opacities. As illness becomes more severe, consolidation involving the terminal and respiratory bronchioles and alveoli results in the development of centrilobular nodular opacities or air-space nodules. The consolidation can develop further and coalesce to give a lobular or lobar pattern of involvement.

3-Focal or diffuse interstitial pneumonia or diffuse interstitial lung disease refers to a large group of lung disorders that affect the interstitium, which is the connective tissue that forms the support structure of the alveoli (air sacs) of the lungs. Normally when one inhales, the alveoli fill with air and oxygen passes into the blood stream. When one exhales, carbon dioxide passes from the blood into the alveoli and is then expelled from the body. When interstitial disease is present, the lung becomes inflamed and stiff, preventing the alveoli from fully expanding. This limits both the delivery of oxygen to the blood stream and the removal of carbon dioxide from the body. As the disease progresses, the interstitium and the walls of the alveoli thicken, which further impedes lung function.

Pneumonia can occur due to infections resulted from bacteria, viruses, mycoplasma, and other infectious agents such as fungi. It is frequently recognized that viral species colonize nasopharynx of patients with community-acquired pneumonia (CAP). Whether they are the main cause or contribute to the pathogenesis by secondary bacterial causes is still being researched. There is an complex balance between the organisms residing in the lower respiratory tract and the local and systemic defense mechanisms (both innate and acquired) which when disturbed

gives rise to inflammation of the lung parenchyma, i.e., pneumonia. Common defense mechanisms that are compromised in the pathogenesis of pneumonia involve:

1-Systemic defense mechanisms like humoral and complement-mediated immunity that is compromised in diseases like common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA, inherited), and functional asplenia (acquired). Impaired cell-mediated immunity predisposes individuals to infection by intracellular organisms like viruses and organisms of low virulence like *Pneumocystis pneumonia* (PJP), fungal causes, among others.

2-The mucociliary clearance that is frequently declined in cigarette smokers, post-viral state, Kartagener syndrome, and other related conditions.

3-Declined cough reflex observed in comatose (relating to or in a state of coma) patients, certain substances of abuse.

4-Collection of secretions as observed in cystic fibrosis or bronchial obstruction. Cystic fibrosis is a hereditary disorder affecting the exocrine glands. It causes the synthesis of abnormally thick mucus, causing the blockage of the pancreatic ducts, intestines, and bronchi and often resulting in respiratory infection, while bronchial obstruction may be localized or generalized. As mentioned, bronchial obstruction may be localized, this indicates that perhaps because of an inhaled foreign body such as a peanut or broken tooth, or obstruction caused by a tumor or enlarged gland. In addition, bronchial obstruction when generalized indicate pneumonia that is slow to resolve owing to whooping cough (a contagious bacterial disease chiefly affecting children, characterized by convulsive coughs followed by a whoop) or measles (an infectious viral disease causing fever and a red rash, typically occurring in childhood). The bronchial obstruction will cause absorption of the air from the lung tissue distal to the obstruction and this area will therefore shrink and collapse.

The resident macrophages ($M\Phi$) function to protect the lung from foreign microbes. Sarcasically, the inflammatory reaction induced by these very macrophages ($M\Phi$) is what is accountable for the histopathological and clinical findings observed in pneumonia. The macrophages ($M\Phi$) engulf these pathogenic microbes and induce signal molecules or cytokines like tumor necrosis factor-alpha ($TNF-\alpha$), interleukin-8 (IL-8), and interleukin-1 (IL-1) that

recruit inflammatory cells like neutrophils to the site of infection. They also function to present these antigens (Ag) to the T cells that induce both cellular and humoral defense mechanisms, activate complement and form antibodies (Ab) against these microorganisms. This, in turn, results in inflammation of the lung parenchyma and makes the lining capillaries leaky, which causes exudative congestion and underlines the pathogenesis of pneumonia. It is valuable to add that congestion stage is characterized by vascular engorgement, intra-alveolar fluid, and numerous microbes. The lung is heavy, boggy, and red. Red hepatization stage is where massive confluent exudation progresses, with red blood cells (RBCs), leukocytes, and fibrin filling the alveolar spaces.

The histopathology in pneumonia can be widely studied under 2 main headings: bronchopneumonia/lobular pneumonia or lobar pneumonia.

Lobar pneumonia is diffuse consolidation involving the entire lobe of the lung. Its evolution can be broken down into 4 stages as follows:

1-Congestion: this stage is represented by exorbitantly heavy and fenny appearing lung tissue, diffuse congestion, vascular engorgement, and the collection of alveolar fluid rich in infectious microorganisms. There are few red blood cells (RBC) and neutrophils at this stage.

2-Red hepatization: marked infiltration of red blood cells (RBCs), neutrophils, and fibrin into the alveolar fluid is recognized. Grossly, the lungs look red and firm akin to a liver, hence the term hepatization.

3-Gray hepatization: the red blood cells (RBC) break down and is correlated with fibrinopurulent exudates leading to a red to gray color transformation.

4-Resolution: represented by clearing of the exudates by resident macrophages ($M\Phi$) with or without residual scar tissue formation.

Bronchopneumonia is characterized by suppurative inflammation localized in patches around bronchi which may or may not be localized to a single lobe of the lung.

Scarcely, severe forms of pneumonia may lead to the formation of lung abscess, a complete breakdown of tissue and formation of pus-filled pockets in focal areas of the lung. Also, the infection may spread to the pleural space forming a fibrinopurulent exudate filling this space-

known as empyema (i.e., the collection of pus in a cavity in the body, especially in the pleural cavity).

Common findings on physical examination for pneumonia comprise: tachypnea, tachycardia, fever with or without chills, decreased or bronchial breath sounds, egophony and tactile fremitus (both suggestive of a consolidative process), crackles on auscultation of the affected regions of the lung, dullness on percussion.

Evaluation of community-acquired pneumonia (CAP) and hospital-acquired Pneumonia (HAP) includes:

1-Clinical Evaluation: includes performing a thorough history and physical checking.

2-Radiological Evaluation: according to the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines, a demonstrable infiltrate by chest x-ray is required and is described the best method (with supportive clinical findings) for the diagnosis of pneumonia. Findings may vary from lobar to interstitial infiltrate, to sometimes cavitory lesions with air-fluid concentrations presumptive of a more severe illness process.

3-Laboratory Evaluation: these involve a series of examinations like blood culture, sputum culture and microscopy, routine blood counts, and lymphocyte count. Special tests such as urinary antigen testing (UAT), bronchial aspirate, or induced sputum may be used for certain pathogenic microbes. Two tests, procalcitonin (PCT) and C-reactive protein (CRP) aid differentiate viral from bacterial causes when clinical and radiological findings may not be obvious. It is also worthy that empiric antibiotic treatment may be initiated in all typical cases of pneumonia, and the entire series of tests is rarely required.

Evaluation of ventilator associated pneumonia (VAP), on the other hand, differs a bit from that of community-acquired pneumonia (CAP). It needs radiological and microbiological evidence prior to starting of antimicrobial management. Ventilator associated pneumonia (VAP) should be suspected in ventilated patients who have new onset dyspnea, fall in oxygen saturation on the same ventilator settings, fevers with chills or new onset lung infiltrates. All suspected patients require a chest x-ray [or a computed tomography (CT) scan if x-ray findings are inconclusive]. This must be followed by invasive sampling techniques like mini broncho-alveolar lavage (mini

BAL) or bronchoscopic broncho-alveolar lavage (BAL) or even protected specimen brush (PSB) to determine accidental microorganisms. To recognize the etiological agent responsible for severe acute respiratory failure (ARF) in patients in mechanical ventilation (MV) is important to determine their treatment and prognosis, and to avoid the excessive use of antibiotics. Mini bronchoalveolar lavage (mini BAL) is a blind, non bronchoscopic procedure, used to obtain samples from the lower respiratory tract from patients on mechanical ventilation (MV). Bronchoalveolar Lavage or BAL is a minimally invasive procedure that involves instillation of sterile normal saline into a subsegment of the lung, followed by suction and collection of the instillation for analysis. This procedure is typically facilitated by the introduction of a flexible bronchoscope into a sub-segment of the lung. The procedure was popularized in 1974 by the work of American physicians, Reynolds and Newball, in Maryland. Today, it serves predominantly as a diagnostic tool for the evaluation of lower respiratory tract pathology and in some uncommon conditions, it also has therapeutic utility. Once the diagnosis is assured, the suitable antimicrobial therapy can be started.

Therapy of community-acquired pneumonia (CAP) includes initial risk stratification of the patient and to decide whether to treat the patient on an outpatient basis, in a general medicine ward, or in an intensive care unit (ICU) setting. The "CURB-65" scale has been used extensively for this occasion. The components of this scale involve confusion, uremia [blood urea nitrogen (BUN) greater than 20 mg/dl], a respiratory rate greater than 30 per minute, blood pressure less than 90 mm Hg systolic or less than 60 mm Hg diastolic, and age greater than 65. One point is awarded for every positive criterion that the patient meets. Patient disposition is determined as follows:

-A score of 0 to 1: outpatient treatment. These patients are managed empirically using fluoroquinolones or beta-lactams+ macrolides if adverse comorbidities are exhibited and with macrolides or doxycycline if no comorbidities are present.

-A score of 2 to 3 refers to admission and treatment in a general medicine ward. The first line of management is a choice between fluoroquinolones or macrolides plus beta-lactams.

-A score of 4 or more warrants treatment in an intensive care unit (ICU). The empiric regimen, in this case, is a choice between a combination of a beta-lactam plus fluoroquinolones or beta-lactams plus macrolides.

Treatment of ventilator associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) is according to the American Thoracic Society / Infectious Diseases Society of America (ATS/IDSA) guidelines. It is much more prolonged, complicated, and includes the administration of broad-spectrum antibiotics as compared to the treatment of community-acquired pneumonia (CAP). It includes early identification of signs of pneumonia and thorough evaluation, before starting empiric treatment. Empiric therapy is guided by resistance patterns predominant in that region as well as patient risk factors for multi-drug resistant organisms.

Differential diagnosis of pneumonia includes asthma, chronic obstructive pulmonary disease (COPD), pulmonary edema, malignancies, non-infective consolidative processes of the lung, pleuritis, pulmonary embolism (PE), aspiration of a foreign body, bronchiectasis, bronchiolitis, and others just to name a few. In case a differentiation becomes difficult, parameters like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT) levels, leucocyte count, and temperature may be used to confirm a diagnosis

Complications of untreated or under-treated pneumonia comprise respiratory failure, sepsis, metastatic infections, empyema, lung abscess, and multi-organ dysfunction.

10.1.1Pneumonia in COVID-19 Infection

Almost all of the serious consequences of coronavirus disease 2019 (COVID-19) experience pneumonia. The World Health Organization (WHO) also reveals that elderly individuals and individuals with underlying problems, such as high blood pressure (HBP, also known as hypertension, HTN), heart and lung problems or diabetes mellitus (DM), are more probable to progress to serious diseases. Regularly, when people with coronavirus disease 2019 (COVID-19) develop cough and fever, this is a result of the infection that affects the bronchial tree. The lining of the bronchi is injured, leading to inflammation. This, in turn, irritates the nerves in the lining of the airways, and in such conditions, just a grain of dust can induce coughing. With the evolution of the condition, the virus reaches the gas exchange units (alveoli), igniting them and, consequently, triggering the filling of such alveoli by liquids, cellular debris and others, due to

the alterations caused in the alveolar-capillary membrane. This condition will therefore be represented as pneumonia, resulting in an inability of gas exchange with consequent hypoxemia and hypercapnia. Hypoxemia is a below-normal level of oxygen in blood, particularly in the arteries. Hypoxemia is a sign of a problem related to breathing or circulation, and may lead to various symptoms, such as shortness of breath. Hypercapnia is when there is too much carbon dioxide in the blood. This is normally resulted from hypoventilation of the body which develops to carbon dioxide retention. Pneumonic conditions are associated with mortality, particularly in the elderly. A study was conducted on 99 patients with pneumonia caused by coronavirus disease 2019 (COVID-19). The average age of the patients was 55.5 years, including 67 males and 32 females. 51% of patients had chronic diseases. The patients presented clinical manifestations of fever (83%), cough (82%), shortness of breath (31%), muscle pain (11%), mental confusion (9%), headache (8%), headache throat (5%), rhinorrhea (an excessive discharge of mucus from the nose) (4%), chest pain (2%), diarrhea (2%) and nausea and vomiting (1%). According to the imaging exam, 75% of patients had bilateral pneumonia, 14% of patients had multiple spots and ground-glass opacity, and 1% of patients had pneumothorax. 17% of patients developed acute respiratory distress syndrome (ARDS) and, among them, 11% of patients worsened in a short period and died from multiple organ failure. It is notable to refer that bilateral pneumonia, also called double pneumonia is an infection of both lungs. A virus, bacteria or fungus causes the tiny sacs of the lungs, called alveoli, to become inflamed and fill with fluid or pus, leading to a range of symptoms, including breathing difficulties. In addition, pneumothorax is the presence of air or gas in the cavity between the lungs and the chest wall, causing collapse of the lung. Furthermore, acute respiratory distress syndrome (ARDS) is a severe lung condition. It occurs when fluid fills up the air sacs in the lungs. Too much fluid in the lungs can lower the amount of oxygen or increase the amount of carbon dioxide in the bloodstream. Acute respiratory distress syndrome (ARDS) can prevent body organs from getting the oxygen they need to function, and it can eventually cause organ failure.

Luo *et al.* (2020) mentioned histopathological findings related to a 66-year-old man who had symptoms of high fever and cough when he returned to Shenzhen City, coming from Wuhan on January 4, 2020. This patient had only hypertension (HTN) as a comorbidity. On macroscopic examination, the surface of the entire lung exhibited a diffuse congestive appearance. There was punctual hemorrhage and partially hemorrhagic necrosis. Hemorrhagic necrosis was found

mostly on the outer edge of the lower right lobe, middle lobe and upper lung lobe. The bronchi were swollen and the mucous surfaces were covered with hemorrhagic exudation. The cut surfaces of the lung showed severe congestive and hemorrhagic changes. Histopathological findings presented extensive interstitial fibrosis with partially hyaline degeneration and pulmonary hemorrhagic infarction. The small vessels showed hyperplasia, thickening of the vessel wall and stenosis / occlusion. Interstitial infiltration of inflammatory cells, involving lymphocytes and mononuclear cells. Pulmonary interstitial fibrosis was established and no other bacterial and fungal infections were present by special staining. There was alveolitis (inflammation of the air sacs of the lungs) with atrophy (A wasting away or diminution), proliferation, desquamation and various changes in the squamous metaplasia of alveolar epithelial cells (mainly type II). The remaining pulmonary alveoli demonstrated a thickened septum, necrosis and desquamation of alveolar epithelial cells. In addition, massive fibrous exudate, giant multinucleated cells and intracytoplasmic viral inclusion bodies. Necrotizing bronchiolitis and manifest necrosis of the bronchiolar wall, with epithelial cells present in the lumen.

Coronavirus disease 2019 (COVID-19) pneumonia manifests with abnormalities in chest computed tomography (CT), even in asymptomatic patients, with rapid evolution of unilateral to diffuse bilateral ground-glass opacities that evolve or coexist with consolidations in 1-3 weeks. Combining the assessment of imaging resources with clinical and laboratory findings can facilitate the early diagnosis of coronavirus disease 2019 (COVID-19) pneumonia.

Shi *et al.* (2020) retrospectively investigated the chest computed tomography (CT) results of 81 patients with assured coronavirus disease 2019 (COVID-19). Patients were subdivided into 4 groups based on the duration of clinical symptoms. Group 1 consisted of 15 patients who underwent a chest computed tomography (CT) scan before any clinical symptoms; group 2 underwent a computed tomography (CT) scan within 7 days after the onset of symptoms; group 3 patients were examined 7 to 14 days after the onset of symptoms. It is important to note that all 81 patients (including those without symptoms) had an abnormal chest computed tomography (CT) consistent with viral pneumonia. In the asymptomatic group, the typical type was ground-glass, multifocal and peripheral opacities. Thickening of the interlobular septum, thickening of the adjacent pleura, nodules, round cystic changes, bronchiectasis, pleural effusion and

lymphadenopathy were scarcely noticed in the asymptomatic group. Still analyzing the study by Shi *et al.* (2020) there was radiographic progression after the first symptoms. In group 2 (that is, in the first 7 days of symptoms), computed tomography (CT) chest lesions became bilateral in 90% and diffuse in more than 50%, predominantly with ground-glass opacities. Pleural effusion and some cases of lymphadenopathy were also detected in group 2. In group 3 (i.e., 7 to 14 days after symptoms), the ground-glass aspect was still the predominant finding on computed tomography (CT) in more than 50% of cases, however, consolidation patterns were also seen in about a third of patients. Finally, in group 4 (that is, more than 14 days after symptoms), ground-glass opacities and reticular patterns were more common.

A valuable study interprets that in the viral replication phase after entering a person's organism, coronavirus ribonucleic acid (CoV RNA) encodes the synthesis of structural proteins (for the structure of the virus) and other non-structural proteins (nsps). One of these non-structural proteins (nsps) invades hemoglobins (Hb), removes the iron atom and binds at the site, preventing oxygen from being carried. This would illustrate the rapidly evolving hypoxia picture. They explain that the lung parenchyma lesions (ground glass) are a consequence of hypoxia and consequent necrosis and not a direct effect of the inflammatory process caused by the virus. This could describe individuals with comorbidities, particularly diabetes mellitus (DM), who decompensate quickly due to hypoxia, sometimes even with supplemental oxygen supply, as these people would have fewer binding sites in hemoglobins (Hb). Theoretically, in individuals without comorbidities, the initial viral load would be responsible for defining the severity of the condition since the higher the viral load, the more theoretically there are compromised hemoglobins (Hb). It is also presumed that the change in the structure of red blood cells (RBCs) would interpret vessel damage and disseminated intravascular coagulation (DIC). Infection of the individual by coronavirus disease 2019 (COVID-19) has the probability to cause considerable changes in ventilatory capacity, causing diffuse pulmonary impairment and worsening gas exchange.

A noteworthy study showed that among 138 hospitalized patients, the most common general symptoms at disease onset included fever (98.6%), dry cough (59.4%), fatigue (69.6%), dyspnea (31.2%), and myalgia (pain in a muscle or group of muscles) (34.8%). Less common symptoms of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) infection involve headache,

abdominal pain, dizziness, nausea, vomiting, and diarrhea. In another study of 41 cases, it was reported several symptoms, involving fever (> 90%), dry cough (80%), shortness of breath (20%), respiratory distress (15%), and fatigue. The researchers found that the lineament signs and symptoms of this disease were stable in the majority of cases. However, investigators detected lymphopenia and leukopenia in these patients. Among the 41 patients, 6 were discharged from the hospital, 7 were transferred to critical care, and 1 died (a 61-year-old man with respiratory failure and severe pneumonia, who also had an abdominal tumor). Wang *et al.* (2020) reported symptoms involving fever (98%), dry cough (76%), dyspnea (55%), and diarrhea (3%). Chen *et al.* (2020) reported clinical symptoms including fever (83%), shortness of breath (31%), confusion (9%), cough (82%), muscle ache (11%), headache (8%), sore throat (5%), rhinorrhea (4%), chest pain (2%), nausea and vomiting (1%), and diarrhea (2%). Chen *et al.* (2020) determined some critical conditions, such as pneumothorax (1%) and acute respiratory distress syndrome (ARDS) (17%). The different symptoms appear of coronavirus disease 2019 (COVID-19) as different days passes. It has been recorded that in severe cases, pneumonia and kidney failure [also called end-stage renal disease (ESRD)] can occur, in the end leading to death. Huang *et al.* (2020) showed that severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) infection may lead to acute respiratory distress syndrome (ARDS) and may require admission to an intensive care unit (ICU), with death being a probability. Infected patients must subject to laboratory examinations. For example, the laboratory test findings for one patient revealed hypoproteinemia. The laboratory test results revealed reduced albumin (alb) (35.70 g/L) and total protein (62.20 g/L) concentrations; irregular liver function [augmented aspartate aminotransferase (AST) (72 U/L)]; augmented alanine aminotransferase (ALT) (79 U/L), C-reactive protein (CRP) (53 mg/L), and procalcitonin (PCT) (0.10 ng/ ml) concentrations; reduced lymphocyte (0.9×10^9 /L) and white blood cell (WBC) (3.72×10^9 /L) counts; reduced hemoglobin (Hb) (131.10 g/L) concentrations; mild anemia with a reduced red blood cell (RBC) count (4.10×10^{12} /L); and decreased hematocrit [i.e., the ratio of the volume of red blood cells (RBCs) to the total volume of blood] concentrations (39.0%).

Shen and Yang (2020) revealed the clinical features in 28 pediatric patients (1 month to 17 years of age) with ascertained infection, comprising dry cough, fever, and fatigue, together with other upper respiratory symptoms, including a runny nose and nasal congestion. Pediatric patients also exhibited some gastrointestinal (GI) symptoms such as vomiting, nausea, and diarrhea. On

biochemical examination, C-reactive protein (CRP) concentrations were normal or temporarily higher; however, routine blood culture results were frequently normal. They concluded that most pediatric patients experienced mild symptoms, without fever or pneumonia.

Patients with suspected severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) infection and/or confirmed disease must be managed in specialized hospitals with protective isolation facilities. For confirmed cases, bed rest is recommended. It is urgent to monitor parameters such as heart rate, blood pressure, pulse oxygen saturation, and respiratory rate. Heart rate indicates the speed at which the heart beats. Oxygen saturation measures how much hemoglobin is currently bound to oxygen compared to how much hemoglobin remains unbound. Due to the critical nature of tissue oxygen consumption in the body, it is essential to be able to monitor current oxygen saturation. A pulse oximeter can measure oxygen saturation. It is a noninvasive device placed over a person's finger. It measures light wavelengths to determine the ratio of the current levels of oxygenated hemoglobin to deoxygenated hemoglobin. Respiratory rate refers to the number of breaths per minute or, more formally, the number of movements indicative of inspiration and expiration per unit time. In practice, the respiratory rate is usually determined by counting the number of times the chest rises or falls per minute. Plan Patients should be administered adequate amounts of liquids, including energy drinks and electrolytes, to balance the body's electrolyte, water, and acid-base levels. The hospital should perform routine tests of different organ systems and function [myocardial and liver enzymes, bilirubin, blood urea nitrogen (BUN), creatinine, and urine volume, among others]. Besides, assessment of procalcitonin (PCT) and C-reactive protein (CRP) levels and coagulation function, routine blood work-up, and chest imaging should be performed. If necessary, patients should be provided with adequate oxygen management or therapy through mask oxygen, a nasal cannula, or high flow nasal oxygen therapy. Similarly, if necessary, patients should be provided with non-invasive ventilation (NIV) or invasive mechanical ventilation. However it is important to demonstrate that noninvasive ventilation (NIV) refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an invasive artificial airway. (endotracheal tube, tracheostomy). The goal is to provide time for the cause of respiratory failure to resolve and improve gas. Invasive mechanical ventilation includes an endotracheal tube (ETT) and a mechanical ventilator (as opposed to noninvasive ventilation in which the interface is a face mask). In addition to serving as the conduit for delivery of mechanical breaths, the endotracheal tube (ETT) protects

the airway, allows for suctioning of secretions, and facilitates select procedures, including bronchoscopy. Invasive mechanical ventilation helps stabilize patients with hypoxemic and hypercapnic respiratory failure, decreases inspiratory work of breathing, redistributes blood flow from exercising respiratory muscles to other tissues in patients with shock, and allows for the implementation of lung-protective (low tidal volume) ventilation in patients with acute respiratory distress syndrome (ARDS). It has been recommended that patients with respiratory distress, severe respiratory infections, shock, or hypoxemia must subject to oxygen therapy as first-line management. The preliminary flow rate should be 5 L/min. The titration flow rate according to target oxygen saturation levels should be adjusted as follows: for children and adults with symptoms, the oxygen saturation (SpO₂) should be $\geq 94\%$. For pregnant patients, oxygen saturation (SpO₂) should be $\geq 92-95\%$, and for non-pregnant patients, $\geq 90\%$. In patients with acute respiratory distress syndrome (ARDS) and/or hypoxic respiratory failure, respiratory support should be offered.

Patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) who undergo mild signs and symptoms can, however, be managed with antibacterial drugs for pneumonia including azithromycin, fluoroquinolones, and amoxicillin. Lu *et al.* (2020) reported that antiviral molecules, nucleoside analogues, neuraminidase inhibitors, therapeutic peptide, ribonucleic acid (RNA) synthesis inhibitors, anti-inflammatory therapies, and Chinese traditional medicine could be therapeutic options for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Among the therapeutic options for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Lu *et al.* (2020) provided antiviral molecules including lopinavir/ritonavir (400 mg/100 mg), a therapeutic peptide comprising enterokinase 1 (EK1), ribonucleic acid (RNA) synthesis inhibitor molecules consisting of tissue differentiation factor (TDF) and lamivudine (also called 3TC), and anti-inflammatory drugs containing hormones and other proteins. Some researchers have recommended alpha-interferon (IFN- α) management for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The dose can be administered as an injection of 5 million International Unit (IU) twice per day in adults. It was recognized that Chloroquine phosphate, a drug for the management of malaria, has exhibited its efficiency against coronavirus disease 2019 (COVID-19). The clinical trial of this drug and its derivative [chloroquine or hydroxychloroquine (HCQ)] is being conducted in 10 hospitals in China to test the efficacy and safety for the treatment of COVID-19 associated pneumonia. A

report showed an improvement in the case of a patient having contracted severe acute respiratory syndrome coronavirus (SARS-CoV) in Wuhan, China and was considered as the first patient in the United States of America for coronavirus disease 2019 (COVID-19), after administration of remdesivir (a nucleotide prodrug). Patients showed a decrease in the severity of the symptoms after its administration. Lim *et al.* (2020) reported that a patient (54-year old male) with coronavirus disease 2019 (COVID-19) infection in South Korea when was administered lopinavir/ ritonavir the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) load in the patient decreased considerably. Additionally, no or little coronavirus (CoV) titers were described in the patient after this drug administration. Remdesivir (GS-5734) is being used for the treatment of Middle East respiratory syndrome-coronavirus (MERS-CoV) infection in the rhesus macaque model and it has been supposed to be a probable cure for coronavirus disease 2019 (COVID-19). Liu *et al.* (2020) suggested four primary therapy candidates for the management of coronavirus disease 2019 (COVID-19), which are remdesivir, novel vinylsulfone protease inhibitor, an ACE2-based peptide, and 3CLpro-144. Chloroquine and hydroxychloroquine (HCQ) looks to be promising therapeutic drugs to fight against coronavirus disease 2019 (COVID-19). Hydroxychloroquine (HCQ) is a less toxic derivative than chloroquine, which can be efficient for inhibiting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. In a non-randomized clinical trial Gautret *et al.* (2020) described azithromycin and hydroxychloroquine (HCQ) as a better therapeutic agent against coronavirus disease 2019 (COVID-19).

Chinese traditional medicine options include Lianhuaqingwen and Shu Feng Jie Du capsules. Chinese medicinal tea may also be administered (agastache leaf [6 g]; perilla leaf [6 g]; stewedamomumtsao-ko [6 g], dehydrated tangerine or orange peel [9 g]; and 3 slices of ginger). Huoxiang Zhengqi capsule or Huoxiang Zhengqi Shui can be used to prevent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (at half dose).

Several potential strategies for blocking the angiotensin-converting enzyme 2 (ACE2) receptor have been indicated and have been considered to prevent severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

10.2 Pulmonary Hypertension

Pulmonary hypertension (PH) is high blood pressure in the heart-to-lung system that delivers fresh (oxygenated) blood to the heart while returning used (oxygen-depleted) blood back to the lungs. Unlike systemic blood pressure (also known as regular hypertension or high blood pressure), which represents the force of blood moving through the blood vessels in the body, pulmonary blood pressure reflects the pressure the heart exerts to pump blood from the heart through the arteries of the lungs. In other words, it focuses on the pressure of the blood flow in the lungs.

Pulmonary hypertension (PH) is a severe condition of multiple etiologies described by an elevation in mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest, measured during right heart catheterization. Augmented right ventricular afterload and strain can result from sustained elevations in pulmonary blood pressure, in the end developing to right ventricular failure (RVF) and death. Right ventricular failure (RVF) is most commonly a result of left ventricular failure (LVF), via pressure and volume overload. In addition to left ventricular failure (LVF), there are other conditions of pressure overload that develop to right ventricular failure (RVF). These include transient processes such as: pneumonia, pulmonary embolism (PE), mechanical ventilation, and acute respiratory distress syndrome (ARDS). Furthermore, chronic conditions of pressure overload may progress to right ventricular failure (RVF). These include: primary pulmonary arterial hypertension (PAH) and secondary pulmonary hypertension (PH) as seen in chronic-obstructive pulmonary disease (COPD) or pulmonary fibrosis, and congenital heart disease. Pulmonary hypertension (PH) is an increasingly recognized comorbidity to numerous common disease processes and is related to poor prognosis, and therefore proper diagnosis of this condition is urgent.

Understanding the physiology and pathophysiology of the pulmonary circulation is definitive in the diagnosis and treatment of pulmonary hypertension (PH). The pulmonary circulation is responsible for carrying deoxygenated blood from the heart to the lungs and returning oxygenated blood back to the heart for delivery to the systemic circulation. Though the pulmonary circulation is faced with the entire cardiac output, low pressure and pulmonary vascular resistance (PVR) is normally preserved due to redundancy of small pulmonary arteries and capillaries with high cross-sectional area. More capillaries are recruited during exercise to

maintain low pulmonary artery (PA) pressure. Elevations in pulmonary vascular resistance (PVR) with subsequent increases in pulmonary artery (PA) pressure are recognized in the progress of pulmonary hypertension (PH). According to the Poiseuille equation, pulmonary vascular resistance (PVR) is directly proportional to the length of the blood vessel and viscosity of the blood and indirectly proportional to the radius of the blood vessel to the fourth power. Therefore, small reductions in the radius of blood vessels can cause dramatic increases in pulmonary vascular resistance (PVR). Structurally, the pulmonary trunk branches into two pulmonary arteries and approximately 15 higher order branches to the pre-capillary level. The pulmonary arteries are composed of three layers: the inner intima comprised of pulmonary artery endothelial cells (PAECs), the middle medial layer comprised on pulmonary artery smooth muscle cells (PASMCs), and the outer adventitial layer comprised mostly of fibroblasts. Abnormalities in the function of all these cell types have been involved in the progress of pulmonary hypertension (PH).

The most current pulmonary hypertension (PH) classifications were defined at the 5th World Symposium on pulmonary arterial hypertension (PAH) in 2013 (Nice, France), with five separate groups identified depending on shared disease histology and pathophysiology, clinical presentation, and therapeutic strategies. The five groups of disorders that cause pulmonary hypertension (PH) are:

- 1-Pulmonary arterial hypertension (PAH) ,
- 2-Pulmonary hypertension (PH) due to left heart disease,
- 3-Pulmonary hypertension (PH) due to chronic lung disease and/or hypoxia,
- 4-Chronic thromboembolic pulmonary hypertension (CTEPH), and
- 5- Pulmonary hypertension (PH) due to unclear or multifactorial mechanisms.

Table 1 – Pulmonary Hypertension Classification

GROUP	PATHOGENESIS	EXAMPLES
1 – Pulmonary arterial hypertension	Vascular remodeling of small pulmonary arteries and proliferation of endothelial cells which increase pulmonary pressures	Idiopathic, familial HIV, drugs, medications, congenital heart disease
2 – Pulmonary hypertension due to left-sided heart disease	Left-sided heart disease increases pulmonary venous pressures and arterial pressures	Chronic LV heart failure, severe mitral disease, severe aortic disease
3 – Pulmonary hypertension due to lung disease or hypoxemia	Chronic lung disease or hypoxemia results in vasoconstriction and loss of pulmonary vasculature	COPD, sleep apnea, obesity hypoventilation syndrome
4 – Pulmonary hypertension due to chronic thromboembolic disease	Pulmonary thromboembolism results in increased pulmonary pressures	Prior PE, recurrent PE, large PE, or pulmonary hypertension at time of diagnosis of PE
5 - Miscellaneous	Varied conditions result in multiple pathologies, causing increased pulmonary pressures	Connective tissue diseases, sarcoidosis, mediastinal tumors, thyroid disorder

Figure(59):Classification of pulmonary hypertension [Long B.; Koyfman A. (2016). Pulmonary hypertension: no ordinary case dyspnea. Emergency Physicians]

Patients with pulmonary hypertension (PH) usually found with symptoms exhibiting poor oxygen transport and impaired cardiac output, involving unexplained dyspnea with exertion, fatigue, chest pain, syncope, hemoptysis, and Raynaud’s phenomenon.

Numerous invasive and noninvasive procedures are demanded for precise diagnosis of pulmonary hypertension (PH), such as electrocardiography, pulmonary function testing, chest radiography, echocardiography, serologic testing, and right heart catheterization (RHC). Despite ameliorations in clinical diagnostics and understanding of the underlying pathogenic mechanisms of pulmonary hypertension (PH), current mainstay treatments are defined to supportive care and targeting pulmonary vasoconstriction.

-Group 1: Pulmonary Arterial Hypertension (PAH): Group 1 pulmonary hypertension (PH), or pulmonary arterial hypertension (PAH), is a group of illnesses with the shared characteristics of

progressively elevated pulmonary vascular resistance (PVR) and mean pulmonary arterial pressure (mPAP) due to obstructive changes within the pulmonary vasculature. The similarities between different types of pulmonary arterial hypertension (PAH) may reflect common underlying pathogenic mechanisms, which can in the end develop to right ventricular failure (RVF) and premature death. The causes of pulmonary arterial hypertension (PAH) involve idiopathic, heritable, drug and toxin triggered, and associated disorders such as connective tissue disorders, human immunodeficiency virus (HIV) infection, portal hypertension (PHT, indicating increased pressure in portal venous system), congenital heart diseases, and schistosomiasis (bilharzia). Pulmonary arterial hypertension (PAH) can also be as a result of pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH) (Group 10) and persistent pulmonary hypertension of the newborn (PPHN, Group 100). Here it is preferred to add that pulmonary capillary hemangiomatosis (PCH) is a rare histological substrate within the spectrum of pulmonary arterial hypertension that possibly represents an unusual manifestation of pulmonary veno-occlusive disease (PVOD). One of the histological hallmarks of pulmonary capillary hemangiomatosis (PCH) is the proliferation of pulmonary capillaries in the alveolar septa that infiltrate adjacent structures such as bronchioles, vessels, and visceral pleura. The hyperplastic process including the smallest vessels of the pulmonary vascular bed might reflect uncontrolled angiogenesis.

-Group 2: Pulmonary hypertension (PH) due to left heart disease (LHD) [left heart disease (LHD) arising in response to increased left ventricular (LV) or left atrial filling pressure in a wide range of cardiac disorders]: group 2 comprises pulmonary hypertension (PH) resulted from left heart diseases, including left ventricular systolic dysfunction (LVSD), left ventricular diastolic dysfunction (LVDD), valvular disease, congenital/acquired left heart inflow/outflow tract obstruction, and congenital cardiomyopathies. It is notable to talk briefly about each of the above mentioned diseases: first, it is seen that left ventricular systolic dysfunction (LVSD) with a resultant increase in left ventricular volume leads to an increase in diastolic filling pressure. The patient with heart failure (HF) after a myocardial infarction (MI) is the classic example of systolic dysfunction. In hypertrophic cardiomyopathy, systolic or contractile function can be normal or even better than normal, but a thick, noncompliant ventricle that cannot readily fill leads to an increased pulmonary wedge pressure; second, diastolic dysfunction is characterized by a normal cardiac output for a given workload, but this output comes at the expense of an

elevated filling pressure. The distinction between systolic and diastolic function requires the measurement of cardiac output; third, valvular disease is characterized by damage to or a defect in one of the four heart valves: the mitral, aortic, tricuspid or pulmonary. The mitral and tricuspid valves control the flow of blood between the atria and the ventricles; third, left ventricular outflow tract obstruction (LVOTO) can occur at the valvular, subvalvular, or supra-valvular level. In general, there is an obstruction to forward flow which increases afterload, and if untreated, can result in hypertrophy, dilatation, and eventual failure of the left ventricle; and finally, fourth, cardiomyopathy is a disease of the heart muscle. It makes it harder for the heart to fill with blood and to pump blood. Cardiomyopathy is a major cause of heart failure and one of the most common conditions leading to heart transplantation. The condition can also cause abnormal heart rhythms.

Most commonly group 2 of pulmonary hypertension (PH) is present in patients with heart failure with preserved or reduced ejection fraction (HFpEF and HFrEF, respectively). Heart failure with preserved ejection fraction (HFpEF) is a form of heart failure in which the ejection fraction - the percentage of the volume of blood ejected from the left ventricle with each heartbeat divided by the volume of blood when the left ventricle is maximally filled - is normal, defined as greater than 50%; this may be measured by echocardiography or cardiac catheterization. Approximately half of people with heart failure (HF) have preserved ejection fraction, while the other half have a reduction in ejection fraction, called heart failure with reduced ejection fraction (HFrEF). Hemodynamically, group 2 is defined by a combination of mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg, a pulmonary artery wedge pressure (PAWP) or left ventricular end-diastolic pressure (LVEDP) > 15 mm Hg, and a normal or reduced cardiac output. The shared pathophysiology of this group includes a passive backward transmission of filling pressures that increases mean pulmonary arterial pressure (mPAP) (e.g., loss of left atrial compliance, diastolic dysfunction, mitral regurgitation), a further increase in mean pulmonary arterial pressure (mPAP) (e.g., endothelial dysfunction, vasoconstriction), and eventual worsening pulmonary vascular remodeling, right ventricular failure (RVF), and death.

The risk factors that best differentiated pulmonary hypertension (PH) with heart failure with preserved ejection fraction (HFpEF) from pulmonary arterial hypertension (PAH) were old age, the presence of hypertension (HTN) and coronary artery (CA) disease, the absence of right atrial

enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output. These results allow for the easier detection of pulmonary hypertension (PH) with heart failure with preserved ejection fraction (HFpEF), though it is still unknown why only some patients with heart failure with preserved ejection fraction (HFpEF) develop pulmonary hypertension (PH).

Although there is no validated management for group 2 pulmonary hypertension (PH), the principal target has been to manage the underlying heart condition found. Previous clinical trials in group 2 pulmonary hypertension (PH) have led to little evidence of efficiency, probably due to the fact that the patients are more heterogeneous than pulmonary arterial hypertension (PAH), and can be divided into subgroups [isolated postcapillary pulmonary hypertension (PH) and combined pre and postcapillary pulmonary hypertension (PH)]. An early trial investigating epoprostenol, a prostacyclin analog, in group 2 pulmonary hypertension (PH) was terminated early due to a trend toward decreased survival. Endothelin receptor antagonists, used in pulmonary arterial hypertension (PAH), have revealed no benefit in heart failure patients. Results in group 2 pulmonary hypertension (PH) using the phosphodiesterase type 5 (PDE5) inhibitor, sildenafil, have emerged. A pilot study demonstrated that sildenafil use in group 2 pulmonary hypertension (PH) related to left heart diastolic dysfunction improved mean pulmonary arterial pressure (mPAP), pulmonary capillary wedge pressure, right ventricular (RV) function, pulmonary function, and quality of life.

The conditions correlated with group 3 pulmonary hypertension (PH) comprise chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILD) [e.g., idiopathic pulmonary fibrosis (IPF), sarcoidosis], other pulmonary diseases with a mixed restrictive and obstructive pattern, sleep-disordered breathing (SDB), alveolar hypoventilation disorders, chronic high altitude exposure, and developmental lung diseases. Given the high dominance of these associated lung illnesses, it is frequently difficult to distinguish idiopathic pulmonary arterial hypertension (PAH) from group 3 pulmonary hypertension (PH). Group 3 pulmonary hypertension (PH) patients usually have moderately to severely impaired ventilatory function, reduced breathing reserve, and characteristic airway and/or parenchymal abnormalities. In general, group 3 pulmonary hypertension (PH) patients have mild-moderate elevations in mean pulmonary arterial pressure (mPAP), associating with the severity of the underlying anomaly.

Given the heterogeneity of this group, the true prevalence is difficult to identify and a high index of suspicion is required clinically. Pulmonary hypertension (PH) in chronic obstructive pulmonary disease (COPD) is ordinarily viewed as common and relatively mild, although some patients experience more severe pulmonary hypertension (PH) out of proportion to their underlying chronic obstructive pulmonary disease (COPD) and have about 50% reduction in 5-year survival. Pulmonary hypertension (PH) correlated with interstitial lung disease (ILD) has a worse prognosis, with idiopathic pulmonary fibrosis (IPF) patients having a fivefold increased 1-year mortality rate in comparison with pulmonary arterial hypertension (PAH). Two key pathophysiologic features underlying pulmonary hypertension (PH) correlated with hypoxia and chronic obstructive pulmonary disease (COPD) are hypoxic vasoconstriction and obliteration of the pulmonary vascular bed. Hypoxia triggers endothelial cell damage, causing release of molecules such as endothelin that cause neighboring smooth muscle cell (SMC) vasospasm and proliferation. Eventual pathologic changes involve arteriolar neo-muscularization, intimal thickening, medial hypertrophy, and adventitial collagen deposition. Although initial hypoxia-induced vasoconstriction is a reversible process, the pulmonary remodeling due to chronic hypoxia is widely irreversible. Treatment for group 3 pulmonary hypertension (PH) primarily involves managing the underlying disease process. Several drugs considered efficient in pulmonary arterial hypertension (PAH) have been examined in group 3 pulmonary hypertension (PH) with mixed findings. Epoprostenol use in chronic obstructive pulmonary disease (COPD)-related acute respiratory failure showed a worsening in oxygenation, whereas iloprost improved gas exchange and exercise tolerance in a small, short-term study of group 3 pulmonary hypertension (PH) patients with associated chronic obstructive pulmonary disease (COPD). Epoprostenol and bosentan both described symptomatic improvement in pulmonary hypertension (PH) correlated with interstitial lung disease (ILD), but only short-term.

Group 4, chronic thromboembolic pulmonary hypertension (CTEPH), includes pulmonary hypertension (PH) due to chronic thromboembolic disease that causes prolonged occlusion of the pulmonary vasculature. These patients are usually underdiagnosed and may have abnormal mechanisms of fibrinolysis or underlying hematological or autoimmune diseases contributing to a hypercoagulable state and poor resolution of thrombi. Underlying pulmonary arteriopathy or in situ thrombosis likely contributes to chronic thromboembolic pulmonary hypertension (CTEPH) progression. This vascular remodeling may happen in the small muscular arteries and arterioles

at the site of vessel occlusion, as well as in spared nonobstructed vessels secondary to the resulting high shear stress. The strict mechanisms of why only a fraction of patients with acute pulmonary emboli develop chronic thromboembolic pulmonary hypertension (CTEPH) are poorly understood. A prospective, longitudinal study presumed the cumulative incidence of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with acute pulmonary embolism (APE) without a history of other venous thromboembolism history to be 3.8% after 2 years. In patients with known pulmonary hypertension (PH), ventilation–perfusion (VQ) scanning is the favored screening exam for chronic thromboembolic disease, whereas pulmonary angiography is the gold standard for illness confirmation and to demonstrate operability. Group 4 pulmonary hypertension (PH) is unique in that surgical intervention with pulmonary thromboendarterectomy is probably curable, although patients with distal vessel illness or considerable comorbidities may not be surgical candidates. Longterm anticoagulation is also indicated, and lung transplant and balloon pulmonary angioplasty have historically been used in select cases of chronic thromboembolic pulmonary hypertension (CTEPH). The use of riociguat, a soluble guanylate cyclase stimulator, has been approved for the management of inoperable or persistent chronic thromboembolic pulmonary hypertension (CTEPH) after thromboendarterectomy.

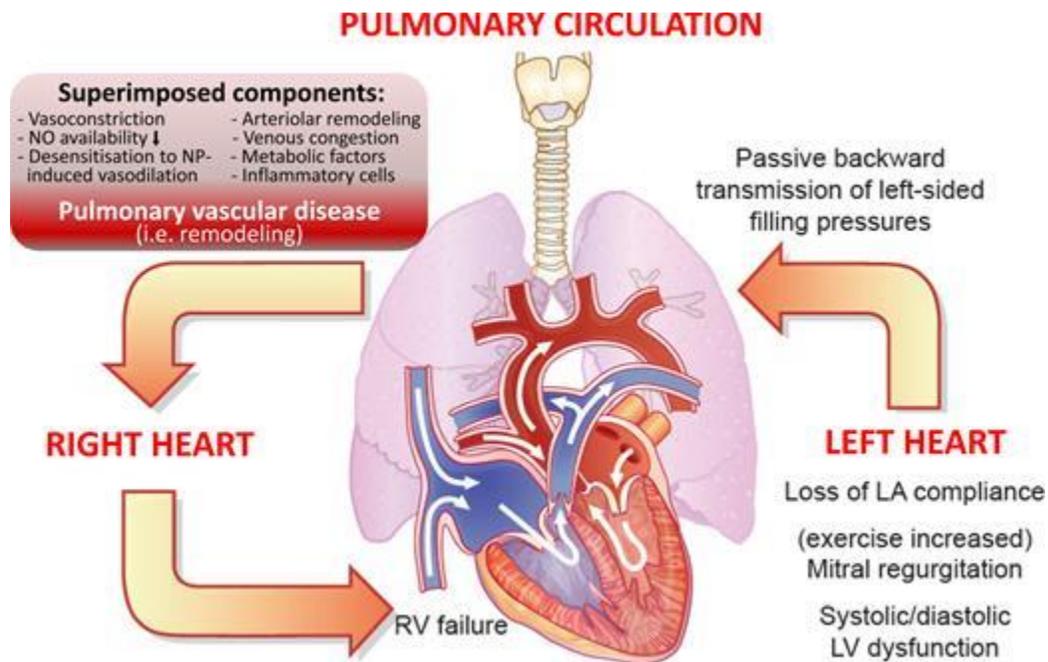
-Group 5, pulmonary hypertension (PH) with unclear multifactorial mechanisms, comprises all other conditions of pulmonary hypertension (PH) that have unclear, multifactorial mechanisms. This encompasses hematologic disorders [sickle cell disease (SCD) or sickle cell anemia, beta-thalassemia, chronic hemolytic anemia, myeloproliferative disorders, splenectomy], systemic disorders [sarcoidosis, lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH)], and metabolic disorders [glycogen storage disease (GSD), Gaucher disease, thyroid disorders]. In addition, causes of tumoral obstruction, fibrosing mediastinitis, chronic renal failure, and segmental pulmonary hypertension are involved. Sickle cell disease (SCD) has been the most well characterized disease associated with group 5 pulmonary hypertension (PH). Postcapillary pulmonary hypertension in sickle cell disease (SCD) is secondary to left ventricular dysfunction (LVD), whereas precapillary pulmonary hypertension (PH) may be resulted from vasculopathy from intravascular hemolysis, chronic pulmonary thromboembolism, or upregulated hypoxic responses. It is worthy to describe pulmonary hypertension (PH) which is defined as an increase of mean pulmonary arterial pressure ≥ 25

mmHg at rest as assessed by right heart catheterization. According to different combinations of values of pulmonary wedge pressure, pulmonary vascular resistance and cardiac output, a hemodynamic classification of pulmonary hypertension has been proposed. Of major importance is the pulmonary wedge pressure which allows to distinguish pre-capillary (pulmonary wedge pressure ≤ 15 mmHg) and post-capillary (pulmonary wedge pressure >15 mmHg) pulmonary hypertension. Pre-capillary pulmonary hypertension includes the clinical groups 1 (pulmonary arterial hypertension), 3 (pulmonary hypertension due to lung diseases and/or hypoxia), 4 (chronic thrombo-embolic pulmonary hypertension) and 5 (pulmonary hypertension with unclear and/or multifactorial mechanisms). Post-capillary pulmonary hypertension corresponds to the clinical group 2 (pulmonary hypertension due to left heart diseases). No randomized trials to date have found drugs to lower pulmonary pressure in sickle cell disease (SCD) patients with precapillary pulmonary hypertension (PH).

While the mechanisms underlying the pathophysiology of group 1 pulmonary arterial hypertension (PAH) have been investigated to a broad extent over the past several decades, leading to the discovery of many new potent therapy targets, much less is currently known about groups 2, 3, 4, and 5. Many of the mechanisms are obviously shared between all groups of pulmonary hypertension (PH), involving vascular remodeling and elevated pulmonary vascular resistance (PVR). The primary mechanisms of elevations in pulmonary vascular resistance (PVR) in pulmonary arterial hypertension (PAH) involve sustained vasoconstriction, uncontrolled pulmonary vascular remodeling, and thrombosis in situ. Pulmonary arterial hypertension (PAH) development is multifactorial and heterogeneous, and a large variety of cell types within the pulmonary artery (PA) vessel walls, involving human pulmonary artery endothelial cells (PAECs), primary pulmonary artery smooth muscle cells (PASMCs), fibroblasts, inflammatory cells, and platelets, are involved in the disease process. Initial vasoconstriction of the pulmonary vasculature causes muscularization of peripheral arteries and medial hypertrophy of muscular arteries. Genetic or toxic risk factors elevate susceptibility to these changes. Pulmonary artery endothelial cell (PAEC) damage and dysfunction due to environmental inductions is also believed to be an early insult in pulmonary arterial hypertension (PAH), and the repair process can develop to neointimal formation, vessel occlusion, and subsequent formation of plexiform lesions that increase pulmonary vascular resistance (PVR). Pulmonary vasoconstriction is an early pathogenic process in pulmonary arterial hypertension

(PAH) and can be stimulated by hypoxia, leading to narrowing of the luminal area of the pulmonary artery (PA) branches. Hypoxia is known to inhibit voltage-gated potassium channels in pulmonary artery smooth muscle cells (PASMCs), which results in opening of voltage gated calcium channels due to membrane depolarization. The resulting rises in cytosolic calcium concentrations can trigger pulmonary artery smooth muscle cell (PASMC) contraction and proliferation, a process particular to the pulmonary vasculature. Down-regulation of potassium channels have been determined in pulmonary artery smooth muscle cells (PASMCs) and lungs of pulmonary artery hypertension (PAH) patients. Several appetite suppressants involved in the development of pulmonary artery hypertension (PAH), involving fenfluramine, directly inhibit potassium channels and lead to pulmonary vasoconstriction. Noticeably, sustained vessel constriction causes dysfunction of pulmonary artery endothelial cell (PAECs), resulting in a chronic reduction in the synthesis of vasodilators prostacyclin and nitric oxide and increased production of the vasoconstrictors endothelin 1 (ET-1) and thromboxane A2. These changes can also stimulate vascular remodeling, and drugs to target these pathways have been used. Modulation of the nitric oxide pathway has been achieved using therapies that inhibit breakdown of cyclic guanosine monophosphate (cGMP) (e.g., phosphodiesterase inhibitors) and induce guanylate cyclase (e.g., riociguat), or by directly inhaled nitric oxide replacement.

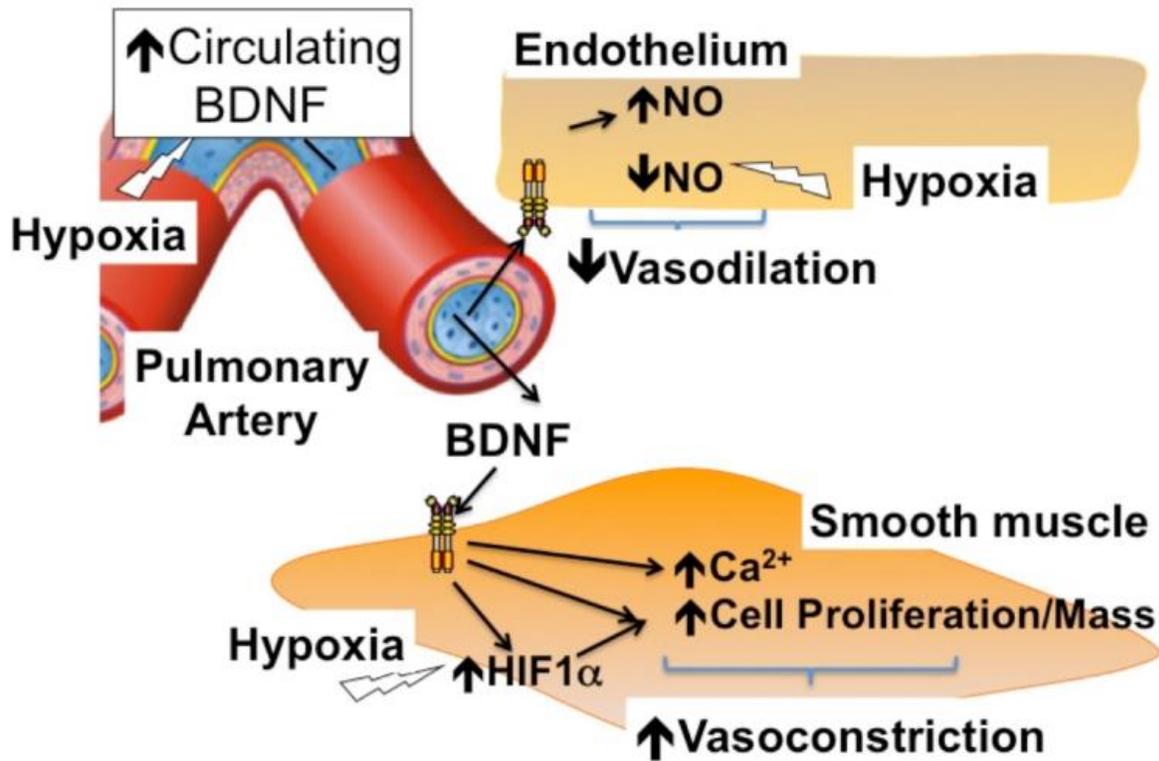
Pulmonary vascular remodeling is associated with marked medial hypertrophy due to unrestrained pulmonary artery smooth muscle cell (PASMC) proliferation and apoptosis resistance and neointimal formation due to pulmonary artery endothelial cell (PAEC) dysfunction and proliferation. These changes can develop to obstructive lesions which narrow the luminal space of vessels and impede blood flow, contributing to increased pulmonary vascular resistance (PVR). Current investigations are underway to elucidate the mechanisms of abnormal cell proliferation contributing to the formation of pathogenic lesions. Other mechanisms of remodeling in pulmonary artery hypertension (PAH) involve elevated adventitial matrix synthesis and impaired proteolysis of extracellular matrix (ECM). Evidence supposes that platelets may also play an important role in pulmonary artery hypertension (PAH) pathogenesis given their ability to occlude vessels via thrombotic lesion formation and production of vasoconstrictive mediators, such as nitric oxide. Platelets from idiopathic pulmonary artery hypertension (PAH) patients have been seen to have decreased levels of endothelial nitric oxide synthase (eNOS), which may contribute to vasoconstriction.



Figure(60):cardiopulmonary interaction and pathobiology of pulmonary hypertension (PH) in left ventricular heart failure [Rosenkranz S.; Gibbs J.; Wachter R.; De Marco T.; Von-Noordegraaf A.; Vachieri JL. (2016). Left ventricular heart failure and pulmonary hypertension. *European Heart Journal*, 37(12):942-954. <https://doi.org/10.1093/eurheartj/ehv512>]

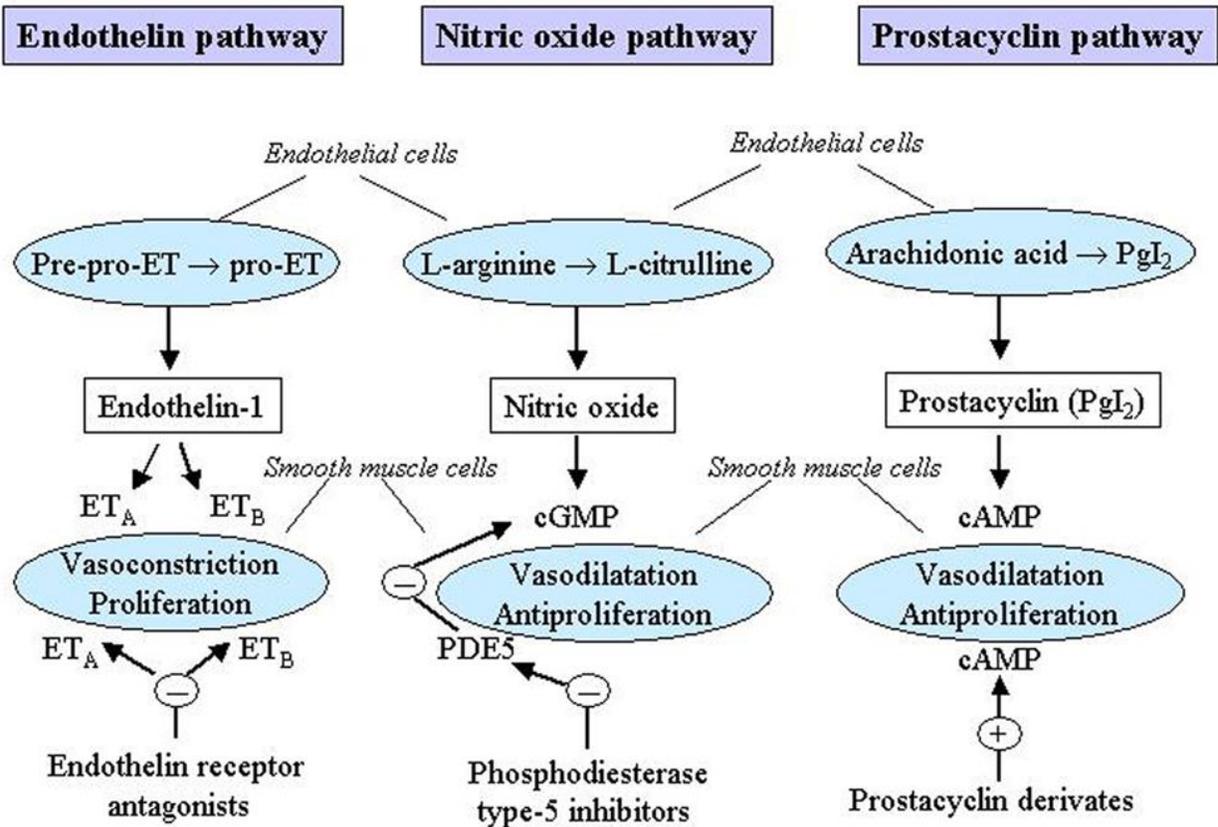
Figure(60) shows (i) the backward transmission of elevated left ventricular filling pressures into the pulmonary circulation (post-capillary hemodynamic profile), (ii) potential superimposed components contributing to the extent of pulmonary hypertension (PH) (leading to a pre-capillary component), which may be associated with (iii) pulmonary vascular remodelling in some patients, thus leading to (iv) right ventricular strain and dysfunction over time. Right ventricular (RV) dilation and increase in wall stress/tension [internal right ventricular (RV) afterload] lead to increased myocardial oxygen consumption, which with concomitant reduction in coronary perfusion gradient leads to right ventricular (RV) ischemia and progressive right ventricle (RV) failure.

Pulmonary Hypertension



Figure(61):Hypoxia and neurotrophins in pulmonary hypertension [Prakash Y. (2020). Pulmonary cell biology. Mayo Foundation for Medical Education and Research (MFMER)]

Figure (61): hypoxia is well-known as a risk factor for pulmonary hypertension (PH). Evidence proposes that neurotrophins and their receptors are expressed in the pulmonary artery (PA). Results from the laboratory indicate that brain-derived neurotrophic factor (BDNF) regulates endothelial nitric oxide synthase (eNOS) and thus modulates pulmonary vasodilation. However, brain-derived neurotrophic factor (BDNF) can worsen vascular smooth muscle contraction and vascular remodeling. Furthermore, hypoxia modulates brain-derived neurotrophic factor (BDNF) and conversely, brain-derived neurotrophic factor (BDNF) worsens hypoxia effects. Studies in the lab are now exploring how these interactions occur in order to test the possibility of interfering with brain-derived neurotrophic factor (BDNF) to blunt pulmonary hypertension (PH).



Figure(62):Therapeutic strategies in pulmonary hypertension [Fuso L.; Baldi F.; Di Perna A. (2011). Therapeutic strategies in pulmonary hypertension. Front Pharmacol. <https://doi.org/10.3389/fphar.2011.00021>]

Figure (62): Mechanisms which induce pulmonary arterial hypertension (PAH) as targets for pharmacological managements. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ET, endothelin; ET_A, endothelin receptor A; ET_B, endothelin receptor B; PDE5, phosphodiesterase type-5; Pgl₂, prostaglandin I₂.

Figure(62) shows two levels of management can be described: primary and specific treatment. Primary treatment is directed at the underlying cause of the pulmonary hypertension (PH). It also involves a supportive management which should be implicated in all patients with pulmonary hypertension (PH). Specific therapy is directed at the pulmonary hypertension (PH) itself and involves therapy with vasodilators such as calcium channel blockers (CCBs) and with vasodilator and pathogenetic drugs such as prostanoids, endothelin receptor antagonists and phosphodiesterase type-5 inhibitors. These drugs act in several pathogenetic mechanisms of the pulmonary hypertension (PH) and are particular for pulmonary arterial hypertension (PAH) although they might be used also in the other groups of pulmonary hypertension (PH).

Supportive therapy which should be considered in all patients with pulmonary hypertension (PH) comprises oxygen supplementation, diuretics, anticoagulation and exercise.

Specific therapy is directed at the pulmonary hypertension (PH) itself and is determined for patients who have evidence of persistent pulmonary hypertension (PH) and a World Health Organization (WHO) functional class II, III, or IV despite proper primary therapy. Specific therapy is often demanded for patients with group 1 pulmonary hypertension (PH), because there are not efficient primary therapies for these patients.

Patients with pulmonary hypertension (PH) who are selected for specific therapy should undergo an invasive hemodynamic assessment, i.e., right heart catheterization (or pulmonary artery catheterization) (RHC), prior to the initiation of treatment. It is recommended that patients with group 1 pulmonary hypertension (PH) also undergo a vasoreactivity exam with intravenous (IV) adenosine, intravenous (IV) epoprostenol, or inhaled nitric oxide. Patients with a positive vasoreactivity exam can be given a trial of oral calcium channel blocker (CCB) therapy. In contrast, patients with a negative vasoreactivity test require therapy with a prostanoid, endothelin receptor antagonist, or phosphodiesterase type-5 inhibitor. Combination specific therapy may be suitable in refractory cases, although data are limited. Some patients are refractory to all medical interventions. In such conditions, lung transplantation or creation of a right to left shunt by atrial septostomy may be considered.

10.2.1 Pulmonary Hypertension in COVID-19 Infection

Angiotensin-converting enzyme 2 (ACE2) is a membrane amino-peptide. Angiotensin-converting enzyme 2 (ACE2) has a multiplicity of physiological roles that revolve around its trivalent function: a negative regulator of the renin-angiotensin system (RAS), facilitator of amino acid (AA) transport, and the severe acute respiratory syndrome-coronavirus (SARS-CoV) and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) receptor. Angiotensin-converting enzyme 2 (ACE2) is broadly expressed, involving, in the lungs, cardiovascular (CV) system, gut, kidneys, central nervous system (CNS), and adipose tissue. It functions as an angiotensin II-degrading enzyme which generates angiotensin (1-7). This latter oligopeptide has vasodilatory, hypotensive and diuretic effects. Angiotensin-converting enzyme 2 (ACE2) has been described as the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) receptor, the infective agent responsible for coronavirus disease 2019 (COVID-19), offering a crucial link between immunity, inflammation, angiotensin-converting enzyme 2 (ACE2), and cardiovascular disease (CVD). Although sharing a close evolutionary relationship with severe acute respiratory syndrome-coronavirus (SARS-CoV), the receptor-binding domain of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) differs in several key amino acid (AA) residues, allowing for stronger binding affinity with the human angiotensin-converting enzyme 2 (ACE2) receptor, which may be responsible for the greater pathogenicity of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The loss of angiotensin-converting enzyme 2 (ACE2) function following binding by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)

is driven by endocytosis and activation of proteolytic cleavage and processing. The angiotensin-converting enzyme 2 (ACE2) system is a crucial protective pathway against heart failure with reduced and preserved ejection fraction involving, myocardial infarction and hypertension, and against lung disease and diabetes mellitus (DM). The binding of coronavirus disease 2019 (COVID-19) spike (S) protein to angiotensin-converting enzyme 2 (ACE2) has been observed to downregulate angiotensin-converting enzyme 2 (ACE2) and, in turn, to decrease angiotensin (1-7) production. This mechanism may be included in the pathogenesis of pulmonary hypertension (PH) and insufficiency caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection. The control of gut dysbiosis and vascular permeability by angiotensin-converting enzyme 2 (ACE2) arose as a crucial mechanism of pulmonary hypertension (PH) and diabetic cardiovascular (CV) complications. Recombinant angiotensin-converting enzyme 2 (ACE2), gene-delivery of Ace2, Ang 1–7 analogs, and Mas receptor agonists enhance angiotensin-converting enzyme 2 (ACE2) action and serve as potential therapies for disease conditions associated with an activated renin-angiotensin system (RAS). Recombinant human angiotensin-converting enzyme 2 (rhACE2) has completed clinical trials and effectively lowered or increased plasma angiotensin II and angiotensin (1-7) levels, respectively.

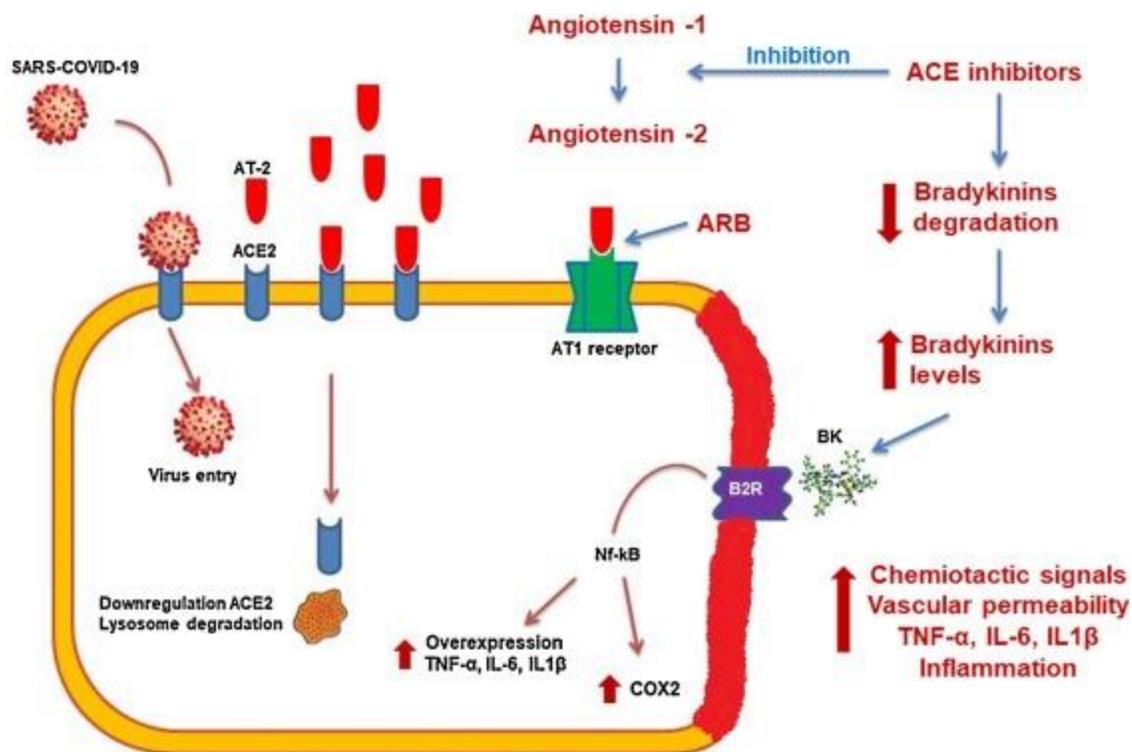
Lung epithelial cells express high levels of angiotensin-converting enzyme 2 (ACE2), which positively correlates with airway epithelial differentiation. Involvement of angiotensin-converting enzyme 2 (ACE2) in acute respiratory distress syndrome (ARDS), which is induced by multiple diseases including severe acute respiratory syndrome-coronavirus (SARS-CoV) and severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has been confirmed in multiple animal models. Age-related loss of angiotensin-converting enzyme 2 (ACE2) in the lungs associates with the increased mortality and worsened phenotype in elderly patients with coronavirus disease 2019 (COVID-19). Angiotensin-converting enzyme 2 (ACE2) has been involved in acute lung injury by triggering an imbalance in the renin-angiotensin system (RAS). Evidence involves that in acute lung injury:

1-A decrease in pulmonary angiotensin-converting enzyme 2 (ACE2) and an increase in angiotensin II (Ang II) levels occurs;

2-Supplementation with angiotensin-converting enzyme 2 (ACE2) or inhibition of angiotensin II (Ang II) improves outcomes; and

3-A lack or decrease of pulmonary angiotensin-converting enzyme 2 (ACE2) aggravates viral-induced acute lung injury.

Angiotensin-converting enzyme 2 (ACE2) is also involved in pulmonary hypertension (PH) and fibrosis. Increasing angiotensin-converting enzyme 2 (ACE2) activity using recombinant human angiotensin-converting enzyme 2 (rhACE2) decreased bleomycin-induced inflammation and fibrosis, leading to improved lung function and exercise capacity, and the angiotensin-converting enzyme 2 (ACE2) activator, DIZE, protects animals from pulmonary hypertension (PH) and fibrosis. Further, oral feeding of a bioencapsulated form of angiotensin-converting enzyme 2 (ACE2) protects and arrests the progression of pulmonary hypertension (PH). Validation of this protective effect comes from a small human study that showed that pulmonary hypertension (PH) is characterized by reduced angiotensin-converting enzyme 2 (ACE2) activity and supplementation of these individuals with recombinant human angiotensin-converting enzyme 2 (rhACE2) improved pulmonary hemodynamics and decreased oxidative and inflammatory markers. Collectively, these studies unequivocally confirm the conceptual framework that angiotensin-converting enzyme 2 (ACE2) is a central player in normal pulmonary function, and its imbalance develops pulmonary diseases.



Figure(63): Potential mechanisms linking angiotensin renin system and COVID-19 infection [Ruocco G.; Feola M.; Palazzuoli A. (2020). Hypertension prevalence in human coronavirus disease: the role of ACE system in infection spread and severity. *International Journal of Infectious Diseases*, 95:373-375. DOI: <https://doi.org/10.1016/j.ijid.2020.04.058>]

Figure(63) demonstrates schematic diagram of the potential mechanisms linking the angiotensin-converting enzyme (ACE) system and coronavirus disease 2019 (COVID-19) infection. The virus could enter directly inside the epithelial cell of the respiratory system via the angiotensin-converting enzyme 2 (ACE2) receptor or trigger an inflammatory cascade by bradykinin escape related to ACEI therapy. The subsequent increase in prostaglandins and cyclooxygenases leads to interleukin production, which causes cell membrane inflammation potentially leading to apoptosis. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT, angiotensin; B2R, bradykinin 2 receptor; BK, bradykinin; COX, cyclooxygenase.

Blockage of the angiotensin-converting enzyme (ACE) system is the basis of management for several situations involving hypertension and heart failure. The inhibition of angiotensin-converting enzyme (ACE) has also described favorable influences in many metabolic diseases, such as diabetes mellitus (DM), obesity, and chronic kidney disease (CKD). In clinical practice, two main drug types capable of modulating the angiotensin-converting enzyme (ACE) system exist: ACE inhibitors (ACEI), which block the conversion of angiotensin 1 (AT1) to angiotensin 2 (AT2), and angiotensin receptor blockers (ARBs), which exhibit their effect via blockage of

the angiotensin 1 (AT1) receptor. Both classes of therapy have an important role in cardiovascular (CV) risk reduction, blood pressure control, and maintenance of cardiac function.

Pathological neurohormonal activation of the renin-angiotensin system (RAS) drives the development and progression of cardiovascular disease (CVD). Current pharmacotherapies purpose to achieve multilevel renin-angiotensin system (RAS) inhibition through distinct modes of action. Although angiotensin-converting enzyme 2 (ACE2) is not the direct cellular target of these therapies, Ace2 gene transcription, translation, and ultimately catalytic activities are modified due to the intricate nature of the renin-angiotensin system (RAS). Blocking the ACE/Ang II/AT1R axis through limiting the formation and actions of angiotensin II (Ang II) potentiates the effects of angiotensin-converting enzyme 2 (ACE2) as the endogenous renin-angiotensin system (RAS) counter-regulator. The angiotensin II receptor blockers (ARBs) consistently increased Ace2 mRNA expression, protein concentrations, and catalytic activities in the heart, kidneys, and thoracic aorta, but the translation to protein levels and activity is different between experimental models and tissues for angiotensin-converting enzyme (ACE) inhibitors. It is suggested that the accumulation of angiotensin II (Ang II) in pathological conditions contributes to the modulatory effects of renin-angiotensin system (RAS) blockade on angiotensin-converting enzyme 2 (ACE2). Angiotensin II (Ang II) can regulate angiotensin-converting enzyme 2 (ACE2) expression through the angiotensin 1 receptor (AT1R). Healthy hearts and kidneys are characterized by high levels of angiotensin-converting enzyme 2 messenger ribonucleic acid (ACE2 mRNA) and protein expression, with moderate expression of angiotensin-converting enzyme (ACE). Renin-angiotensin system (RAS) overactivation in cardiovascular disease (CVD) increases angiotensin 1 receptor (AT1R) stimulation by angiotensin II (Ang II), promoting extracellular signal-regulated protein kinase(ERK)1/2 and P38 mitogen-activated protein kinase (p38 MAPK) signaling pathways to downregulate angiotensin-converting enzyme 2 (ACE2) while upregulating angiotensin-converting enzyme (ACE) expression. Activation of P38 mitogen-activated protein kinase (p38 MAPK) upregulates A disintegrin and metalloproteinase 17(ADAM17) activity though posttranslational phosphorylation of the cytoplasmic domain leads to shedding of surface angiotensin-converting enzyme 2 (ACE2) in a positive feedback loop and could explain the observed effects of angiotensin II receptor blockers (ARBs) in increasing angiotensin-converting enzyme 2 (ACE2) protein levels and activity. Mechanisms behind the augmentation of angiotensin-converting

enzyme 2 messenger ribonucleic acid (ACE2 mRNA) levels by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) require further characterization. Spironolactone, a nonselective mineralocorticoid receptor antagonist, prevented the increase in both angiotensin-converting enzyme (ACE) and angiotensin 1 receptor messenger ribonucleic acid (AT1 R mRNA) levels, and the associated increase in angiotensin 1 receptor (AT1R) density from aldosterone signaling in cardiomyocytes. Activation of mineralocorticoid receptors also stimulates overlapping downstream signaling pathways with angiotensin 1 receptor (AT1R), involving the extracellular signal-regulated protein kinase(ERK)1/2 and P38 mitogen-activated protein kinase (p38 MAPK) pathways. Blocking these signaling pathways contributes to the recognized effect of mineralocorticoid receptor antagonist on angiotensin-converting enzyme 2 (ACE2) gene expression, surface protein levels, and activity.

Promoting the ACE2/Ang 1–7/Mas signaling by recombinant human angiotensin-converting enzyme 2 (rhACE2) or the angiotensin (1-7) (Ang 1–7) receptors agonist AVE 0991 can have salutary therapeutic effects in cardiovascular disease (CVD) and lung disease from diverse etiologies. The angiotensin (1-7) (Ang 1–7) receptors agonist AVE 0991 has been seen to exhibit cardiorenal and pulmonary protective effects, and management with recombinant human angiotensin-converting enzyme 2 (rhACE2) improved the symptoms of acute lung injury, cardiovascular disease (CVD), and kidney injury in various preclinical models. Maintaining angiotensin-converting enzyme 2 (ACE2) levels in patients with or predisposed to common cardiovascular disease (CVD) states such as diabetes mellitus (DM), hypertension (HTN), and obesity wards off the advancement of these comorbidities in instances where the patient contracts severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by maintaining a level of ACE2/Ang1–7/ MasR negative counter-regulation. Recombinant human angiotensin-converting enzyme 2 (rhACE2) functionally sequesters circulating viral particles to prevent spike (S)-protein interactions with endogenous angiotensin-converting enzyme 2 (ACE2), while simultaneously regulating the systemic renin-angiotensin system (RAS) may provide therapeutic benefits in coronavirus disease 2019 (COVID-19) and is moving into phase II clinical trials in Europe. A potential limitation of recombinant human angiotensin-converting enzyme 2 (rhACE2) is the restricted penetrance and activity against tissue renin-angiotensin system (RAS) owing to its large molecular size. Pharmacological renin-angiotensin system (RAS) blockade agents, angiotensin II receptor blockers (ARBs), particularly, are able to modulate both systemic

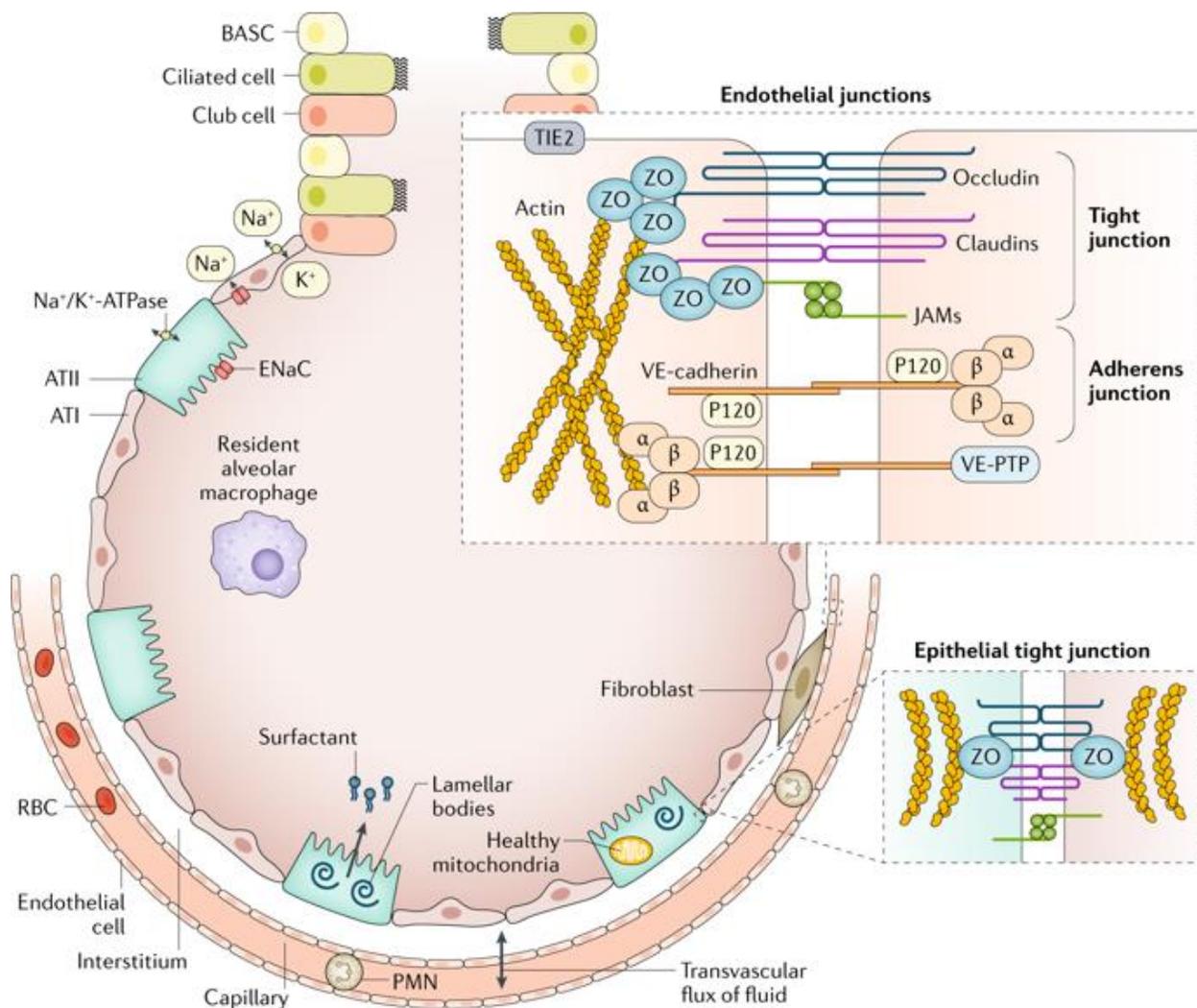
and tissue renin-angiotensin system (RAS), and simultaneously increasing angiotensin-converting enzyme 2 (ACE2) expression and activity in experimental models. The direct implications of renin-angiotensin system (RAS) inhibition in patients with coronavirus disease 2019 (COVID-19) with hypertension (HTN) remain elusive, and clinical evidence is desperately needed to determine the relative benefits and risks associated with usage of these medications. Nonetheless, introducing angiotensin II receptor blockers (ARBs) to patients already infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may be an effective therapeutic option in addressing the viral-mediated renin-angiotensin system (RAS) imbalance and is currently under investigation in several clinical trials. Potential for angiotensin-converting enzyme 2 (ACE2) as a treatment is also facilitated by using the probiotic species *Lactobacillus paracasei* (LP), which can be engineered to express recombinant proteins. Mice managed with the recombinant LP expressing the secreted angiotensin-converting enzyme 2 (ACE2) in fusion with the nontoxic subunit B of cholera toxin (acts as a carrier to facilitate transmucosal transport) demonstrated elevated angiotensin-converting enzyme 2 (ACE2) activities in serum and tissues and decreased diabetic retinopathy. These findings provide proof of concept for using bioengineered probiotic species as live vectors for delivery of human angiotensin-converting enzyme 2 (ACE2) with enhanced tissue bioavailability for managing diabetic complications but could potentially be repurposed for managing cardiovascular disease (CVD) and coronavirus disease 2019 (COVID-19) infection.

10.3 Acute Respiratory Distress Syndrome

The normal lung is structured to facilitate carbon dioxide excretion and oxygen transfer across the distal alveolar capillary unit. The selective barrier to fluid and solutes in the uninjured lung is established by a single layer lining of endothelial cells linked by plasma membrane structures, including adherens and tight junctions. The vast surface of the alveolar epithelium is lined by flat alveolar type I (ATI) cells along with cuboidal shaped alveolar type II (ATII) cells, forming a very tight barrier that restricts even the passage of small solutes but allows diffusion of carbon dioxide and oxygen. The alveolar type II (ATII) cells produce surfactant, the critical factor that decreases surface tension, enabling the alveoli to remain open and facilitating gas exchange. Both alveolar type I (ATI) and alveolar type II (ATII) cells have the capacity to absorb excess fluid from the airspaces by vectorial ion transport, primarily by apical sodium channels and

basolateral Na^+/K^+ -ATPase pumps. Thus, when alveolar oedema develops, reabsorption of the oedematous fluid depends on junctions between alveolar type I (ATI) and alveolar type II (ATII) cells and intact ion transport channels in the epithelial cells. Once the oedematous fluid is absorbed into the lung interstitium, the fluid can be cleared primarily by lymphatics and the lung microcirculation. The cellular makeup of the normal alveolus involves alveolar macrophages ($\text{M}\Phi$) but not polymorphonuclear leukocytes (neutrophils), although they can be rapidly recruited from the circulation. Alveolar macrophages ($\text{M}\Phi$), neutrophils and other immune effector cells, involving monocytes and platelets, are critical in defence of the normal lung and have key activities in acute lung injury (ALI).

The intact alveolar epithelium is linked by intercellular tight junctions. Tight junctions are responsible for barrier function and regulating the movement of fluid and ions across the epithelium and are composed of transmembrane claudins and occludins and cytoplasmic zonula occludens (ZO) proteins that anchor tight junctions to the actin cytoskeleton.



Figure(64): Normal alveolus [Matthay M.; Zemans R.; Zimmerman G.; Arabi Y.; Beitler J.; Mercat A.; Herridge M.; Randolph A.; Calfee C. (2019). Acute respiratory distress syndrome. Nature Reviews Disease Primers, 5, 18. <https://doi.org/10.1038/s41572-019-0069-0>]

Acute respiratory distress syndrome (ARDS) is an acute life threatening inflammatory lung injury manifested by hypoxia and stiff lungs due to increased pulmonary vascular permeability and almost always requiring mechanical ventilation support. Acute respiratory distress syndrome (ARDS) represents an acute response to diverse provoking trigger factors and etiologies, resulting bilateral lung opacities on radiography and hypoxemia.

Acute respiratory distress syndrome (ARDS) was first described in 1994 by the American-European Consensus Conference (AECC) as the acute onset of hypoxemia [arterial partial

pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ≤ 200 mm Hg] with bilateral infiltrates on frontal chest radiograph, with no evidence of left atrial hypertension and acute lung injury (ALI) was defined using similar criteria, but having arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ≤ 300 mm Hg. It is important to say that the ratio of partial pressure arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2), known as the Horowitz index or Carrico index, refers to a comparison between the oxygen level in the blood and the oxygen concentration that is breathed. Over the years, with the ongoing research on this topic, issues considering the validity and reliability of the definition of acute respiratory distress syndrome (ARDS) arose. A panel of experts assembled in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) and developed the Berlin Definition of acute respiratory distress syndrome (ARDS) using a consensus process. The Berlin definition require all four criteria's to be found for diagnosis of acute respiratory distress syndrome (ARDS):

1-Timing: Respiratory symptoms must have begun within one week of a known clinical insult, or the patient must have new or worsening symptoms during the past week;

2-Chest imaging: Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or computed tomographic (CT) scan, which is not fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules;

3-Origin of edema: The patient's respiratory failure must not be fully explained by cardiac failure or fluid overload. An objective assessment (e.g., echocardiography) to exclude hydrostatic pulmonary edema is required if no risk factors for acute respiratory distress syndrome (ARDS) are present; and

4-Oxygenation: A moderate to severe impairment of oxygenation must be present, as defined by the arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio.

The severity of the hypoxemia defines the severity of the acute respiratory distress syndrome (ARDS):

1-Mild acute respiratory distress syndrome (ARDS): the arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) is > 200 mmHg, but ≤ 300 mmHg, on a ventilator with

a positive end-expiratory pressure (PEEP) or continuous positive airway pressure ≥ 5 cm H₂O. Positive end-expiratory pressure (PEEP) is described as the positive pressure that will remain in the airways at the end of the respiratory cycle (end of exhalation) that is greater than the atmospheric pressure in mechanically ventilated patients;

2-Moderate acute respiratory distress syndrome (ARDS): the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) is > 100 mmHg, but ≤ 200 mmHg, on a ventilator with a positive end-expiratory pressure (PEEP) ≥ 5 cm H₂O;

3-Severe acute respiratory distress syndrome (ARDS): the arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) is ≤ 100 mmHg on a ventilator with a positive end-expiratory pressure (PEEP) ≥ 5 cm H₂O. In comparison with the American-European Consensus Conference (AECC) definition, the Berlin Definition had a better prediction for mortality with elevated rate of mortality correlated with increasing stages of acute respiratory distress syndrome (ARDS): mild 27%, moderate 32%, and severe 45% with 95% CI.

Berlin Criteria for Acute Respiratory Distress Syndrome (ARDS)

Respiratory symptoms must have begun within one week of a known clinical insult OR the patient must have new or worsening symptoms during the past week.

Bilateral opacities consistent with pulmonary edema must be present on a chest radiograph or computed tomographic (CT) scan.

These opacities must not be fully explained by pleural effusions, lobar collapse, lung collapse, or pulmonary nodules

A moderate to severe impairment of oxygenation must be present, as defined by the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO₂/FiO₂). The severity of the hypoxemia defines the severity of the ARDS:

- Mild ARDS – The PaO₂/FiO₂ is > 200 mm Hg, but ≤ 300 mm Hg, on ventilator settings that include positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) ≥ 5 cm H₂O.
- Moderate ARDS – The PaO₂/FiO₂ is > 100 mm Hg, but ≤ 200 mm Hg, on ventilator settings that include PEEP ≥ 5 cm H₂O.
- Severe ARDS – The PaO₂/FiO₂ is ≤ 100 mm Hg on ventilators setting that include PEEP ≥ 5 cm H₂O.

Figure(65): Berlin criteria for diagnosis of acute respiratory distress syndrome (www.google.com)

Acute respiratory distress syndrome (ARDS) progresses most commonly in the setting of pneumonia (bacterial and viral; fungal is less common), nonpulmonary sepsis (with sources that include the peritoneum, urinary tract, soft tissue and skin), aspiration of gastric and/or oral and

oesophageal contents (which may be complicated by subsequent infection) and major trauma (such as blunt or penetrating injuries or burns). Several other less common scenarios are also related to the development of acute respiratory distress syndrome (ARDS), comprising acute pancreatitis; transfusion of fresh frozen plasma, red blood cells (RBCs) and/or platelets (that is, transfusion-associated acute lung injury (TRALI); drug overdose with various agents; near drowning (inhalation of fresh or salt water); haemorrhagic shock or reperfusion injury (including after cardiopulmonary bypass and lung resection); and smoke inhalation (often associated with cutaneous burn injuries). Other causes of noncardiogenic pulmonary oedema that are frequently regarded as additional aetiologies of acute respiratory distress syndrome (ARDS) involve primary graft dysfunction following lung transplantation, high-altitude pulmonary oedema, neurogenic oedema (following a central nervous system insult or injury) and drug-induced lung injury.

Acute respiratory distress syndrome manifests as rapidly progressive dyspnea, tachypnea, and hypoxemia. Diagnostic criteria comprise acute onset, profound hypoxemia, bilateral pulmonary infiltrates, and the absence of left atrial hypertension.

The initial pathological stage is the exudative stage, characterized by diffuse alveolar damage. The second stage of proliferation develops after approximately 10–14 days, characterized by resolution of pulmonary edema, proliferation of type II alveolar cells, squamous metaplasia, interstitial infiltration by myofibroblasts, and early deposition of collagen. Some patients progress to the third stage of fibrosis, characterized by obliteration of normal lung architecture, diffuse fibrosis, and cyst formation.

CLINICAL MANIFESTATIONS

- **Early signs/symptoms**
 - Restlessness
 - Dyspnea
 - Low blood pressure
 - Confusion
 - Extreme tiredness
 - Change in patient's behavior
 - Mood swing
 - Disorientation
 - Change in LOC
 - If pneumonia is causing ARDS then client may have
 - Cough
 - Fever

Figure(66): Early symptoms in acute respiratory distress syndrome (www.google.com)

CLINICAL MANIFESTATIONS

CONTD.....

Late signs & symptoms

- Severe difficulty in breathing i.e., labored, rapid breathing.
- Shortness of breath.
- Tachycardia
- Cyanosis (blue skin, lips and nails)
- Thick frothy sputum
- Metabolic acidosis
- Abnormal breath sounds, *like crackles*
- ↓PaCO₂ with respiratory alkalosis.
- ↓PaO₂

Mr sanjay. M. Peerapur, Principal, KLES Institute of Nursing Sciences, Hubli

13

Figure(67): Late symptoms in acute respiratory distress syndrome (www.google.com)

Acute respiratory distress syndrome (ARDS) happens as a consequence of an alveolar injury due to various causes leading to diffuse alveolar damage. This causes the release of pro-inflammatory cytokines [tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8)], which recruit neutrophils to the lungs, where they get activated and secrete toxic mediators [reactive oxygen species (ROS) and proteases] that destruct the capillary endothelium and alveolar epithelium causing alveolar edema. This, eventually, leads to impairment of gas exchange, decreased lung compliance, and elevated pulmonary arterial pressure.

Acute respiratory distress syndrome (ARDS) is deemed to happen when a pulmonary or extrapulmonary insult leads to the secretion of inflammatory mediators, promoting neutrophil accumulation in the microcirculation of the lung. Neutrophils destruct the vascular endothelium and alveolar epithelium, causing pulmonary edema, hyaline membrane formation, decreased lung compliance, and difficult air exchange. Most cases of acute respiratory distress syndrome

(ARDS) are correlated with pneumonia or sepsis. It is estimated that 7.1 percent of all patients admitted to an intensive care unit (ICU) and 16.1 percent of all patients on mechanical ventilation progress acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). In-hospital mortality related to these situations is between 34 and 55 percent, and most deaths are due to multiorgan failure. Acute respiratory distress syndrome (ARDS) frequently has to be differentiated from congestive heart failure, which usually has signs of fluid overload, and from pneumonia. Patients who survive acute respiratory distress syndrome (ARDS) are at risk of diminished functional capacity, mental disease, and decreased quality of life; ongoing care by a primary care physician is of benefit for these patients.

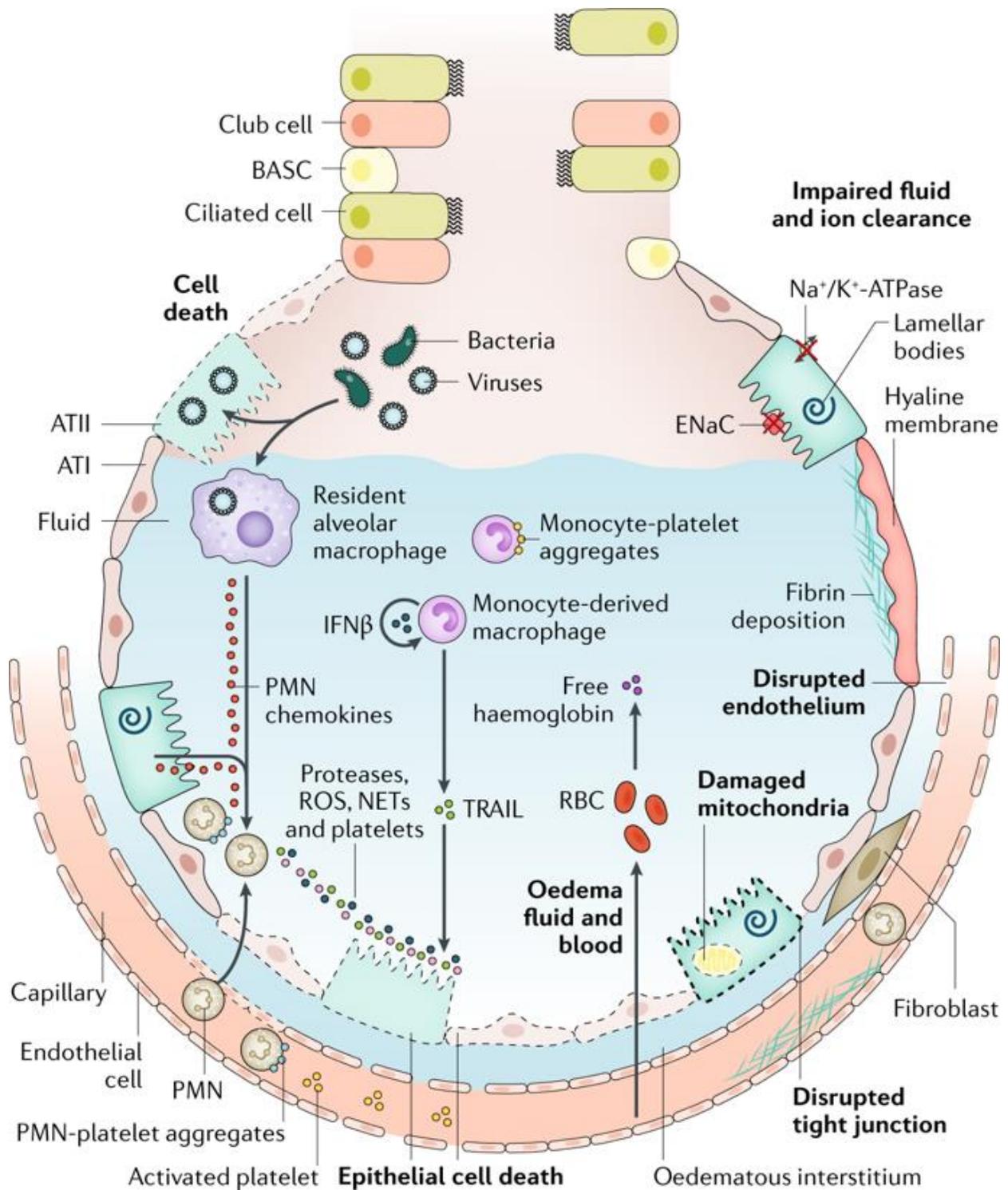
In acute respiratory distress syndrome (ARDS), there is increased permeability to liquid and protein across the lung endothelium, which then develops oedema in the lung interstitium. Next, the oedematous fluid translocates to the alveoli, often facilitated by injury to the normally tight barrier properties of the alveolar epithelium. Increased alveolar–capillary permeability to fluid, proteins, neutrophils and red blood cells (RBCs) (resulting in their accumulation into the alveolar space) is the hallmark of acute respiratory distress syndrome (ARDS). Arterial hypoxaemia in patients with acute respiratory distress syndrome (ARDS) is resulted from ventilation-to-perfusion mismatch as well as right-to-left intrapulmonary shunting. Further, impaired excretion of carbon dioxide is a major component of respiratory failure, leading to elevated minute ventilation that is associated with an increase in pulmonary dead space (that is, the volume of a breath that does not participate in carbon dioxide excretion). Elevation of pulmonary dead space and a decrease in respiratory compliance are independent predictors of mortality in acute respiratory distress syndrome (ARDS).

Interstitial and alveolar oedema are key characteristics of diffuse alveolar damage (DAD) in the acute exudative phase (~7 days) of acute respiratory distress syndrome (ARDS). Eosinophilic depositions termed hyaline membranes are also describing characteristics of diffuse alveolar damage (DAD), the classic histopathological hallmark of acute respiratory distress syndrome (ARDS). The other findings involve alveolar haemorrhage, accumulation of white blood cells (WBCs) (usually predominantly neutrophils), fibrin deposition and some areas of alveolar atelectasis (collapse). After the initial exudative phase, alveolar type II (ATII) cell hyperplasia follows in a proliferative phase that can last >3 weeks in survivors; interstitial fibrosis can also

happen in this phase. The original description of diffuse alveolar damage (DAD) was relied heavily on analyses of lungs of patients dying with oxygen toxicity, although similar histological changes were identified in lungs from patients with a variety of issues that underlie acute respiratory distress syndrome (ARDS). Recent reports reveal that diffuse alveolar damage (DAD) is found in only a subset of patients with clinical acute respiratory distress syndrome (ARDS), and pathological heterogeneity is evident.

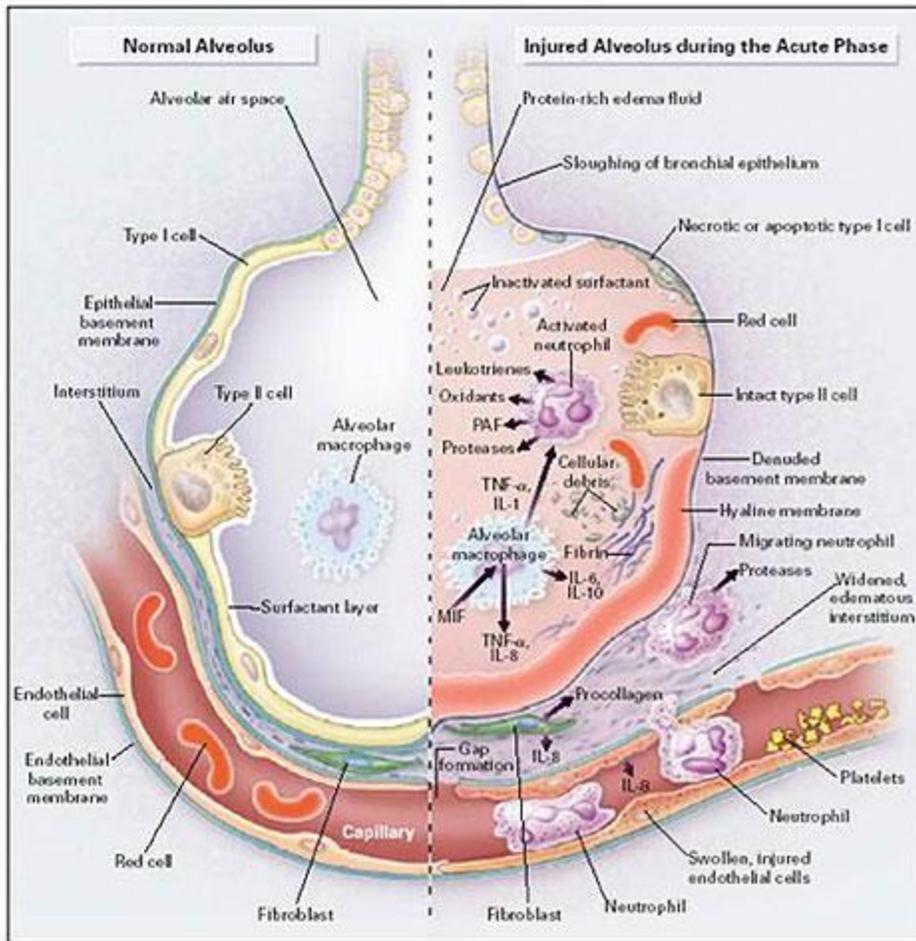
Classic electron microscopic analyses demonstrate that alterations in endothelial and epithelial cells are critical characteristics of acute alveolar injury in acute respiratory distress syndrome (ARDS). For example, early involvement of alveolar type I (ATI) cells is often dramatic and involves focal epithelial destruction and denudation of the alveolar basement membrane. Epithelial cell necrosis is usually defined in the exudative phase, although evidence for apoptosis has also been mentioned. Early epithelial injury is followed rapidly by alveolar type II (ATII) cell proliferation. Endothelial damage and injury are commonly described, and an evidence proposes that apoptosis and alternative cell death pathways such as pyroptosis might be included. Conceptually, an increase in lung vascular permeability can happen because of a functional breakdown in endothelial junctions or by death of endothelial cells. Ultrastructural alterations of alveolar endothelial cells are often subtle in comparison with the dramatic epithelial cell disruption recognized in autopsy analysis, supposing functional barrier impairment. Experimental evidence has revealed that endothelial cell activation can happen, stimulated by inflammatory signals from microorganisms [including lipopolysaccharide (LPS) and other toxins] and lung white blood cells (WBCs) in response to pathogens (as in pneumonia or nonpulmonary sepsis), injury from aspiration syndromes, ischaemia-reperfusion (as in trauma-induced shock) or blood product transfusions as in transfusion-associated acute lung injury (TRALI). Endothelial cell activation may lead to mediator generation [such as angiopoietin 2, (Ang2)] and leukocyte accumulation [accompanied by upregulation of P-selectin and E-selectin (cell adhesion molecules) in the lung microvessels, especially in the post-capillary venules]. Platelet and neutrophil deposition characteristically occur, mostly as neutrophil-platelet aggregates, as a result of endothelial cell activation. Neutrophils and platelets look to play a synergistic role in causing an increase in lung vascular permeability to protein. Endothelial disruption can be resulted from pathogens and their toxins; endogenous danger-associated

molecular patterns; barrier-destabilizing factors generated by alveolar macrophages, circulating leukocytes and platelets; and pro-inflammatory signalling molecules such as tumour necrosis factor (TNF), the inflammasome product interleukin-1beta (IL-1 β), angiopoietin 2 (Ang2), vascular endothelial growth factor (VEGF), platelet-activating factor [also known as PAF, PAF-acether or AGEPC (acetyl-glycerol-ether-phosphorylcholine)] and others. Increased systemic vascular permeability often occurs, mainly contributing to hypovolaemia (a decreased volume of circulating blood in the body) and multiple organ failure.



Figure(68): Injured alveolus in acute respiratory distress syndrome [Matthay M.; Zemans R.; Zimmerman G.; Arabi Y.; Beitler J.; Mercat A.; Herridge M.; Randolph A.; Calfee C. (2019). Acute respiratory distress syndrome. *Nature Reviews Disease Primers*, 5, 18. <https://doi.org/10.1038/s41572-019-0069-0>]

A variety of insults [such as acid, viruses, ventilator-associated lung injury, hyperoxia or bacteria] can injure the epithelium, either directly or by inducing inflammation, which in turn injures the epithelium. Direct injury is inevitably exacerbated by a secondary wave of inflammatory injury. Activation of Toll-like receptors (TLRs) on alveolar type II (ATII) cells and resident macrophages (M Φ) induces the secretion of chemokines, which recruit circulating immune cells into the airspaces. As neutrophils migrate across the epithelium, they release toxic mediators, including proteases, reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), which have an important role in host defence but cause endothelial and epithelial injury. Monocytes also migrate into the lung and can cause injury, including epithelial cell apoptosis via interferon-beta (IFN β)-dependent release of tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), which activates death receptors. Activated platelets form aggregates with polymorphonuclear (PMN) leukocytes, which are involved in neutrophil extracellular trap (NET) formation, and monocyte-platelet aggregates. Red blood cells (RBCs) release cell-free haemoglobin (Hb), which exacerbates injury via oxidant-dependent mechanisms. Angiopoietin 2 (Ang2) inhibits receptor tyrosine kinase Tie2-stabilization of vascular endothelial cadherin [VE-cadherin, also known as CD144 (Cluster of Differentiation 144)]; vascular endothelial growth factor [VEGF, originally known as vascular permeability factor (VPF)] and other permeability-promoting agonists also destabilize vascular endothelial cadherin (VE-cadherin) via dissociation from p120-catenin, resulting in its internalization and enhanced paracellular permeability. Additionally, loss of cell-cell adhesion in the setting of actomyosin contraction results in the formation of occasional gaps between endothelial cells. Epithelial injury also includes wounding of the plasma membrane, which can be induced by bacterial pore-forming toxins or mechanical stretch, and mitochondrial dysfunction. Together, these effects result in endothelial and epithelial permeability, which further facilitate the transmigration of leukocytes and lead to the influx of oedematous fluid and red blood cells (RBCs). Airspace filling with oedematous fluid causes hypoxaemia, resulting in the need for mechanical ventilation. The vascular injury and alveolar oedema contribute to the decreased ability to excrete carbon dioxide (hypercapnia), accounting for the elevated pulmonary dead space in acute respiratory distress syndrome (ARDS). In turn, hypoxaemia and hypercapnia impair vectorial sodium transport, reducing alveolar oedema clearance.



Figure(69): Acute respiratory distress syndrome and acute lung injury (www.google.com)

Phases of injury in acute respiratory distress syndrome (ARDS) includes: first, exudative: characterized by acute development of decreased pulm compliance and arterial hypoxemia; second, fibroproliferative: characterized by increased alveolar dead space fraction (AVDSf), chronic inflammation, and scarring of alveolar-capillary unit; third, recovery : characterized by restoration of the alveolar epithelial barrier, gradual improvement in pulm compliance, resolution of arterial hypoxemia, and eventual return of pulm function.

For decades, clinicians and researchers have wondered whether preventive therapies involved early in the development of acute lung injury (ALI), before patients meet acute respiratory distress syndrome (ARDS) diagnostic criteria, could improve clinical outcomes. Unfortunately,

most trials focused on prevention using pharmacotherapies have met disappointing outcomes. In the earliest trials to test this approach, corticosteroids (CSs) were estimated for acute respiratory distress syndrome (ARDS) prevention in at-risk patients, with no evidence of benefit. Then, a phase IIb clinical trial testing aspirin as a preventive therapy in at-risk patients was negative, although a subsequent re-analysis of the data raised important issues. A smaller phase IIa trial of aerosolized budesonide (a corticosteroid) and formoterol (a long-acting β_2 -agonist that may improve alveolar fluid clearance) demonstrated improved oxygenation and a decreased percent of development to acute respiratory distress syndrome (ARDS) in the management group, although baseline randomization imbalances may have affected this finding. In contrast to these results with pharmacotherapy trials, studies assessing the use of low tidal volume ventilation in mechanically ventilated patients without acute respiratory distress syndrome (ARDS) have provided more beneficial evidence, but a large clinical trial comparing low with intermediate tidal volumes in patients without acute respiratory distress syndrome (ARDS) was negative. Several studies have noted reductions in nosocomial acute respiratory distress syndrome (ARDS) incidence thought to be correlated with improvements in supportive care.

Although true prevention trials have been challenging to conduct because of the quick progress and decreased incidence of acute respiratory distress syndrome (ARDS), an alternative approach has been to exam the value of early management in patients with incipient acute hypoxaemic respiratory failure, which in many cases develops to acute respiratory distress syndrome (ARDS). A French trial interpreted the potential value of this approach, comparing high-flow nasal cannula to noninvasive ventilation and face-mask oxygen in 310 non-intubated patients with a $\text{PaO}_2/\text{FiO}_2 < 300$ mmHg. The majority of patients (64%) had pneumonia, and 79% had bilateral radiographic opacities on chest radiography, indicating that they probably had early acute respiratory distress syndrome (ARDS). High-flow nasal cannula did not impact the principal outcome of endotracheal intubation but did cause statistically considerable lower mortality than both noninvasive ventilation and face-mask oxygenation. This trial may serve as a useful paradigm for future early management trials in selected patient populations, particularly emphasizing the opportunity to identify patients in the early phase of acute lung injury (ALI) before endotracheal intubation. Notably, the potential benefit of high-flow nasal cannula (HFNC) may not be generalizable across all patients in intensive care. A randomized controlled study

demonstrated that high-flow oxygen medicine did not considerably decrease 28-day mortality compared with standard oxygen treatment among critically ill immunocompromised patients with acute respiratory failure (ARF).

Treatment of acute respiratory distress syndrome (ARDS) concentrates on the diagnosis and management of infections, respiratory support, careful fluid treatment (which is especially important if the patient is in shock) and general supportive measures such as nutritional supplementation.

Historically, the focus of mechanical ventilation in acute respiratory failure (ARF) has been to maintain adequate oxygenation and carbon dioxide elimination. Several preclinical studies showed that the common clinical practice of using relatively high tidal volumes and elevated airway pressures for acute respiratory distress syndrome (ARDS) patients might exacerbate the degree of lung injury. Investigators boosted by the United States National Heart Lung and Blood Institute acute respiratory distress syndrome (ARDS) Network completed a randomized phase III clinical trial in which a tidal volume of 6 ml per kg predicted body weight (PBW), compared with the more common higher tidal volume of 12 ml per kg predicted body weight (PBW), improved survival, shortened duration of mechanical ventilation, attenuated systemic inflammation and accelerated recovery of extra-pulmonary organ failures, and the biologic findings were reported in other studies. Thus, with the discovery of the main role that mechanical forces play in the pathogenesis of lung injury, optimizing ventilator support to minimize ventilator-associated lung injury (VALI) has become central to clinical treatment of acute respiratory distress syndrome (ARDS), developing the concept of lung-protective ventilation [protective lung ventilation, the current standard of care for mechanical ventilation. It is synonymous with low tidal volume ventilation (4-8 mL/kg) and often includes permissive hypercapnia].

The acute respiratory distress syndrome (ARDS) lung is non-uniformly aerated, with nonaerated areas predominantly in gravity-dependent regions, owing to the superimposed weight of inflammatory pulmonary oedematous fluid. Aerated lung volume is much smaller than normal, a phenomenon termed baby lung, described and interpreted first with computed tomography (CT)

scans; this concept of the baby lung accounts for the low compliance of the respiratory system because it identifies the areas of the lung that are consolidated with oedema and inflammation and associated atelectasis. Thus, lower tidal volumes are necessary in acute respiratory distress syndrome (ARDS) to inhibit regional overdistension. However, scaling tidal volume to predicted body weight (PBW) targets evaluated healthy lung size, although aerated baby lung volume can differ substantially between patients. Although the crucial importance of the use of a low tidal volume is now universally accepted, the best method for scaling tidal volume to patient-specific surrogates of stress or strain is still debated and warrants further investigation. Targeting airway driving pressure is one strategy for tailoring tidal volume to patient-specific mechanics that has garnered significant attention, but a universally safe threshold has yet to be validated in a prospective trial. For patients with mild lung injury at lower risk of biophysical injury, the benefit conferred by lowering tidal volume should be weighed against risks of more aggressive sedation or use of paralytics if required to perform the intended tidal volumes. Real-time bedside imaging techniques such as electrical impedance tomography hold some potential to identify overdistension or tidal recruitment with each breath, which could be useful for monitoring protective ventilation and to individualize ventilator strategy.

Positive end-expiratory pressure (PEEP) (5–20 cmH₂O) is a key element of protective ventilation and is routinely applied in all patients with acute respiratory distress syndrome (ARDS) to facilitate adequate oxygenation and keep alveolar recruitment. The ideal positive end-expiratory pressure (PEEP) might be sufficiently high to prevent cyclic opening and collapse of distal airspaces during tidal ventilation yet low enough to avoid tidal overdistension. Unfortunately, there is still not a reliable method to estimate at the bedside the risk-to-benefit ratio of different positive end-expiratory pressure (PEEP) levels in individual patients. Titrating positive end-expiratory pressure (PEEP) to offset oesophageal pressure, a surrogate of pleural pressure, showed promise in a single-centre study, but the findings from a follow-up multicentre trial reveal no benefit for clinical results for titrating positive end-expiratory pressure (PEEP) by an oesophageal-guided strategy, in comparison with empirical high positive end-expiratory pressure (PEEP) in patients with moderate or severe acute respiratory distress syndrome (ARDS). No multicentre clinical trials to date have definitively exhibited that any one positive end-expiratory pressure (PEEP) titration strategy provides superior patient-centred outcomes.

However, in accordance with data from studies assessing lung recruitability with computed tomography (CT) scan, a meta-analysis of these trials presumes that higher levels of positive end-expiratory pressure (PEEP) might be preferable in moderate or severe acute respiratory distress syndrome (ARDS) but not in patients with mild acute respiratory distress syndrome (ARDS). Recruitability is a term used to identify distal airspaces of the lung that may be collapsed or oedematous that could be inflated with higher levels of positive end-expiratory pressure (PEEP), therefore, participating in gas exchange. However, a recent study reported worse results with a strategy of aggressive recruitment manoeuvres (to open the collapsed lung) and very high positive end-expiratory pressure (PEEP) in patients with moderate or severe acute respiratory distress syndrome (ARDS) receiving 6 ml per kg predictive body weight (PBW) tidal volume. To maximize benefit and limit the risk of overdistension, further reduction in tidal volume may be necessary when using high positive end-expiratory pressure (PEEP). The role of recruitment manoeuvres [recruitment manoeuvres are transient, sustained increases in transpulmonary pressure designed to open up collapsed airless alveoli. Primarily used in severe acute respiratory distress syndrome (ARDS) They can be used as part of an open lung approach (OLA) to mechanical ventilation] in treating acute respiratory distress syndrome (ARDS) is uncertain at this time; whereas a brief recruitment manoeuvre (for example, 30 seconds of continuous airway pressure applied at 30 cmH₂O) may transiently enhance oxygenation in some patients, the effect of repeated manoeuvres with higher airway pressures and for a longer duration on clinical outcomes remains unclear.

By modifying the regional distribution of transpulmonary pressure, prone positioning decreases regional heterogeneity of lung aeration, causing an improvement of gas exchange and a decreased risk of mechanical lung injury. In the multicentre Prone Positioning Severe ARDS Patients (PROSEVA) trial, prone positioning improved survival and shortened the duration of mechanical ventilation compared with supine positioning. Unlike prior trials that gave mixed results, Prone Positioning Severe acute respiratory distress syndrome (ARDS) Patients (PROSEVA) included only patients with moderate or severe acute respiratory distress syndrome (ARDS) the ratio of arterial oxygen partial pressure to fractional inspired oxygen (P_{aO_2}/F_{iO_2}) <150 mmHg, used prone positioning early in the patient's course, prescribed the prone position for at least 16 hours per day, tailored treatment course to patient recovery and used concomitant low tidal volume ventilation- all

potential requisites for therapeutic efficacy. Long sessions of the prone position are now recommended in most patients with severe acute respiratory distress syndrome (ARDS).

In spontaneously breathing patients with acute lung injury (ALI), it is adequate that elevated transpulmonary pressures may exacerbate the degree of lung injury, thereby raising the question of whether intubation and ventilation with lower tidal volumes and reduced transpulmonary pressure might be of benefit. Moreover, owing to a high respiratory drive, ventilated patients with acute respiratory distress syndrome (ARDS) often show strong respiratory effort even when receiving high doses of sedatives. This respiratory effort may lead to severe patient–ventilator dyssynchronies and increased mechanical lung injury owing to high transpulmonary pressures and/or cyclic atelectasis. Paralysis can inhibit these effects; thus, neuromuscular blockade may decrease mechanical lung injury. In a multicentre trial in patients with severe acute respiratory distress syndrome (ARDS), infusion with the neuromuscular-blocking drug cisatracurium for 48 hours improved adjusted survival and ventilator-free days compared with deep sedation without cisatracurium. Results are expected soon for a follow-up multicentre trial comparing cisatracurium to protocolized sedation treated according to usual care.

For patients with mild acute respiratory distress syndrome (ARDS), avoiding invasive mechanical ventilation altogether may be of benefit. Invasive positive-pressure ventilation and the related co-interventions carry their own risks: sedative infusions that predispose to delirium, decreased mobility that predisposes to neuromuscular weakness and risk of ventilator-associated pneumonia, among other complications. Noninvasive positive-pressure ventilation improves oxygenation and is used more in patients with mild acute respiratory distress syndrome (ARDS) but without a clear benefit on outcome; device interface may affect patient tolerance and efficiency. High-flow oxygen (for example, up to 60 l per min) via large-bore nasal cannula is safe, well tolerated and effective in supporting patients with mild acute respiratory distress syndrome (ARDS), in part by providing low level end-expiratory pressure (PEEP) and modestly increasing carbon dioxide excretion. One study found that high-flow nasal cannula led to lower mortality than noninvasive ventilation or usual care. The optimal threshold to proceed to intubation and the drawbacks of delaying invasive support in patients who are progressing towards such have not been well described.

Dating back to 1978, several preclinical studies referred that elevated lung vascular hydrostatic pressure would increase the quantity of pulmonary oedema in animal models of acute respiratory distress syndrome (ARDS). In 2006, a randomized clinical trial in 1,000 patients with acute respiratory distress syndrome (ARDS) defined that adopting a fluid-conservative approach after vasopressor-dependent shock had resolved led to an increase in ventilator-free days and improved oxygenation index. In the trial, the fluid-conservative arm was guided by a detailed algorithm that required measurement of central venous or pulmonary wedge pressure (PWP) measurements every 4 hours to determine the use of diuretics to achieve lower vascular filling pressures. Since that trial, a simplified fluid-conservative approach has been recommended to reduce overall fluid balance by 500–1,000 ml per day in patients with acute respiratory distress syndrome (ARDS) who no longer have shock by decreasing intravenous (IV) fluids and using diuretics. In the presence of haemodynamic instability, transpulmonary thermodilution estimation of extravascular lung water could help specify risk of exacerbating pulmonary oedema with a volume challenge, potentially helping inform resuscitation. Some have cautioned against overly conservative fluid therapy, as a small study proposed that a fluid-conservative strategy might be correlated with long-term cognitive impairment; however, methodological issues, potential survivorship bias and underpowering limit definitive conclusions. This trial also demonstrated no value in using a pulmonary arterial catheter compared with a central venous fluid catheter to guide fluid treatment. No randomized controlled trial has evaluated conservative fluid therapy in children with acute respiratory distress syndrome (ARDS), but one study observed that elevated cumulative fluid balance on day 3 of pediatric acute respiratory distress syndrome (PARDS) was associated with higher mortality, particularly in patients with concomitant acute kidney injury (AKI).

To maximize efficiency, managements for acute respiratory distress syndrome (ARDS) should be instituted early in the patient's course. Some patients experience continued clinical deterioration despite optimized standard therapies; in this scenario, clinicians may advice use of so-called rescue therapies.

Veno-venous extracorporeal membrane oxygenation (ECMO) is a management in which blood is circulated outside of the body for oxygenation on a gas-permeable membrane. Veno-venous extracorporeal membrane oxygenation (ECMO) has been supposed as a rescue therapy (rescue

therapy also known as salvage therapy, is a form of therapy given after an ailment does not respond to standard therapy) for patients with confirmed very severe acute respiratory distress syndrome (ARDS); for these trials, patients are usually those with severe acute respiratory distress syndrome (ARDS) in whom sufficient correction of gas exchange is inconsistent with lung-protective ventilation. Observational data from the 2009 influenza A H1N1 virus epidemic proposed that veno-venous extracorporeal membrane oxygenation (ECMO) rescue may have a role for patients with refractory hypoxaemia due to isolated pulmonary failure. One trial in 249 patients with very severe acute respiratory distress syndrome (ARDS), refractory hypoxaemia and/or hypercapnia randomly assigned participants to veno-venous extracorporeal membrane oxygenation (ECMO) or continued conventional treatment. The trial reported an 11% absolute reduction in 60-day mortality with veno-venous extracorporeal membrane oxygenation (ECMO) with ventilator settings targeting very low tidal volumes to achieve a plateau airway pressure less than 24 cmH₂O, compared with the now conventional strategy of 6 ml per kg predicted body weight (PBW) tidal volumes and plateau airway pressures up to 30 cmH₂O. However, this clinically substantial effect for survival did not achieve statistical significance ($P=0.09$), leaving the role of veno-venous extracorporeal membrane oxygenation (ECMO) in very severe acute respiratory distress syndrome (ARDS) open for debate. The best potential candidates for veno-venous extracorporeal membrane oxygenation (ECMO) are patients with very severe acute respiratory distress syndrome (ARDS) within the first week of mechanical ventilation and without multiple organ failure. To optimize the risk-to-benefit ratio, veno-venous extracorporeal membrane oxygenation (ECMO) should be offered only in centres experienced in both the care of severe acute respiratory distress syndrome (ARDS) and the use of extracorporeal support.

Extracorporeal carbon dioxide (CO₂) removal partially removes carbon dioxide from the venous blood using a moderate (0.5-1 l per min) extracorporeal blood flow. This method permits the use of very low tidal volume [3-4 ml per kg predicted body weight (PBW)] without causing severe respiratory acidosis. This so-called ultra-protective strategy has been shown to attenuate biomarkers of inflammation in bronchoalveolar lavage and blood in pilot trials in humans, regarding that some patients suffer ongoing ventilator-associated lung injury (VALI) with

conventional protective ventilation. As with all extracorporeal methods, extracorporeal carbon dioxide removal carries its own risks, especially bleeding.

Methylprednisolone acetate is the acetate salt of a synthetic glucocorticoid receptor agonist with immunosuppressive and antiinflammatory effects. Methylprednisolone acetate is converted into active prednisolone in the body, which activates glucocorticoid receptor mediated gene expression. This includes inducing synthesis of anti-inflammatory protein I kappa B-alpha and inhibiting synthesis of nuclear factor kappaB (NF-kappaB). As a result, proinflammatory cytokine production such as interleukin-1 (IL-1), interleukin-2 (IL-2) and interleukin-6 (IL-6) is down-regulated and cytotoxic T-lymphocyte activation is inhibited. Therefore, an overall reduction in chronic inflammation and autoimmune reactions may be achieved. Methylprednisolone was among the first managements examined in trials for preventing acute lung injury (ALI), conjecturally appealing for its anti-inflammatory properties. Up to one-fifth of patients with acute respiratory distress syndrome (ARDS) receive systemic steroids. Although some have reported a positive effect of steroids on survival, a multicentre trial of methylprednisolone versus placebo for persistent moderate to severe acute respiratory distress syndrome (ARDS) observed no survival benefit (7–28 days duration). Steroids accelerated resolution of respiratory failure and circulatory shock but also increased risk of neuromuscular weakness; patients initiating steroids >14 days after acute respiratory distress syndrome (ARDS) onset underwent increased mortality. Thus, steroids should likely not be initiated 2 weeks after acute respiratory distress syndrome (ARDS) onset and have an uncertain risk-to-benefit ratio even when initiated earlier, unless the specific cause of acute respiratory distress syndrome (ARDS) is *Pneumocystis carinii* pneumonia. On balance, the role for corticosteroids (CSs) in early acute respiratory distress syndrome (ARDS) remains controversial owing to mixed results from existing researches and no described large-scale trial in the era of lung-protective ventilation.

Inhaled nitric oxide and prostaglandin achieve selective vasodilation of the pulmonary circulation, improving ventilation-perfusion matching and, transiently, oxygenation in patients with acute respiratory distress syndrome (ARDS). However, a benefit in patient-centred outcomes such as mortality has not been demonstrated. Pulmonary vasodilation could benefit patients with acute respiratory distress syndrome (ARDS) in whom associated acute cor

pulmonale (right heart failure) is contributing to circulatory failure. However, it is noteworthy to say that pulmonary vasodilators reduce pulmonary artery pressure; improve hemodynamic function; alter ventilation/perfusion matching in the lungs; and improve functional quality of life, exercise tolerance, and survival in.

High-frequency oscillatory ventilation (HFOV) is a mode of ventilation support that uses very rapid respiratory rates and very low tidal volumes in an attempt to maximize lung recruitment and avoid cyclic alveolar collapse. Lung collapse is still a concern during the critical care of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Experimental evidence describes the presence of airspace collapse and cyclic recruitment as pivotal elements in the development of ventilator-induced lung injury. When compared with injury caused by overdistension, cyclic alveolar recruitment and collapse due to insufficient recruitment and positive end-expiratory pressure (PEEP) show to have similar or even greater impact on lung injury. In two worthy trials in adults with acute respiratory distress syndrome (ARDS), high-frequency oscillatory ventilation (HFOV) conferred no benefit compared with conventional ventilation, and in one trial mortality was increased. Thus, high-frequency oscillatory ventilation (HFOV) should be used with extreme caution, if at all, in adult acute respiratory distress syndrome (ARDS). High-frequency oscillatory ventilation (HFOV) is more commonly used in children with acute respiratory distress syndrome (ARDS), and there is currently evaluating its effectiveness using a factorial design. Ventilation modes that combine controlled breaths and unassisted spontaneous breaths, such as airway pressure release ventilation (APRV), may improve oxygenation and haemodynamics while decreasing the need for sedation. Airway pressure release ventilation (APRV) was described as a continuous positive airway pressure (CPAP) with an intermittent release phase. Airway pressure release ventilation (APRV) applies continuous positive airway pressure (CPAP) (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or (release time) where most of ventilation and CO₂ removal occurs.

10.3.1 Acute Respiratory Distress Syndrome in COVID-19 Infection

Severe acute respiratory syndrome coronavirus (SARS-CoV) spike (S) protein has a strong binding affinity to human angiotensin-converting enzyme 2 (ACE2), relied on biochemical interaction researches and crystal structure analysis. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and severe acute respiratory syndrome coronavirus (SARS-CoV) spike (S) proteins share 76.5% identity in amino acid (AA) sequences and, remarkably, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and severe acute respiratory syndrome coronavirus (SARS-CoV) spike (S) proteins have a high degree of homology.

Further analysis supposed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) realizes human angiotensin-converting enzyme 2 (ACE2) more effectively than severe acute respiratory syndrome coronavirus (SARS-CoV) increasing the ability of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to transmit from person to person. Thus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein was foreseen to also have a potent binding affinity to human angiotensin-converting enzyme 2 (ACE2).

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein directly binds with the host cell surface angiotensin-converting enzyme 2 (ACE2) receptor facilitating virus entry and replication.

A key question is why the lung looks to be the most vulnerable target organ. One cause is that the vast surface area of the lung makes the lung highly susceptible to inhaled viruses, but there is also a biological factor. Using normal lung tissue from eight adult donors, Zhao *et al.* (2020) demonstrated that 83% of angiotensin-converting enzyme 2 (ACE2)-expressing cells were alveolar epithelial type II cells (AECII), suggesting that these cells can serve as a reservoir for viral invasion. Moreover, gene ontology enrichment analysis indicated that the angiotensin-converting enzyme 2 (ACE2)-expressing alveolar epithelial type II cells (AECII) have high levels of multiple viral process-related genes, involving regulatory genes for viral processes, viral life cycle, viral assembly, and viral genome replication, presuming that the angiotensin-converting enzyme 2 (ACE2)-expressing alveolar epithelial type II cells (AECII) facilitate coronaviral replication in the lung.

Expression of the angiotensin-converting enzyme 2 (ACE2) receptor is also present in many extrapulmonary tissues comprising heart, kidney, endothelium, and intestine. Remarkably, angiotensin-converting enzyme 2 (ACE2) is highly expressed on the luminal surface of intestinal epithelial cells, functioning as a co-receptor for nutrient uptake, particularly for amino acid (AA) resorption from food. It is therefore foreseen that the intestine might also be a main entry site for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and that the infection might have been initiated by eating food from the Wuhan market, the putative site of the outbreak. Whether severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can really infect the human gut epithelium has crucial implications for fecal–oral transmission and containment of viral spread. Angiotensin-converting enzyme 2 (ACE2) tissue distribution in other organs could explain the multi-organ dysfunction seen in patients.

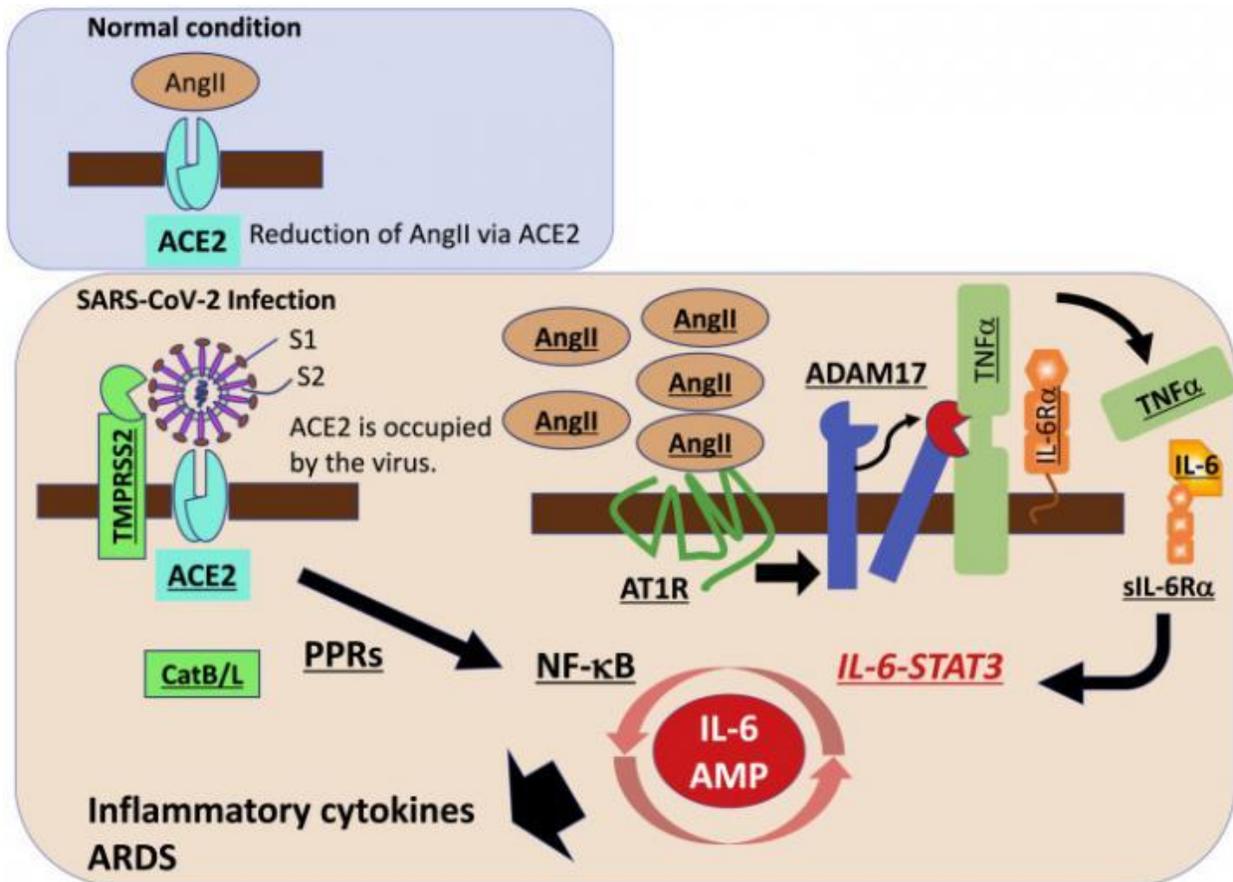
The symptom of patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) ranges from minimal symptoms to severe respiratory failure with multiple organ failure. On Computed tomography (CT) scan, the characteristic pulmonary ground glass opacification can be observed even in asymptomatic patients. Because angiotensin-converting enzyme 2 (ACE2) is highly expressed on the apical side of lung epithelial cells in the alveolar space, this virus can probably enter and destroy them. This matches with the fact that the early lung injury was usually observed in the distal airway. Epithelial cells, alveolar macrophages (AMs) and dendritic cells (DCs) are three main components for innate immunity in the airway. Dendritic cells (DCs) reside underneath the epithelium. Macrophages (M Φ) are found at the apical side of the epithelium. Dendritic cells (DCs) and macrophages (M Φ) serve as innate immune cells to fight against viruses till adaptive immunity is included. T cell mediated responses against coronaviruses (CoVs) have been reviewed. T cell responses are initiated by antigen presentation via dendritic cells (DCs) and macrophages (M Φ). Dendritic cells (DCs) and macrophages (M Φ) can phagocytize apoptotic cells infected by virus. For example, virus-infected apoptotic epithelial cells can be phagocytized by dendritic cells (DCs) and macrophages (M Φ), which results in antigen presentation to T cells. Based on the Immunological Genome database, the expression of angiotensin-converting enzyme 2 (ACE2) on (splenic) dendritic cells (DCs) and alveolar macrophages (AMs) is present but restricted. Determining whether or not severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses another protein to bind to antigen presenting cells (APCs) helps to answer this question. Severe acute respiratory syndrome

coronavirus (SARS-CoV) can also bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) and dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN)-related protein (DC-SIGNR, L-SIGN) in addition to angiotensin-converting enzyme 2 (ACE2). Dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) is highly expressed on dendritic cells (DCs) and macrophages (MΦ). Another target for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), if any, can aid the virus to directly infect dendritic cells (DCs) and alveolar macrophages (AMs). This needs future research. These antigen presenting cells (APCs) move to the draining lymph nodes to present viral antigens to T cells. CD4⁺ and CD8⁺ T cells play a critical role. CD4⁺ T cells activate B cells to induce the synthesis of virus-specific antibody, while CD8⁺ T cells can kill viral infected cells. Immunological studies were primarily reported in severe coronavirus disease 2019 (COVID-19) patients. Patients with severe diseases showed lymphopenia, particularly the reduction in peripheral blood T cells. Patients with severe diseases were mentioned to have increased plasma levels of proinflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein-1alpha (MIP-1α), and tumor necrosis factor-alpha (TNF-α). The more severe statuses patients were in, the elevated their interleukin-6 (IL-6) concentration were. CD4⁺ and CD8⁺ T cells were activated in those patients as proposed by higher expression of CD69, CD38 and CD44. Higher percentage of checkpoint receptor Tim3⁺PD-1⁺ subsets in CD4⁺ and CD8⁺ T cells showed that T cells were also exhausted. A study found that T cell immunoglobulin mucin (Tim) 3 is expressed on CD8⁺ tumor-infiltrating lymphocytes (TILs) in mice bearing solid tumors. All Tim-3⁺ TILs coexpress PD-1, and Tim-3⁺PD-1⁺ TILs represent the predominant fraction of T cells infiltrating tumors. Tim-3⁺PD-1⁺ TILs exhibit the most severe exhausted phenotype as defined by failure to proliferate and produce interleukin-2 (IL-2), tumor necrosis factor (TNF), and interferon-gamma (IFN-γ). In addition, this study demonstrated that exhausted T cells fail to proliferate and exert effector functions such as cytotoxicity and cytokine secretion in response to antigen stimulation. Further studies identified that exhausted T cells are characterized by sustained expression of the inhibitory molecule PD-1 (programmed cell death 1) and that blockade of PD-1 and PD-L1 (PD-1 ligand) interactions can reverse T cell exhaustion and restore antigen-specific T cell responses in lymphocytic choriomeningitis virus (LCMV)-infected mice. T cell exhaustion also occurs

during chronic infections in humans. It was demonstrated that inhibitory receptors (IRs) function as critical regulators of immune responses by tempering T cell activity. In humans, several persisting viruses as well as cancers exploit inhibitory receptor (IR) signaling by upregulating inhibitory receptor (IR) ligands, resulting in suppression of T cell function (i.e., exhaustion). This allows escape from immune surveillance and continuation of disease. NK group 2 member A (NKG2A), another marker for exhaustion was elevated on CD8⁺ T cells. Exhaustion of T cells could have led to the progression of the disease. The NK group 2 member A (NKG2A) receptor transduces inhibitory signalling, suppressing NK cytokine secretion and cytotoxicity. Overexpression of NK group 2 member A (NKG2A) has been observed on CD8⁺ and natural killer (NK) cells of coronavirus disease 2019 (COVID-19) infected patients compared to healthy controls, while NK group 2 member A (NKG2A) overexpression also functionally exhausts CD8⁺ cells and natural killer (NK) cells, developing a severely compromised innate immune response. A recently proposed mechanism via which severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) overrides innate immune response of the host is by over-expressing NK group 2 member A (NKG2A) on CD⁺ T and natural killer (NK) cells, culminating in functional exhaustion of the immune response against the viral pathogen. Monalizumab is an inhibiting antibody against NK group 2 member A (NKG2A) which can restore the function of CD8 + T and natural killer (NK) cells in cancers, successfully ceasing tumor progression with no considerable side effects in Phase 2 clinical trials. It is hypothesized that patients with severe coronavirus disease 2019 (COVID-19) have a severely compromised innate immune response and could be managed via the administration of monalizumab, interferon α , chloroquine, and other antiviral agents. Another interesting finding was that aberrant pathogenic CD4⁺ T cells with coexpressing interferon-gamma (IFN- γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed in coronavirus disease 2019 (COVID-19) patients with severe disease. Granulocyte-macrophage colony-stimulating factor (GM-CSF) release from T cells has been previously reported as a response to virus infection. Granulocyte-macrophage colony-stimulating factor (GM-CSF) can help to differentiate innate immune cells and augment T cell function, but it can initiate tissue damage at excess. Granulocyte-macrophage colony-stimulating factor + interferon-gamma+CD4⁺ T cells (GM-CSF+IFN- γ + CD4⁺ T cells) were previously observed upon potent T cell receptor (TCR) responses in experimental autoimmune encephalomyelitis (EAE) models, where CD8⁺ T cells

expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) were present at higher percentage and produced interleukin-6 (IL-6). It is worth mentioning that these immunological studies were exclusively reported from adult patients. Immunological responses in pediatric population needs to be examined. The study of severe acute respiratory syndrome coronavirus (SARS-CoV) showed that virus infected lung epithelial cells produced interleukin-8 (IL-8) in addition to interleukin-6 (IL-6). Interleukin-8 (IL-8) is a well-known chemoattractant for neutrophils and T cells. Infiltration of a large number of inflammatory cells were recognized in the lungs from severe coronavirus disease 2019 (COVID-19) patients, and these cells presumably consist of a constellation of innate immune cells and adaptive immune cells. Among innate immune cells, it is expected the majority to be neutrophils. Neutrophils can function as double-edged sword as neutrophils can promote lung injury. The majority of the observed infiltrating adaptive immune cells were potentially T cells, regarding that the significant reduction in circulating T cells was recorded. CD8⁺ T cells are primary cytotoxic T cells. Severe patients also exhibited pathological cytotoxic T cells derived from CD4⁺ T cells. These cytotoxic T cells can kill virus but also contribute to lung injury. Circulating monocytes respond to granulocyte-macrophage colony-stimulating factor (GM-CSF) secreted from these pathological T cells. CD14⁺CD16⁺ inflammatory monocyte subsets, which scarcely exist in healthy controls and were also present at notably higher percentage in coronavirus disease 2019 (COVID-19) patients. These inflammatory CD14⁺CD16⁺ monocytes had high expression of interleukin-6 (IL-6), which probably accelerated the development of systemic inflammatory response. It is important to refer to systemic inflammatory response syndrome (SIRS) which is an exaggerated defense response of the body to a noxious stressor (infection, trauma, surgery, acute inflammation, ischemia or reperfusion, or malignancy to name a few) to localize and then eliminate the endogenous or exogenous source of the insult. It includes the secretion of acute-phase reactants which are direct mediators of widespread autonomic, endocrine, hematological and immunological alteration in the subject. Even though the purpose is defensive, the dysregulated cytokine storm has the potential to cause massive inflammatory cascade progressing to reversible or irreversible end-organ dysfunction and even death. An interesting note is that angiotensin-converting enzyme2 (ACE2) was significantly expressed on innate lymphoid cells 2 (ILC2) and innate lymphoid cells 3 (ILC3). Natural killer (NK) cells are a member of innate lymphoid cells 1 (ILC1), which constitute a large portion of innate lymphoid

cells (ILCs) in the lung (~95%). Innate lymphoid cells 2 (ILC2) and innate lymphoid cells 3 (ILC3) work for mucous homeostasis. So far there is a very limited study of innate lymphoid cells 2 (ILC2) and innate lymphoid cells 3 (ILC3) in coronavirus (CoV) infection. In addition to respiratory symptoms, thrombosis and pulmonary embolism (PE) have been seen in severe diseases. This is in line with the finding that elevated D-dimer (DD) and fibrinogen concentrations were seen in severe diseases. The function of the endothelium comprises stimulation of vasodilation, fibrinolysis, and anti-aggregation. Because endothelium plays a considerable role in thrombotic regulation, hypercoagulable profiles observed in severe diseases potentially refer to considerable endothelial injury. Endothelial cells also express angiotensin-converting enzyme2 (ACE2). Of note, the endothelial cells represent the one third of lung cells. Microvascular permeability as a result of the endothelial injury can facilitate viral invasion.



Figure(70):COVID-19 cytokine storm: possible mechanisms for acute respiratory distress syndrome (www.google.com)

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus principally affects the respiratory system, although other organ systems are also involved. Lower respiratory tract infection related symptoms including fever, dry cough and dyspnea were mentioned in the initial case series from Wuhan, China. Further, headache, dizziness, generalized weakness, vomiting and diarrhea were recognized. It is now broadly seen that respiratory symptoms of coronavirus disease 2019 (COVID-19) are extremely heterogeneous, ranging from minimal symptoms to significant hypoxia with acute respiratory distress syndrome (ARDS). In a report from Wuhan, the time between the onset of symptoms and the development of acute respiratory distress syndrome (ARDS) was as short as 9days, supposing that the respiratory symptoms could develop rapidly. This disease could be also fatal. A growing number of patients with severe diseases have continued to succumb worldwide. Epidemiological studies have shown that mortalities are higher in elder people and the incidence is much lower in children.

There is an immense range in the reported incidence of acute respiratory distress syndrome (ARDS) or critical illness from coronavirus disease 2019 (COVID-19). Initial studies from hospitals in Wuhan, China report an alarming incidence of acute respiratory distress syndrome (ARDS) (17 - 29%) and critical illness requiring intensive care unit (ICU) admission (23–32%). The incidence may even be underestimated, considering that in some studies the majority of patients remained hospitalized. Conversely, the reported incidence of critical illness in areas away from the epicentre of the disease outbreak appears to be lower. A study of 1,099 patients from 30 provinces in China and reported an incidence of 3–5% for acute respiratory distress syndrome (ARDS) or admission to intensive care unit (ICU). In this study, the vast majority (94%) of patients remained hospitalized at the time of analysis, again proposing that results may be considerably disparaged and the study better defined as a cross sectional survey of hospitalized patients. Differences in age and comorbidities may also consider for these differences as well. In addition, patients included in some of these studies may have milder disease. In Zhejiang province, all persons with respiratory symptoms or significant contact history were advised to go to hospitals, and acute respiratory distress syndrome (ARDS) was seen in only 1 of 62 hospitalized patients. Nevertheless, it is clear that the clinical spectrum of coronavirus disease 2019 (COVID-19) ranges broadly from asymptomatic or mild illness to critical illness with a high risk of mortality.

A case study showed the rapid clinical deterioration observed in the patient. Acute respiratory distress syndrome (ARDS) and critical illness seem to progress mostly between 1–2 weeks after the onset of symptoms. The patient experienced acute respiratory distress syndrome (ARDS) at day 9 of symptoms, similar to published literature . The patient's age (64 years old) and presenting symptom of dyspnoea definitely shaped disturbing characteristics. Moreover, there was significant lymphopenia on initial blood tests, which has been mentioned to be related to critical disease. Neutrophilia, hypoalbuminemia, elevated levels of lactate dehydrogenase (LDH) and D-dimer (DD) were other described markers of critical illness in coronavirus disease 2019 (COVID-19) that were observed in the patient. These observations look to be consistent with severe acute respiratory syndrome (SARS), where multivariate analysis defined elevated lactate dehydrogenase (LDH) and neutrophilia as markers combined with worse outcomes. However, these markers are non-specific and are commonly present in critically ill patients. It remains to be seen if trends in the viral load can serve as a surrogate for disease recovery and more investigations are needed in this field. In the patient, computed tomography (CT) chest showed extensive multilobar ground-glass changes with intralobular septal thickening and more confluent consolidation in the dependent portions of the lungs. Despite the peripheral location of the groundglass changes, there were thin rims of subpleural sparing. Nevertheless, ground-glass opacities with or without consolidation, with posterior and peripheral predominance, seem to be the commonest finding in coronavirus disease 2019 (COVID-19) pneumonia, as well as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS). The lack of thoracic lymphadenopathy and pleural effusions in the patient is also consistent with reported findings with coronavirus disease 2019 (COVID-19). Despite the rapid deterioration seen in the patient, only subtle ground-glass and interstitial changes were observed on the initial chest radiograph. A limitation of this observation is that it is relied on a single case report. Interestingly, the patient also remained in a semi-conscious state for almost 4 days despite preventing sedation and opioid therapy. No abnormalities were observed on computed tomography (CT) brain, and no considerable metabolic disturbances could interpret the degree of unconsciousness. The patient regained full consciousness with no neurological deficit over the next few days. While septic encephalopathy is a potential diagnosis, a postulation was also the possible accumulation of fentanyl due to inhibition of cytochrome P450 (CYP) by ritonavir, which is another important consideration for intensivists managing these patients. It is important

here to mention that cytochrome P450 enzymes are mainly present in liver cells but are also located in cells throughout the body. Within cells, cytochrome P450 enzymes are located in a structure involved in protein processing and transport (endoplasmic reticulum) and the energy-producing centers of cells (mitochondria). In addition, Cytochrome P450 (CYP) is a heme protein that plays a key role in the metabolism of drugs and other xenobiotics. Drug metabolism occurs in many sites in the body involving the liver, intestinal wall, lungs, kidneys, and plasma. As the primary site of drug metabolism, the liver functions to detoxify and facilitate excretion of xenobiotics (foreign drugs or chemicals) by enzymatically converting lipid-soluble compounds to more water-soluble compounds. Drug metabolism is achieved through phase I reactions, phase II reactions, or both. The most common phase I reaction is oxidation, which is catalyzed by the Cytochrome P450 (CYP) system.

Normal chest imaging, however, does rule out the development of severe illness. Similar with Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS), patients with older age, presence of comorbidities [cardiovascular (CV) and cerebrovascular diseases], and dyspnoea appear to have worse outcomes. The reported median age of patients who required intensive care unit (ICU) admission was 63–66 years, compared to 46–51 years of age for non-intensive care unit (ICU) patients. Similar differences in age were also noted between survivors and non-survivors. While fever and cough was recognized in most patients, dyspnoea was reported in about 30–50, and depending on studies from Wuhan, China, approximately half of patients with dyspnoea required admission to the intensive care unit (ICU). Pre-existing chronic lung disease (CLD) is also of interest. In a recognized study more than half of patients with chronic obstructive pulmonary disease (COPD) and coronavirus disease 2019 (COVID-19) infection were admitted to intensive care unit (ICU) or required mechanical ventilation. What will be useful to clinicians would be an early surrogate of disease severity, ideally before the onset of critical illness. Whether the degree of lymphopenia or lactate dehydrogenase (LDH) elevation can function as early markers of illness severity or even a surrogate for disease recovery from coronavirus disease 2019 (COVID-19) is still unclear. In a study involving non-critically ill patients, it was demonstrated a decline in viral loads [based on reverse transcriptase polymerase chain reaction (RT-PCR) cycle thresholds] after reaching a peak soon after the onset of symptoms. It was valuably reported that up to 23% and 12% of patients requiring intensive care unit (ICU) admission had a normal chest radiograph and computed

tomography (CT) imaging, respectively. It will be prudent for clinicians to closely monitor patients with advanced age, comorbidities or dyspnoea, particularly at 1–2 weeks from symptom onset.

While the estimated case fatality rate of 3.4% for coronavirus disease 2019 (COVID-19) seems to be considerably lower than Middle East respiratory syndrome coronavirus (MERS-CoV) (34.4%) and severe acute respiratory syndrome (SARS) (11%), critical illness from coronavirus disease 2019 (COVID-19) is correlated with a high risk of mortality. Reported mortality rates of intensive care unit (ICU) patients in Jin YinTan Hospital are between 38–62%, with more than 10% requiring extracorporeal membrane oxygenation (ECMO). Yang *et al.* (2020) reported a 28-day mortality rate of 62% in patients who required intensive care unit (ICU) care; among patients who experienced acute respiratory distress syndrome (ARDS), 28-day mortality rate was reported to be 74%. The in-hospital mortality rate is probably to be even higher considering that at the time of analysis, the majority of survivors were still hospitalized, with 3 patients on mechanical ventilation, including 1 patient on extracorporeal membrane oxygenation (ECMO). These reported mortality rates are really alarming, and even higher than mortality rates commonly observed in severe acute respiratory distress syndrome (ARDS) from other causes. It is possible that overwhelmed healthcare resources in Wuhan may affect quality of care, resulting in poorer outcomes. In a publication by Xie *et al.* (2020) it was reported that there were severe shortages in ventilators and only about 25% of patients who died received invasive mechanical intubation. Additionally, the majority of patients were supported with high flow nasal cannula (HFNC) and non-invasive ventilation (NIV) and received systemic corticosteroids (CSs). It is unclear if delayed intubation or systemic corticosteroids may have adversely affected the outcomes of some patients. Remarkably, up to a third of critically ill patients underwent nosocomial or secondary bacterial infections, and intensivists managing these patients will need to remain vigilant as early administration of antibiotics may probably improve the results.

There are several potential therapeutic approaches include:

1-Spike (S) protein-based vaccine: development of a spike1 subunit protein-based vaccine may base on the fact that angiotensin-converting enzyme 2 (ACE2) is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) receptor. Cell lines that facilitate viral replication in the

presence of angiotensin-converting enzyme 2 (ACE2) may be most effective in large-scale vaccine production.

2-Inhibition of transmembrane protease serine 2 (TMPRSS2) activity: Hoffman *et al.* (2020) revealed that initial spike (S) protein priming by transmembrane protease serine 2 (TMPRSS2) is crucial for entry and viral spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) through interaction with the angiotensin-converting enzyme 2 (ACE2) receptor. The serine protease inhibitor camostat mesylate, approved in Japan to manage unrelated diseases, has been shown to block transmembrane protease serine 2 (TMPRSS2) activity and is thus an interesting candidate.

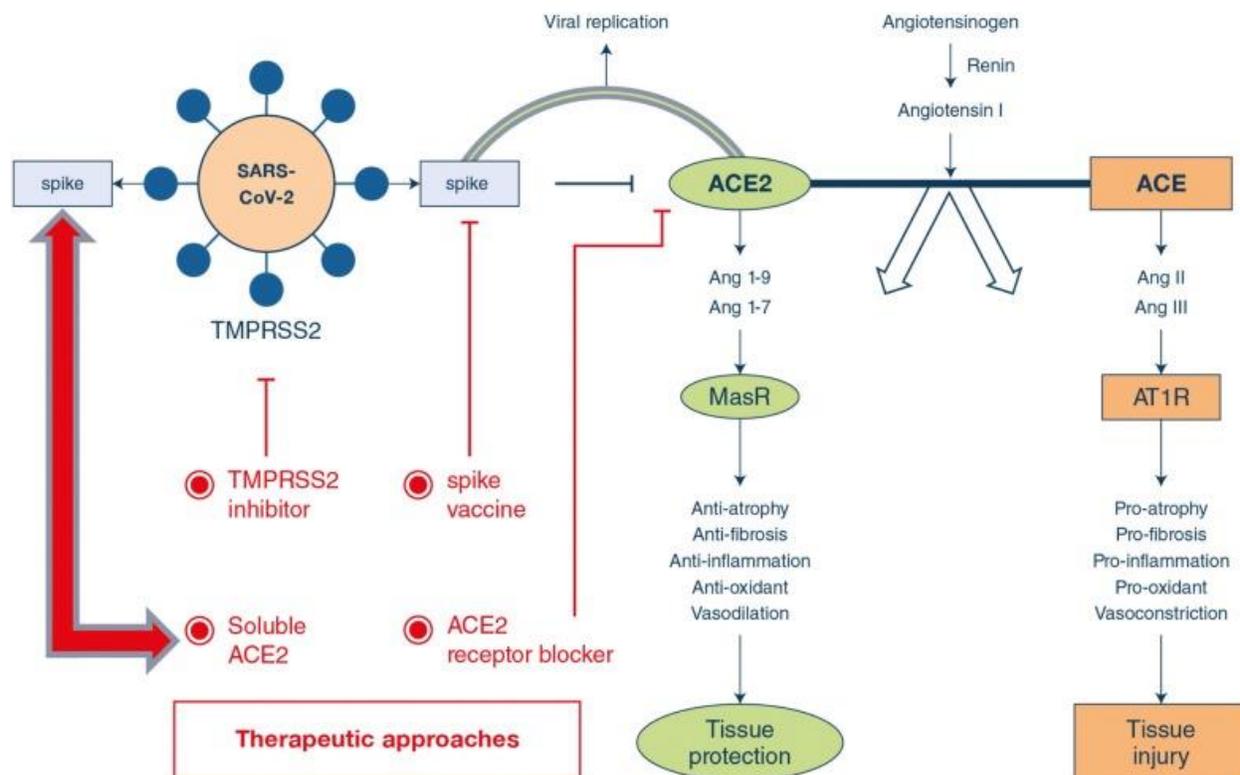
3-Blocking angiotensin-converting enzyme 2 (ACE2) receptor: the interaction sites between angiotensin-converting enzyme 2 (ACE2) and severe acute respiratory syndrome coronavirus (SARS-CoV) have been identified at the atomic level and from studies to date should also hold true for interactions between angiotensin-converting enzyme 2 (ACE2) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Thus, one could target this interaction site with antibodies or small molecules.

4-Delivering excessive soluble form of angiotensin-converting enzyme 2 (ACE2): it was demonstrated in mice that severe acute respiratory syndrome coronavirus (SARS-CoV) downregulates angiotensin-converting enzyme 2 (ACE2) protein [but not angiotensin-converting enzyme (ACE)] by binding its spike (S) protein, contributing to severe lung injury. This supposes that excessive angiotensin-converting enzyme 2 (ACE2) may competitively bind with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) not only to neutralize the virus but also rescue cellular angiotensin-converting enzyme 2 (ACE2) activity which negatively regulates the renin-angiotensin system (RAS) to protect the lung from injury. Indeed, enhanced angiotensin-converting enzyme (ACE) activity and decreased angiotensin-converting enzyme 2 (ACE2) availability contribute to lung injury during acid- and ventilator-induced lung injury. Thus, treatment with a soluble form of angiotensin-converting enzyme 2 (ACE2) itself may exert dual functions:

- (1) Slow viral entry into cells and hence viral spread; and
- (2) Protect the lung from injury.

Notably, a recombinant human angiotensin-converting enzyme 2 (rhACE2; APN01, GSK2586881) has been found to be safe, with no negative hemodynamic effects in healthy

volunteers and in a small cohort of patients with acute respiratory distress syndrome (ARDS). The administration of APN01 rapidly decreased concentrations of its proteolytic target peptide angiotensin II, with a trend to lower plasma interleukin-6 (IL-6) concentrations. A previous work on severe acute respiratory syndrome coronavirus (SARS-CoV) pathogenesis makes angiotensin-converting enzyme 2 (ACE2) a rational and scientifically validated therapeutic target for the current coronavirus disease 2019 (COVID-19) pandemic. The availability of recombinant angiotensin-converting enzyme 2 (ACE2) was the impetus to assemble a multinational team of intensivists, scientists, and biotech to rapidly initiate a pilot trial of recombinant human angiotensin-converting enzyme 2 (rhACE2) in patients with severe coronavirus disease 2019 (COVID-19).



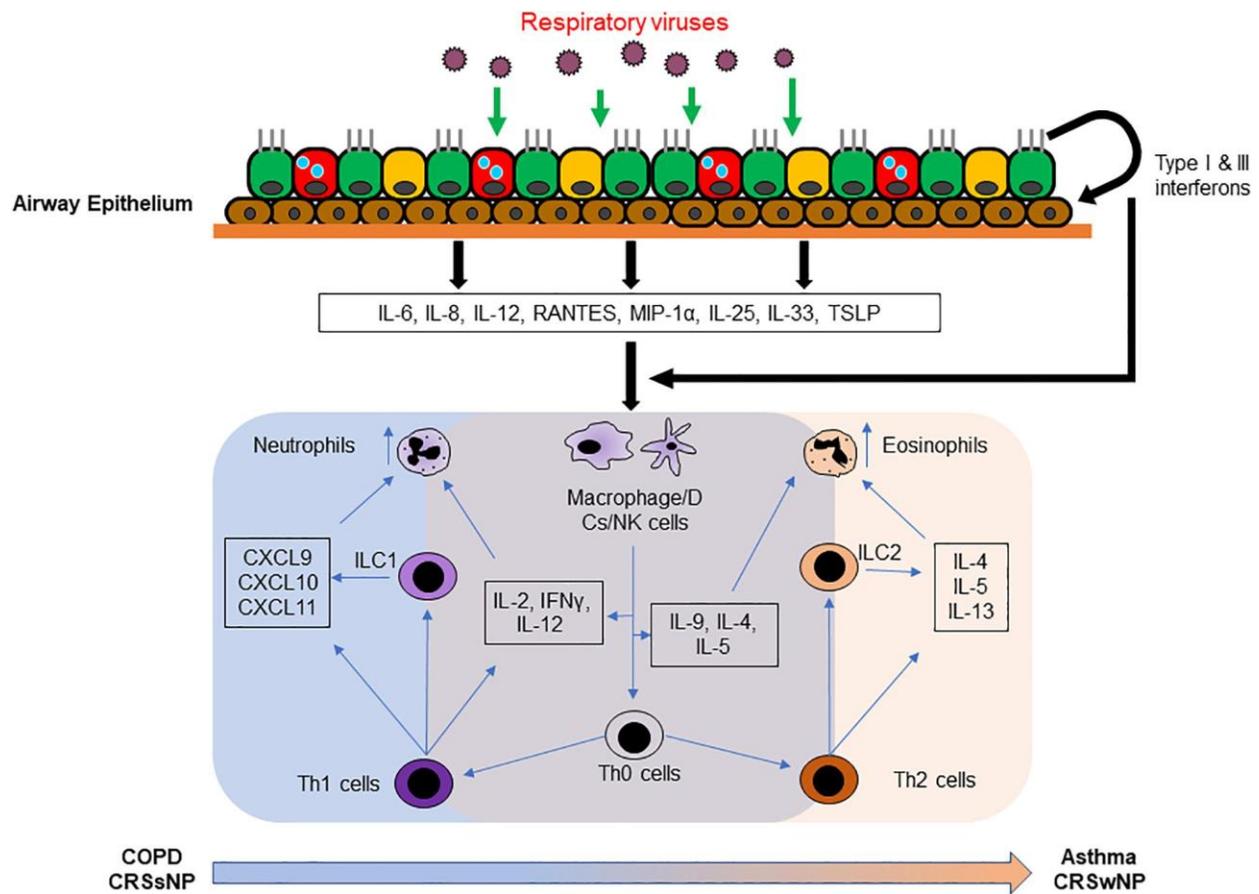
Figure(71): Angiotensin-converting enzyme2 as a SARS-CoV-2 receptor and therapeutic target [Zhang H.; Penninger JM.; Li Y.; Zhong N.; Slutsky AS. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Medicine, 46(4):586-590. DOI: [10.1007/s00134-020-0598-9](https://doi.org/10.1007/s00134-020-0598-9)]

Figure(71): TMPRSS2: transmembrane protease serine 2, AT1R: angiotensin II type 1 receptor, MasR: mitochondrial assembly receptor.

Potential approaches to address angiotensin-converting enzyme 2 (ACE2)-mediated coronavirus disease 2019 (COVID-19) following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. The finding that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and severe acute respiratory syndrome coronavirus (SARS-CoV) use the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry has important implications for understanding severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmissibility and pathogenesis. Severe acute respiratory syndrome coronavirus (SARS-CoV) and likely severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) lead to downregulation of the angiotensin-converting enzyme 2 (ACE2) receptor, but not angiotensin-converting enzyme (ACE), through binding of the spike (S) protein with angiotensin-converting enzyme 2 (ACE2).

This leads to viral entry and replication, as well as severe lung injury. Potential therapeutic approaches include a SARS-CoV-2 spike (S) protein-based vaccine; a transmembrane protease serine 2 (TMPRSS2) inhibitor to block the priming of the spike (S) protein; blocking the surface angiotensin-converting enzyme 2 (ACE2) receptor by using anti- angiotensin-converting enzyme 2 (ACE2) antibody or peptides; and a soluble form of angiotensin-converting enzyme 2 (ACE2) which should slow viral entry into cells through competitively binding with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and hence decrease viral spread as well as protecting the lung from injury through its unique enzymatic function.

10.4 Chronic Obstructive Pulmonary Disease



Figure(72):Viral induced exacerbation of chronic airway inflammatory diseases [Tan K.; Lim R.; Liu J.; Ong H.; Tan V.; Lim H.; Chung K.; Adcock I.; Chow V.; Wang D. (2020). Respiratory viral infections in exacerbation of chronic airway inflammatory diseases: novel mechanisms and insights from the upper airway epithelium. *Frontiers in Cell and Developmental Biology*. <https://doi.org/10.3389/fcell.2020.00099>]

Figure (72) reveals current understanding of viral stimulated exacerbation of chronic airway inflammatory illness. Upon virus infection in the airway, antiviral status will be activated to clear the invading pathogenic agent from the airway. Immune response and injury factors released from the infected epithelium normally would stimulate a rapid type 1 immunity that facilitates viral clearance. However, in the inflamed airway, the cytokines and chemokines released instead augmented the inflammation present in the chronically inflamed airway, strengthening the neutrophilic infiltration in chronic obstructive pulmonary disease (COPD) airway, and eosinophilic infiltration in the asthmatic airway. The effect is also more compounded by the participation of Th1 and type1 innate lymphoid cells (ILC1) cells in the chronic obstructive pulmonary disease (COPD) airway; and Th2 and type 2 innate lymphoid cells cells in the asthmatic airway. However, it is noteworthy to to talk about innate lymphoid cells (ILC). Innate lymphoid cells (ILCs) is the collective term for a group of lymphoid cells lacking rearranged antigen-specific receptors. Group 1 innate lymphoid cells (ILC1) include both cytotoxic natural killer (NK) cells and non-cytotoxic helper type1 innate lymphoid cells (ILC1). Type1 innate lymphoid cells (ILC1) are commonly described as interferon-gamma (IFN- γ)-producing cells, which depend on the transcription factor T-box expressed in T cells TBET (also called T-box transcription factor TBX21, a protein which regulates the development of naive T lymphocyte and may play a role in the development of asthma in humans as well, encoded by *Tbx21*) for their development and function whereas natural killer (NK) cells additionally express eomesodermin [EOMES, a T-box transcription factor with high homology to T-bet and is expressed by activated CD8⁺ T cells as well as in resting and activated natural killer (NK) cells]. Human helper type1 innate lymphoid cells (ILC1) are activated by the cytokines interleukin-12 (IL-12) and interleukin-18 (IL-18), promoting the release of interferon-gamma (IFN- γ) and tumor necrosis factor (TNF). Of interest, helper type1innate lymphoid cells (ILC1), defined as Lin⁻CD127⁺ cells lacking markers of type2 innate lymphoid cells (ILC2) and type3 innate lymphoid cells (ILC3), comprising CD117, CRTH2, and NKp44, were observed to be enriched in inflamed mucosa of patients with Crohn's disease; cells within the type1 innate lymphoid cells (ILC1) population express surface proteins typically expressed by T cells, including CD4, CD5, CD8, and CD28 and several transcripts of T cell receptor (TCR) and CD3, albeit absent on the cell surface; In summary, the human Lin⁻CD127⁺CD117⁻CRTH2⁻NKp44⁻ population, which is usually regarded as helper type1 innate lymphoid cells (ILC1), is probably a heterogenous mix of yet undefined cells and true helper type1 innate lymphoid cells (ILC1) with the capacity to express TBET and produce interferon-gamma (IFN- γ) . Type2 innate lymphoid cells (ILC2), a type of innate lymphoid cell. They are derived from common lymphoid progenitor and belong to the lymphoid lineage. These cells lack antigen specific B or T cell receptor because of the lack of recombination activating gene. Type2 innate lymphoid cells (ILC2) produce type 2 cytokines [e.g. interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-9 (IL-9), interleukin-13 (IL-13)]. Type 2 innate lymphoid cells (T2 ILC) were first characterized as interleukin-13 (IL-13)-producing innate lymphocytes in a number of different tissues in the mouse. They were later also discovered in human intestinal and nasal tissue, peripheral blood, adipose tissue, and lung as cells depending on GATA3 (GATA-binding protein 3 (GATA3), a transcription factor of the GATA family; GATA3 is involved in the regulation of development and differentiation of a variety of human tissues including T cells, skin, kidney, mammary gland, and the central nervous system) and expressing the prostaglandin D₂ receptor CRTH2 (Chemoattractant Receptor-homologous molecule expressed on Th2 cells) and CD161; Human type2 innate lymphoid cells (ILC2) are activated by

cell surface ligands, including ICOS (inducible costimulator-ligand) and NKp30 [natural cytotoxicity receptor 3 (NCR3)] and soluble factors such as lipid mediators, including PGD₂ (prostaglandin D2) and cytokines interleukin-25 (IL-25), interleukin-33 (IL-33), and thymic stromal lymphopoietin (TSLP). Human type2 innate lymphoid cells (ILC2) have been seen to release the typical type 2 cytokines interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-9 (IL-9), and interleukin-13 (IL-13) but also interleukin-6 (IL-6), interleukin-8 (IL-8), and granulocyte-macrophage colony-stimulating factor (GM-CSF). The major physiological role for type2 innate lymphoid cells (ILC2) is probably in immune defense against helminth infections. Type2 innate lymphoid cells (ILC2) have been indicated to be enriched in several human tissues during type 2-mediated inflammation [describes an inflammatory pathway involving a subpopulation of CD4⁺ T cells known as T helper2 (Th2) cells that secrete interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) and stimulate Type 2 immunity, which is characterized by high immunoglobulin E (IgE) antibody titers and eosinophilia]. In patients with chronic rhinosinusitis with nasal polyps [CRSwNP, a subgroup of chronic rhinosinusitis (CRS) characterized by the presence of fleshy swellings (nasal polyps) that develop in the lining of the nose and paranasal sinuses], type2 innate lymphoid cells (ILC2)-producing interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) are found to be significantly accumulated as compared to the healthy nasal mucosa. In asthmatic patients, type2 innate lymphoid cells (ILC2) are found to be enriched in bronchoalveolar lavage fluid and sputum. Type2 innate lymphoid cells (ILC2) also play a role in skin repair, where they were found to be enriched in repaired skin near a wound compared to healthy skin before wounding; Really, a study demonstrates the existence of a regulatory type2 innate lymphoid cells (ILC2) population in chronic rhinosinusitis with nasal polyps (CRSwNP). These regulatory type2 innate lymphoid cells (ILC2reg) develop under the influence of retinoic acid (RA) express interleukin-10 (IL-10) and CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4, also known as CD152 (cluster of differentiation 152), A protein found on T cells) and suppress the activity of CD4⁺ T cells and type2 innate lymphoid cells (ILC2).

The prevalence of chronic airway inflammatory disease is increasing worldwide particularly in developed nations. This disease is characterized by airway inflammation causing complications such as coughing, wheezing and shortness of breath. The disease can manifest in both the upper airway (such as chronic rhinosinusitis, CRS) and lower airway (such as asthma and chronic obstructive pulmonary disease, COPD) which widely impact the patients' quality of life. Treatment and management vary greatly in efficacy due to the complexity and heterogeneity of the disease. This is further complicated by the effect of episodic exacerbations of the disease, described as worsening of disease symptoms involving wheeze, cough, breathlessness and chest tightness. Such exacerbations are attributed to the effect of enhanced acute airway inflammation impacting upon and worsening the symptoms of the existing illness. These acute exacerbations are the major cause of morbidity and sometimes mortality in patients, as well as leading to primary economic burdens worldwide. However, due to the complex interactions between the

host and the exacerbation agents, the mechanisms of exacerbation may vary significantly in different patients under various promoters.

Acute exacerbations are often due to the presence of environmental factors such as allergens, pollutants, smoke, cold or dry air and pathogenic microorganisms in the airway. These agents elicit an immune response resulting in infiltration of activated immune cells that further produce inflammatory mediators that lead to acute symptoms such as increased mucus production, cough, wheeze and shortness of breath. Among these agents, viral infection is one of the main drivers of asthma exacerbations responsible of up to 80–90% and 45–80% of exacerbations in children and adults respectively. Viral involvement in chronic obstructive pulmonary disease (COPD) exacerbation is also equally high, having been detected in 30–80% of acute chronic obstructive pulmonary disease (COPD) exacerbations. One of the reasons for the involvement of respiratory viruses' in exacerbations is their ease of transmission and infection. In addition, the high diversity of the respiratory viruses may also contribute to exacerbations of different nature and severity. It is notable to describe the exact mechanisms underpinning viral exacerbations in susceptible subjects in order to adequately treat exacerbations via supplementary treatments that may alleviate the exacerbation symptoms or prevent severe exacerbations.

While the lower airway is the site of dysregulated inflammation in most chronic airway inflammatory illnesses, the upper airway remains the first point of contact with sources of exacerbation. Therefore, their interaction with the exacerbation agents may directly contribute to the subsequent responses in the lower airway.

Respiratory viruses primarily infect and replicate within airway epithelial cells. During the replication process, the cells release antiviral factors and cytokines that alter local airway inflammation and airway niche. In a healthy airway, the inflammation normally leads to type 1 inflammatory responses consisting of activation of an antiviral state and infiltration of antiviral effector cells. This eventually leads to the resolution of the inflammatory response and clearance of the viral infection. However, in a chronically inflamed airway, the responses against the virus may be impaired or aberrant, causing sustained inflammation and erroneous infiltration, leading to the exacerbation of their symptoms. This is often further compounded by the increased susceptibility of chronic airway inflammatory disease patients toward viral respiratory infections, thereby increasing the frequency of exacerbation as a whole.

Furthermore, due to the different replication cycles and response against the myriad of respiratory viruses, each respiratory virus may also contribute to exacerbations via different mechanisms that may alter their severity.

Once the link between viral infection and acute exacerbations of chronic airway inflammatory disease was confirmed, there have been many reports on the mechanisms underlying the exacerbation stimulated by respiratory viral infection. Upon infecting the host, viruses trigger an inflammatory response as a means of counteracting the infection. In general, infected airway epithelial cells secrete type I [interferon-alpha/beta, (IFN α/β)] and type III [interferon-lambda, (IFN λ)] interferons, cytokines and chemokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-12 (IL-12), RANTES, macrophage inflammatory protein-1alpha (MIP-1 α), and monocyte chemoattractant protein-1 (MCP-1). These, in turn, enable infiltration of innate immune cells and of professional antigen presenting cells (APCs) that will then in turn produce specific mediators to facilitate viral targeting and clearance, involving type II interferon (interferon-gamma, IFN γ), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-9 (IL-9), and interleukin-12 (IL-12). These factors heighten local inflammation and the infiltration of granulocytes, T-cells and B-cells. The increased inflammation, in turn, worsens the symptoms of airway illnesses.

Patients with chronic obstructive pulmonary disease (COPD) are more neutrophilic in nature due to the expression of neutrophil chemoattractants such as CXCL9, CXCL10, and CXCL11. The pathology of these airway diseases is characterized by airway remodeling due to the presence of remodeling factors such as matrix metalloproteinases (MMPs) secreted from infiltrating neutrophils. Viral infections in such states will then lead to increased neutrophilic activation; worsening the symptoms and airway remodeling in the airway thereby exacerbating chronic obstructive pulmonary disease (COPD).

An epithelial-centric alarmin pathway around interleukin-25 (IL-25), interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP), and their interaction with type 2 innate lymphoid cells (ILC2) has also been described. Interleukin-25 (IL-25), interleukin-33 (IL-33), and thymic stromal lymphopoietin (TSLP) are type 2 inflammatory cytokines expressed by the epithelial cells upon injury to the epithelial barrier. Type 2 innate lymphoid cells (ILC2) are a group of lymphoid cells lacking both B and T cell receptors but play a crucial role in secreting type 2

cytokines to perpetuate type 2 inflammation when activated. In viral infection, cell death and injury to the epithelial barrier will also trigger the expression of interleukin-25 (IL-25), interleukin-33 (IL-33), and thymic stromal lymphopoietin (TSLP), with heighten expression in an inflamed airway. These 3 cytokines then function in concert to activate type 2 innate lymphoid cells (ILC2) to further release type 2 cytokines interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13) which further aggravate the type 2 inflammation in the airway resulting in acute exacerbation. In chronic obstructive pulmonary disease (COPD), increased type 2 innate lymphoid cells (ILC2) activation, which retain the capability of differentiating to type 1 innate lymphoid cells (ILC1), may also further augment the neutrophilic response and further aggravate the exacerbation. Of interest, these factors are not produced to any great extent and do not activate an type 2 innate lymphoid cells (ILC2) response during viral infection in healthy individuals; despite augmenting a type 2 exacerbation in chronically inflamed airways.

On the other end of the spectrum, viruses that trigger strong type 1 inflammation and cell death such as certain coronaviruses (CoV) [including the recently emerged coronavirus disease 2019 (COVID-19) virus], may not cause prolonged inflammation due to potent induction of antiviral clearance. These infections, however, lead to massive damage and cell death to the epithelial barrier, so much so that areas of the epithelium may be completely absent post infection. The massive cell death induced may cause worsening of the acute exacerbation due to the release of their cellular content into the airway, further triggering an inflammatory response in the airway. Further, the destruction of the epithelial barrier may cause further contact with other pathogens and allergens in the airway which may then prolong exacerbations or develop new exacerbations. Epithelial destruction may also induce further epithelial remodeling during its regeneration as viral infection triggers the expression of remodeling genes such as matrix metalloproteinases (MMPs) and growth factors. Infections that cause massive destruction of the epithelium, often cause severe acute exacerbations with non-classical symptoms of chronic airway inflammatory diseases.

Another mechanism that viral infections may use to drive acute exacerbations is the induction of vasodilation or tight junction opening factors which may increase the rate of infiltration. Infection with a multitude of respiratory viruses causes disruption of tight junctions with the resulting increased rate of viral infiltration. This also increases the chances of allergens coming

into contact with airway immune cells. Moreover, the expression of vasodilating factors and fluid homeostatic factors such as angiopoietin-like 4 (ANGPTL4) and bactericidal/permeability-increasing fold-containing family member A1 (BPIFA1) are also correlated with viral infections and pneumonia progress, which may worsen inflammation in the lower airway. These factors may act as targets to prevent viral-induced exacerbations during the treatment of acute exacerbation of chronic airway inflammatory illnesses.

Another area of interest is the relationship between asthma and chronic obstructive pulmonary disease (COPD) exacerbations and their association with the airway microbiome. The development of chronic airway inflammatory diseases is usually linked to specific bacterial species in the microbiome which may thrive in the inflamed airway environment. In addition, viral infection may disrupt biofilm colonies in the upper airway (e.g., *Streptococcus pneumoniae*) microbiome to be released into the lower airway and worsening the inflammation. Further, a viral infection may also alter the nutrient profile in the airway through release of previously inaccessible nutrients that will alter bacterial growth. In addition, the destabilization is further compounded by impaired bacterial immune response, either from direct viral influences, or use of corticosteroids (CSs) to suppress the exacerbation symptoms. All these may gradually cause more far reaching effect when normal flora is replaced with opportunistic pathogenic agents, altering the inflammatory profiles. These changes may in turn develop more severe and frequent acute exacerbations due to the interplay between virus and pathogenic bacteria in exacerbating chronic airway inflammatory diseases.

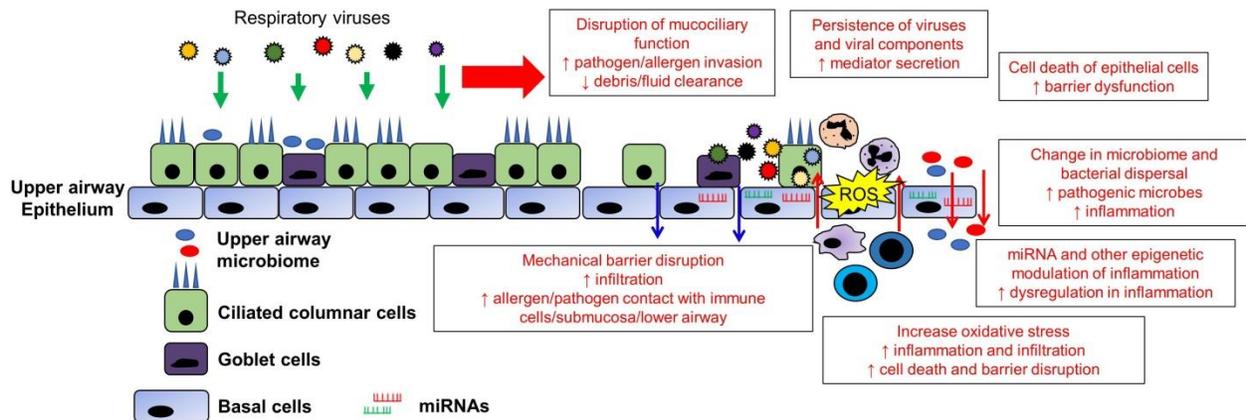
Viral infections can cause the disruption of mucociliary function, an important component of the epithelial barrier. Ciliary proteins that aid in the proper function of the motile cilia in the airways are aberrantly expressed in ciliated airway epithelial cells which are the major target for viral infection. Such form of secondary cilia dyskinesia appears to be present with chronic inflammations in the airway, but the exact mechanisms are still unknown. Nevertheless, it was shown that in viral infection, there can be a change in the metabolism of the cells as well as alteration in the ciliary gene expression, mostly in the form of down-regulation of the genes such as dynein axonemal heavy chain 5 (DNAH5) and multiciliate differentiation and deoxyribonucleic acid (DNA) synthesis associated cell cycle protein [multiciliate differentiation and DNA synthesis-associated cell cycle protein (MCIDAS)]. Severe acute respiratory syndrome

coronavirus-2 (SARS-CoV-2) was found to reduce ciliary beating in infected airway epithelial cell model. Furthermore, viral infections were shown to directly destroy the cilia of the ciliated cells and almost all respiratory viruses infect the ciliated cells. In addition, mucus overproduction may also disrupt the equilibrium of the mucociliary function following viral infection, developing symptoms of acute exacerbation. Hence, the disruption of the ciliary movement during viral infection may cause more foreign material and allergen to enter the airway, aggravating the symptoms of acute exacerbation and making it more difficult to manage. The mechanism of the occurrence of secondary cilia dyskinesia can also therefore be explored as a means to limit the effects of viral induced acute exacerbation.

Micro-ribonucleic acids (miRNAs) are short non-coding ribonucleic acids (RNAs) involved in post-transcriptional modulation of biological processes, and implicated in a number of diseases. Micro-ribonucleic acids (miRNAs) are found to be stimulated by viral infections and may play a role in the modulation of antiviral responses and inflammation. In the case of chronic airway inflammatory diseases, circulating micro-ribonucleic acids (miRNAs) changes were seen to be linked to exacerbation of the diseases. Therefore, it is probably that such micro-ribonucleic acids (miRNAs) changes originated from the infected epithelium and responding immune cells, which may function to further dysregulate airway inflammation causing exacerbations. Non-coding ribonucleic acids (RNAs) also found as targets to modulate viral induced airway changes as a means of managing exacerbation of chronic airway inflammatory diseases. Other than micro-ribonucleic acids (miRNAs) modulation, other epigenetic modification such as deoxyribonucleic acid (DNA) methylation may also play a role in exacerbation of chronic airway inflammatory diseases. Recent epigenetic studies have indicated the association of epigenetic modification and chronic airway inflammatory diseases, and that the nasal methylome was shown to be a sensitive marker for airway inflammatory changes.

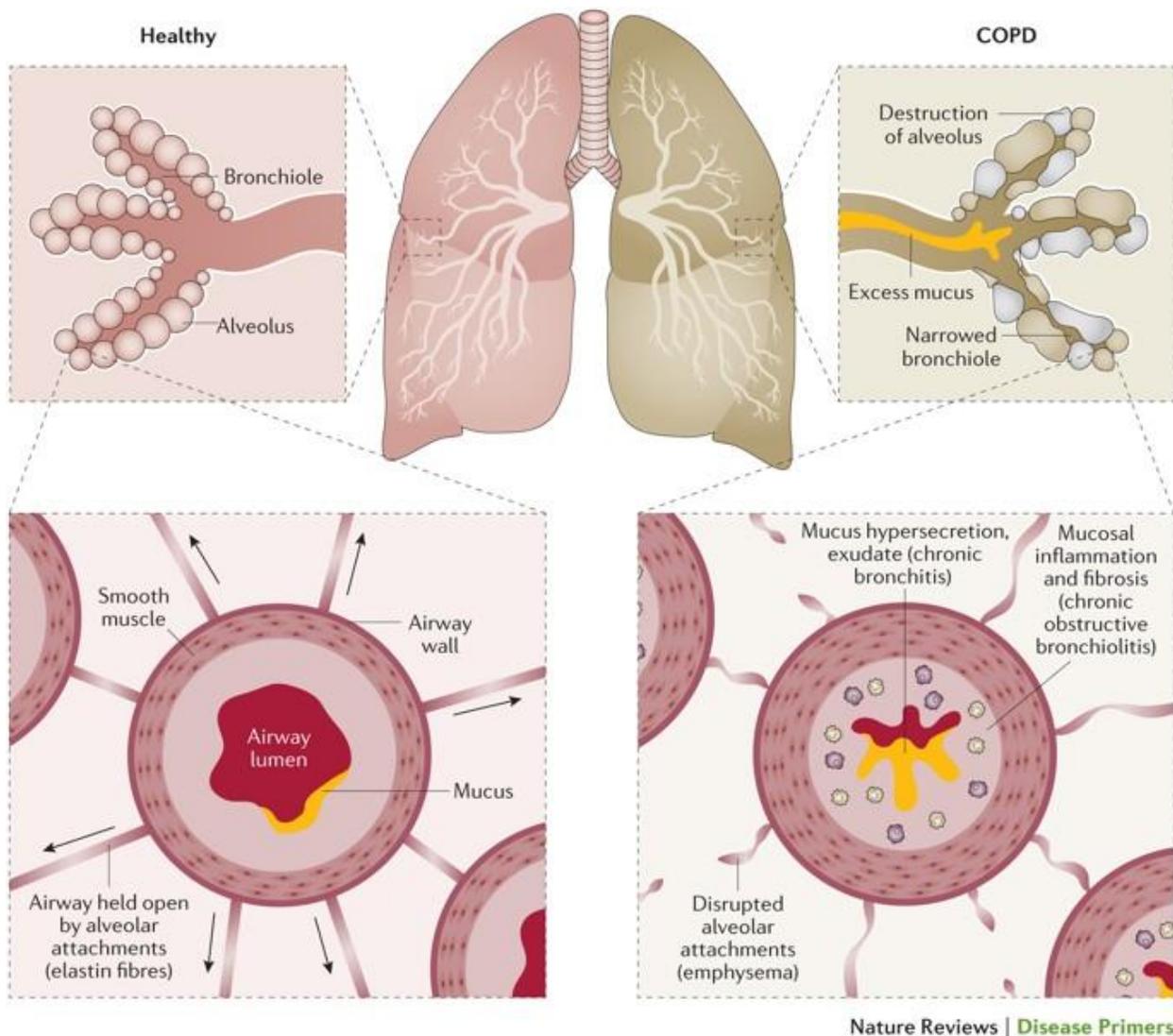
Finally, viral infection can lead to enhanced production of reactive oxygen species (ROS), oxidative stress (OS) and mitochondrial dysfunction in the airway epithelium. The airway epithelium of patients with chronic airway inflammatory diseases are often under a condition of constant oxidative stress (OS) which sustains the inflammation in the airway. Viral infections of the respiratory epithelium may induce the further production of reactive oxygen species (ROS) as an antiviral mechanism. Moreover, infiltrating cells in response to the infection such as

neutrophils will also evoke respiratory burst as a means of increasing the reactive oxygen species (ROS) in the infected region. The increased reactive oxygen species (ROS) and oxidative stress (OS) in the local environment may serve as a trigger to promote inflammation thereby aggravating the inflammation in the airway.



Figure(73):Changes in the upper airway epithelium contributing to viral exacerbation in chronic airway inflammatory diseases [Tan K.; Lim R.; Liu J.; Ong H.; Tan V.; Lim H.; Chung K.; Adcock I.; Chow V.; Wang D. (2020). Respiratory viral infections in exacerbation of chronic airway inflammatory diseases: novel mechanisms and insights from the upper airway epithelium. *Frontiers in Cell and Developmental Biology*. <https://doi.org/10.3389/fcell.2020.00099>]

Figure (73) shows changes in the upper airway epithelium contributing to viral exacerbation in chronic airway inflammatory diseases. The upper airway epithelium is the primary contact/infection site of most respiratory viruses. Therefore, its infection by respiratory viruses may have far reaching consequences in augmenting and synergizing current and future acute exacerbations. The destruction of epithelial barrier, mucociliary function and cell death of the epithelial cells serves to increase contact between environmental triggers with the lower airway and resident immune cells. The opening of tight junction increasing the leakiness further augments the inflammation and exacerbations. In addition, viral infections are usually accompanied with oxidative stress (OS) which will further increase the local inflammation in the airway. The dysregulation of inflammation can be further compounded by modulation of micro-ribonucleic acids (miRNAs) and epigenetic modification such as deoxyribonucleic acid (DNA) methylation and histone modifications that induce dysregulation in inflammation. Finally, the change in the local airway environment and inflammation stimulates growth of pathogenic bacteria that may replace the airway microbiome. Furthermore, the inflammatory environment may also disperse upper airway commensals into the lower airway, further causing inflammation and alteration of the lower airway environment, leading to prolonged exacerbation episodes following viral infection.



Nature Reviews | Disease Primers

Figure(74):Chronic obstructive pulmonary disease[Barnes P.; Burney P.; Silverman E.; Celli B.; Vestbo J.; Wedzicha J.; Wouters E. (2015). Chronic obstructive pulmonary disease. Nature Reviews Disease Primers. <https://doi.org/10.1038/nrdp.2015.76>]

Chronic obstructive pulmonary disease (COPD) comprises a diverse group of clinical syndromes that share the common characteristic of limitation of expiratory airflow. The American Thoracic Society defines chronic obstructive pulmonary disease (COPD) in terms of chronic bronchitis and emphysema. Chronic bronchitis is characterized by the clinical symptoms of excessive cough and sputum production; emphysema refers to chronic dyspnea, resulting from enlarged air spaces and destruction of lung tissue. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a disease state

characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Asthma is also characterized by airflow obstruction and inflammation, but in addition it involves hyperresponsiveness of the airways to stimulus; therefore, the reversibility of functional deficits in asthma differentiates it from chronic obstructive pulmonary disease (COPD).

Cigarette smoking is the main risk factor for chronic obstructive pulmonary disease (COPD). However, about 1 of 6 Americans with chronic obstructive pulmonary disease (COPD) has never smoked. Occupational and environmental exposures to chemical fumes, dusts, and other lung irritants account for 10% to 20% of patients. Patients with a history of severe lung infections in childhood are more probable to develop chronic obstructive pulmonary disease (COPD). Alpha-1 antitrypsin deficiency (AATD) is a scarce cause of chronic obstructive pulmonary disease (COPD) but should be suspected in individuals in whom emphysema develops before the age of 40 or those who lack the common risk factors. Alpha-1 antitrypsin deficiency (AATD), also known as alpha-1 proteinase inhibitor deficiency, is a genetic condition that causes increased risk of lung and liver disease and several other conditions. Alpha-1 antitrypsin deficiency (AATD) lung disease is due to the relative deficiency in the blood and lungs of the alpha-1 antitrypsin (AAT) protein, a major circulating serine proteinase inhibitor. Although recent evidence suggests a more complicated cascade of proteolytic and inflammatory factors as the cause of emphysema in alpha-1 antitrypsin deficiency (AATD), unopposed neutrophil elastase activity within the pulmonary interstitium with resultant connective tissue (CT) destruction remains an important contributor to the pathogenesis of emphysema. In addition, neutrophil elastase has been implicated in the mucus hypersecretion correlated with chronic bronchitis. There is a high prevalence of anatomic bronchiectasis in persons with alpha-1 antitrypsin deficiency (AATD), with some persons manifesting signs and symptoms of clinical bronchiectasis. Overall, the pulmonary manifestations of alpha-1 antitrypsin deficiency (AATD) involve the entire spectrum of disorders correlated with chronic obstructive pulmonary disease (COPD).

Chronic obstructive pulmonary disease (COPD) is a slowly progressing disease with a long asymptomatic phase, during which lung function continues to decline. Persistent cough, particularly with mucus production, is a common symptom. Dyspnea, especially with exercise,

wheezing, and chest tightness may also be present. Patients often present with the first acute exacerbation of chronic obstructive pulmonary disease (COPD) at an advanced stage. Symptoms do not usually occur until forced expiratory volume in 1 second (FEV1) is approximately 50% of the predicted normal value. It is notable to identify forced expiratory volume in 1 second (FEV1) as the maximum amount of air that the subject can forcibly expel during the first-second following maximal inhalation. As the disease progresses, exacerbations may become more frequent and lifethreatening complications may develop. End-stage chronic obstructive pulmonary disease (COPD) is featured by severe airflow limitation, severely limited performance, and systemic complications. Patients frequently succumb to respiratory failure or pulmonary infection. Extrapulmonary effects associated with chronic obstructive pulmonary disease (COPD) involve weight loss, nutritional abnormalities, and muscle atrophy.

Cigarette smoking or exposure to noxious agents triggers an inflammatory process in the lungs and airways of the bronchial tree that develops to small airway disease and parenchymal destruction. Loss of elasticity of the alveolar attachments, or their destruction, is a hallmark of emphysema. The inability of the lungs to empty causes air trapping and hyperinflation, manifested as dyspnea on exertion. Over time, this can cause the diaphragm to flatten and the rib cage to enlarge. In the late stages of chronic obstructive pulmonary disease (COPD), hypoxemia develops. Pulmonary hypertension (PH) is a consequence of thickening of the intima and vascular smooth muscle and indicates a poor prognosis.

The net result of the pathophysiologic processes of chronic obstructive pulmonary disease (COPD) is increased resistance to airflow and decreased expiratory flow rate. Removing the inflammatory stimulus (eg, stopping smoking) does not diminish the inflammatory process. The inflammatory process in asthma is notably different from that in chronic obstructive pulmonary disease (COPD), but since approximately 10% of chronic obstructive pulmonary disease (COPD) patients also have asthma, some of the pathologic characteristics may overlap.

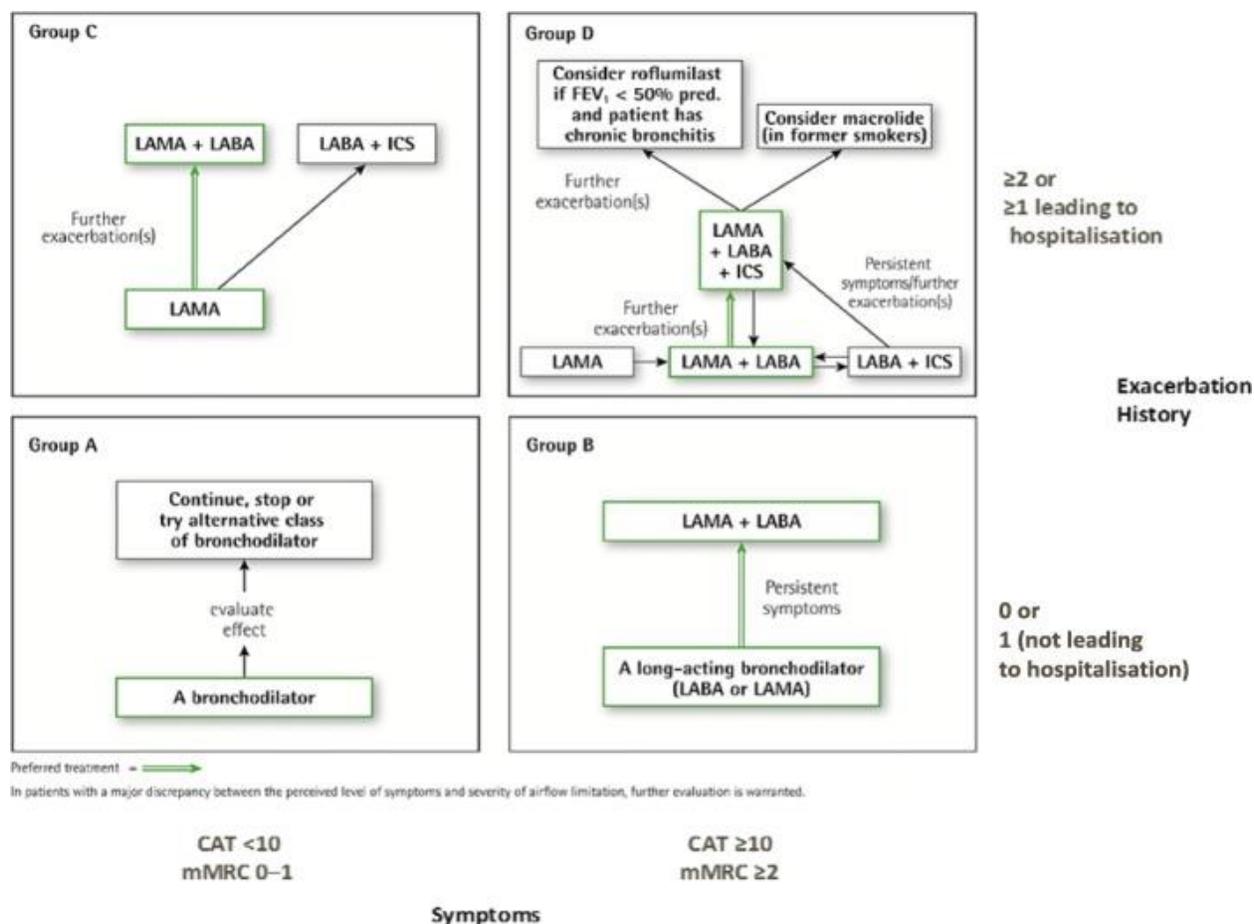
Clinicians need to be aware of comorbidities in patients with chronic obstructive pulmonary disease (COPD), which can adversely impact health status and complicate treatment. Chronic obstructive pulmonary disease (COPD) is associated not only with other respiratory diseases (eg, pneumonia) but also with diseases affecting organ systems, such as the musculoskeletal system (e.g., osteoporosis) and the cardiovascular system (e.g., angina).

Regarding the different chronic obstructive pulmonary disease (COPD) phenotypes, a question remains as to which pharmacologic agent(s), i.e. β_2 agonists, antimuscarinics, inhaled or systemic corticosteroids, theophylline, phosphodiesterase-4 (PDE4) inhibitors, mucolytics, and macrolides would be optimal for a given phenotype. Beta-agonist is a bronchodilator medicine that opens the airways by relaxing the muscles around the airways that may tighten during an asthma attack or in chronic obstructive pulmonary disease (COPD). Antimuscarinic (anticholinergic) inhibiting the action of acetylcholine, a neurotransmitter in the parasympathetic nervous system. Antimuscarinic drugs relax smooth muscle, decrease the secretion of saliva, sweat, and digestive juice, and dilate the pupil of the eye. A Dictionary of Nursing. Systemic and local inflammation is central to the pathophysiology of chronic obstructive pulmonary disease (COPD) and increased levels of inflammation have been linked to a more progressive course in chronic obstructive pulmonary disease (COPD) and have been shown to be present during an exacerbation, thus decreases in inflammatory cytokines, C-reactive protein (CRP), and inflammatory cells have been recognized with corticosteroid (CS) use, proposing a possible mechanism for a therapeutic benefit of steroids. Theophylline, also known as 1,3-dimethylxanthine, is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of brand names; as a member of the xanthine family, it bears structural and pharmacological similarity to theobromine and caffeine, and is readily found in nature, being present in tea (*Camellia sinensis*) and cocoa (*Theobroma cacao*). A phosphodiesterase type 4 inhibitor, commonly referred to as a PDE4 inhibitor, is a drug used to block the degradative action of phosphodiesterase 4 (PDE4) on cyclic adenosine monophosphate (cAMP); it is a member of the larger family of phosphodiesterase (PDE) inhibitors; the phosphodiesterase-4 (PDE4) family of enzymes are the most prevalent phosphodiesterase (PDE) in immune cells; they are predominantly responsible for hydrolyzing cyclic adenosine monophosphate (cAMP) within both immune cells and cells in the central nervous system (CNS). Mucolytics are medicines that thin mucus, making it less thick and sticky and easier to cough up; they are used to manage respiratory conditions characterized by excessive or thickened mucus, such as a chesty (productive) cough. Macrolide, class of antibiotics characterized by their large lactone ring structures and by their growth-inhibiting (bacteriostatic) effects on bacteria. The macrolides were first discovered in the 1950s, when scientists isolated erythromycin from the soil

bacterium *Streptomyces erythraeus*. In the 1970s and 1980s synthetic derivatives of erythromycin, including clarithromycin and azithromycin, were developed.

An approach to chronic obstructive pulmonary disease (COPD) pharmacotherapy used by Spanish investigators utilizes an easy table of four major phenotypes [non exacerbators, asthma and COPD overlap (ACO), exacerbators with emphysema, exacerbators without emphysema] with five treatments options [bronchodilators, inhaled corticosteroids (ICS), mucolytics, phosphodiesterase-4 (PDE4) inhibitors, macrolides], linking each of the four phenotypes with the appropriate management(s). In addition, a paper emphasizes the notion of phenotyping chronic obstructive pulmonary disease (COPD) patients before starting management, by recommending that inflammatory phenotypes, such as chronic bronchitis, frequent exacerbators and those with multiple co-morbidities need inhaled corticosteroids (ICS) treatment; and patients that are emphysematous with dyspnea and lung hyperinflation, fast decliners, need dual bronchodilation with long-acting β 2-agonist/long-acting muscarinic antagonist (LABA/LAMA).

The 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document presumes treatment recommendations depending on chronic obstructive pulmonary disease (COPD) phenotypes described by symptoms and exacerbation history with preferred treatments.



Figure(75):Pharmacologic treatment algorithms by GOLD grade [Candela M.; Costorella R.; Stassaldi A.; Maestrini V.; Curradi G.(2019). Treatment of COPD: the simplicity is a resolved complexity. Multidisciplinary Respiratory Medicine, 14:8. doi:[10.1186/s40248-019-0181-8](https://doi.org/10.1186/s40248-019-0181-8)]

Furthermore, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) also states probable consideration should be given to step down from triple therapy to a non-inhaled corticosteroids (ICS) treatment in case of ascertained pneumonia risk [e.g. on an inhaled corticosteroids (ICS)-containing regimen] or lack of marked clinical improvement. Bronchodilators, including dual bronchodilators, figure prominently into the treatment guidelines. This is most likely due to the increasing amount of evidence supporting the benefits long-acting muscarinic antagonist/ long-acting β_2 -agonist (LAMA/LABA) combinations on lung and symptom improvement with no increase in side effects compared to long-acting muscarinic antagonist (LAMA) or long-acting β_2 -agonist (LABA) alone. Findings from the Effect of Indacaterol–Glycopyrronium Versus Fluticasone–Salmeterol on COPD Exacerbations (FLAME)

study also demonstrated an exacerbation benefit with long-acting muscarinic antagonist/ long-acting β 2-agonist (LAMA/LABA) vs inhaled corticosteroids/long-acting β 2-agonist (ICS/LABA). On the other hand, combination inhaled corticosteroids/long-acting β 2-agonist (ICS/LABA) have also shown benefit in reducing exacerbations and improving lung function and health-related quality of life compared to placebo, inhaled corticosteroids (ICS) and long-acting β 2-agonist (LABA) alone. However, inhaled corticosteroids (ICS)-containing therapy is associated with an increased risk of pneumonia with no association with an increase in mortality supporting a favorable benefit/risk profile in patients at risk of exacerbations.

As with all therapeutic choices, an assessment of benefit/risk should be made on an individual patient level and those with chronic obstructive pulmonary disease (COPD) receiving inhaled corticosteroids should be carefully evaluated to identify concomitant osteoporosis and diabetes mellitus (DM), and monitored for progression of these diseases for early implementation of appropriate management.

The publication of the InforMing the Pathway of COPD Treatment (IMPACT) Study has shown new evidences about the role of single inhaler triple therapy inhaled corticosteroids/long-acting β 2-agonist/long-acting muscarinic antagonist (ICS/LABA/LAMA) compared to inhaled corticosteroids/long-acting β 2-agonist (ICS/LABA) and long-acting muscarinic antagonist/ long-acting β 2-agonist (LAMA/LABA). The main results of this study were obtained on: reduction of exacerbation rate, lung function improvement [in terms of trough forced expiratory volume in 1 second (FEV1) improvement], mortality data and incidence of pneumonia. Single inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) demonstrated a significant reduction of moderate/severe exacerbation rate and prolonging the time to first exacerbation on-treatment compared to both fluticasone furoate/vilanterol (FF/VI) and umeclidinium/vilanterol (UMEC/VI). A reduction in the number hospitalizations was seen with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) vs umeclidinium/vilanterol (UMEC/VI) but not fluticasone furoate/vilanterol (FF/VI). There was a significant improvement in lung function with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) compared with both dual treatments [inhaled corticosteroids/long-acting β 2-agonist (ICS/LABA) and long-acting muscarinic antagonist/ long-acting β 2-agonist (LAMA/LABA)]; this result reinforces the need for maximum bronchodilation to optimize lung function improvements.

Some debate was made on the asthmatic patient enrolled in the InforMing the Pathway of COPD Treatment (IMPACT) study: only patients with chronic obstructive pulmonary disease (COPD) diagnosis, based on American Thoracic Society/European Respiratory Society (ATS/ERS) criteria were included and patients were permitted to enter the study if they also had a prior history of asthma, without an ongoing diagnosis of asthma, associated to other parameters as 65 years of age, substantial smoking history and a high frequency of exacerbations noted during the 52-week management period (~ 1 event/patient/year). Furthermore, of the population enrolled in InforMing the Pathway of COPD Treatment (IMPACT), 18% had airflow limitation that was reversible to salbutamol and this proportion is lower than that shown in other studies in chronic obstructive pulmonary disease (COPD) population.

Taken together, these features should be obviously ascribed to chronic obstructive pulmonary disease (COPD) population rather than to an asthma population. For over a decade the respiratory community has debated the potential mortality benefits of inhaled corticosteroids (ICS)-containing treatments in chronic obstructive pulmonary disease (COPD), but until now this benefit has not been prospectively shown.

Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and fluticasone furoate/vilanterol (FF/VI) are the only chronic obstructive pulmonary disease (COPD) therapies available that have prospective data showing a reduction in the risk of all-cause mortality vs long-acting muscarinic antagonist/ long-acting β 2-agonist (LAMA/LABA) umeclidinium/vilanterol (UMEC/VI).

There was an increase in the risk of pneumonia seen with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and fluticasone furoate/vilanterol (FF/VI) vs umeclidinium/vilanterol (UMEC/VI) which was expected and consistent with the class of inhaled corticosteroids (ICS) containing therapy. As indicated previously pneumonia and exacerbations are key events during chronic obstructive pulmonary disease (COPD) disease, with different implications for individual patients. It is important to consider both events, as viewing them in tandem may provide a better picture of the overall benefit/risk profile of a particular chronic obstructive pulmonary disease (COPD) therapy.

The InforMing the Pathway of COPD Treatment (IMPACT) trial is the only clinical study which has directly compared all three major inhaled therapy combinations available [inhaled corticosteroids/long-acting β 2-agonist (ICS/LABA), long-acting muscarinic antagonist/ long-

acting β 2-agonist (LAMA/LABA) and inhaled corticosteroids/ long-acting muscarinic antagonist/ long-acting β 2-agonist (ICS/LAMA/LABA)] in the management of chronic obstructive pulmonary disease (COPD). The direct comparison between these medications has helped to better understand the role of inhaled corticosteroids (ICS) on top of maximal bronchodilation with long-acting muscarinic antagonist/ long-acting β 2-agonist (LAMA/LABA).

Macrolides have shown a recognizable efficiency in preventing exacerbations. However, their use in a chronic/preventive manner needs to be decided carefully balancing the potential efficacy in the right patients with the potential risk connected to an antibiotic overuse and probable antibiotic resistance in a single patient and/or a community.

Roflumilast, the first phosphodiesterase-4 inhibitor available, is indicated for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) [forced expiratory volume in 1 second (FEV1) post-bronchodilator less than 50% predicted] associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. In fact, a *post-hoc* pooled analysis showed that roflumilast reduced exacerbation frequency mainly in a subset of chronic obstructive pulmonary disease (COPD) patients whose features included chronic bronchitis with/without concurrent inhaled corticosteroids (ICS).

In terms of oxygen supplementation, it's well known and accepted that in patients with chronic obstructive pulmonary disease (COPD) and chronic hypoxemia long-term oxygen administration can improve pulmonary hypertension (PH) and increase exercise performance. However only two studies have shown in the early 1980s that the use of long term oxygen therapy (LTOT) can lower mortality in patient with chronic obstructive pulmonary disease (COPD) associated to chronic hypoxemia. In the Medical Research Council trial, 87 chronic obstructive pulmonary disease (COPD) patients were randomized to an long term oxygen therapy (LTOT) group that received oxygen for at least 15 h per day or to a no-oxygen control group. Within the 5-year study period, 19 out of 42 died in the treated group versus 30 out of 45 in the control group (probability of survival was 55% versus 33% respectively with a $p < 0.05$).

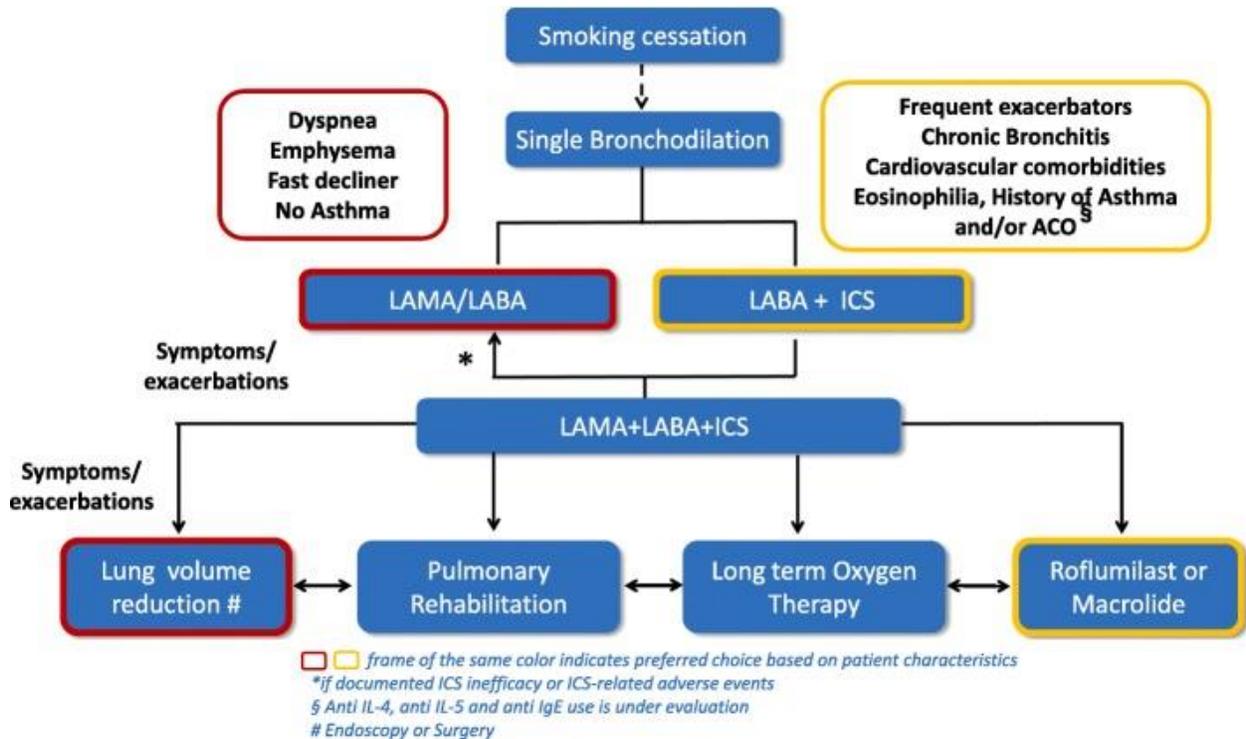
The Nocturnal Oxygen Therapy Trial (NOTT) compared continuous (24-h) oxygen administration with 12-h nocturnal oxygen supplementation over a period of two years; patients treated with 24 oxygen showed a significant improvement in survival versus those given 12-h nocturnal oxygen (mean annual death rate was 11,9% and 20,6% respectively with a $p < 0.05$).

Currently the British Thoracic Society (BTS) guidelines propose using long term oxygen therapy (LTOT) in patients with stable chronic obstructive pulmonary disease (COPD) and a resting partial pressure of oxygen $\text{PaO}_2 \leq 55$ mmHg and in patients with stable chronic obstructive pulmonary disease (COPD) with a resting partial pressure of oxygen (PaO_2) ≤ 60 kilopascal (kPa) associated with evidence of peripheral edema, polycythemia (hematocrit $\geq 55\%$) or pulmonary hypertension (PH) independently if patient is a prevalent bronchitis or emphysema.

As shown in an important review, a quite limited and well selected group of chronic obstructive pulmonary disease (COPD) patients can benefit from surgical and endoscopic lung volume reduction [lung volume reduction surgery (LVRS) and endobronchial lung volume reduction (ELVR)]. These treatments should be considered in presence of heterogeneous emphysema (upper lobe predominant), severe obstruction [forced expiratory volume in 1 second (FEV_1) $\leq 45\%$ but $> 20\%$ predicted], limited exercise capacity with hyperinflated lung and moderate impairment of the lung diffusion capacity [at least diffusing capacity of the lungs for carbon monoxide (D_LCO) $> 20\%$ predicted]. However, to date, there are no data comparing the two techniques and other studies should be conducted in order to clarify long term outcomes, side effect and costs linked to these different approaches.

A non-pharmacological treatment for chronic obstructive pulmonary disease (COPD) patients is represented by the pulmonary rehabilitation. Pulmonary rehabilitation (PR) has been defined as a multi-disciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy. As lung reserve declines, dyspnea worsens and independent daily activity performance erodes. Pulmonary rehabilitation (PR) provides multidisciplinary training to improve the patient's ability to manage and cope with progressive dyspnea. Pulmonary rehabilitation (PR) services include critical components of assessment, physical reconditioning, skills training, and psychological support. Additional pulmonary rehabilitation (PR) services may include vocational evaluation and counseling. The topic is still debated and controversial especially in chronic obstructive pulmonary disease (COPD) patients after a recent exacerbation due to conflicting evidences emerged from more recent trials: these last showed no benefit of rehabilitation on hospital readmissions and mortality versus older studies. Nevertheless, the British Thoracic Society (BTS) guidelines suggest the use of respiratory rehabilitation in chronic obstructive pulmonary

disease (COPD) patients having a view to improving: exercise capacity, dyspnea, health status and psychological wellbeing . To date, the advantages of respiratory rehabilitation do not seem to be associated with the prevalent bronchitis or emphysematous status.



Figure(76):Treatment algorithm with COPD[Candela M.; Costorella R.; Stassaldi A.; Maestrini V.; Curradi G.(2019). Treatment of COPD: the simplicity is a resolved complexity. Multidisciplinary Respiratory Medicine, 14:8. doi:10.1186/s40248-019-0181-8]

10.4.1 Chronic Obstructive Pulmonary Disease in COVID-19 Infection

Chronic Obstructive Pulmonary Disease (COPD) is correlated with elevated risk of morbidity and mortality in community-acquired pneumonia (CAP). Alterations in local/systemic inflammatory response, impaired host immunity, microbiome imbalance, persistent mucus production, structural damage, and use of inhaled corticosteroids have been hypothesized to be associated with such risk. With respect to coronavirus disease 2019 (COVID-19), levels of angiotensin converting enzyme 2 (ACE2), the reported host receptor of the virus responsible of coronavirus disease 2019 (COVID-19) [severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] have been seen to be elevated in patients with chronic obstructive pulmonary disease (COPD). However, early coronavirus disease 2019 (COVID-19) researches have not

proportionately reported a considerably elevated percent of severe coronavirus disease 2019 (COVID-19) in chronic obstructive pulmonary disease (COPD) patients.

Coronavirus disease 2019 (COVID-19) infection was correlated with fundamental severity and mortality rates in chronic obstructive pulmonary disease (COPD). Compared to former and never smokers, current smokers were at higher risk of severe complications and increased mortality rate. Efficient preventive measures are needed to decrease coronavirus disease 2019 (COVID-19) risk in chronic obstructive pulmonary disease (COPD) patients and current smokers.

Chronic obstructive pulmonary disease (COPD) exacerbations are a main event in the natural history of the disease related to worsening of symptoms usually leading to hospitalisation and poor prognosis. Various factors have been defined to associate with acute worsening of chronic obstructive pulmonary disease (COPD), however, viral infection remains the major trigger, involving seasonal coronaviruses. Seven studies that comprised 35 chronic obstructive pulmonary disease (COPD) patients mentioned coronavirus disease (COVID) severity in their analysis. With 63% (22/35) patient reported as severe compared to 37% (13/35) non-severe, this indicates that chronic obstructive pulmonary disease (COPD) patients are at elevated risk of more severe coronavirus disease 2019 (COVID-19) in comparison with patients without chronic obstructive pulmonary disease (COPD) 33.4% (409/1224). Data from two studies including chronic obstructive pulmonary disease (COPD) patients with assured coronavirus disease 2019 (COVID-19) reveal 60% (6/10) mortality rate in comparison with mortality rate in patients without chronic obstructive pulmonary disease (COPD) 55% (86/157).

In a study, the major outcomes show that the prevalence of chronic obstructive pulmonary disease (COPD) in coronavirus disease 2019 (COVID-19) patients was low, but that the risk of severity (63%) and mortality (60%) were high, which means that chronic obstructive pulmonary disease (COPD) patients with confirmed coronavirus disease 2019 (COVID-19) are at a higher risk of severe complications and death. Moreover, the prevalence of current smokers in coronavirus disease 2019 (COVID-19) patients was 9%, and this was also combined with higher severity (22.30%) and mortality (38.5%). It is reported a low prevalence of chronic obstructive pulmonary disease (COPD) patients in coronavirus disease 2019 (COVID-19) case series in comparison with the latest chronic obstructive pulmonary disease (COPD) prevalence rate in China, which was 13.6% and the global prevalence of chronic obstructive pulmonary disease

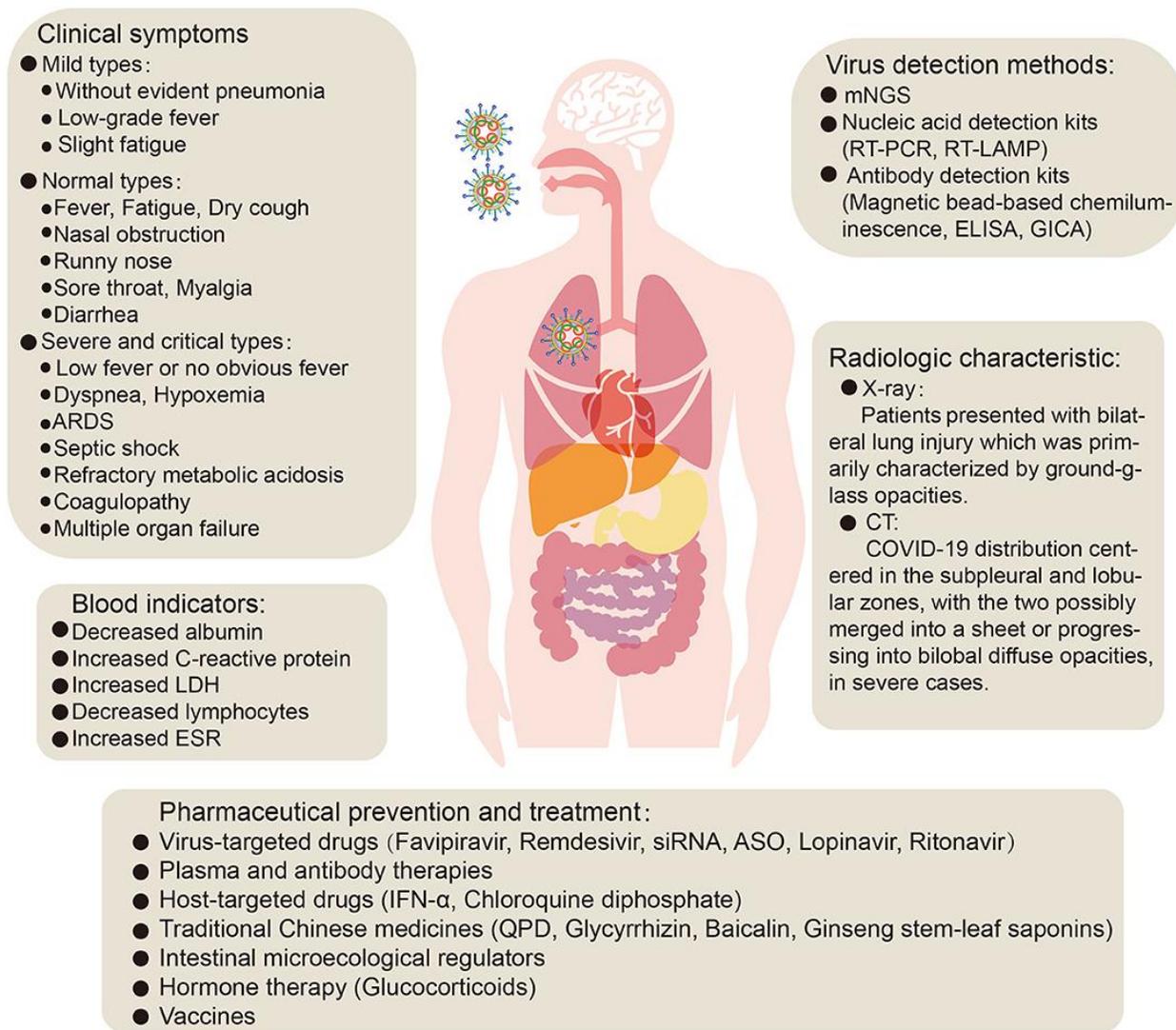
(COPD) (9-10%). It is considered that patients may have not been diagnosed. Having a reliable assess of the prevalence of chronic obstructive pulmonary disease (COPD) in coronavirus disease 2019 (COVID-19) cases, and probably outcomes, is essential to ascertain particular successful global preventive and treatment strategies for chronic obstructive pulmonary disease (COPD) patients.

Although the chronic obstructive pulmonary disease (COPD) prevalence was not high in the involved assured coronavirus disease 2019 (COVID-19) patients, coronavirus disease 2019 (COVID-19) causes a crucial burden on chronic obstructive pulmonary disease (COPD) patients with elevated severity of illness. Viral diseases in chronic obstructive pulmonary disease (COPD) patients elevate systemic inflammation with slow recovery of reported symptoms. Furthermore, patients with chronic obstructive pulmonary disease (COPD) have various comorbidities, some of which are related to higher hospitalization risk. A worthy study showed the prevalence of comorbidities in coronavirus disease 2019 (COVID-19) patients was high and these comorbidities were correlated with higher severity of illness. Most of the studies that reported chronic obstructive pulmonary disease (COPD) severity described severe illness patients as those who were admitted to intensive care unit (ICU), had severe oxygenation, required mechanical ventilation or death. Generally, those with severe state of coronavirus disease 2019 (COVID-19) were older and had more coexisting comorbidities than those with mild disease.

Studies described chronic obstructive pulmonary disease (COPD) patients with confirmed coronavirus disease 2019 (COVID-19) showed an elevated mortality percent at 60%. Despite the small number of patients that were analyzed, this increases regard about the prognosis of this vulnerable people. However, this high mortality rate could be attributed to several factors. The majority of chronic obstructive pulmonary disease (COPD) patients have various comorbidities that may also be correlated with mortality and associated conditions may have been underreported because of the difficulties finding the particular contributor of mortality. Further, in patients with severe chronic obstructive pulmonary disease (COPD), respiratory failure is the major cause of mortality and this needs intensive care unit (ICU) intervention. It is probable that restricted approach to respiratory support as part of coronavirus disease 2019 (COVID-19) treatment may be contributing to this mortality, dependent on critical care capacity in each

hospital or region. According to a coronavirus disease 2019 (COVID-19) report from Italy, the surge in patients demanding intensive care has been unmanageable, with 12% of positive patients demanding intensive care unit (ICU) admission, more than that reported in China. As a consequence, patients were dying because mechanical ventilation could not be offered, on top of acute shortage of clinicians who were able to treat those patients. Concerning smoking and coronavirus disease 2019 (COVID-19), data showed a pooled prevalence of 9% current smokers, (95%), lower than the reported prevalence of smoking in China that was 25.2%. Of interest, it was found that 22.30% of current smokers and 46% of ex-smokers had severe complications associated and greater mortality reaching 38.5% in current smokers. Two studies showed that current smokers were 1.45 times more likely to have severe complications compared to former and never smokers. The impact of smoking history on vulnerability to coronavirus disease 2019 (COVID-19) has been explored. A systematic review on coronavirus disease 2019 (COVID-19) and smoking comprising five studies found that smoking was most likely associated with the negative outcomes. Evidence from other respiratory viruses, respiratory syncytial virus (RSV), has demonstrated that inhaled tobacco smoke increases the transmission rate and severity of viral respiratory tract infectious diseases. It looks there is underlying mechanisms behind this prevalence, as smoking has been bound to higher expression of angiotensin-converting enzyme2 (ACE2) . A meta-analysis was performed using a random impacts model to calculate the pooled prevalence of chronic obstructive pulmonary disease (COPD) in confirmed coronavirus disease 2019 (COVID-19) and tested the findings. It was shown that chronic obstructive pulmonary disease (COPD) and smoking in coronavirus disease 2019 (COVID-19) were associated with greater illness severity and elevated mortality.

In summary, though chronic obstructive pulmonary disease (COPD) prevalence in reported coronavirus disease 2019 (COVID-19) patients is low, coronavirus disease 2019 (COVID-19) infection is related to significant severity and mortality in chronic obstructive pulmonary disease (COPD). There was also elevated risk of severe illness and mortality in current smokers. Effective preventive measures are urgently required to reduce coronavirus disease 2019 (COVID-19) risk on chronic obstructive pulmonary disease (COPD) patients and current smokers.



Figure(77):Clinical symptoms, treatment and prevention of COVID-19. [Guo G.; Ye L.; Pan K.; Chen Y.; Xing D.; Yan K.; Chen Z.; Ding N.; Li W.; Huang H.; Zhang L.; Li X.; Xue X. (2020). New insights of emerging SARS-CoV-2: epidemiology, etiology, clinical features, clinical treatment, and prevention. *Frontiers in Cell and Developmental Biology*. <https://doi.org/10.3389/fcell.2020.00410>]

Figure (77) shows the clinical symptoms, treatment and prevention of coronavirus disease 2019 (COVID-19) pneumonia. ARDS: acute respiratory distress syndrome; LDH: lactate dehydrogenase; ESR: erythrocyte sedimentation rate; mNGS: metagenomic next-generation sequencing; RT-PCR: reverse transcription- polymerase chain reaction; RT-LAMP: reverse transcription loop-mediated isothermal amplification; ELISA: enzyme-linked immunosorbent assay; GICA: gold immunochromatography assay; siRNA: small interfering ribonucleic acid; ASO: antisense oligonucleotides; IFN- α : Interferon-alpha; QPD, *qingfei paidu* decoction.

11. Pancreas Damage

The pancreas is unique in that it's both an endocrine and exocrine gland. In other words, the pancreas has the dual function of releasing hormones into blood (endocrine) and producing enzymes through ducts (exocrine). Approximately 80% of the gross weight of the pancreas favors exocrine function, while the remaining 20% is included with endocrine function. Enzymes are synthesized within the pancreatic acinar cells, packaged into storage vesicles called zymogens, and then secreted via the pancreatic ductal cells into the pancreatic duct, from where they are released into the small intestine to begin the metabolic process required to affect the major digestive activity of the gastrointestinal tract (GIT). The pancreas produces 1500-3000 mL of iso-osmotic alkaline (pH 8.0) fluid per day containing many enzymes and zymogens.

Following ingestion of food, the vagal nerves, vasoactive intestinal peptide, gastrin releasing peptide (GRP), secretin, cholecystokinin (CCK), and encephalins stimulate enzymatic release into the pancreatic duct. The pancreas produces amylolytic, lipolytic, and proteolytic enzymes. Amylase, the major amylolytic enzyme, hydrolyzes starch to oligosaccharides. The lipolytic enzymes include lipase, phospholipase A (PLA), and cholesterol esterase (CE). Proteolytic enzymes which include trypsin, chymotrypsin (Chy or α -Chy), carboxypeptidases (CP), aminopeptidases, and elastases act on peptide bonds of proteins and polypeptides. The proteolytic enzymes are released as inactive precursors (zymogens). These precursor enzymes reach the duodenum where trypsinogen, the proenzyme for trypsin, is activated by the brush border enzyme enterokinase (EK). Trypsin then facilitates the conversion of the other proenzymes to their active form. Autodigestion of the pancreas is inhibited by the packaging of proteases in precursor form and by the synthesis of protease inhibitors, such as pancreatic secretory trypsin inhibitor (PSTI) and serine protease inhibitor (SPINK1). Moreover, the acidic pH and a low calcium concentration in the zymogen granules guard against premature activation of the proenzymes. Whenever there is a loss of any of these protective mechanisms, zymogen activation and autodigestion happen, developing to acute pancreatitis (AP). Pancreatic enzyme secretion is controlled by a negative feedback mechanism stimulated by the presence of active unbound proteases in the duodenum.

The production of pancreatic hormones, including insulin, somatostatin [SST, also known as growth hormone-inhibiting hormone (GHIH)], gastrin, and glucagon, play an important role in

maintaining sugar and salt balance in the bodies. Primary hormones produced by the pancreas comprise:

1-Gastrin: this hormone aids digestion by stimulating certain cells in the stomach to produce acid.

2-Glucagon: this hormone helps insulin maintain normal blood glucose (Glc) by working in the opposite way of insulin. It stimulates the cells to release glucose (Glc), and this raises the blood glucose (Glc) concentrations.

3-Insulin: this hormone regulates blood glucose (Glc) by allowing many of the body's cells to absorb and use glucose (Glc). In turn, this drops blood glucose (Glc) concentrations.

4-Somatostatin (SST): when levels of other pancreatic hormones, such as insulin and glucagon, get too high, somatostatin is released to maintain a balance of glucose (Glc) and/or salt in the blood.

5-Vasoactive intestinal peptide (VIP): this hormone helps control water secretion and absorption from the intestines by stimulating the intestinal cells to release water and salts into the intestines.

The pancreas maintains the body's blood glucose (Glc) balance. Diabetes mellitus (DM) is the most common disorder associated with the pancreas.

Pancreatic inflammatory disease may be classified as acute pancreatitis (AP) and chronic pancreatitis. Acute pancreatitis (AP) causes acute inflammation typically presenting as abdominal pain with elevated levels of pancreatic enzymes. The pathologic spectrum of acute pancreatitis (AP) varies from a mild self-limited form of interstitial pancreatitis to a severe systemic form of necrotizing pancreatitis.

Acute pancreatitis (AP) is defined by the presence of 2 of the 3 criteria:

1-Abdominal pain characteristic of acute pancreatitis (AP);

2-Serum amylase and/or lipase 3 times the upper limit of normal; and

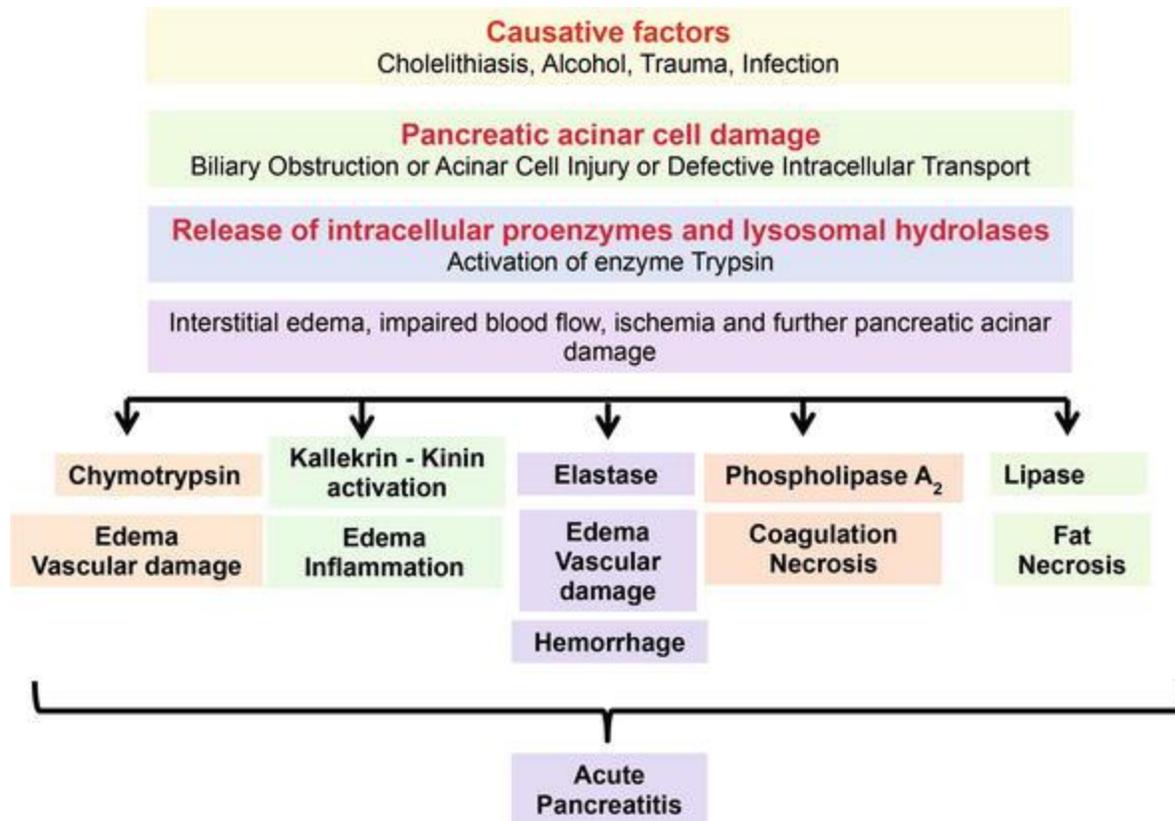
3-Characteristic findings of acute pancreatitis (AP) on computed tomography (CT) scan. In computed tomography (CT) scan acute interstitial pancreatitis shows normal enhancing pancreas with swelling and little peripancreatic fat stranding; for acute necrotizing pancreatitis, computed tomography (CT) shows nonenhancing parts of pancreatic head, neck, and body with normal enhancing tail asterisk, in addition, stones in the gallbladder; for pancreatic necrosis,

computed tomography (CT) performed on the day of admission shows a normal enhancing pancreatic parenchyma with little peripancreatic fluid, follow-up computed tomography (CT) on day 5 shows necrosis of pancreatic head and neck and an acute necrotic collection in the left retroperitoneal space.

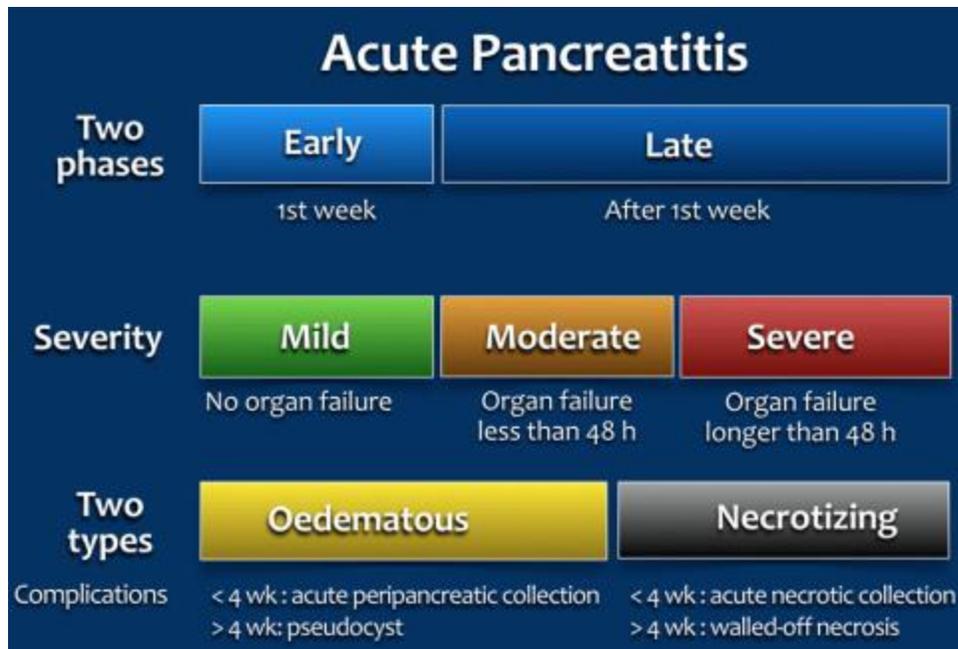
In 1992, the Atlanta International Symposium classified acute pancreatitis (AP) into mild acute pancreatitis (AP) (edematous/interstitial pancreatitis), which has a mortality of 1%, and severe acute pancreatitis (AP) (necrotizing pancreatitis), which constitutes about 20% to 30% of the acute pancreatitis (AP) with a mortality rate around 20% to 30%.

Infection is a seldom cause of pancreatitis. Immunocompromised patients are more susceptible to have infection-related pancreatitis.

Determining the etiology of acute pancreatitis (AP) is crucial in the management of an acute episode and in the prevention of recurrent pancreatitis. Biliary and alcoholic pancreatitis constitute the majority of cases. In up to 30% of cases, etiology cannot be determined and they are labeled as idiopathic pancreatitis. The label of idiopathic pancreatitis (IP) was originally designated to patients experiencing pancreatitis wherein a diagnosis could not be made through a thorough history, physical examination, laboratory studies, and noninvasive imaging modalities such as abdominal ultrasonography/computed tomography (CT) scan.



Figure(78):Aetiopathogenesis of acute pancreatitis [Chanda A. (2017). Severe acute pancreatitis and its management. Open access peer-reviewed chapter. DOI:[10.5772/intechopen.69217](https://doi.org/10.5772/intechopen.69217)]



Figure(79):Acute pancreatitis (www.google.com)

In the standard definition of acute pancreatitis (AP), abdominal pain characteristic of acute pancreatitis (AP) is a key feature in the diagnosis of acute pancreatitis (AP). Pain is often acute, constant, and localized to the epigastric area or the right upper quadrant, usually radiating to the back. Gallstone pancreatitis is characterized by sudden, sharp pain, whereas the pain in pancreatitis due to alcoholic, metabolic, and hereditary pancreatitis is poorly localized and less abrupt in onset. Pain is usually associated with nausea and vomiting.

Physical examination results may be variable and comprise severe abdominal tenderness, fever, hypotension, guarding, and respiratory distress. In the mild form, abdominal palpation may elicit tenderness in the epigastric region. Patients are usually restless and may go into a knee-chest position in an effort to reduce the pain because lying supine exacerbates the intensity of symptoms. In the case of necrotizing pancreatitis, the exudates from a necrotic pancreas can track down along the falciform ligament into the retroperitoneum, which can be seen as bruising in the periumbilical region (Cullen's sign) or in the flank (Grey-Turner's sign). Although these signs are observed in only around 3% of patients with acute pancreatitis (AP), they predict a severe attack of pancreatitis with high mortality rate rising to 37%. However, these signs may be observed in any condition leading to retroperitoneal hemorrhage. Extension of exudates to the diaphragm can lead to shallow respiration. Shallow breathing, or chest breathing is the drawing

of minimal breath into the lungs, usually by drawing air into the chest area using the intercostal muscles rather than throughout the lungs via the diaphragm. Shallow breathing can result in or be symptomatic of rapid breathing and hypoventilation.

The main targets in the treatment of acute pancreatitis (AP) are adequate fluid resuscitation and the prevention of organ failure. It is noticeable to define fluid replacement or fluid resuscitation as the medical practice of replenishing bodily fluid lost through sweating, bleeding, fluid shifts or other pathologic processes. Failure to do so increases the risk of pancreatic necrosis and multiple organ failure. Hypovolemia which is a decreased volume of circulating blood in the body, can impair the pancreatic microcirculation, leading to further pancreatic damage. Another implication of hypovolemia is intestinal ischemia which occurs when the blood flow through the major arteries that supply blood to the intestines slows or stops, causing bacterial translocation and secretion of cytokines, which can result in pancreatic infection and inflammation, respectively. Monitoring vital signs with pulse oximetry at least every 4 hours is crucial in the first 24 hours, especially when the patient is receiving parenteral narcotics. Supplemental oxygen in the first 24 to 48 hours is also necessary.

Once the diagnosis of acute pancreatitis (AP) is made, triaging the patient to the proper unit is very important. Evidence of organ failure, such as sustained hypoxemia, hypotension refractory to intravenous (IV) fluid boluses, renal insufficiency (creatinine 2 mg/dL), persistent tachycardia (120/min), urine output 50 mL/h, encephalopathy, and increasing need for intravenous (IV) narcotics warrant an intensive care unit (ICU) transfer.

Fluid treatment is the cornerstone in the management of acute pancreatitis (AP). Hemoconcentration (Hct 44) is a marker of poor prognosis and indicates the need for fluid resuscitation. Crystalloids (Ringer lactate or normal saline) are the most commonly used fluid for resuscitation. The first 48 to 72 hours after onset after admission is the crucial period. The amount and rate of fluids should be determined by the factors like urine output, vital signs, and serial hematocrit.

Acute pancreatitis (AP) is a hyperdynamic, hypermetabolic state that leads to increased protein catabolism, increased ureagenesis, glucose intolerance, and increased lipolysis. This results in negative nitrogen balance, resulting in increased mortality. In mild pancreatitis the inflammation

resolves within 5-7 days and the patient can resume oral intake. However, in severe pancreatitis and pancreatic necrosis, this process of healing takes a longer time, which limits oral intake. In the past, parenteral nutrition was used increasingly in severe pancreatitis, which inhibited pancreatic stimulation but was correlated with higher incidence of metabolic and electrolyte disturbances. Total parenteral nutrition (TPN) is also associated with hyperglycemia and catheter-related sepsis. In critically ill patients the gastrointestinal tract (GIT) serves as a probable source of immunoinflammatory process as the gut absorbs the endotoxins and bacterial products, leading to the stimulation of endogenous cytokines. This forms the basis for initiating early enteral nutrition in severe acute pancreatitis (AP) to preserve the gut barrier. A notable review showed that enteral nutrition when compared with parenteral nutrition was associated with considerable reduction in mortality, multiorgan failure, operative interventions, and systemic infections.

The risk of pancreatic stimulation is overcome by feeding via nasojejunal tube and thus delivering the tube feeds beyond the ligament of Treitz into the jejunum. Trouble might arise with enteral nutrition when there is a proximal tube migration, resulting in pancreatic stimulation and ileus. The 3 major categories of tube feeds include elemental/semielemental, polymeric, and immunoenhanced. Elemental feeds have a theoretical advantage of superior intestinal absorption, lesser pancreatic stimulation, and better tolerance. A review in 2009 showed no significant feeding intolerance between elemental and polymeric tube feeds. Polymeric feeds are cheaper than elemental feeds. Also, the polymeric feeds significantly decreased the infectious complication and mortality rates, similar to elemental tube feeds. The immunoenhanced feeds specifically contain glutamine (Gln, neutral amino acid), arginine (Arg, basic amino acid), and omega-3 fatty acids [the three main omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)]. So far, there is no evidence to use immunoenhanced feeds or probiotics. The fiber-enhanced formulas have a lower incidence of diarrhea when compared with the elemental feeds.

According to the 2006 American College of Gastroenterology (ACG) practice guidelines, the pain in acute pancreatitis (AP) should be treated with parenteral narcotics. Parenteral administration of drugs is any technique in which the route of administration bypasses the gastrointestinal tract. These routes include, but are not limited to, intravenous (IV)

administration, intramuscular (IM) and subcutaneous injections and the use of medication patches and nasal sprays. The most commonly used medications are hydromorphone, morphine, meperidine, and fentanyl. Hydromorphone hydrochloride is a drug used to manage moderate to severe pain; it may also be used to treat certain types of cough. Hydromorphone hydrochloride is made from morphine and binds to opioid receptors in the central nervous system; it is a type of opioid and a type of analgesic agent. Morphine is an analgesic and narcotic therapy obtained from opium and used medicinally to relieve pain. Pethidine, also called meperidine and sold under the brand name Demerol among others, is a synthetic opioid pain drug of the phenylpiperidine class. Fentanyl is a powerful opioid medication used in the management of severe pain. There is no proven superiority of one therapy over the other. The dose and frequency of administration should be adjusted according to the pain. Patient-controlled analgesia can be used if needed. The vital signs and pulse-oximetry which is a test used to measure the oxygen level (oxygen saturation) of the blood, should be monitored at least every 4 hours when using narcotics.

Somatostatin is a peptide that is synthesized in the gastrointestinal tract (GIT) and has an inhibitory action on gastrointestinal (GI) motility and pancreatic secretion. Octreotide is the pharmacologic analogue of somatostatin. Studies have shown no recognizable difference in the management results with octreotide. A meta-analysis done in 2007 by Andriulli *et al.* did not show any benefit of octreotide in preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) but it did not include a study published in 2007 by Li *et al.*, which showed a reduced incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) with octreotide. However, it is important to refer to endoscopic retrograde cholangiopancreatography (ERCP) which has been a prominent technological innovation that has advanced in the field of gastrointestinal (GI) endoscopy since its inception in 1968. Endoscopic retrograde cholangiopancreatography (ERCP), a comparatively more complicated integral therapeutic modality among endoscopic techniques, is clinically the most common and specialized procedure used for the diagnosis and management of pancreatic and biliary system disorders. Although it is superior to the traditional operation due to limited trauma, simplicity of the operation, and short recovery time in the treatment and diagnosis of duodenal and pancreatobiliary disorders, diagnostic and therapeutic endoscopic retrograde cholangiopancreatography (ERCP) can lead to various complications such as pancreatitis,

cholangitis, perforation, hemorrhage (especially postsphincterotomy), cholecystitis, cardiopulmonary depression, asymptomatic hyperamylasemia, aspiration, hypoxia, bleeding, sepsis, adverse medication reactions, and death. Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP) and it is a crucial factor in morbidity and mortality. Chemical, mechanical, enzymatic, hydrostatic and thermal causes are considered as the pathophysiology of the post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). Although its determinants are unclear, development of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) is thought to be based on a pro-inflammatory cascade caused by pancreatic acinar cell injury that induces to systemic cytokine release.

Gabexate is a protease inhibitor that could decrease physiologically the synthesis of pancreatic enzymes. There is a difference of opinion in the use of gabexate between different societies. The American College of Gastroenterology (ACG) guidelines do not recommend it in the management of acute pancreatitis (AP), whereas the Japanese guidelines recommend its use for both mild and severe pancreatitis. It is also widely used in certain countries for prophylaxis of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP).

N-Acetylcysteine (NAC) is an antioxidant that theoretically can decrease the oxidative stress (OS) in the early phases of acute pancreatitis (AP) and thus decrease pancreatic injury. So far, studies show no benefit of N-acetylcysteine (NAC) in either management or prophylaxis.

Steroid is a nonspecific anti-inflammatory agent, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic as well as anti-inflammatory properties. There is no evidence for the use of steroids in the management or prophylaxis of acute pancreatitis (AP). However, steroids are the mainstay in the treatment of autoimmune pancreatitis, which is a form of chronic pancreatitis. Interestingly nonsteroidal anti-inflammatory drugs (NSAIDs) (indomethacin, diclofenac) have been shown to decrease the incidence of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) when compared with placebo in a select group of patients undergoing pancreatic duct injection. When used in the therapy of acute pancreatitis (AP), the nonsteroidal anti-inflammatory drugs (NSAID) group demanded less opiates as analgesics during hospitalization.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine released by the T-helper cells. There is no evidence for its use in either treatment or prophylaxis of acute pancreatitis (AP).

Tumor necrosis factor-alpha (TNF- α) is synthesized in the macrophages (M Φ) of secretory acinar cells and is included in mediating the inflammatory process. There are no human studies done so far using tumor necrosis factor (TNF) inhibitors. One of main reasons for this is the elevated risk of bacterial infection in patients with acute pancreatitis (AP). A study done in acute alcoholic hepatitis using infliximab demonstrated increased rates of bacterial infection and mortality.

Intestinal permeability is increased in acute pancreatitis (AP) and the probiotics are deemed to exhibit beneficial effects by replenishing the gut flora, thereby preventing bacterial infection. So far there is no potent evidence in the use of probiotics in acute pancreatitis (AP).

Endoscopic retrograde cholangiopancreatography (ERCP) is a useful tool in the diagnosis and treatment of acute pancreatitis (AP). The main role of endoscopic retrograde cholangiopancreatography (ERCP) is in gallstone disease and other etiologies that cause pancreatic duct obstruction like pancreatic divisum, sphincter of Oddi dysfunction, and occult tumors. Gallstones are the most common cause of acute pancreatitis (AP) in the western world, accounting for one-half of the cases. Most of the stones cause transient obstruction and pass into duodenum spontaneously. Pancreatic edema and necrosis is incident when there is a persistent ampullary obstruction because of impacted stone or peri-ampullary edema. Urgent endoscopic retrograde cholangiopancreatography (ERCP) is indicated in patients who fail to demonstrate improvement in bilirubin by 24 to 48 hours after admission, show persistent choledocholithiasis on imaging, or have cholangitis. Recurrence of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy for gallstone pancreatitis is scarce. Cholecystectomy vs endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy is a controversial topic. In general, cholecystectomy is performed if the patient is a surgical candidate. Selective postcholecystectomy endoscopic retrograde cholangiopancreatography (ERCP) is performed if choledocholithiasis is found intraoperatively. Microlithiasis or biliary sludge as a cause of pancreatitis is still controversial. Microlithiasis is a viscous precipitate of mucin, cholesterol, and calcium bilirubinate found in biliary sludge. Ultrasound is only 55% sensitive in detecting biliary sludge. Bile analysis with microscopic

examination is the gold standard in diagnosing microlithiasis. It can be done by endoscopic retrograde cholangiopancreatography (ERCP) with bile aspirate, which is 83% sensitive. Endoscopic retrograde cholangiopancreatography (ERCP) is often performed 4 to 6 weeks after the episode of acute pancreatitis (AP) when microlithiasis is suspected as the culprit. Pancreatic divisum is found in 7% to 10% of the population. It is correlated with increased prevalence of pancreatitis. The role of endoscopic retrograde cholangiopancreatography (ERCP) is majorly therapeutic using sphincterotomy with or without pancreatic duct stent placement, which decreased the recurrence rate of pancreatitis. Sphincter of Oddi dysfunction (SOD) is the abnormality in sphincter of Oddi contractility, leading to intermittent biliary and pancreatic duct obstruction. It is the cause of pancreatitis in about one-third of recurrent unexplained pancreatitis. If sphincter of Oddi dysfunction (SOD) is suspected, sphincter of Oddi manometry is done. Sphincter of Oddi manometry (SOM) is performed during endoscopic retrograde cholangiopancreatography (ERCP) to evaluate elevated sphincter pressures. A resting pressure more than 40 mm Hg is the best predictor of response to endoscopic sphincterotomy. Endoscopic retrograde cholangiopancreatography (ERCP) is also beneficial in the diagnosis of ampullary and intraductal papillary mucinous tumors. Pancreatic duct stent placement helps in relieving the obstruction.

11.1 Acute Pancreatitis in COVID-19 Infection

A study collected public datasets [bulk RNA sequencing (RNA-seq) and single-cell RNA sequencing (scRNA-seq)] to indicate the expression and the distribution of angiotensin-converting enzyme2 (ACE2) in pancreas (in both exocrine glands and islets). And further, clinical data including mild and severe patients with coronavirus disease 2019 (COVID-19) demonstrated there showed mild pancreatitis. In the 67 severe cases, 11 patients (16.41%) exhibited higher levels of both amylase and lipase, and 5 patients (7.46%) revealed imaging alterations. Only one patient (1.85%) demonstrated elevated levels of both amylase and lipase in 54 mild patients, without imaging changes. This study indicated the phenomenon and possible cause of mild pancreatic injury in patients with coronavirus disease 2019 (COVID-19). This presumes that pancreatitis after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection should also be paid attention in clinical work. In the clinical observation in this study, authors also found that some patients exhibited signs of pancreatic injury, such as elevated levels

of amylase and lipase in serum and urine. In this study, authors concentrated on the expression of angiotensin-converting enzyme2 (ACE2) in pancreas and the damage to the pancreas in a proportion of patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This study revealed angiotensin-converting enzyme2 (ACE2) was mostly expressed in the pancreas of normal people, and it was slightly elevated in the pancreas than in the lungs, demonstrating that when severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in the circulation, it might also combine with angiotensin-converting enzyme2 (ACE2) in the pancreas to enter cells and cause pancreatic injury. Moreover, authors performed single-cell RNA sequencing (scRNA-seq) datasets of the pancreas to explore the localized expression of angiotensin-converting enzyme2 (ACE2) in the pancreas. Angiotensin-converting enzyme2 (ACE2) is expressed in both exocrine glands and islets. At the same time, analysis results from single-cell RNA sequencing (scRNA-seq) data were consistent with higher plasma amylase and lipase levels of the enrolled patients. In this study, about 1-2% of the non-severe patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had pancreatic lesions, and about 17% of the severe patients experienced pancreatic injuries. Although their imaging alterations proposed that pancreatitis was not severe, the problem should not be ignored, particularly in severely infected patients. In the clinic, the consequences of pancreatic injury can still be very serious, such as aggravating systemic inflammation, especially in the lungs and accelerating the occurrence of acute respiratory distress syndrome (ARDS), and even progressing to chronic pancreatitis without early intervention, which will have a serious impact on the health and quality of life of patients. On the other hand, it was reported that patients infected with severe acute respiratory syndrome coronavirus (SARS-CoV) who had never used glucocorticoids suffered from hyperglycemia, which might be caused by severe acute respiratory syndrome coronavirus (SARS-CoV) damaging the pancreatic islets through angiotensin-converting enzyme2 (ACE2). Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has the same receptor as severe acute respiratory syndrome coronavirus (SARS-CoV), whether this result will occur requires more attention and regard. Therefore, increased attention should be paid to the pancreas in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, particularly in severely infected patients. The systemic inflammatory response in severe coronavirus disease 2019 (COVID-19) patients might also cause mild damage to the pancreas.

Hadi *et al.* (2020) in a case report describes three first-degree relatives with severe coronavirus disease 2019 (COVID-19), two of which developed severe acute pancreatitis. Data were collected from three family members admitted with coronavirus disease-19 (COVID-19) to the intensive care unit (ICU) at Copenhagen University Hospital Hvidovre in the Capital Region of Denmark in March 2020. Diagnosis of acute pancreatitis was according to the Atlanta classification. The revised Atlanta classification requires that two or more of the following criteria be met for the diagnosis of acute pancreatitis:

- (a) Abdominal pain suggestive of pancreatitis;
- (b) Serum amylase or lipase level greater than three times the upper normal value; or
- (c) Characteristic imaging findings.

Throat swab samples and tracheal aspirates were collected from all patients and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was detected using real time transcription–polymerase chain reaction assay. Blood samples and diagnostic imaging were done according to the best clinical practice.

Two of the three family members were diagnosed with acute pancreatitis associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Other causes of acute pancreatitis were excluded for both patients (including alcohol, biliary obstruction/gall stones, drugs, trauma, hypertriglyceridemia, hypercalcemia, and hypotension).

A 47-year old previously healthy woman (the daughter) was admitted to the emergency department (ED) at the hospital with a fever, headache and neck pain for one week and anorexia, sore throat and dyspnea for a couple of days. The patient had a minimal alcohol intake and did not smoke. At admission, she was awake and hemodynamically stable with a mean arterial pressure of 93 mmHg. She exhibited signs of acute respiratory distress syndrome (ARDS) with a respiratory rate of 40/min, an oxygen-saturation (SaO₂) of 80% on 15L of oxygen/min requiring intubation and mechanical ventilation. A chest X-ray showed bilateral massive opacities with air bronchograms. She tested positive for severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA). She developed acute kidney failure (AKF) and continuous veno-venous hemodialysis (CVVHD) was initiated at day two. The respiratory changes worsened over the next two weeks and the chest X-ray showed increasing perihilar involvement and consolidation. Fifteen days after admission, severe hypercapnia [partial

pressure of carbon dioxide ($p\text{CO}_2 > 8,5$ kilopascal (kPa)] was resolved with extracorporeal membrane oxygenation, which was maintained for three days. Extracorporeal membrane oxygenation (ECMO), also called extracorporeal life support (ECLS), is an extracorporeal technique of providing prolonged cardiac and respiratory support to individuals whose heart and lungs are unable to provide an adequate amount of gas exchange or perfusion to sustain life. The technology for extracorporeal membrane oxygenation (ECMO) is largely derived from cardiopulmonary bypass, which provides shorter-term support with arrested native circulation. Extracorporeal membrane oxygenation (ECMO) works by temporarily drawing blood from the body to allow artificial oxygenation of the red blood cells (RBCs) and removal of carbon dioxide. Tracheostomy which is an incision in the windpipe made to relieve an obstruction to breathing, was performed at day 25 as clinical progress was observed. Treatments included fluid resuscitation and intravenous antibiotics. At admission, pancreas-specific plasma amylase was increased to 173 U/L. The value increased rapidly to >1500 U/L after 11 h. Abdominal ultrasound revealed evidence of acute pancreatitis (AP) with a diffusely voluminous pancreas without focal lesions or gallstones. The Modified Glasgow Acute Pancreatitis Score was 5 points indicating severe acute pancreatitis. Plasma levels of triglycerides (TGs) and calcium were normal. The amylase decreased from day four and reached the normal range at day 21. As of last update, she was still in intensive care.

The second case was the mother whom she was a 68-year old and was admitted to the Gastrounit at the hospital two days after the daughter. Comorbidities involved hypertension (HTN), hypothyroidism (occurring when the body doesn't produce enough thyroid hormones) and osteoporosis treated with losartan, levothyroxine, alendronate and cyanocobalamin. The mother was admitted with epigastric pain and fever as well as vomitus, diarrhea, fatigue and polydipsia [abnormally great thirst as a symptom of disease (such as diabetes mellitus) or psychological disturbance]. At admission, she had a temperature of 39.7 °C rectally, a C-reactive protein (CRP) of 77 mg/L, tachypnea (30 breaths/min), hypoxia [8.5 kilopascal (kPa)] and hypocapnia [3.8 kilopascal (kPa)] on 4L of oxygen/min. Initial chest radiograph showed diffuse interstitial opacities. The respiratory insufficiency (The condition in which the lungs cannot take in sufficient oxygen or expell sufficient carbon dioxide to meet the needs of the cells of the body; also called pulmonary insufficiency) progressed during the first two days and the patient was intubated and admitted to the intensive care unit (ICU) for mechanical ventilation. The patient

tested positive for severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA). On day 3, she developed acute kidney failure (AKF) and continuous veno-venous hemodialysis (CVVHD) treatment was initiated. Renal function did not recover, and the respiratory distress continued to worsen with bilateral progression of opacities peripherally and perihilar with consolidation. Treatment included fluid resuscitation and intravenous (IV) antibiotics. At admission, she suffered from abdominal pain and the clinical assessment demonstrated direct epigastric and periumbilical tenderness. Slight abdominal distension was noted at day four and remitted afterwards. The amylase-level increased from 85 U/L on the day of admission to 934U/L on day six. The Modified Glasgow Acute Pancreatitis Score was 5 points indicating severe acute pancreatitis. Calcium-levels were normal and earlier measurements of triglycerides (TGs) were also normal. A daily decline of amylase was measured afterwards until normal range was reached at day 22. As of last update, the patient was still in intensive care unit (ICU).

One week after the daughter was admitted, the father, a 71-year old was admitted to the emergency department (ED). He was previously healthy, had a very low alcohol intake and did not smoke. Three days before admission he suffered from gastrointestinal (GI) symptoms with anorexia and diarrhea as well as a fever (38.9 °C), dry cough, general malaise and fatigue. Initially, he was hypoxic, but reached a normal respiratory rate of 17 breaths/min and saturation [9.7 kilopascal (kPa)] after management with oxygen (8L/min). A chest X-ray revealed bilateral perihilar and interstitial opacities. The respiratory problems worsened and on day three, he developed acute respiratory distress syndrome (ARDS). He was transferred to the intensive care unit (ICU) and received invasive mechanical ventilation and intravenous (IV) antibiotics. Due to bradycardia and hypotension, noradrenaline and dopamine (DA) was added. After three weeks, he progressed increasing creatinine and oliguria. The outcome was fatal. He did not show evidence of acute pancreatitis (AP).

This study reports two first-line relatives with acute pancreatitis (AP) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. According to the current guidelines, the diagnosis of acute pancreatitis requires at least two of the three following signs:

- 1-Abdominal pain;
- 2-Amylase or lipase >3 times the upper normal limit; and
- 3-Characteristic findings on diagnostic imaging.

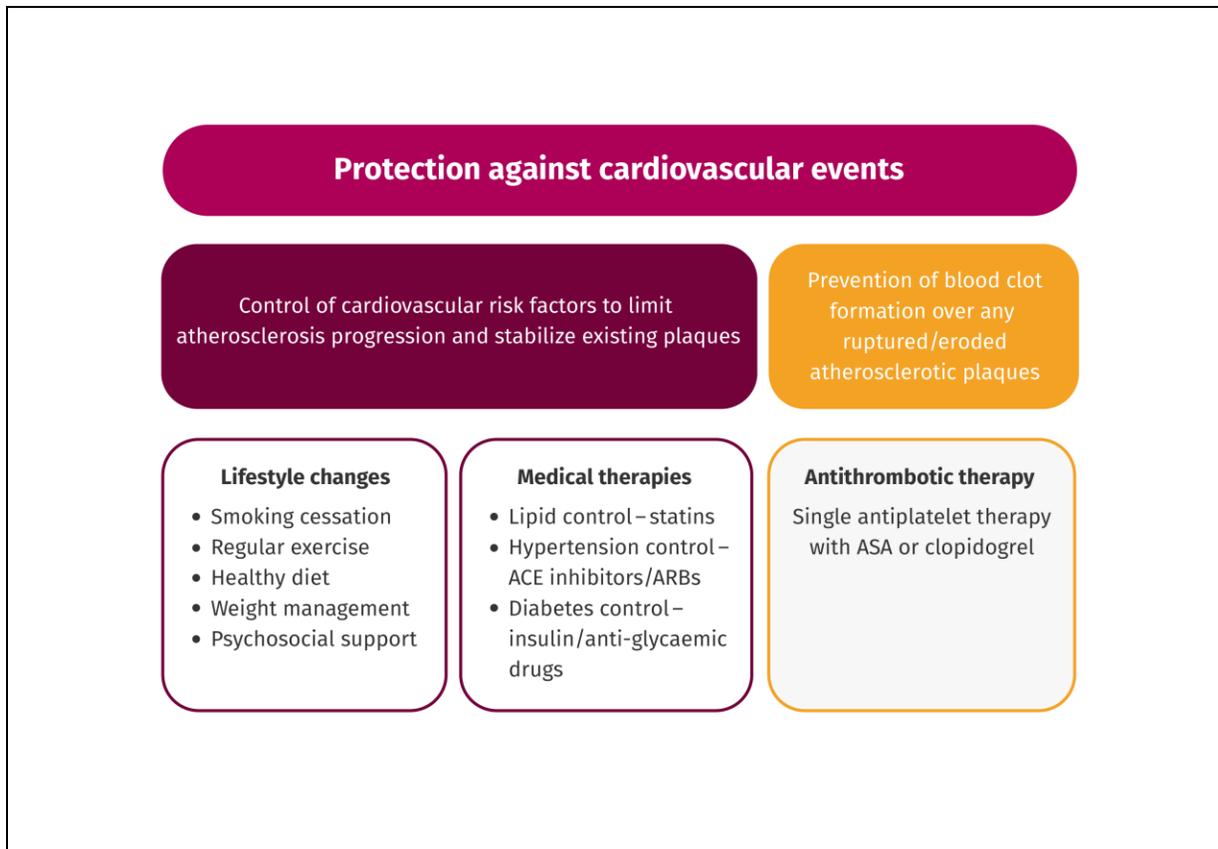
The two patients with acute pancreatitis (AP) defined in this research had severe acute pancreatitis, which itself may develop to multiorgan failure involving adult respiratory distress and kidney failure as seen in both patients, the daughter and the mother. On the other hand, coronavirus disease-19 (COVID-19) may also lead to same organ failures and it is therefore not possible to evaluate if the acute pancreatitis contributed to the severe course of the disease. The third family member, i.e. the father, who was admitted to the intensive care unit (ICU) with coronavirus disease-19 (COVID-19) had respiratory distress and gastrointestinal (GI) symptoms, but not acute pancreatitis (AP). Additional two family members (not described) tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), but only had mild symptoms and did not require hospitalization.

Previous studies have verified that coronavirus disease-19 (COVID-19) may be associated with gastrointestinal (GI) symptoms involving abdominal pain and have identified viral ribonucleic acid (RNA) in the gastrointestinal tract (GIT). Wang *et al.* (2020) reported at admission 17% of 52 patients with coronavirus disease-19 (COVID-19) had slightly abnormal amylase or lipase. Several factors may contribute to the development of acute pancreatitis (AP) including pancreatic autodigestion, enzyme activation, complement system activation, microcirculation disturbance theory, leukocyte excessive activation, and pancreatic acinar cell apoptosis and necrosis. Theoretically viral pancreatitis develops due to direct destruction of pancreatic acinar cells by inflammation and edema. Alternatively, damage to the pancreatic acinar cells by the virus could cause a leaking intracellular enzyme or precipitates a process of cell death. The entry receptor angiotensin-converting enzyme 2 (ACE2) for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been identified in the gastrointestinal epithelium of infected patients. During the 2002–2004 outbreak, severe acute respiratory syndrome coronavirus (SARS-CoV) used angiotensin-converting enzyme2 (ACE2) for entry to host cells. Increased expression in pancreatic islets were recognized, leading eventually to acute diabetes. Genome sequences of severe acute respiratory syndrome coronavirus (SARS-CoV) have indicated that 79.6% are shared with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The expression of angiotensin-converting enzyme2 (ACE2) in the pancreas during severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection could therefore lead to acute inflammation.

Nevertheless, the presented cases underline the importance of measuring lipase or amylase in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections, particularly if infected individuals suffer from abdominal pain.

12. Cardiac Injury

Coronary artery disease (CAD) is characterized by an atherosclerotic process occurring on the coronary vasculature. The first signs of atherosclerosis can be seen in infants, followed by a regression in childhood, reappearance in puberty and progression over time. Asymptomatic illness can become symptomatic anytime with angina, exertional or at rest, myocardial infarction (MI) or sudden death. However, Angina can be described as a type of chest pain resulted from reduced blood flow to the heart. It is a symptom of coronary artery disease (CAD). Angina, also called angina pectoris, is usually described as squeezing, pressure, heaviness, tightness or pain in the chest. Some people with angina symptoms say angina feels like a vise squeezing their chest or a heavy weight lying on their chest. The prevalence of angina increases with age and is higher in middle-aged women than men. The incidence and prevalence of coronary artery disease (CAD) are difficult to evaluate and its detection is based upon symptom appearance. In general, stable coronary artery disease (CAD) is characterized by episodes of reversible myocardial demand/supply mismatch, related to ischemia, i.e. decreased blood flow and oxygen to the heart muscle, or hypoxia, i.e. deficiency in the amount of oxygen reaching the tissues, which are often inducible by exercise, emotion or other types of stress and are commonly correlated with transient chest discomfort. Stable coronary artery disease (CAD) can manifest itself due to plaque-related obstruction of coronary arteries, their spasms, microvascular dysfunction or left ventricular dysfunction (LVD).



Figure(80): Coronary artery disease treatment (www.google.com)

Myocardial infarction (MI) is defined as myocardial cell death attributed to prolonged ischemia. Clinically, the term myocardial infarction (MI) is used when there is evidence of myocardial necrosis in a clinical setting, consistent with acute myocardial ischemia and with an elevation in cardiac troponin (cTn) concentration. It is distinguished between two types of myocardial infarction (MI) on which clinical decision-making is based: ST-elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). In contrast to non-ST-segment elevation myocardial infarction (NSTEMI) individuals, individuals with ST-elevation myocardial infarction (STEMI) are referred to immediate reperfusion management strategies. Acute coronary syndrome (ACS) can be divided into subgroups of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. It is worthy to add the followings: first, ST-elevation myocardial infarction (STEMI) is a very serious type of heart attack during which one of the heart's major arteries (one of the arteries that supplies oxygen and nutrient-rich blood to the heart

muscle) is blocked, ST-segment elevation is an abnormality detected on the 12-lead electrocardiogram (ECG); second, non-ST-segment elevation myocardial infarction (NSTEMI) may be correlated with other electrocardiogram (EKG) changes such as ST segment depression.

Myocardial infarction (MI) is classified into 5 types based on its pathophysiology, clinics and prognostics:

1-Type I: spontaneous myocardial infarction (MI): atherosclerotic plaque disturbance leading to thrombus formation and reduced myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis;

2-Type II: myocardial infarction (MI) secondary to an ischemic imbalance: imbalance between myocardial oxygen supply and/or demand attributed to other states [not coronary artery disease (CAD)], e.g. coronary endothelial dysfunction, coronary artery spasm, tachy-/brady-arrhythmias, heart failure (HF), anemia, respiratory failure, hypotension, hypertension (HTN), renal failure or major procedures, and coronary embolism (CE). The case definition of coronary embolism (CE) used consisted of major and minor criteria according to Shibata *et al.* (2015). The 3 major criteria involved:

- (a)-Angiographic evidence of coronary artery thrombosis without atherosclerotic components;
- (b)-Concomitant multisite coronary embolism (CE); and
- (c)-Concomitant systemic embolization excluding left ventricular thrombus attributable to ST-elevation myocardial infarction (STEMI).

The 3 minor criteria involved:

- (a)-Coronary angiography showing <25% luminal stenosis, except for the culprit lesion. However, coronary angiography is a procedure that uses a particular dye (contrast material) and x-rays to observe how blood flows through the arteries in the heart;
- (b)-Evidence of an embolic source detected by any imaging modality; and
- (c)-Coexistence of a potential for thromboembolic disease such as intracardiac tumor, infective myocarditis, prosthetic valve implantation, atrial fibrillation (AF), any pathology or hemostasis disorder favoring hypercoagulable state, patent foramen ovale (PFO), or atrial septal defect

(ASD). The diagnosis of definite coronary embolus was based on the presence of ≥ 2 major criteria, 1 major criterion plus ≥ 2 minor criteria, or 3 minor criteria;

3-Type III: myocardial infarction (MI) resulting in death when biomarker values are unavailable;

4-Type IVa: myocardial infarction (MI) related to percutaneous coronary intervention (PCI). According to the revised universal definition, a percutaneous coronary intervention (PCI)-related myocardial infarction (MI) (type 4a) was defined as an elevation in cardiac troponin (cTn) concentration to $>5\times$ the 99th percentile of the upper reference limit (URL) during the first 48 h following percutaneous coronary intervention (PCI) [in patients with normal baseline cardiac troponin (cTn) concentrations], plus either:

(a) evidence of prolonged ischemia as demonstrated by prolonged chest pain; or (b) ischemic ST-segment changes or new pathological Q waves; or (c) angiographic evidence of a flow limiting complication; or

(d) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Cardiac troponin (cTn) was regarded as the preferred biomarker for detection of myonecrosis (a condition of necrotic damage, specific to muscle tissue);

5-Type IVb: myocardial infarction (MI) related to stent thrombosis. Stent thrombosis is described as a thrombotic occlusion of a coronary stent. Stent thrombosis is a main complication correlated with stent placement in percutaneous coronary intervention (PCI). ; and

6-Type V: myocardial infarction (MI) related to coronary artery bypass grafting (CABG). Coronary artery bypass grafting, are also called heart bypass surgery. Coronary artery bypass grafting (CABG) is a procedure to improve poor blood flow to the heart. It may be required when the arteries supplying blood to heart tissue, called coronary arteries, are narrowed or blocked.

With aging, plaques can progress and grow to become so capacious that coronary artery lumen is reduced beyond the critical point at which blood flow to cardiomyocytes is not sufficient, exposing them to anaerobic environment and causing ischemia to set in. With the onset of ischemia, stable angina pectoris develops. Stable angina, also called angina pectoris, is the most common type of angina. Stable angina is a predictable pattern of chest pain. Stable angina takes

place when the heart muscle doesn't get the oxygen it needs to function properly. However, certain plaques do not reduce lumen/flow significantly and therefore do not cause symptoms. The severity of flow obstruction depends on plaque size, vasospasms and a phenomenon called arterial remodeling, consisting of two instances, positive and negative remodeling. Positive or expansive remodeling is thought to be in part a consequence of homeostatic responses of the adjacent preserved vessel wall to maintain normal shear stress. Another theory supposes that it is predominantly a pathophysiologic process in which proteolytic enzymes degrade the media and the external elastic membrane which consequently expands. Non-stenotic plaque is clinically silent and cannot be seen on angiography. Therefore, it can only be managed by conservative therapy. Negative or constrictive remodeling is thought to be a consequence of plaque rupture followed by healing. Stenotic lesions cause angina pectoris and are managed not only with drug therapy, but frequently also call for revascularization treatment. In affected patients, plaques with positive and negative remodeling often coexist. Moreover, they usually lie in between those extremes. Flow through coronary arteries is restricted when there is more than an 80% reduction in the luminal area or more than a 50% reduction in diameter as seen on coronary angiography. In lower grade stenosis, only flow reserve is reduced. In stable coronary artery disease (CAD), plaques develop gradually, sometimes complicated by plaque ruptures that are majorly clinically silent, resulting in non-occlusive thrombus formation. Many complicated plaques have several plaque rupture sites. The non-occlusive thrombus is partly removed by natural lysis; the remaining part is then covered with natural heparinoids to neutralize the thrombogenicity of the exposed collagen. After 36 hours, smooth muscle cells (SMCs) migrate to this area and cover the surface with newly produced connective tissue (CT), restoring plaque integrity. With the restoration of the fibrous cap (thickening), the affected plaque increases in size and contracts by healing smooth muscle cells (SMCs)- negative remodeling. For this reason, plaque progression is usually not linear, but phasic.

In the vast majority of cases, myocardial infarction (MI) and unstable angina are resulted from the formation of thrombus on ruptured or eroded plaque with or without simultaneous vasospasm. It is regarded to refer that unstable angina is chest pain that occurs at rest or with exertion or stress. The pain worsens in frequency and severity. Unstable angina means that blockages in the arteries supplying the heart with blood and oxygen have reached a critical level. The thrombus causing unstable angina and non-ST-elevation myocardial infarction (NSTEMI) is

often nonocclusive and dynamic, whereas an occlusive and persistent thrombus is present in ST-elevation myocardial infarction (STEMI) patients. Other more scarce reasons for acute coronary syndromes (ACSs) are spasms, emboli, spontaneous coronary artery dissection, vasculitis, cocaine abuse, trauma and compressions of the coronary artery by myocardial bridges. Plaque rupture is the main cause of thrombosis in coronary vasculature and is more often in males. When plaque ruptures, the fibrous cap tears and exposes the highly thrombogenic lipid core to blood. The lipid core contains a tissue factor, collagens and lipid microcrystals, all of which accelerate thrombosis, which starts in the plaque itself and extends intraluminally. When there is no sign of fibrous cap rupture, term plaque erosion is used. In plaque erosion, subendothelial tissue, such as the basal membrane, is exposed to blood, and the thrombus that forms is therefore adherent to the plaque surface. The underlying mechanism of both processes is an enhanced vascular inflammatory activity within the plaque itself. Macrophages ($M\Phi$) within the plaque are highly activated, leading to endothelial and smooth muscle cell (SMC) inhibition and death by apoptosis, secretion of a wide range of metalloproteinases degrading the connective tissue matrix (CTM) involving collagen. Apoptosis of endothelial tissue with lysis of adhesion proteins are basis of endothelial erosion. Apoptosis of smooth muscle cells (SMCs) with fibrous cap lysis causes endothelial rupture. Metalloproteinase secretion by macrophages ($M\Phi$) is upregulated by inflammatory cytokines. Plaque rupture/erosion is therefore recognized as an auto-destructive process related to the inflammation.

The development of thrombus and its extent is highly variable and depends on: local flow disturbances, blood coagulability and thrombogenicity of the exposed tissue – the Virchow triad. The most important factor in plaque rupture looks to be the thrombogenicity of the expelled tissue; however, in plaque erosion, the exposed tissue is not as thrombogenic as the lipid core or particles containing the tissue factor, thus the major mechanism is likely the disturbance in systemic and local thrombogenic factors. The thrombus may develop rapidly or can progress over the course of days, with intermittent flow disturbances due to dynamic processes: thrombosis, thrombolysis with or without vasospasms. Moreover, as thrombus starts to form, blood continues to flow through the plaque washing away tissue factor-rich debris resulting in microembolisation. Microembolisation may also be incident with percutaneous coronary intervention (PCI). Microemboli then obstruct small coronary arteries in the size range of 50-100 μ m distal to the plaque and prevent myocardial perfusion despite the possible recanalization

of the culprit artery. A thrombus can form predominantly intraluminally or inside the plaque. A large occlusive thrombotic mass can form on a small ruptured plaque on the one hand, whereas on the other hand, a thrombus can expand the plaque from within and, in extreme cases, cause complete disintegration.

Myocarditis is described as an inflammatory disease of the heart muscle cells and is pathologically defined by conventional histology and immunohistochemical techniques as an infiltration of mononuclear cells to the myocardium. Myocarditis can be acute, subacute, or chronic and may either include focal or diffuse areas of the myocardium.

Individuals of suspected myocarditis are clinically evaluated to distinguish fulminant lymphocytic myocarditis from acute lymphocytic myocarditis. In the case of fulminant myocarditis, individuals show New York Heart Association class IV symptoms, such as flu-like symptoms with left ventricle (LV) systolic dysfunction and cardiogenic shock. Other characteristics involve leukocytosis, eosinophilia (including rare cases of eosinophilic myocarditis), higher erythrocyte sedimentation rate (ESR), and elevated concentrations of cardiac troponin (cTn) or the creatine kinase (CK) level biomarker. Fulminant myocarditis may possess multiple foci of active myocarditis that principally can resolve within 6 months. Less frequently, giant cell myocarditis has been correlated with fulminant acute myocarditis. In contrast, nonfulminant myocarditis may be acute or chronic myocarditis that usually progresses in an insidious manner. Although both acute and chronic myocarditis can be inferred on echocardiography as heart failure (HF) with left ventricular dysfunction (LVD), acute myocarditis may cause complete resolution or stable dilated cardiomyopathy (DCM), whereas chronic active myocarditis is described as an ongoing myocarditis with visible fibrosis and may involve giant cells. The development of new molecular techniques such as micro ribonucleic acid (miRNA) profiling, nested polymerase chain reaction (Nested PCR), and in situ hybridization (ISH) has improved accuracy of diagnosis and prognostic value of eosin methylene blue (EMB) specimens recognizably, allowing for improved definitions of the various types of myocarditis, including less prevalent subtypes of myocarditis such as eosinophilic and giant cell myocarditis.

The clinical manifestations of myocarditis are heterogeneous, ranging from virtually asymptomatic states with vague signs and symptoms to severe myocardial destruction by virus and immune cells leading to cardiogenic shock and arrhythmias.

Myocarditis can be resulted from a wide range of pathogens, involving viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa, as well as noninfectious triggers, such as toxins and hypersensitive reactions. Among these triggers, viral infection has been recorded to form the most prevalent cause of myocarditis, especially in children. A broad spectrum of viral genomes in the endomyocardial samples of individuals with clinically suspected myocarditis or dilated cardiomyopathy (DCM) has been identified by polymerase chain reaction (PCR) and virus-specific in situ hybridization (ISH), which includes enterovirus, parvovirus B19 (PVB19), adenovirus, influenza A virus, human herpes virus (HHV), Epstein–Barr virus (EBV), cytomegalovirus (CMV), hepatitis C virus, and human immunodeficiency virus (HIV).

Cardiac arrhythmias often persist with a slow or a fast heartbeat consisting of irregular rhythm. The necrosis of the cells of a heart can be attributed to a long-term ischemic impact from a complete absence of oxygen. This results in an abnormal re-entry of the electrical impulses, which leads to arrhythmia. In the case of fibrosis, ageing and cardiac channel mutation the irregular cardiac action potential is progressed which may make the affected individual susceptible to cardiac arrhythmias. Pacemaker, the electrical device activates the electrical signal in the presence of specific cardiac structure for generating, conduction, and distribution to the contractile myocardium. In heart, electric impulse is generated from the sinus node and deputed to specific ionic channels explicitly situated in cells and another part of the heart. Secondary pacemaker show activity in crisis condition. Capacity to generate a frequent depolarisation's reduces the sinoatrial (SA) node, and is minimum in ventricle. The primary pacemaker receives essential neuro vegetative inputs, were depolarisation are often regulated change it to needs of the organism for the metabolic. By conduction system, impulse from sinus node is deputed to the heart; the sinus node and atrioventricular (AV) node are connected through the inter-nodal tracts that constitute the physiologically decelerator the electromechanical delay between the atrial and ventricular conduction. One of the major causes of casualties in cardiovascular disease (CVD) is the arrhythmia, thus monitoring the patient periodically by using an electrocardiogram (ECG) tool can aid to restraint such casualty provoked by arrhythmia. The development of tele-electrocardiogram (Tele-ECG) has reduced the casualties caused by the arrhythmia, which is a disorder that takes place in the normal rhythm of the heart. The ventricular fibrillation (V-fib or VF) is very fatal and can lead death in the victims. The ventricular fibrillation (VF) is an abnormal heart rhythm in which the ventricles of the heart quiver instead of pumping normally.

It is attributed to disorganized electrical activity. Ventricular fibrillation (VF) causes cardiac arrest with loss of consciousness and no pulse. This signal processing can be applied to improve the diagnosis through cardiac electrical signals.

Fibrillation involves a numerous irregular and diverse quivers, atrial flutter is from part of the atrium is not directly legitimately, and because of this, the anomalous heart conduction is occurring in the heart. Nor a perfect directing blood through the heart, the few patients might experience flutter and fibrillation. Atrial flutter beats 250 to 350 beats/min, and untreated of atrial flutter leads to fibrillation.

Atrial fibrillation (AF) is sporadic beats of the atrial chamber-almost rapid in every case. Atrial fibrillation (AF) is mostly affecting more in geriatric individuals. Atrial chamber rather than the single and robust contraction, chamber fibrillates (shudder). The chamber fibrillate 350 beats/min in some cases and 600 beats/min in extreme cases.

Supraventricular tachycardia (SVT) patient experiences the burst of a rapid pulse which last for seconds to hour. It is regular and sporadic heartbeats. Heart rate range between 160-200 beats/min, from the supraventricular tachycardia (SVT) only atrial fibrillation (AF) and flutter are classified.

Ventricular tachycardia its origin is from ventricles and causes a sporadic and rapid heartbeat. It usually occurs if the heart has experienced the prior heart attack. Ventricle contract is more than 200 times/min.

Ventricular fibrillation (VF) is uncoordinated fluttering contraction and very fast sporadic rhythm of the ventricles. Pumping ability of blood in ventricle will be improper shudder. Ventricular fibrillation (VF) is life threatening it was triggered by a heart attack.

An individual will suffer from these symptoms of cardiac arrhythmia: palpitations, a slow heartbeat, sporadic heartbeat, and a feeling of pauses between heartbeats. More serious signs and symptoms involve: anxiety, weakness, dizziness and light-headedness, fainting or nearly fainting, sweating, shortness of breath, and chest pain. The condition that weakens the heart, such as: heart attack, heart failure (HF) or cardiomyopathy, heart tissue that is too thick or stiff, leaking or narrowed heart valves, and congenital problems. Other conditions also can increase

the chances of arrhythmia, such as: high blood pressure, damages of the heart muscle or sac around the heart due to infection, diabetes mellitus (DM), sleep apnoea, overactive or underactive thyroid, drugs for heart surgery like cocaine or amphetamine, and imbalance of chemicals in a body (e.g., potassium, magnesium).

The heart is present in the centre of the thoracic cavity, and its function is to pump blood throughout the body by the continuous rhythmic contractions. An increase in the intracellular potentials is accompanied by the electrical activation of the myocardial cells which happens through the contraction of the heart. The membrane of the myocardial cells has a specific ion channel which generates a sequence of ion fluxes known as the action potential. Sinoatrial node (also known as the SA node or the sinus node) is located on the right atrium act as the pacemaker in a healthy heart. Electrical impulse proliferates through atrial wall and reaches a ventricle for the contraction respectively. The electrical activity can be measured indirectly by electrocardiogram (ECG). It reflects the many deflections of the electrical activity of the heart chamber.

Class I therapy (anti-arrhythmic agents) for cardiac arrhythmia treatment involves the most class of antiarrhythmic agent. This agent reduces the sodium influx which is responsible for conduction of cardiac action potential. Also they reduce and block intra cardiac conduction. Class IA drugs are such as quinidine, disopyramide and procainamide. Quinidine is used most broadly upon these drugs because it has same electrophysiology property in both in-vivo and in-vitro. It blocks the influx of the sodium current (responsible for the repolarization of the cardiac potential action) and efflux of potassium current (liable to the repolarization of the Cardiac Potential Action) at the concentration near to the therapeutic level. Class I B Drugs re such as Lidocaine, phenytoin, and mexiletine. These drugs diminish automaticity and conduction; though, they quick repolarization diminished action potential duration (APD) even though effective refractory period (ERP) is increased and Lidocaine is generally utilized agent in intense ventricular arrhythmia (VA) due to its high efficiency and negligible side effects. Also, it has a two mechanism of action to diminishing the automaticity (phase 4) and ensuing ectopic, reentry arrhythmia caused by conduction of impulse (phase 0). Recalcitrance (phase 3) is insignificantly influenced, with a decline in action potential duration (APD) counterbalanced by an elevate effective refractive period (ERP). Class IC Drugs are such as Flecainide, Propafenone, and

Moricizine. These drugs are especially reduced (phase 4) and conduction (phase 0) in a nonselective equivalent in ordinary and ischemic tissue, whereas action potential duration and the effective refractory period (ERP) is unaffected. Encainide has no effect on the effective refractory period (ERP) but slows the conduction velocity and diastolic depolarisation (phase 4), that elevates the PR, QRS, and QT periods. Encainide is also (30-60%) successful to treat ventricular tachycardia (VT) or Atrial fibrillation (AF). In electrocardiography, the PR interval is the period, measured in milliseconds, that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization); it is normally between 120 and 200 ms in duration. The QRS duration represents the time for ventricular depolarization. The duration is normally 0.06 to 0.10 seconds. Q waves are inscribed when the initial QRS vector is directed away from the positive electrode. The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, efficiently the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

Class II therapy for cardiac arrhythmia treatment involves sympathetic antagonists such as propranolol, Timolol, metoprolol, atenolol, and esmolol. In 1958 this class of drug used as an antagonist for isoproterenol and a multitude of effects. Beta antagonist have diminished the action potential of phase 4, phase 0 and phase 3 by the impact on exogenous autonomic induce to maintenance of internal membrane. Some equal characterisation on this agents is sinoatrial (SA) node reduction, Atrioventricular (AV) conduction and inotropic state this results in a decrease of myocardial oxygen utilisation. Each drug has specific characterisation like lipid solubility relational to the side effects in central nervous system (CNS).

Class III therapy for cardiac arrhythmia treatment includes antifibrillatory agents such as Amiodarone, sotalol, Ibutilide, and dofetilide. These drugs are to re-establish automaticity (Phase 4), Covert the multiple to uniform morphology of heterogeneous action potential, and moderate re-entry recuperation by delaying the Phase 3. Amiodarone is examined first as anti-anginal coronary artery vasodilator, this agent comprises of a procainamide-Lidocaine congener part, physiological effect on diethyl amine group. And thyroid function effects on iodine group. Amiodarone inhibits the calcium and sodium channel in sinoatrial (SA) and atrioventricular

(AV) nodes and Purkinje's fibres respectively, it causes falls of conduction in Phase-0. These action extent the action potential duration (APD) and effective refractive period (ERP), demonstrated as differed bundle of His atrial (AH) and ventricle's (HV) intervals associating in elevating the intervals between PR and QT in electrocardiogram (ECG).

Class IV therapy for cardiac arrhythmia treatment involves calcium channel rival such as Nifedipine, Verapamil, and Diltiazem. This type of drug acts as calcium channel blocker, which inhibits the calcium entry in sinoatrial (SA) and atrioventricular (AV) nodes. To treat specifically conduction disorder like Supra-Hissian (Verapamil > Diltiazem > Nifedipine). The cardiovascular (CV) effect are decreases diastolic depolarisation (Phase-4), activity potential incline and sufficiency (phase-0).cardiovascular (CV) sequence unwind (N>D>V), reduces contraction in intracellular calcium, and bad chronotropic effect atrioventricular (AV) > (SA) sinoatrial nodes. These class drug are used to treat violent supraventricular tachycardia (SVT) 90% and atrial fibrillation (AF)10% typical sinus rhythm. (Wolff- Parkinson- white disorder).

Palpitations-sensations of a rapid or irregular heartbeat-are usually resulted from cardiac arrhythmias or anxiety. Most patients with arrhythmias do not complain of palpitations. However, any arrhythmia, involving sinus tachycardia (ST, also colloquially known as sinus tach or sinus tachy), atrial fibrillation (AF), premature ventricular contractions (PVCs), or ventricular tachycardia (VT), can cause palpitations. Palpitations should be considered as possibly more serious if they are associated with dizziness, near-syncope, or syncope. Presyncope or near-syncope is usually ill-defined and may have different meanings to different providers but denotes near fainting or a prodrome of syncope. The most uniform definition is feeling like one was going to pass out but without actual loss of consciousness. Near syncope can last for seconds to minutes. Near syncope is usually resulted from a drop in the blood pressure that occurs when one stands up quickly. The following can elevate the risk for near syncope:certain medicines, such as medicine to lower person blood pressure, dehydration, low sodium or blood sugar levels, an abnormal heart rhythm, hyperventilation (breathing too quickly). Syncope is a temporary loss of consciousness often associated with insufficient blood flow to the brain. It's also known as fainting or passing out. It most frequently happens when blood pressure is too low (hypotension) and the heart doesn't pump enough oxygen to the brain. Nonarrhythmic cardiac problems, such as mitral valve prolapse, pericarditis, and congestive heart failure, and noncardiac problems, such

as hyperthyroidism, vasovagal syncope, and hypoglycemia, can cause palpitations. Palpitations also can be caused by stimulant drugs, and over-the-counter and prescription medications. No cause for the palpitations can be found in up to 16 percent of patients. Ambulatory electrocardiographic (ECG) monitoring often is indicated if the etiology of palpitations cannot be determined from the patient's history, physical examination, and resting electrocardiogram (ECG). When palpitations happen unpredictably or do not happen daily, an initial two-week course of continuous closed-loop event recording is indicated. Holter monitoring for 24 to 48 hours may be suitable in affected individuals with daily palpitations. Trans-telephonic event monitors are more efficient and cost-effective than Holter monitors for most affected individuals.

Apoptosis is described as a caspase-dependent, genetically controlled form of cell death. This definition considers apoptosis is a biological process that can be modulated by genetic or pharmacologic interventions. In addition to apoptosis, multiple forms of regulated cell death are present, such as autophagic cell death that is correlated with lipidation of microtubule-associated protein light chain 3 (LC3) and degradation of sequestosome 1 (SQSTM1, also known as p62) and necroptosis that is dependent on receptor-interacting protein kinases 1 and 3 (RIPK1/RIPK3). It is worthy to show that necroptosis is a programmed form of necrosis, or inflammatory cell death. Conventionally, necrosis is related to unprogrammed cell death resulting from cellular damage or infiltration by pathogens, in contrast to orderly, programmed cell death via apoptosis. Receptor-interacting protein kinases 1 and 3 (RIPK1 and RIPK3) are key arbitrators in tumor necrosis factor (TNF)-induced cell fate regulation. Receptor-interacting protein kinases 1 (RIPK1) can activate the nuclear factor κ B (NF- κ B) transcription factors causing cell proliferation and differentiation. Alternatively, it can form a cytosolic complex engaging the Fas-associated death domain (FADD) and caspase-8 to initiate apoptosis. In other circumstances, receptor-interacting protein kinases 1 (RIPK1) can be in association with receptor-interacting protein kinases 3 (RIPK3) through receptor-interacting protein (RIP) homotypic interaction motifs (RHIM) to form a necrosome and trigger necroptosis.

Apoptosis is crucial during heart development and has long been bound to a number of cardiovascular diseases (CVDs) such as ischemic heart disease (IHD), reperfusion injury, chemotherapy-induced cardiomyopathy (CCM), and heart failure (HF). Noticeable apoptosis was detected in embryonic heart at the time of outflow tract shortening, and inhibition of apoptosis

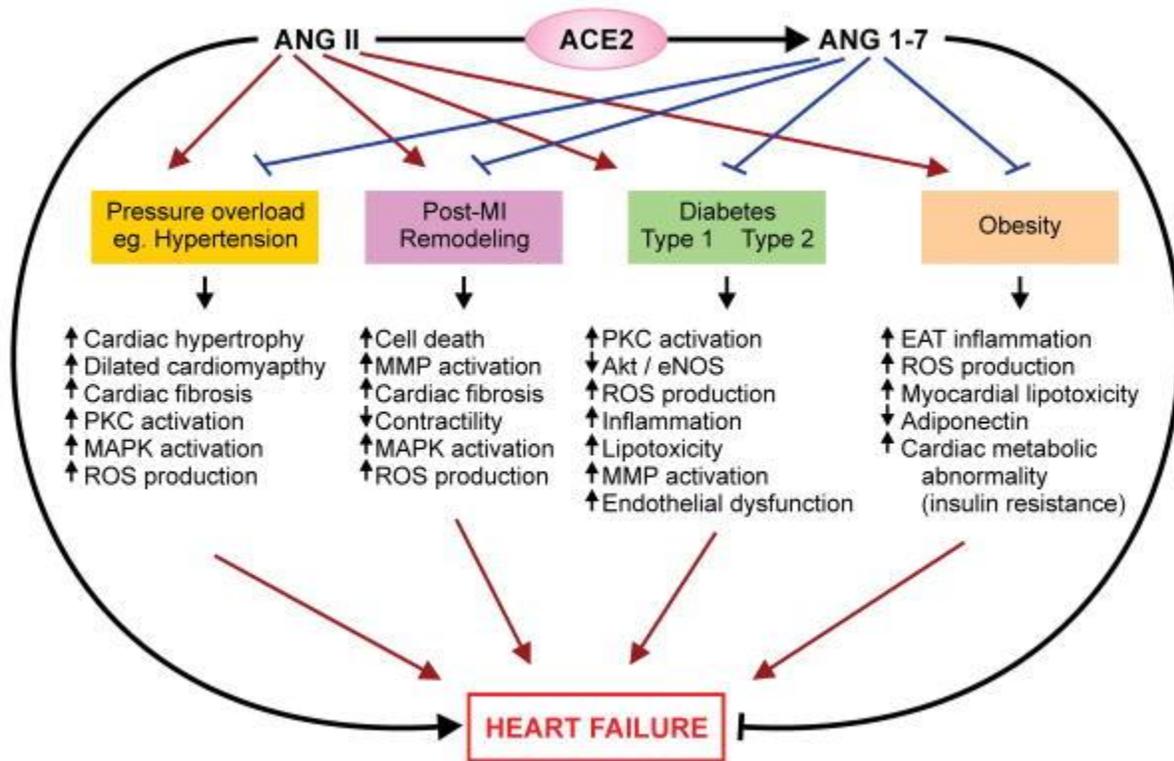
using the pan-caspase inhibitor zVAD-fmk or adenoviral mediated expression of X-linked inhibitor of apoptosis protein resulted in excessive outflow tract above the base of the ventricles, indicating that apoptosis is imperative for morphogenesis of the outflow tract myocardial tissue. Although apoptosis seems to be dispensable for physiological homeostasis in normal adult heart, it can cause cardiomyocyte loss that is correlated with life-threatening cardiac dysfunction in multiple pathological settings. Therefore, modulation of apoptosis is a promising therapeutic strategy for cardiovascular diseases (CVDs).

Cardiac myocytes, which represent ~85% of total heart mass, are the major contracting cells in the heart. Cardiovascular diseases (CVDs), the number 1 cause of death worldwide, are often associated with apoptotic death of cardiac myocytes. Since cardiomyocyte apoptosis is a highly regulated process, pharmacological intervention of apoptosis pathways may represent a promising therapeutic strategy for a number of cardiovascular diseases (CVDs) and disorders involving myocardial infarction (MI), ischemia/reperfusion injury (IRI), chemotherapy-induced cardiotoxicity (CTX), and end-stage heart failure.

Heart block is associated with pulmonary hypertension (PHT). The hypothesis that the heart block is the result of a change in the ion channel transcriptome of the atrioventricular (AV) node. Pulmonary hypertension (PHT) leads to a derangement of the ion channel transcriptome in the atrioventricular (AV) node, and this is the possibly cause of atrioventricular node dysfunction in this disease. Pulmonary hypertension (PHT) has a poor prognosis especially leading to progressive right ventricular failure and death. Patients with pulmonary hypertension (PHT) have a high burden of arrhythmias, involving heart block. Pulmonary hypertension (PHT) is a disease characterized by elevated pulmonary vascular resistance (PVR). It has a poor prognosis particularly causing progressive right ventricular failure and death. The incidence of arrhythmias in patients with pulmonary hypertension (PHT) is high. All forms of supraventricular tachycardia (SVT) are more common in pulmonary hypertension (PHT) with studies proposing an incidence of $\approx 3\%$ per year and a prevalence of supraventricular arrhythmia of $\approx 12\%$. Atrial flutter, atrial fibrillation (AF), and atrioventricular nodal reentrant tachycardia (AVNRT) are common.

A noticeable study demonstrates widespread downregulation of the ion channel transcriptome in the atrioventricular (AV) node in response to an illness process. Previously, atrioventricular (AV) node disease has been commonly attributed to idiopathic fibrosis and sclerosis. However,

there are indications pointing to the importance of ion channels in normal atrioventricular (AV) conduction. A genome-wide association study has revealed several loci that are correlated with a prolonged PR interval, involving genes for ion channels and developmental genes known to be beneficial for the patterning of ion channels during embryogenesis. There is also a recognition that several disease-causing ion channel mutations that have been characterized as causing Brugada syndrome and long QT syndrome are also correlated with conduction system disturbances and heart block. In addition to these findings in affected individuals, gene knockout studies in mice have pointed to the importance of several ion channels, involving voltage-dependent Ca^{2+} channels and hyperpolarization activated cyclic nucleotide gated potassium channel 4 (HCN4) in maintaining normal atrioventricular (AV) conduction.



Figure(81): ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure [Patel VB.; Zhong JC.; Grant MB.; Oudit GY. (2016). Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. *Circulation Research*, 118(8):1313-1326. DOI:[10.1161/circresaha.116.307708](https://doi.org/10.1161/circresaha.116.307708)]

Congestive heart failure is a common condition that increases in prevalence with increasing age. In 2003, guidance from the National Institute for Health and Clinical Excellence acknowledged that the rising epidemic of heart failure (HF) is partly the result of people living longer and the more effective treatments for coronary artery disease (CAD) now available. It also acknowledged, however, that average life expectancy is only about three years after diagnosis, which is much worse than for many other serious diseases such as cancer of the breast or colon. The condition is associated with poor quality of life, frequent hospital admissions, and poor survival, although this may have changed with the advent of better managements. About 1% of males experience heart failure (HF) after age 75 and almost 2% after 80 years. Heart failure (HF) is a clinical syndrome comprising reduced cardiac output, tissue hypoperfusion, and congestion. In hospital, patients with heart failure (HF) typically present with shortness of breath, exercise intolerance, and leg swelling. Dyspnoea, fatigue, exercise intolerance, and fluid retention are common, but some of the other characteristics may not be found. In the community, patients often present with less acute symptoms and fewer clinical signs, and the clinical diagnosis of heart failure (HF) can be difficult. Fluid retention may be present in patients who have dyspnoea, an increase in weight from baseline of more than 2 kg in under three days, raised jugular venous pressure, crepitations on chest auscultation, hepatomegaly, or signs of peripheral oedema. Disease classification may change—for example, during an acute exacerbation a patient may have class IV disease but have class I disease (asymptomatic) after recovery. Patients with heart failure (HF) may have impaired left ventricular (LV) systolic function, which is usually assessed on echocardiography by measuring the left ventricular ejection fraction (LVEF). However, as many as 50% of patients with the syndrome may have preserved left ventricular ejection fraction (usually defined as $>50\%$), and currently little evidence is available to guide management in these patients. It is important to distinguish between those with a low ejection fraction and those with a preserved ejection fraction because most of the research into treatment has been done on those with low ejection fraction. Ejection fraction (EF) is a measurement doctors use to calculate the percentage of blood flowing out of these ventricles with each contraction. As one ages, the hearts do too. Heart walls thicken and lose some of their capacity to contract and relax as the years go on. But, a low ejection fraction (EF) reading can also refer to some form of heart damage, involving: cardiomyopathy, heart attack [also known as a myocardial infarction (MI)], coronary artery disease (CAD), systolic heart failure (SHF), and heart valve disease (HVD).

Heart failure with preserved ejection fraction (HFpEF) occurs when the lower left chamber (left ventricle) is not able to fill properly with blood during the diastolic (filling) phase. The amount of blood pumped out to the body is less than normal. It is also called diastolic heart failure (DHF). Many descriptive studies have shown that affected individuals with diagnosed heart failure (HF) in the community are undertreated. A person with heart failure (HF) may present in several different ways. Affected individuals who are acutely unwell are often admitted to hospital urgently. They may have acute pulmonary oedema (APE). A bedside clinical assessment is usually sufficient to make a diagnosis without the need for further investigations. An echocardiogram will help to guide management for those with heart failure (HF) and low ejection fraction. In patients with less acute symptoms who have a constellation of clinical symptoms and signs suggestive of heart failure (HF) the clinician might have a high degree of clinical certainty. Early therapy may be initiated and the affected individual referred for electrocardiography, chest radiography, and echocardiography. Although access to echocardiography may be delayed or limited in some locations, refer as a priority for echocardiography patients who are at high risk of heart failure (HF) [if they have a history of myocardial infarction (MI), basal lung crepitations (abnormal breath sounds (crackles) heard on auscultation only in the bases of the lungs), or are male and have swollen ankles]. In patients presenting in the community who have coexisting respiratory disease or are elderly, the diagnosis of heart failure (HF) is frequently difficult to make. Such a diagnosis can be improved by incorporating brain natriuretic peptide (BNP) in clinical decision making pathways. The 2009 Health Technology Assessment group considers brain natriuretic peptide [measured using brain natriuretic peptide or N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) assays] better than electrocardiography for diagnosing congestive cardiac failure. Low brain natriuretic peptide (BNP) particularly rules out congestive heart failure (HF) as a cause of dyspnoea and guides investigation towards other causes, such as respiratory disease. All patients with confirmed congestive heart failure (HF) should undergo echocardiography to estimate cardiac structure and function. It is proposed that when there is a strong clinical suspicion of congestive heart failure (HF) (with or without presumed characteristics on chest radiography and electrocardiography) but no access to echocardiography, patients should be given an angiotensin converting enzyme (ACE) inhibitor and a β blocker, titrated up to maximal doses. This means that individuals with heart failure (HF) with low ejection fraction will be managed optimally and

those with preserved ejection fraction will have their risk of cardiovascular disease (CVD) lowered by virtue of a lower blood pressure. For those with heart failure (HF) with preserved ejection fraction a change to candesartan could be regarded once the diagnosis is confirmed. Although this approach is not ideal and extends beyond the current evidence, it is a pragmatic and reasonable approach to patient care in a resource poor environment because the adverse effects of angiotensin-converting enzyme (ACE) inhibitors and β blockers are not serious enough to limit their use. Consider treatment with diuretics in patients with heart failure (HF) who have dyspnoea or ankle or pulmonary oedema. These drugs should be given before or at the same time as angiotensin-converting enzyme (ACE) inhibitors, and both should precede the start of β blockers. Diuretics are used on an individual basis to reduce fluid retention. There should avoid overtreatment, which can cause dehydration and renal dysfunction, particularly with loop diuretics. Hypovolaemia can be assessed by measuring supine and standing blood pressures. A postural drop in blood pressure that leads to light headedness or unconsciousness indicates hypovolaemia, especially in elderly patients with heart failure (HF). Bumetanide, furosemide, and torasemide (loop diuretics) act at the loop of Henle, whereas thiazides, metolazone, and potassium sparing agents (such as spironolactone) act in the distal portion of the tubule. The addition of a thiazide diuretic or a potassium sparing diuretic (or both) to loop diuretics can be beneficial if pulmonary or ankle oedema persists, because the different classes of diuretic are believed to have an additive effect. It is crucial to monitor electrolytes in the early phase of diuretic administration. The side effects of diuretics, such as frequent micturition, are unpleasant, particularly for elderly patients, and in those with stable symptoms [ideally on maximum doses of angiotensin-converting enzyme (ACE) inhibitor and β blocker] consider lowering the dose of the loop diuretic, stepping down to a thiazide diuretic, or stopping diuretics completely. A systematic review of randomised trials in patients with heart failure (HF) with low ejection fraction found that in those categorised as New York Heart Association class III or IV an aldosterone antagonist such as spironolactone may be life saving. Hyperkalaemia [an elevated level of potassium (K^+) in the blood. Normal potassium levels are between 3.5 and 5.0 mmol/L (3.5 and 5.0 mEq/L) with levels above 5.5 mmol/L defined as hyperkalemia] is a recognized adverse effect, particularly when starting the drug, so patients need to be monitored. Doses of spironolactone higher than 25 mg daily should be used with caution. The combination of spironolactone and an angiotensin-converting enzyme (ACE) inhibitor can cause worsening renal

function or hyperkalaemia (or both), which can occur many months after starting therapy, and may happen at the time of intercurrent disease such as diarrhoea and vomiting. There should advise patients to stop the drug themselves if such an illness happens. If dyspnoea remains a problem despite the treatment recommended above, digoxin may be used even in patients who are in sinus rhythm. A Cochrane systematic review revealed that digoxin reduces the combined end point of death and hospital admission in those with both heart failure with low ejection fraction and heart failure with preserved ejection fraction (HFpEF), but most studies have been done on patients who were not taking a β blocker. One large randomised controlled trial published in 2003 found that the angiotensin receptor blocker candesartan may reduce readmissions in patients with heart failure and preserved ejection fraction (HFpEF). In this trial about 20% of patients were already taking an angiotensin-converting enzyme (ACE) inhibitor and about 50% were taking a β blocker. Another randomized trial showed that the angiotensin receptor blocker irbesartan made no difference to mortality or readmissions when used in patients with heart failure and preserved ejection fraction (HFpEF). However, because evidence to guide the use of other drugs is limited and management is largely empirical, treatment is possibly best guided by advice from secondary care. Heart failure with preserved ejection fraction (HFpEF) is commonly associated with hypertension (HTN), so effective treatment of blood pressure is beneficial. Atrial fibrillation (AF) can also contribute to the heart failure (HF) syndrome in those with a preserved ejection fraction, and effective treatment of heart rate and anticoagulation is necessary in patients with atrial fibrillation (AF). Other drugs Scottish Intercollegiate Guidelines Network (SIGN) guidelines state that hydralazine and isosorbide dinitrate are options for patients who are intolerant of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers but should not be considered first line except in African-Americans. Statins to lower cholesterol reduced ischaemic heart events in the Heart Protection Study and could be referred to those with suspected ischaemic heart disease (also called coronary artery disease, CAD). The usefulness of antiplatelet agents for those without evidence of ischaemic heart disease (or coronary artery disease, CAD) is unclear.

Several non-drug treatments are available but most are not depending on evidence from randomized trials. Approaches comprise sodium restriction, fluid restriction, daily weighing,

avoiding alcohol and tobacco, and losing weight. Systematic reviews of exercise have shown benefits in terms of exercise tolerance and quality of life.

Sudden cardiac arrest (SCA) is a condition in which the heart suddenly and unexpectedly stops beating. If this occurs, blood stops flowing to the brain and other vital organs. Sudden cardiac arrest (SCA) usually leads to death if it is not treated within minutes. Ventricular fibrillation (VF) causes most sudden cardiac arrests (SCAs). Ventricular fibrillation (VF) is a type of arrhythmia. During ventricular fibrillation (VF), the ventricles (the heart's lower chambers) don't beat normally. Instead, they quiver very rapidly and irregularly. When this happens, the heart pumps little or no blood to the body. Ventricular fibrillation (VF) is fatal if not treated within a few minutes. Other problems with the heart's electrical system also can cause sudden cardiac arrest (SCA). For example, sudden cardiac arrest (SCA) can occur if the rate of the heart's electrical signals becomes very slow and stops. Sudden cardiac arrest (SCA) also can occur if the heart muscle doesn't respond to the heart's electrical signals. Certain illnesses and conditions can cause the electrical problems that cause sudden cardiac arrest (SCA). Examples include ischemic heart disease [also called coronary heart disease or coronary artery disease (CAD)], severe physical stress, certain inherited disorders, and structural changes in the heart.

The risk of sudden cardiac arrest (SCA) increases: with age, males are more probable than females to have sudden cardiac arrest (SCA), some studies show that blacks-especially those with underlying conditions such as diabetes mellitus (DM), high blood pressure, heart failure (HF), and chronic kidney disease (CKD) or certain cardiac findings on tests such as an electrocardiogram-have a higher risk for sudden cardiac arrest (SCA).

The major risk factor for sudden cardiac arrest (SCA) is ischemic heart disease. Most people who have sudden cardiac arrest (SCA) have some degree of ischemic heart disease; however, many people may not know that they have heart disease until sudden cardiac arrest (SCA) occurs. Usually their heart disease is silent-that is, it has no signs or symptoms. Because of this, doctors and nurses have not detected it. Many people who have sudden cardiac arrest (SCA) also have silent, or undiagnosed, heart attacks before sudden cardiac arrest (SCA) happens. These people have no clear signs of heart attack, and they don't even realize that they've had one.

Other risk factors for sudden cardiac arrest (SCA) involve: a personal history of arrhythmias, a personal or family history of sudden cardiac arrest (SCA) or inherited disorders that make one prone to arrhythmias, drug or alcohol abuse, heart attack, and heart failure (HF).

Usually, the first sign of sudden cardiac arrest (SCA) is loss of consciousness (fainting). At the same time, no heartbeat (or pulse) can be felt. Some people may have a racing heartbeat or feel dizzy or light-headed just before they faint. Within an hour before sudden cardiac arrest (SCA), some people have chest pain, shortness of breath, nausea (feeling sick to the stomach), or vomiting.

Sudden cardiac arrest (SCA) is an emergency. A person having sudden cardiac arrest (SCA) needs to be treated with a defibrillator right away. This device sends an electric shock to the heart. The electric shock can restore a normal rhythm to a heart that's stopped beating. To work well, defibrillation must be done within minutes of sudden cardiac arrest (SCA). With every minute that passes, the chances of surviving sudden cardiac arrest (SCA) drop rapidly.

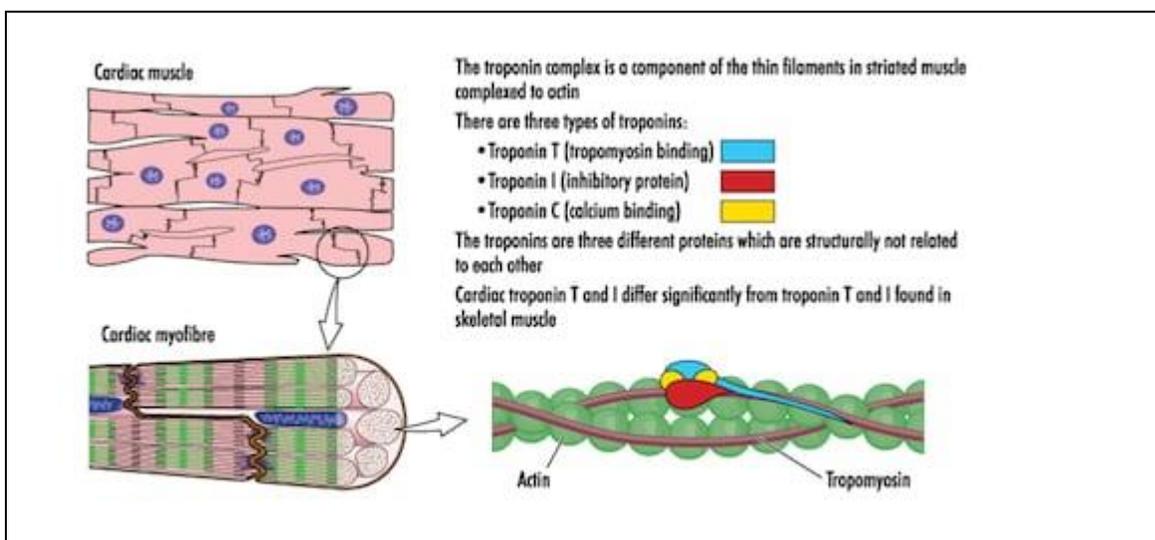
Police, emergency medical technicians, and other first responders usually are trained and equipped to use a defibrillator. If one survives sudden cardiac arrest (SCA), the person will possibly be admitted to a hospital for ongoing care and treatment. In the hospital, person's medical team will closely watch the heart. They may give the person medicines to try to reduce the risk of another sudden cardiac arrest (SCA). While in the hospital, patient's medical team will try to find out what caused the sudden cardiac arrest (SCA). If individual is diagnosed with ischemic heart disease, the individual may have percutaneous coronary intervention, also known as coronary angioplasty, or coronary artery bypass grafting. These procedures help restore blood flow through narrowed or blocked coronary arteries. Often, individuals who have sudden cardiac arrest (SCA) get a device called an implantable cardioverter defibrillator (ICD). This small device is surgically placed under the skin in your chest or abdomen. An implantable cardioverter defibrillator (ICD) uses electric pulses or shocks to help control dangerous arrhythmias.

12.1 Cardiac Troponins

The contractile complex in cardiac muscle contains the contractile proteins actin and myosin, and the regulatory proteins troponins (Tn) and tropomyosin (Tpm). Troponin (Tn) is imperative for the calcium mediated regulation of skeletal and cardiac muscle contraction. The troponin (Tn) complex is a heteromeric protein located with tropomyosin (Tpm) on the actin filament. It consists of three single chain polypeptides: troponin T (cTnT), which binds the other troponin (Tn) components to tropomyosin (Tpm); troponin I (cTnI), which inhibits adenosine triphosphate (ATP) activity when bound to actin; and troponin C (cTnC), which contains binding sites for calcium. Most troponin (Tn) is found as this three unit complex but there is also a small percentage (2–8%) of unbound troponin (Tn) in the cytoplasm of the cardiac muscle cell. When myocyte damage happens, cardiac troponin (cTn) is released into the serum both as the individual troponin (Tn) proteins I, T, and C and as binary and tertiary complexes such as TC and ITC. There are tissue-specific isoforms of troponin I, T, and C. Troponin C (TnC) is not of benefit for diagnosing cardiac injury because the cardiac isoform is shared by skeletal muscle. Multiple cardiac troponin T (cTnT) isoforms are expressed in the human heart [predominantly cardiac troponin T3 (cTnT3)] whereas troponin C (TnC) and troponin I (TnI) are expressed as single isoforms. There are essential differences between the amino acid (AA) sequences of the cardiac isoforms of troponin I (TnI) and troponin T (TnT) and other isoforms and it has been likely to produce highly specific monoclonal antibodies without cross reactivity with other non-cardiac forms.

Detectable increases in the troponin (Tn) biomarkers are indicative of cardiac injury but do not determine the mechanism. The Joint European Society of Cardiology and American College of Cardiology Committee have recommended the cardiac troponin (cTn) as the biomarkers of choice in the diagnosis of myocardial infarction (MI). Cardiac troponin (cTn) have nearly absolute myocardial tissue specificity and reflect even microscopic zones of myocardial necrosis but cardiac troponin (cTn) elevations are not always attributable to acute coronary syndromes (ACSs) and a troponin (Tn) increase in isolation cannot be used to diagnose myocardial infarction (MI). After myocardial cell damage, unbound cytoplasmic troponin (Tn) is released from cardiac myocytes. Both troponin I (TnI) and troponin T (TnT) exhibit biphasic release kinetics. Release from the cytosolic pool gives increase to blood concentrations rising 4-6 h after

the onset of damage and peaking at 12-24 h after myocardial injury. Structural protein release leads to a second peak 2-4 days after injury. Continuing breakdown of myofibrillary-bound complex explains the prolonged elevation of both troponins (i.e., TnI and TnT) for up to 10 days after infarction. This accounts for increased detection of cardiac events using troponin (Tn) and its increased sensitivity but can make diagnosis of reinfarction more difficult and CK-MB test has valuable role here. The CPK-MB test is a cardiac marker used to assist diagnosis of an acute myocardial infarction (MI). It measures the blood level of CK-MB (creatine kinase myocardial band), the bound combination of two variants (isoenzymes CKM and CKB) of the enzyme phosphocreatine kinase.

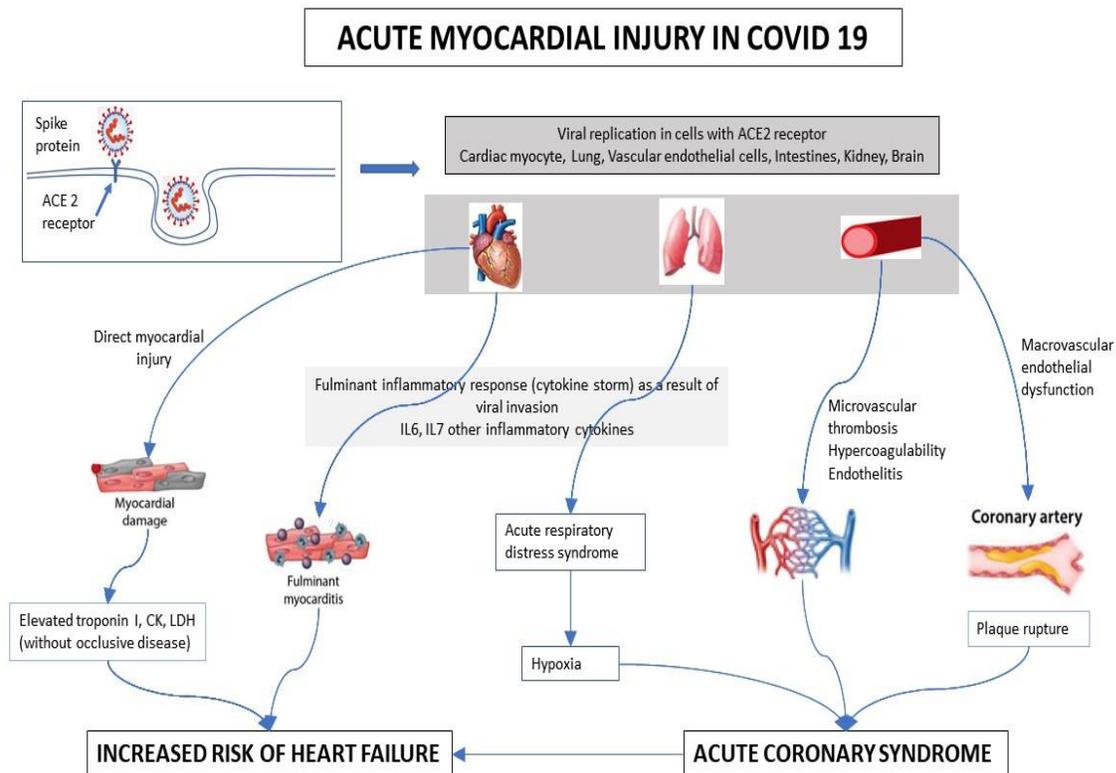


Figure(82):Cardiac troponin (www.google.com)

High-sensitivity cardiac troponin (hs-cTn) assays are increasingly being used in many countries worldwide, however, a generally accepted definition of high-sensitivity is still pending. These assays enable cardiac troponin (cTn) measurement with a high degree of analytical sensitivity with a low analytical imprecision at the low measuring range of cardiac troponin (cTn) assays [coefficient of variation of < 10% at the 99(th) percentile upper reference limit]. One of the most important advantages of these new assays is that they allow novel, more rapid approaches to rule in or rule out acute coronary syndromes (ACSs) than with previous cardiac troponin (cTn) assay generations which are still more commonly used in practice worldwide. High-sensitivity cardiac troponin (hs-cTn) is also more sensitive for the detection of myocardial damage unrelated to

acute myocardial ischemia. Therefore, the increase in early diagnostic sensitivity of high-sensitivity cardiac troponin (hs-cTn) assays for acute coronary syndrome (ACS) comes at the cost of a reduced acute coronary syndrome (ACS) specificity, because more patients with other causes of acute or chronic myocardial injury without overt myocardial ischemia are detected than with previous cardiac troponin (cTn) assays.

12.2 Cardiac Injury in COVID-19 Infection



Figure(83): COVID-19 associated myocardial injury (www.google.com)

It is known that persons at greatest risk of serious disease sufficient to require intensive care and those at greatest risk of mortality are older persons, especially older persons with underlying comorbid disease, including cardiovascular disease (CVD). However, severe disease requiring hospitalization and even deaths have been reported in younger adults. Patients with heart failure (HF) are also prone to hemodynamic decompensation during the stress of severe infectious

diseases. Thus, it is expected that patients with underlying cardiovascular diseases (CVD), which are more prevalent in older adults, would be susceptible to higher risks of adverse outcomes and death during the severe and aggressive inflammatory responses to coronavirus disease 2019 (COVID-19) than persons who are younger and healthier. A study, of 138 hospitalized coronavirus disease 2019 (COVID-19) patients compared patients admitted to the intensive care unit (ICU) and non-intensive care unit (non-ICU) patients. Higher rates of hypertension (HTN) (58.3% vs. 21.6%, $p < 0.001$) and cardiovascular disease (CVD) (25.0% vs. 10.8%, $p = 0.04$) were seen in intensive care unit (ICU) patients. This indicates that patients with pre-existing cardiovascular disease (CVD) may have a worse prognosis than others although age could be one of the confounders. Moreover, it is also particular to understand that although most clinical presentations associate with the respiratory system, the illness may also impact on the cardiovascular (CV) system. Although coronavirus disease 2019 (COVID-19) clinical manifestations are principally respiratory, with the growing number of infected patients, major cardiac complications have been mentioned in a notable number of patients with coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is correlated with a variety of proinflammatory mediators that may play important roles in the pathophysiology of cardiac and arrhythmic complications. In a cohort of 138 hospitalized coronavirus disease 2019 (COVID-19) patients, cardiac injury [defined as elevated high sensitivity troponin I (hs-cTnI) or electrocardiogram (ECG) or echocardiographic abnormalities] was present in 7.2% of patients [22% of patients requiring intensive care unit (ICU) care]. In addition, a report of the National Health Commission (NHC) of China showed that raised troponin (Tn) concentrations and cardiac arrest during hospitalization was prevalent in almost 12% of patients without known cardiovascular disease (CVD).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) as its entry receptor, and subsequently downregulates angiotensin-converting enzyme 2 (ACE2) expression. In addition to the heart and lung, angiotensin-converting enzyme 2 (ACE2) is localized in the intestinal epithelium, vascular endothelium, and the kidneys. In the renin angiotensin aldosterone system (RAAS), angiotensin-converting enzyme 2 (ACE2) catalyzes the conversion of angiotensin II (Ang II) to angiotensin 1-7 (Ang-1-7), which opposes the vasoconstrictor, pro-inflammatory, pro-oxidant, pro-proliferative and pro-fibrotic actions exerted by angiotensin II (Ang II) via angiotensin II type 1 receptors (AT1 receptors). As a

result, suppression of angiotensin-converting enzyme 2 (ACE2) expression and subsequent raise in angiotensin II (Ang II) levels may represent another threat to heart and vessels in individuals with coronavirus disease 2019 (COVID-19).

A clinical trial testing recombinant human angiotensin-converting enzyme 2 (ACE2) as a treatment for individuals with coronavirus disease 2019 (COVID-19) is currently ongoing. This therapy may play a double role, both by acting as a decoy and competitively reducing viral cell entry, and by restoring angiotensin-converting enzyme 2 (ACE2) activity and its important role. Given the interaction with host angiotensin-converting enzyme 2 (ACE2) type II pneumocytes receptors, dysregulation of the renin-angiotensin system (RAS) may serve a central role both in the onset and progression of lung injury. The complex severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) glycoprotein and angiotensin-converting enzyme 2 (ACE2) receptor primed by the cellular protease TMPRSS2 is a critical step for ectodomain virion entry by suppressing angiotensin-converting enzyme 2 (ACE2) activity and altering the angiotensin-converting enzyme/ angiotensin-converting enzyme 2 (ACE2) (ACE/ACE2) balance to a predominant angiotensin-converting enzyme/angiotensin II (ACE/AngII) axis with a reduction of angiotensin 1-7 [Ang(1-7)]-Mas (Mas is G coupled protein) complex and subsequent vasoconstriction (the constriction of blood vessels, which increases blood pressure), cytokines-bradykinin inflammatory response, Fas-induced apoptosis, fibrogenesis and oxidative damage. It is better to refer that bradykinin (BK) is a chemical inflammatory mediator, nanopptide created from plasma Kinin–Kallikrein system . Two or more distinct receptors are present for bradykinins (BKs) which have been titled B1 and B2. Bradykinin (BK) and Lys-BK (kallidin) are vasoactive peptides generated via the cleavage of kininogen by the action of kallikrein proteases (enzymes capable of cleaving peptide bonds in proteins). Both have a half-life of only seconds within the circulation, being rapidly hydrolyzed to biologically active des-Arg kinin derivatives. BK and Lys-BK cause the classical signs of inflammation – redness, local heat, swelling, and pain-whereas their des-Arg derivatives induce increased collagen synthesis, fibroblast proliferation, and cytokine release from macrophages. The effects of these peptides are mediated by two distinct G-coupled receptors. The kinin system has been implicated in the pathophysiology of human airway inflammation. Respiratory viral infections are also associated with increase levels of bradykinin (BK) and Lys-BK within the airway. **Bradykinins**

are essential peptide mediators of a diverse range of physiological and pathological functions of the cardiovascular (CV) system. The kinin peptides exhibit their effects by selective activation of two distinct G-protein coupled receptors termed B₁ and B₂. The principal kinin peptides included in the acute regulation of cardiovascular (CV) function during normal physiology are bradykinin (BK) and Lys-BK which produce their effects via activation of B₂ receptors. The B₁ receptor is activated by the des-Arg⁹kinin metabolites namely des-Arg⁹BK and Lys-des-Arg⁹BK, the synthesis of which are raised during inflammation. The B₁ receptor, which is not constitutively expressed, is induced in various pathologies relating to inflammation. Recent investigations into the molecular mechanisms of B₁ receptor induction and their distribution and function in the cardiovascular (CV) system have shown that following an inflammatory stimulus the B₁ receptor is induced and may play an important role in modulation of cardiovascular (CV) function. Fas (APO-1/CD95) is a member of the tumor necrosis factor-R (TNF-R) family, a group of type I transmembrane proteins. Fas and some members of this family (death receptors) have a death domain (DD) in their cytoplasmic region, which is crucial for their induction of apoptosis. The only known physiological ligand of Fas, FasL (CD95L or APO-1L), belongs to the family of tumor necrosis factor (TNF)-related cytokines. Like most of its relatives, FasL is synthesized as a transmembrane molecule and soluble FasL trimers can be generated through processing by a metalloprotease. Fas signaling plays a critical role in lymphocyte homeostasis. Repeated activation of antigen receptors on T cells induces FasL expression, leading to Fas-transduced apoptosis. Failure of this process, caused by mutations in Fas (lpr or Fas gene deletion) or FasL (gld), evokes lymphadenopathy and autoimmunity. Fibrogenesis is a mechanism of wound healing and repair. However, prolonged injury causes deregulation of normal processes and results in extensive deposition of extracellular matrix (ECM) proteins and fibrosis.

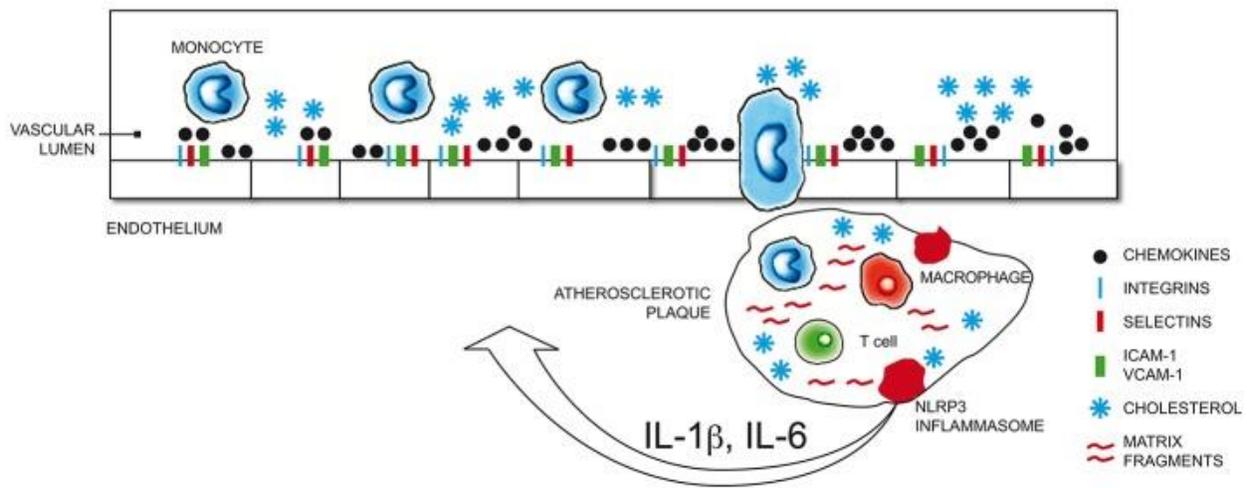
Khan A *et al.*, (2017) in a double-blind two-part phase II trial comparing the effect of the administration of a recombinant form of human angiotensin-converting enzyme 2 (GSK2586881) in forty-six patients with acute respiratory distress syndrome (ARDS), showed a noticeable reduction of angiotensin II (Ang II) levels after scalar infusion with a long standing 48-hours plateau phase. Moreover, surfactant protein D increased as far as interleukin-6 (IL-6) levels decreased. The authors reported no significant differences in either peak or plateau pressures between recombinant human angiotensin-converting enzyme 2 (rhACE2) and placebo

group in the first 72 hours, but an equally increase at the end of the five-day observation period. No adverse haemodynamic effects were observed; however, hypernatremia, rash and dysphagia were noticed. The adoption of a target medication for coronavirus disease 2019 acute respiratory distress syndrome (COVID-19 ARDS) is promising as it could ensure both an anti-inflammatory (like interleukin-inhibitors, such as Tocilizumab) and regenerative (restoration of surfactant homeostasis, prevention of post-injury fibrotic remodelling) effects. The development of target drugs acting on the renin-angiotensin system (RAS) appear promising .

A registry of 1099 patients with coronavirus disease 2019 (COVID-19) demonstrated a higher prevalence of hypertension (HTN) (23.7% vs. 13.4%) and coronary artery disease (CAD) (5.8% vs. 1.8%) in severely affected versus non-severely affected individuals. Individuals with long-term coronary artery disease (CAD) and those with risk factors for atherosclerotic cardiovascular disease (CVD) have a heightened risk of progressing an acute coronary syndrome (ACS) during acute infections, which has been shown previously in epidemiologic and clinical studies of influenza and other acute inflammatory conditions. Such acute coronary events could result from the severe increase in myocardial demand triggered by infections that precipitate myocardial infarction (MI) or injury, akin to type 2 myocardial infarction (MI). Alternatively, circulating cytokines secreted during a severe systemic inflammatory stress could result in atherosclerotic plaque instability and rupture. Pathological conditions that include common cardiovascular (CV) risk factors [such as hypertension (HTN), hyperlipidaemia, hyperglycaemia, and smoking] and stress-related conditions (i.e. depression, anxiety) can elicit immune responses that stimulate the production of leukocyte adhesion molecules and chemotactic factors, inducing monocyte adhesion to endothelial cells and transmigration into the subintimal space. Initial atherosclerotic lesions begin with the differentiation of monocytes into macrophages ($M\Phi$) that engulf cholesterol-rich oxidized lipoproteins to become foam cells that organize into fatty streaks. The perpetuation of pro-inflammatory and oxidizing atherosclerotic stimuli leads to the recruitment of further macrophages ($M\Phi$), mast cells, and activated T and B cells that raise vascular lesions, which, in turn, secreting cytokines [i.e., interleukin-1beta ($IL-1\beta$), tumor necrosis factor-alpha ($TNF-\alpha$)], increases monocytes migration into the subintimal space. Initial atherosclerotic lesions begin with the differentiation of monocytes into macrophages ($M\Phi$) that engulf cholesterol-rich oxidized low density lipoproteins (LDL-ox) to become foam cells that organize into fatty streaks. The perpetuation of pro-inflammatory and oxidizing atherosclerotic

stimuli results in the recruitment of further macrophages (MΦ), mast cells, and activated T and B cells that increase vascular lesions. The fibrous atherosclerotic plaque cap maintains its stability due to interstitial collagen. Cytokines and inflammatory immune cells interfere with the integrity of the collagen matrix, impairing the synthesis of new collagen fibers and inducing the reabsorption of existing ones through the secretion and activation of specific enzymes (metalloproteinases); this process makes the cap weaker and prone to rupture. The broken cup exposes the atheronecrotic core to coagulation factors and platelets circulating into the arterial blood and induces arterial thrombosis, thus developing an acute cardiovascular event [i.e., acute myocardial infarction (MI), stroke (stroke: the sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain)]. A growing body of evidence defines atherosclerosis as a complex and systemic pathology in which hyperlipidaemia is a considerable factor; the persistence of inflammation is needed for plaque evolution and destabilization and plays a decisive role in the pathogenesis and worsening of coronary artery disease (CAD).

INFLAMMATION IN ATHEROSCLEROSIS



Figure(84):Atherosclerosis and inflammation [Fioranelli M.; Bottaccioli A.; Bottaccioli F.; Bianchi M.; Rovesti M.; Rocchia M. (2018). Stress and inflammation in coronary artery disease: a review psychoneuroendocrineimmunology-based. *Frontiers in Immunology*, 9, 2031. doi:10.3389/fimmu.2018.02031]

Abbreviations in figure(84): ICAM-1: Intercellular Adhesion Molecule 1; VCAM-1: Vascular cell adhesion protein 1; NLRP3: nucleotide-binding domain and leucine-rich repeat containing

(NLR) family member pyrin domain-containing protein 3; IL-1 β : Interleukin 1 beta; IL-6: Interleukin 6.

In the afore-mentioned study of 138 hospitalized coronavirus disease 2019 (COVID-19) patients, arrhythmia was mentioned in 17% of total patients and in 16 of 36 patients admitted to the intensive care unit (ICU). Therefore, an arrhythmogenic effect of coronavirus disease 2019 (COVID-19) could be anticipated, possibly contributing to disease outcome. This may be of importance for patients with an elevated risk for cardiac arrhythmias, either secondary to acquired conditions, co-morbidities, or consequent to inherited syndromes. Management of patients with inherited arrhythmia syndromes such as Long QT syndrome (LQTS), Brugada syndrome (BrS), Short QT syndrome (SQTS), and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) in the setting of the coronavirus disease 2019 (COVID-19) pandemic may prove especially challenging. However it is worthy to define the followings: first, long QT (LQT) syndrome represents a heterogeneous family of cardiac electrophysiologic disorders characterized by QT prolongation and T-wave abnormalities on the electrocardiogram, It is commonly associated with syncope, however, sudden cardiac death can occur due to torsades de pointes, long QT (LQT) is a clinical diagnosis and should be suspected in persons on the basis of clinical presentation, family history and electrocardiogram (ECG) characteristics, advanced age, hypokalemia, a history of heart failure (HF), and structural heart disease are often factors associated with long QT (LQT) syndrome; second, the Brugada syndrome (BrS) is a form of cardiac arrhythmia, characterized by electrocardiographic ST-Segment elevation in right precordial leads that affect young male patient, predisposing to malignant ventricular arrhythmia and sudden cardiac deaths, the majority of the patients with Brugada syndrome (BrS) remain asymptomatic, however, patient can present with symptom like syncope, palpitation and aborted sudden cardiac death; third, Short QT syndrome (SQTS) is a highly malignant inherited cardiac disease characterized by ventricular tachyarrhythmias developing to syncope and sudden cardiac death, it is responsible of lethal episodes in young people, mainly infants, international guidelines establish diagnostic criteria with the presence of a $QT_c \leq 340$ ms in the electrocardiogram despite clinical diagnostic values remain controversial; fourth, Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disorder that leads to syncopal episodes related with stress or emotion and even sudden cardiac deaths. Signs and symptoms usually begin in childhood, a suspicion of Catecholaminergic

polymorphic ventricular tachycardia (CPVT) should be kept in mind when a child or an adolescent suddenly loses consciousness, especially if this happens upon physical exercise or sudden mental stress. Depending on the inherited defect included, these affected individuals may be susceptible to pro-arrhythmic effects of coronavirus disease 2019 (COVID-19)-related issues such as fever, stress, electrolyte disturbances and use of antiviral drugs. Hence, additional precautions and preventive measures are recommended, including electrocardiogram (ECG) monitoring, aggressive antipyretic (antipyretic, a substance that reduces fever) treatment, and more stringent social distancing to prevent infection. In a single center study cardiac injury was observed in 19% of hospitalized patients with coronavirus disease 2019 (COVID-19), and it was related to higher risk of inhospital mortality. Therefore, it is plausible that these individuals have an elevated risk of cardiac arrhythmias.

Myocarditis is identified as an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. Many viruses are cardiotropic, meaning they bind directly on molecular targets in the myocardium. Myocardial damage may be due to different mechanisms. In the initial phase of viral myocarditis, direct virus-mediated lysis of cardiomyocytes occurs. This is usually followed by a robust T-cell response that can develop further heart injury and ventricular dysfunction. In coronavirus disease 2019 (COVID-19), special attention has been given to the role of angiotensin converting enzyme 2 (ACE2), the binding receptor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cellular entry. Angiotensin-converting enzyme 2 (ACE2) is highly expressed in pericytes of adult human hearts, which indicates an intrinsic susceptibility of heart to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) seems to not only gain initial entry through angiotensin-converting enzyme 2 (ACE2) but also to subsequently downregulate angiotensin-converting enzyme 2 (ACE2) expression, leading to reduced conversion of angiotensin II (Ang-II) to angiotensin 1-7 (Ang-1-7). The latter physiologically mediates protective cardiovascular (CV) effects in target organs.

In autopsies of patients who died from the severe acute respiratory syndrome (SARS) outbreak in 2002, 35% of heart samples indicated the presence of viral ribonucleic acid (vRNA) in the myocardium, which in turn was combined with reduced angiotensin-converting enzyme 2

(ACE2) protein expression. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may share the same mechanism with the first severe acute respiratory syndrome coronavirus (SARS-CoV) because the two viruses are highly homologous in genome.

Myocarditis represents one of the most challenging diagnoses in cardiology. Suspicion rises with the number of criteria fulfilled. However, diagnostic certainty is depending on endomyocardial biopsy or autopsy, where histological analyses [infiltration, lymphocytes, macrophages (MΦ), and cellular inflammatory types] or molecular methods of viral genome identification can be performed.

A case study describes the autopsy of a patient with severe coronavirus disease 2019 (COVID-19) who died from sudden cardiac arrest (SCA). Interestingly, there were no obvious histological changes seen in heart tissue.

A number of mechanisms have been put forward whereby severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may cause myocardial injury. These include mechanisms involving derangement of angiotensin-converting enzyme 2 (ACE2) signal pathways [animal studies have shown that cellular angiotensin-converting enzyme 2 (ACE2) levels decrease upon severe acute respiratory syndrome coronavirus (SARS-CoV) infection], cytokine storm and myocarditis. Occurrence of myocardial involvement and severity thereof varies among patients. Myocardial damage evidenced by high cardiac markers such as high-sensitivity troponin I (hs-TnI) has been recognized and fulminant myocarditis has been reported. Early reports suppose that there are two patterns of myocardial injury with coronavirus disease 2019 (COVID-19). A retrospective cohort study in 191 patients hospitalized in Wuhan, China showed that high-sensitivity cardiac troponin I (hs-cTnI) was above the 99th percentile upper reference limit in 46% of non-survivors, and in only 1% of survivors. At day 4 after symptom onset, median high-sensitivity cardiac troponin I (hs-cTnI) levels were 8.8 pg/mL in non-survivors vs. 2.5 pg/mL in survivors. Median high-sensitivity cardiac troponin I (hs-cTnI) did not change significantly among survivors in the following days (2.5-4.4 pg/mL). In contrast, in non-survivors the median high-sensitivity cardiac troponin I (hs-cTnI) increased over time (24.7 pg/mL on day 7, 55.7 pg/mL on day 13, 134.5 pg/mL on day 19, and 290.6 pg/mL on day 22). Similar patterns were seen in D-dimer (DD), ferritin, interleukin-6 (IL-6), and lactate dehydrogenase (LDH) levels. This may also point to potential cytokine storm or secondary

hemophagocytic lymphohistiocytosis instead of an isolated myocardial injury. Other case studies of patients with cardiac symptoms suppose a different pattern of possible viral myocarditis or stress cardiomyopathy.

Acute myocarditis (AMC) and fulminant myocarditis (FMC) as well as heart failure (HF) have been reported with Middle East respiratory syndrome coronavirus (MERS-CoV) and could be expected to occur with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), given the similar pathogenicity. Two articles published in JAMA Cardiology from 2 academic hospitals in Wuhan, China, the epicenter of the coronavirus disease 2019 (COVID-19) pandemic, boost these concepts while also providing novel insights into the incidence and consequences of myocardial injury associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Shi *et al.* (2020) present a cohort study of 416 hospitalized individuals with coronavirus disease 2019 (COVID-19) confirmed by reverse transcriptase–polymerase chain reaction (rtPCR), of whom 82 (19.7%) had evidence of myocardial injury manifested by elevation of high-sensitivity troponin I (TnI) levels. Patients with myocardial injury had a significantly higher in-hospital mortality rate [42 of 82 (51.2%)] in comparison with those without myocardial injury [15 of 335 (4.5%)], and among those with myocardial injury, greater degrees of troponin I (TnI) elevation were associated with higher mortality rates. Similar recognitions were documented by Guo *et al.* (2020) in 187 patients hospitalized with laboratory-confirmed coronavirus disease 2019 (COVID-19), of whom 52 (27.8%) had myocardial injury as shown by elevated levels of troponin T (TnT). In-hospital mortality was 59.6% (31 of 52) in those with elevated troponin T (TnT) levels compared with 8.9% (12 of 135) in those with normal troponin T (TnT) levels. Of note, the highest mortality rates were seen in those with elevated troponin T (TnT) levels who had underlying cardiovascular disease (CVD) [25 of 36 (69.4%)], but mortality rates were also considerable in those with elevated troponin T (TnT) levels without prior cardiovascular disease (CVD) [6 of 16 (37.5%)]. In contrast, patients with known cardiovascular disease (CVD) without elevation of troponin T (TnT) levels had a relatively favorable but still worrisome prognosis [mortality of 13.3% (4 of 30)]. Guo *et al.* (2020) provide additional novel insights that troponin T (TnT) levels are recognizably associated with levels of C-reactive protein (CRP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), thus binding myocardial injury to severity of inflammation and ventricular dysfunction. It is valuable to show that N-terminal (NT)-pro hormone BNP (NT-proBNP) is a non-active prohormone that is released from the same

molecule that produces brain natriuretic peptide (BNP). Both brain natriuretic peptide (BNP) and N-terminal (NT)-pro hormone BNP (NT-proBNP) are released in response to changes in pressure inside the heart. These changes can be related to heart failure (HF) and other cardiac problems. Guo *et al.* (2020) also show progressive serial increases in both troponin T (TnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels during hospitalization in patients who follow a deteriorating clinical course toward death, whereas those with a more favorable outcome with less severe illness, successful treatment, and hospital discharge show stable low levels of these biomarkers. Shi *et al.* (2020) and Guo *et al.* (2020) report notably similar characteristics of patients who develop myocardial injury [as assessed by elevated levels of troponin I (TnI) or troponin T (TnT)] associated with coronavirus disease 2019 (COVID19). Patients at risk of myocardial injury are older and have a higher prevalence of hypertension (HTN), coronary artery disease (CAD), heart failure (HF), and diabetes mellitus (DM) than those with normal levels of troponin I (TnI) or troponin T (TnT). Patients with myocardial injury also have evidence of more severe systemic inflammation, involving greater leukocyte counts and elevated levels of C-reactive protein (CRP) and procalcitonin (PCT) [procalcitonin (PCT), a protein that consists of 116 amino acids, is the peptide precursor of calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Procalcitonin arises from endopeptidase-cleaved preprocalcitonin] as well as high levels of other biomarkers of myocardial injury and stress, such as elevated creatine kinase (CK) [creatinine kinase (CK) is an enzyme found in the heart, brain, skeletal muscle, and other tissues. Increased amounts of creatine kinase (CK) are released into the blood when there is muscle damage. This test measures the amount of creatine kinase (CK) in the blood], myoglobin (a red protein containing haem, which carries and stores oxygen in muscle cells. It is structurally similar to a subunit of haemoglobin), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Further, patients who develop myocardial injury with coronavirus disease 2019 (COVID-19) have clinical evidence of higher acuity, with a higher incidence of acute respiratory distress syndrome (ARDS) and more frequent need for assisted ventilation than those without myocardial injury. Thus, a consistent picture emerges from these 2 reports that older patients with preexisting cardiovascular (CV) comorbidities and diabetes mellitus (DM) are prone to develop a higher acuity of illness after contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) associated with higher risk of myocardial injury and a noticeably

higher short-term mortality rate. Yang and Zin (2020) discussed the collision between the acute coronavirus disease 2019 (COVID-19) epidemic and the underlying cardiovascular (CV) epidemic in China. They acknowledged the observations that patients with preexisting cardiovascular disease (CVD) were susceptible to the most adverse complications of coronavirus disease 2019 (COVID-19), including death. Importantly, they also reasonably emphasized that there had thus far been insufficient attention to understanding the mechanisms responsible for these outcomes beyond the obvious recognition that severe infections could destabilize patients with coronary artery disease (CAD) or heart failure (HF). The observations of Shi *et al.* (2020) and Guo *et al.* (2020) considering the important association of myocardial injury (MI) with adverse outcomes began to provide insights into other possible mechanisms, including demand ischemia that devolved into myocardial injury or plaque disruption stimulated by intense systemic inflammatory stimuli. As with other coronaviruses (CoVs), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can elicit the intense release of multiple cytokines and chemokines that can lead not only to vascular inflammation and plaque instability but also to myocardial inflammation. Direct viral infection of the myocardium is another potential causal pathway of myocardial damage and one that requires further investigation. It is noteworthy that the articles from China by Shi *et al.*, (2020) Guo *et al.* (2020), and Yang and Zin (2020) address the unique remarked affinity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) for the host angiotensin-converting enzyme 2 receptor (ACE2R), which has been shown previously for other coronaviruses (CoVs), raising the probability of direct viral infection of vascular endothelium and myocardium. It is thus likely that in some patients with or without preexisting cardiovascular disease (CVD), coronavirus disease 2019 (COVID-19)–associated myocardial injury could represent myocarditis. The well-documented case of acute myocarditis following a coronavirus disease 2019 (COVID-19)–associated respiratory infection in a 53-year-old Italian woman with no previous heart disease, also reported in this issue by Inciardi *et al.*, supports this hypothesis. The association of myocardial injury with outcomes of coronavirus disease 2019 (COVID-19) in the Chinese cohorts represent early data from patients hospitalized at the outset of the epidemic in Wuhan, during which a rapidly escalating number of patients with previously unknown serious respiratory diseases was beginning to stretch and overwhelm local healthcare systems.

It has been presumed that, in individuals with coronavirus disease 2019 (COVID-19), microvascular damage occurring in the heart causes perfusion defects, vessel hyperpermeability and vasospasm, causing myocardial injury.

Despite not being particularly lethal, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is very contagious. In a published clinical cohort of patients with coronavirus disease 2019 (COVID-19), they showed that acute cardiac injury, shock, and arrhythmias were present in 7.2%, 8.7%, and 16.7% of patients, respectively, with higher prevalence amongst patients requiring intensive care. In this report, myocardial injury biomarkers levels were significantly higher in patients requiring intensive care unit (ICU) admission than in those not treated in the intensive care unit (ICU) (median creatine kinase (CK)-MB level 18 U/l vs 14 U/l; $P < .001$; and high-sensitivity cardiac troponin I [hs-cTnI] level 11.0pg/mL vs 5.1pg/mL; $P = .004$), supposing that individuals with severe symptoms usually have complications including acute myocardial injury. Overall, arrhythmia rate was also more frequent in intensive care unit (ICU) patients (44.4% vs 6.9%; $P < .001$). Despite the relevance of these initial data, the authors did not provide any arrhythmia classification or definition. A study from Shi *et al.* (2020) evaluated a single-center cohort of 416 patients hospitalized due to coronavirus disease 2019 (COVID-19). He observed that cardiac lesion, defined by high-sensitivity cardiac troponin I (hs-cTnI) >99 th percentile of on admission, was present in 19.7%, with median value of 0.19 (0.08-1.12) μ g/L in this group. Compared with those without cardiac injury, patients with cardiac injury required more noninvasive ventilation (46.3% vs 3.9%; $P < .001$) and invasive mechanical ventilation (IMV) (22.0% vs 4.2%; $P < .001$), and also had a higher mortality (51.2% vs 4.5%; $P < .001$). It is notable that the elevated troponin (Tn) group was older and significantly more ill, but after adjustment for all the possible confounding factors, still the cardiac injury was a predictor of mortality (HR: 4.26; 95% CI: 1.92-9.49).¹ In another small report, Huang *et al.* (2020) demonstrated that severe acute respiratory syndrome coronavirus-2 (SAR-SCoV-2) associated myocardial injury occurred on 5 out of 41 patients, and was manifested as an increase in high-sensitivity cardiac troponin I (hs-cTnI) levels (>28 pg/mL). Among these five patients, intensive care unit (ICU) management was required in four, revealing the severe nature of the myocardial injury in patients with coronavirus disease 2019 (COVID-19). In a study by Guo *et al.* (2020), 187 patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) positive were analyzed, stratified by the level of troponin (Tn), which was elevated in 27.8%. During hospitalization, patients with

elevated troponin T (TnT) levels developed more frequently complications as acute respiratory distress syndrome (ARDS) (57.7% vs 11.9%), malignant ventricular arrhythmias (VAs) (11.5% vs 5.2%), acute coagulopathy (65.8% vs 20.0%), and acute kidney injury (AKI) (36.8% vs 4.7%), compared with those with normal troponin T (TnT) levels. But the most impressive recognition is that mortality was significantly higher in patients with elevated plasma troponin T (TnT) levels than in patients with normal troponin T (TnT) levels (59.6% vs 8.9%). Contrary to the above mentioned studies Zhou *et al.* (2020) comparing survivors and non-survivors in a cohort of 191 patients from two hospitals in Wuhan, found that, despite more frequent in non-survivors (46% vs 1%; $P < .001$), high-sensitivity cardiac troponin I (hs-cTnI) $> 28 \text{ pg/mL}$ was not associated with mortality in multivariate analysis. Acute myocarditis, as well as ventricular arrhythmias (VAs) might represent the first clinical manifestation of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. In the epicenter of the current Italian epidemic, sudden cardiac death (SCD) likely occurred in many nonhospitalized patients with mild symptoms who were found dead home while in quarantine. Myocardial biomarkers should be evaluated in all patients with coronavirus disease 2019 (COVID-19) for risk stratification and prompt intervention. Even after hospital discharge, there should consider that myocardial injury might result in atrial or ventricular fibrosis, the substrate for subsequent cardiac arrhythmias. The extent of myocardial scar, as assessed with cardiac magnetic resonance, might be a powerful tool to better stratify the arrhythmic risk in patients recovered from coronavirus disease 2019 (COVID-19) who had evidence of myocardial injury at the time of infection. Another relevant aspect of coronavirus disease 2019 (COVID-19) infection is that early diagnosis can be confounded in patients with chronic cardiac conditions, once the most frequent symptoms, like fatigue (51%, 95% CI: 34%-68%), dyspnea (30%, 95% CI: 21%-40%), and cough (67%, 95% CI: 59%-76%)²⁵ can also be manifestations of acute decompensated heart failure (ADHF) or arrhythmic syndrome. Corroborating this concern, the National Health Commission of China (NHC) reported that among severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection confirmed cases, cardiovascular (CV) symptoms were the first presentation in some patients. The problem behind these atypical presentations is that patients suffering from heart palpitations and chest tightness rather than respiratory symptoms, such as fever and cough, had a delayed coronavirus disease 2019 (COVID-19) diagnosis. Still according to the National Health Commission of China (NHC), among the people who died from coronavirus disease 2019

(COVID-19), 11.8% had substantial heart damage, with elevated troponin I (TnI) levels or cardiac arrest during hospitalization. Explanatory theories regarding coronavirus disease 2019 (COVID-19) cardiovascular (CV) affection postulate that chronic cardiovascular diseases (CVDs) may become unstable in the setting of a viral infection as a consequence of the imbalance between the infection-induced increase in metabolic demand and reduced cardiac reserve. This imbalance, concurrent with an accentuated inflammatory response and myocardial damage, could heighten the risk of acute coronary syndromes (ACSs), heart failure (HF), and arrhythmias. The deleterious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection myocardial effects could also be perpetuated by the prompt and severe downregulation of myocardial and pulmonary angiotensin-converting enzyme 2 (ACE2) pathways, thereby mediating myocardial inflammation, lung edema, and acute respiratory failure (ARF). Angiotensin-converting enzyme 2 (ACE2) is broadly expressed not only in the lungs but also in the cardiovascular (CV) system and, therefore, angiotensin-converting enzyme 2 (ACE2)-related signaling pathways might even have a role in heart injury. Other proposed mechanisms of myocardial injury include a cytokine storm triggered by an imbalanced response by type 1 and 2 T-helper cells, strong interferon (IFN)-mediated immunopathological events, and respiratory dysfunction and hypoxemia caused by coronavirus disease 2019 (COVID-19), leading to damage to myocardial cells. Therapeutic use of corticosteroids (CSs), in this context, would further augment the possibility of adverse cardiovascular (CV) events. Regarding hypoxemia caused by coronavirus disease 2019 (COVID-19), it is relevant to highlight that this condition can trigger atrial fibrillation (AF), which is the most common arrhythmia among elderly individuals, and that atrial fibrillation (AF) can become persistent even before pulmonary improvement. In addition, the systemic inflammatory response would make anticoagulation therapy for atrial fibrillation (AF) very complex.

Patients with pre-existing coronary artery disease (CAD) and those with risk factors for atherosclerotic cardiovascular disease (CVD) are at an increased risk of developing an acute coronary syndrome (ACS) during acute infections, as demonstrated previously in epidemiologic and clinical studies of influenza and other acute inflammatory conditions. This could result from imbalance between oxygen supply and demand in the acute setting, so that the troponin (Tn) elevation may be interpreted as a type 2 myocardial infarction (MI). Reduced oxygen supply in patients with coronavirus disease 2019 (COVID-19) is typically caused by hypoxic respiratory

failure, a feature that is more common in deceased patients than in patients who recover and is a marker of disease severity. On the other hand, infectious states are usually accompanied by fever, tachycardia and endocrine dysregulation, which cause a noticeable increase in myocardial oxygen demand. Moreover, hypoxemia also causes excessive intracellular calcium with consequent cardiac myocyte apoptosis. By definition, a type 2 myocardial infarction (MI) can occur with or without underlying coronary artery disease (CAD). However, considering the higher prevalence of elevated troponin (Tn) in patients with coronavirus disease 2019 (COVID-19) with previous cardiovascular disease (CVD), it is possible that the type 2 myocardial infarction (MI) when underlying stable coronary artery disease (CAD) is unmasked by the acute infection. Type 1 myocardial infarction (MI), caused by plaque rupture with thrombus formation, may also be precipitated by coronavirus disease 2019 (COVID-19). Circulating cytokines secreted during a severe systemic inflammatory stress could cause atherosclerotic plaque instability and rupture. In addition, the suppression of angiotensin-converting enzyme 2 (ACE2) expression and angiotensin II (Ang II) increase may elevate cardiovascular (CV) risk through mechanisms such as oxidative stress (OS), endothelial dysfunction, and vasoconstriction. Moreover, as angiotensin-converting enzyme 2 (ACE2) is expressed in vascular endothelial cells (VECs), direct viral vascular infection leading to plaque instability may also play a role in type 1 myocardial infarction (MI) in patients with coronavirus disease 2019 (COVID-19). The occurrence of acute coronary syndrome (ACS) and myocardial infarction (MI) in infected patients during the first severe acute respiratory syndrome (SARS) outbreak has been described. However, there are very seldom data about symptoms and electrocardiogram (ECG or EKG) changes related to myocardial infarction (MI) in coronavirus disease 2019 (COVID-19). Chest pain has been broadly reported and is also associated with cardiac injury, but it has a very low specificity due to the primary lung disease (i.e. pleuritic pain). Interestingly, Guo *et al.* (2020) reported that on admission no patients showed evidence of acute myocardial infarction (MI).

Another crucial aspect to be discussed is about chloroquine cardiovascular (CV) side effects since this is one of the promising drugs that have been tested in patients with coronavirus disease 2019 (COVID-19). It is well-reported that long-term chloroquine use may increase depolarization length duration and Purkinje fiber refractory period (functional refractory period of Purkinje tissue exceeds that of the ventricular muscle, an early premature discharge in the Purkinje system or an impulse transmitted from the A-V node could not excite the ventricles

sufficiently early), ultimately leading to atrioventricular nodal and/or His system malfunction. As an antimalarial drug, both chloroquine and hydroxychloroquine (HCQ) are accumulated in lysosomes, directly inhibiting phospholipase activity, inducing cytoplasmic inclusion body formation (inclusion bodies, sometimes called elementary bodies, are nuclear or cytoplasmic aggregates of stable substances, usually proteins. They typically represent sites of viral multiplication in a bacterium or a eukaryotic cell and usually consist of viral capsid proteins), increasing lysosomal pH, and causing protein inactivity. Due to these properties, drug-induced atrial and ventricular arrhythmias (VAs) have been associated with their use. The most usual electrocardiographic alteration is fascicular block, which can lead to advanced types of atrioventricular block, generally associated with syncope. However, fascicular blocks were previously referred to as hemiblocks, but the latter term has been deprecated. The left bundle branch is subdivided into the following two fascicles:

1-The anterior (anterosuperior) fascicle, which delivers the electrical impulse to the anterior wall of the left ventricle;

2-The posterior (posteroinferior) fascicle which delivers the electrical impulse to the posterior and inferior walls of the left ventricle.

Anatomical or functional block in the anterior fascicle leads to left anterior fascicular block. Similarly, left posterior fascicular block is due to block in the posterior fascicle. Approximately 5-10% of all individuals have a third fascicle-the median or centroseptal fascicle-which gives off Purkinje fibers to the interventricular septum.

Hydroxychloroquine (HCQ) can also induce QT interval prolongation, an extremely rare but potential fatal side effect, due to the risk of induced polymorphic ventricular tachycardia (PVT) and sudden cardiac death (SCD). It is worthy to describe that the QT interval is a measurement made on an electrocardiogram (ECG) used to assess some of the electrical properties of the heart. It is calculated as the time from the start of the Q wave to the end of the T wave, and approximates to the time taken from when the cardiac ventricles start to contract to when they finish relaxing. An abnormally long or abnormally short QT interval is associated with an increased risk of developing abnormal heart rhythms and sudden cardiac death (SCD). The proposed mechanism by which hydroxychloroquine (HCQ) causes QT interval prolongation is

not well understood. Capel *et al.* (2015) demonstrated, in guinea pig sinoatrial node myocytes, an inhibitory effect of the hydroxychloroquine (HCQ) on the hyperpolarization-activated current ion channels (also known as funny current channels), along with delayed rectifier potassium currents, and L-type calcium ion currents. Inhibitory effects on pacemaker cells were recognized to cause delayed rates in depolarization leading to decreased heart rates. These findings may associate with a supposed mechanism by which refractory action potentials in cardiac myocytes may cause prolongation of QT interval due to delayed depolarization and repolarization from abnormal ion currents. It noticeable to describe pacemaker cells as the cells that create these rhythmic impulses, setting the pace for blood pumping, are called , and they directly control the heart rate. They make up the cardiac pacemaker, that is, the natural pacemaker of the heart. In most humans, the concentration of pacemaker cells in the sinoatrial (SA) node is the natural pacemaker, and the resultant rhythm is a sinus rhythm. QT prolongation in individual medical therapy is not always predictable, dose adjustments and/or additional monitoring with electrocardiograms (ECGs) may be proper in some cases. Hydroxychloroquine (HCQ) proarrhythmic risk must be monitored in patients with underlying cardiovascular (CV) or renal disorders, and high caution should be posed in the case of electrolyte imbalance, dysrhythmias or concurrent use of QTc-prolonging drugs.

13.Liver Injury

The liver helps broadly in the maintenance of metabolic homeostasis by processing dietary amino acids (AAs), carbohydrates, lipids, and vitamins; metabolizing cholesterol and toxins; producing clotting factors; and storing glycogen. Injury to the liver parenchyma correlated with an influx of acute or chronic inflammatory cells is called hepatitis. Cirrhosis refers to a progressive, diffuse, fibrosing, nodular condition that disrupts the entire normal architecture of the liver. Fibrosis previously was believed to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence proposes that fibrosis may be reversible in some patients with chronic hepatitis B after antiretroviral therapy. Any chronic insult to the liver can progress to cirrhosis. Although numerous pathophysiologic mechanisms of injury are present, the final common pathway is persistent wound healing causing hepatic parenchymal fibrosis. In most individuals, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically. When complications

of cirrhosis occur, they typically are in relation with impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma.

Jaundice is a medical condition with yellowing of the skin or whites of the eyes, arising from excess of the pigment bilirubin and typically caused by obstruction of the bile duct, by liver disease, or by excessive breakdown of red blood cells. Numerous liver diseases are accompanied by jaundice caused by augmented levels of bilirubin in the body. Bilirubin is the result of degradation of hemoglobin of dead red blood cells (RBCs) which are normally removed by the liver and excreted via bile. In hepatitis, inflammation of the liver, is caused by different viruses, but also some toxic substances, autoimmune diseases and inherited conditions.

Fatty liver (steatosis) is a common histological finding in human liver biopsies which is usually attributed to the effects of alcohol excess, obesity, diabetes, or drugs. The distribution of lipid can be macrovesicular, with hepatocytes being distended by a single vacuole displacing the nucleus or it can be microvesicular with numerous droplets surrounding a centrally placed nucleus. Widespread microvesicular steatosis is characteristically an acute condition in which impairment of fatty acid β -oxidation² reflects a more general perturbation of mitochondrial and ribosomal function both within and outside the liver. Regardless of the etiology, microvesicular steatosis is broadly acknowledged as having a poor prognosis with death caused by both liver failure and extra-hepatic causes. Macrovesicular steatosis, by contrast, is associated with a more long-standing disturbance of hepatic lipid metabolism and has been referred as a benign condition. There is now little doubt that macrovesicular steatosis of both alcohol and nonalcoholrelated etiologies is associated with the development of more advanced disease: necroinflammation (steatohepatitis), fibrosis, and cirrhosis.

How might oxidative stress (OS) and endotoxin/cytokines interpret the association between the severity of steatosis and advanced disease? One probability is that these factors play independent roles in the pathogenesis of steatosis and necroinflammation/fibrosis. Free fatty acids (FFAs), which are able to initiate oxidative stress (OS), also offer the substrate for elevated synthesis of triglyceride (TG); in fact, any induction of oxidative stress (OS), by damaging mitochondrial deoxyribonucleic acid (DNA), may result in an elevation in substrate supply through impaired mitochondrial β -oxidation of fatty acids (FAs). The peroxidation end-products, malondialdehyde

and 4-hydroxynonenal, may also contribute to the pathogenesis of steatosis by impairing the export of triglyceride (TG) from the liver by forming adducts with tubulin in microtubules.

A second and more interesting interpretation for the association between steatosis severity and the risk of advanced disease is that the presence of steatosis influences the liver's response to at least some of the notable triggers of necroinflammation and/or fibrosis. It is clear that the more fat in the liver, the greater the pool of substrate available for any oxidative stress (OS) to initiate lipid peroxidation. Studies have revealed a striking relationship between the degree of lipid peroxidation and the severity of steatosis in both animal and human models with alcohol and nonalcohol-related fatty liver. The increase in lipid peroxidation would generate more possible reactive and cytotoxic intermediates which are able to induce inflammation and fibrosis at least in part via activation of nuclear factor- κ B (38) (NF- κ B38) and/or immunological mechanisms. Studies reveal a number of inflammatory mediators have been shown to contribute to the progression of chronic liver disease (CLD), many of which are either targets or activators of nuclear factor- κ B (NF- κ B). Nuclear factor- κ B (NF- κ B) is a key transcriptional regulator of the inflammatory response, and plays an important role in the regulation of inflammatory signaling pathways in the liver. First, nuclear factor- κ B (NF- κ B) is activated in virtually every chronic liver disease (CLD), involving alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), viral hepatitis and biliary liver disease. Second, nuclear factor- κ B (NF- κ B) regulates multiple essential functions in hepatocytes, Kupffer cells and hepatic stellate cells (HSCs). Third, genetic inactivation of different nuclear factor- κ B (NF- κ B) signaling components leads to liver phenotypes that involve spontaneous injury, fibrosis and carcinogenesis suggesting that nuclear factor- κ B (NF- κ B) makes a crucial contribution to liver homeostasis and wound-healing processes.

Authors presume that the relationship between the severity of steatosis and the risk of advanced liver disease is at least, in part, illustrated by steatosis increasing the sensitivity of the liver to the triggers of necroinflammation and fibrosis common to both alcoholic steatohepatitis and non-alcoholic steatohepatitis (NASH), as follows: oxidative stress, endotoxin, and possibly hypoxia.

The term acute liver failure (ALF) is usually applied as a generic expression to define individuals presenting with or developing an acute episode of liver dysfunction. It is characterised by a deterioration in liver function tests, and possibly associated with dysfunction in other organs.

Acute liver failure (ALF) is frequently, but often incorrectly used to describe both acute deterioration in liver function in patients with chronic liver disease (a condition that should be termed acute-on-chronic liver failure [AoCLF]), or liver involvement in systemic disease processes. Liver injury secondary to alcohol, which presents as alcoholic hepatitis, and other forms of acute-on-chronic liver failure (AoCLF), can be difficult to distinguish from acute liver failure (ALF) on occasion. However, there are clear differences, and different forms of management and treatment are needed.

In the context of hepatological practice, acute liver failure (ALF) indicates to a highly particular and seldom syndrome, characterised by an acute abnormality of liver blood tests in a person without underlying chronic liver disease (CLD). The disease process is associated with development of a coagulopathy of liver aetiology, as opposed to the coagulation disturbance seen in sepsis, and clinically apparent altered level of consciousness due to hepatic encephalopathy (HE). The condition of patients who progress coagulopathy, but do not have any alteration to their level of consciousness is identified as acute liver injury (ALI). Thus, the term acute liver failure (ALF) is adequately used to define patients who develop both coagulopathy and altered mentation and will be the subject of these clinical practice guidelines. The characteristics of coagulopathy, increased serum transaminases, abnormal bilirubin and altered levels of consciousness may be observed in individuals with a variety of systemic disease processes. Therefore, if there is no primary liver insult, these patients should be considered to have a secondary liver injury and not acute liver failure (ALF); management should concentrate on the treatment of any underlying disease processes.

The clinical course of acute liver failure (ALF) is initiated with a severe acute liver injury (ALI). This is characterised by a two- to three times elevation of transaminases (as a marker of liver damage) associated with impaired liver function, i.e., jaundice and coagulopathy, in a patient without a chronic liver disease (CLD). This clinical description originated from observations of drug related hepatotoxicity, but is applicable to all presentations.

Acute liver failure (ALF) is an uncommon but complex and often catastrophic disease manifesting as coagulopathy (International Normalized ratio, INR \geq 1.5) and altered mental status (hepatic encephalopathy, HE) due to rapid decline of liver function in a patient without preexisting liver disease. The onset and duration of disease must be less than 26 weeks

duration.¹ Acute liver failure (ALF) is a challenging medical emergency requiring immediate attention. Progression is associated with multiple organ failure and need for urgent liver transplant, a life-saving option for many acute liver failure (ALF) patients. The etiology of acute liver failure (ALF) plays an important role in the management and survival of patients with acute liver failure (ALF). Terms previously used to describe acute liver failure (ALF) involved fulminant hepatic failure, fulminant hepatitis or acute hepatic necrosis. Others have described subtypes based on the time interval of onset of jaundice to the development of hepatic encephalopathy (HE), which may be of some prognostic consideration. Thus, hyperacute liver failure (< 7 days), acute (7-21 days) and subacute (> 21 days and < 26 weeks) have been supposed. However, this terminology has not been generally adopted. Generally, the more acute the onset of acute liver failure (ALF), the less hepatic fibrosis and better chances of hepatic regeneration, however, with greater incidence of cerebral edema.

Advanced acute liver failure (ALF) frequently includes dysfunction of multiple organ systems. The presenting symptoms of acute liver failure (ALF) are usually non-specific and involve fatigue, malaise, anorexia, abdominal pain, fever and jaundice. These symptoms develop in no special order to coagulopathy preceding the development of encephalopathy, both of which are the hallmark of acute liver failure (ALF). Acute liver failure (ALF) should be managed in an intensive care unit (ICU) at a tertiary care center because of the unpredictable and rapid manner in which patients may deteriorate. Frequent neurological and hemodynamic monitoring is of primary importance.

The liver has a central role in the synthesis of most coagulation factors and some inhibitors of coagulation and fibrinolysis. Deficiencies of fibrinogen, factors II, V, VII, IX and X, and platelet are often present in acute liver failure (ALF). Reduced levels of coagulation inhibitors such as antithrombin, protein C, and protein S fail to completely balance their effect on coagulopathy. Consumption of clotting factors and platelets occur particularly when associated with disseminated intravascular coagulation (DIC). These derangements are manifested as prolongation of prothrombin time, which is widely used as an indicator of the severity of hepatic injury. Infusion of fresh frozen plasma is indicated only for control of active bleeding or during invasive procedures such as insertion of intracranial pressure monitor, to maintain an international normalised ratio (INR < 1.5). Cryoprecipitate can be administered if fibrinogen

levels are < 100 mg/dL. Platelet transfusion is indicated only to aid in controlling active bleeding or during invasive procedures if the count is < 50 x 10⁹/L or prophylactically if < 10-20 x 10⁹/L. Increased intrahepatic cholestasis of pregnancy (ICP, formerly known as obstetric cholestasis or OC, is a liver disorder that occurs in pregnancies, where the normal flow of bile out of the liver is reduced) due to volume overload is a concern with liberal transfusion of blood products. Factor VII replacement is promising. Vitamin K, 5 to 10 mg subcutaneous should be administered to correct any underlying vitamin K deficiency. Risk factors for gastrointestinal (GI) bleeding involve mechanical ventilation for more than 48 hours and coagulopathy in critically ill acute liver failure (ALF) patients. Other risk factors include renal failure, sepsis and shock. Proton pump inhibitors and H₂ blockers have been proven to be effective in decreasing the risk of significant bleeding.

Infectious complications are a leading cause of mortality in acute liver failure (ALF) individuals. High vigilance with blood cultures, urine cultures and sputum cultures must be performed at admission and as indicated clinically. Particularly, venous line infection has to be looked for in these patients. All acute liver failure (ALF) cases with ascites, unexplained fever and leukocytosis need a diagnostic paracentesis. Empirical broad-spectrum antibiotics should be administered to patients with acute liver failure (ALF) who develops signs of systemic inflammatory response syndrome, or unexplained progression to higher grades of encephalopathy.

Liver transplantation is the only intervention with known survival benefit in patients with acute liver failure (ALF). The outcome of liver transplantation is defined by the pretransplant condition of the patient and the quality of graft used. Five year survival post transplant for acute liver failure (ALF) (70%) has been lower than transplantation for chronic liver failure (85%) due to the emergent nature and condition of the recipients. Comorbid cardiovascular (CV), respiratory and systemic conditions have a negative affect on patient outcomes. Psychosocial and family support for compliance and substance abuse have important role in patient evaluation for transplant.

The term liver function tests (LFTs) is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly. Although liver function tests (LFTs) may

not correlate exactly with hepatic function, explaining abnormal biochemical patterns in conjunction with the clinical picture may suppose certain liver diseases. When a liver abnormality is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time (PT) test should be done. Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (Alp), and γ -glutamyltransferase (GGT); total, direct, and indirect serum bilirubin; and serum albumin (alb). It is worthy to reveal that gamma-glutamyl transferase (GGT) is an enzyme that is found in many organs throughout the body, with the highest concentrations found in the liver. Gamma-glutamyl transferase (GGT) is elevated in the blood in most diseases that cause damage to the liver or bile ducts. This test measures the level of gamma-glutamyl transferase (GGT) in a blood sample. Normally, gamma-glutamyl transferase (GGT) is present in low levels, but when the liver is injured, the gamma-glutamyl transferase (GGT) level can rise. Gamma-glutamyl transferase (GGT) is usually the first liver enzyme to rise in the blood when any of the bile ducts that carry bile from the liver to the intestines become obstructed, for example, by tumors or stones. This makes it the most sensitive liver enzyme test for detecting bile duct problems. However, the gamma-glutamyl transferase (GGT) test is not very specific and is not useful in differentiating between various causes of liver damage because it can be elevated with many types of liver diseases, such as liver cancer and viral hepatitis, as well as other non-hepatic conditions, such as acute coronary syndrome. For this reason, the gamma-glutamyl transferase (GGT) test is not recommended for routine use by itself. However, it can be useful in conjunction with other tests and in determining the cause of a high alkaline phosphatase (ALP) level, another enzyme found in the liver. Both gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) are increased in liver diseases, but only alkaline phosphatase (ALP) will be increased with diseases affecting bone tissue. Therefore, gamma-glutamyl transferase (GGT) can be used as a follow up to an elevated alkaline phosphatase (ALP) to help determine if the high alkaline phosphatase (ALP) result is due to liver or bone disease. The alanine transaminase (ALT) is thought to be the most cost-effective screening test for describing metabolic or drug-induced liver injury (DILI), but like other liver function tests (LFTs), it is of limited use in predicting degree of inflammation and of no use in evaluating severity of fibrosis.

13.1 Liver Injury in COVID-19 Infection

Reports on coronavirus disease 2019 (COVID-19) infection shed light that beyond severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a complex course of the illness or even viral infection itself can cause involvement of other organs and multiorgan failure. The liver is the primary organ for detoxification and metabolism, and maintaining an optimal function is urgent to engage all available therapeutic modalities in the management of coronavirus disease 2019 (COVID-19). Abnormal liver function needs clinical estimation, continuous surveillance and, possibly, particular medication. Emerging data from small clinical case studies have suggested that liver injury in coronavirus disease 2019 (COVID-19) is often observed, but the extent and underlying mechanisms remain undetermined. In a report by Chen *et al.* (2020) (5%) of coronavirus disease 2019 (COVID-19) patients progressed acute liver injury (ALI) during the course of the disease of whom 10 (76.9%) passed away. Although the numbers are small, but this transfer a noticeable message on coronavirus disease 2019 (COVID-19) patients with hepatic dysfunction.

The liver does an essential function in host defense against microbial agents and is included in most systemic infections as it receives both the portal and systemic circulation. Certain viruses lead to a direct cytopathic impact on hepatocytes and cholangiocytes although, in most conditions, the pathogenesis looks multifactorial. It was reported that severe acute respiratory syndrome coronavirus (SARS-CoV) could result in direct cytopathic liver injury rather than stimulating cellular stress from low oxygen supplies or cytokines as observed in sepsis. Autopsy studies in patients demonstrated that severe acute respiratory syndrome coronavirus (SARS-CoV) was revealed in 41% of the liver tissue, with a maximum viral load of 1.6×10^6 copies/g of tissue. The pathological results of liver biopsy specimens from severe acute respiratory syndrome (SARS) patients indicated hepatocellular necrosis (death of liver cells), mitoses, cellular infiltration, and fatty degeneration. In a notable study of autopsy analysis of liver tissue from a patient with coronavirus disease 2019 (COVID-19), moderate microvesicular steatosis and mild inflammation in the lobular and portal area was recorded. However, this pattern of histological injury is not particular for one etiology but can also be recognized during sepsis or drug-induced liver injury (DILI). It is important to refer that during sepsis, the liver plays a key role. It is implicated in the host response, engaging in the clearance of the infectious

microbes/products. Sepsis also triggers liver damage through hemodynamic alterations or through direct or indirect assault on the hepatocytes or through both. Accordingly, liver dysfunction stimulated by sepsis is realized as one of the components that contribute to the severity of the illness. However, Sands *et al.* (1997) defined liver failure as a combination of a total bilirubin level of greater than 2 mg/dL ($> 34 \mu\text{mol/L}$) and either an alkaline phosphatase (Alp) or serum aminotransferase (AST) level of greater than twice the normal value. Drug-induced liver injury (DILI; also known as drug-induced hepatotoxicity) is resulted from medications (prescription or OTC), herbal and dietary supplements (HDS), or other xenobiotics that cause abnormalities in liver tests or in hepatic dysfunction that cannot be interpreted by other causes. There are two types of drug-induced liver injury (DILI): intrinsic and idiosyncratic. Intrinsic drug-induced liver injury (DILI) refers to liver toxicity induced by a drug in a predictable and dose-related manner; idiosyncratic drug-induced liver injury (DILI), which occurs less frequently, is associated with a less consistent dose-toxicity relationship and a more varied presentation.

Hepatic distribution of angiotensin-converting enzyme 2 (ACE2) is distinctive. It is highly expressed in the endothelial layer of small blood vessels, but not in the sinusoidal endothelium. A considered study found a higher expression of angiotensin-converting enzyme 2 (ACE2) cell surface receptor in cholangiocytes (59.7%) than hepatocytes (2.6%). The level of angiotensin-converting enzyme 2 (ACE2) in cholangiocytes was similar to type 2 alveolar cells of the lungs, referring to that the liver could be a possible target for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Immunohistochemistry stains for angiotensin-converting enzyme 2 (ACE2) were negative on Kupffer cells, T and B lymphocytes. Other studies have noticed that angiotensin-converting enzyme 2 (ACE2) expression in the cell clusters of cholangiocytes was significantly higher than that in the hepatocytes population (59.7% vs. 2.6%). The authors concluded that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may directly bind to angiotensin-converting enzyme 2 (ACE2) positive cholangiocytes, but not hepatocytes, to reveal a cytopathic effect. Cholangiocytes are involved in many aspects of liver physiology, involving regeneration and adaptive immune response mechanisms, and the disruption of cholangiocyte function can develop hepatobiliary damage. This is supported by cholestatic markers, including gamma-glutamyl transferase (GGT), that can be found in some, but not all, case series of coronavirus disease 2019 (COVID-19). Notably, a review done by Zhang *et al.*

(2020) reported data with gamma-glutamyl transferase (GGT) elevations in 54% of infected individuals with coronavirus disease 2019 (COVID-19). In a human organoid model of liver ductal organoids, permissiveness to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was seen. Viral infection destructed the barrier and bile acid transporting functions of cholangiocytes through dysregulation of genes involved in tight junction formation and bile acid transportation, boosting the susceptibility of cholangiocytes in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-related liver injury.

Dysregulation of the innate immune response can be one manifestation of liver injury in coronavirus disease 2019 (COVID-19). Patients with coronavirus disease 2019 (COVID-19) show noticeable activation of inflammatory markers, involving abnormal concentrations of C-reactive protein (CRP), lymphocytes, neutrophils and cytokines, especially interleukin-6 (IL-6). These mechanisms may contribute to pulmonary and extrapulmonary injuries and the control of cytokine dysregulation at an early stage could be of benefit to control the disease progression. Hepatic inflammation including activation of innate immune cells and the production of cytokines is a well-established driver of liver injury from various causes. In some of the available case series of coronavirus disease 2019 (COVID-19), a relationship between lymphopenia and liver injury was realized and C-reactive protein (CRP) 20 mg/L and a lymphocyte count $<1.1 \times 10^9/L$ were independent risk factors for liver injury. Of note, lymphopenia in coronavirus disease 2019 (COVID-19) studies was reportedly seen in 63% to 70.3% of patients and those with lower lymphocyte counts more susceptible to fatal outcomes.

Many articles reported abnormal levels of aminotransferases in patients with coronavirus disease 2019 (COVID-19). A systematic review and meta-analysis on liver function test (LFT) abnormalities provided a pooled elevation of aspartate aminotransferase (AST) in 33.3% and alanine aminotransferase (ALT) in 24.1% of patients. Many authors across different studies reported a correlation between the severity of coronavirus disease 2019 (COVID-19) and the degree of liver dysfunction. In one retrospective study, one patient suffered from severe hepatitis with alanine aminotransferase (ALT) of 7590 U/L and aspartate aminotransferase (AST) of 1445 U/L. In a report from Shanghai, 50.7% of patients showed elevated liver function tests (LFTs) at the time of hospitalization. Of interest, these were more possibly to have a moderate-to-highgrade fever when compared with the patients with normal liver function test (LFT) (44% vs. 27.4%; $p = 0.035$). On the other hand, mild and moderate cases experienced only discrete

abnormal liver function test (LFT) values. These reports support the concept that the disease severity and an older age predispose to more severe liver injury from coronavirus disease 2019 (COVID-19). Relied on these case series, patients with severe coronavirus disease 2019 (COVID-19) and pre-existing liver conditions-but also elderly patients-should undergo surveillance and individually tailored therapeutic approaches for possible liver injury. A published research by Bangash *et al.* (2020) argued after careful review of seven relevant studies that elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) might not necessarily be of hepatic origin alone. The authors have given a timely reminder that it is common for other respiratory viruses to create similar liver function test (LFT) elevations and thus more prospective data related to the clinical relevance coronavirus disease 2019 (COVID-19) and liver injury is required and needed. The previous pathogenic coronaviruses (CoVs), such as severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), were also reported to show with elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In general, non-hepatotropic viruses may cause hepatic injury that can range from mild and transient elevation of aminotransferases to acute hepatitis and occasionally acute liver failure and fulminant hepatitis. However, in the majority of patients, recovery from viral disease is usually sufficient to resolve liver injury.

Like in severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections, abnormal levels of albumin and lactate dehydrogenase (LDH) were also recorded in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, with the maximum of 98% and 76% of the patients affected as reported in the study by Chen *et al.* (2020). It is notable to refer to that lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) elevation could be from muscle damage and not necessarily reflect liver injury.

The current treatment recommendations for coronavirus disease 2019 (COVID-19) involve anti-viral drugs, antibiotics, intravenous (IV) fluids and corticosteroids (CSs). Oseltamivir was utilized in 89.9% of patients in the Wuhan series this current pandemic situation. Remdisivir has revealed good results with coronavirus disease 2019 (COVID-19). Being a ribonucleic acid (RNA) virus, one would expect broad spectrum ribavirin to work; unfortunately, during severe

acute respiratory syndrome (SARS) outbreak ribavirin was correlated with recognizable toxicity involving severe haemolysis. A literature found interferon alpha 2A (IFN- α 2A) in combination with ribavirin exhibited higher initial survival (70% vs 17%, $P=0.004$) by day 14 but not in 28 days (30% vs 17%, $p=0.054$) in Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak. Lopinavir/Ritonavir, approved for human immunodeficiency virus (HIV) infection showed in vitro activity against coronavirus (CoV) and was advantageous in Middle East respiratory syndrome coronavirus (MERS-CoV). These medications are being tried in coronavirus disease 2019 (COVID-19). Lopinavir, a protease inhibitor has been shown efficient in controlling severe acute respiratory syndrome (SARS). Ritonavir was added to increase lopinavir trough level through cytochrome P450 (CYP450) enzyme inhibition in liver. An open labelled, randomized controlled trial on 199 patients with severe coronavirus disease 2019 (COVID-19) revealed no benefit of lopinavir and ritonavir (99 patients). It was debated whether the trial should have been conducted in less sick patient and treatment should have been initiated early phase of coronavirus disease 2019 (COVID-19). In this study, 20.5% and 41% of patients had elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) prior to randomisation, respectively; however, presence of cirrhosis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 times upper limit normal were exclusion criteria in this trial. Increased bilirubin and elevated aspartate aminotransferase (AST) were recognized in 3.2% and 2.1%, respectively in the managed group. Usage of this drug Inhibition of cytochrome P450 (CYP450) will increase the trough levels of calcineurin inhibitor (CNI), the most commonly used immunosuppression in solid organ transplant recipients. This can cause possible drug toxicity. Antibiotics such as fluoroquinolones, third generation cephalosporins were used to reduce secondary infection. Corticosteroids (Methyl prednisolone) has been used in 44.9% of coronavirus disease 2019 (COVID-19) patients to curtail inflammation. Recently, dexamethasone has been found to reduce mortality. Chronic Hepatitis B can reactivate with the use of corticosteroids (CSs). Hepatitis B surface antigen (HBSAg, also known as the Australia antigen) positive patients should be covered with antiviral reedy in case of prolonged corticosteroids (CSs) usage. Authors recommended to check Hepatitis B core antibody status and positive should be managed with antiviral therapy for the duration of steroid treatment. Chen *et al.* (2020) constructed a 3-dimensional crystal structure model of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) proteases. Virtual screening inhibition of the

active viral site as a therapeutic measure identified Hepatitis C nonstructural protein 5A (Hepatitis C NS5A) inhibitor to be effective in controlling severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus infection. Ledipasvir and velpatasvir readily inhibited severe acute respiratory syndrome coronavirus (SARS-CoV) proteases in their model. However, this requires more evidence.

Given the fact that the liver is included in the metabolism of many therapies, involving nucleoside analogs and protease inhibitors that are currently used to manage coronavirus disease 2019 (COVID-19), hepatotoxicity from these drugs can arise. A randomized controlled trial of lopinavir and ritonavir in severe coronavirus disease 2019 (COVID-19) reported that elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin occurred as adverse effects in a few patients. Another case series from Wuhan reported that 55.4% of patients experienced liver injuries after treatment with lopinavir and ritonavir. Fan *et al.* (2020) published a retrospective study on coronavirus disease 2019 (COVID-19) and recognized that the utilization rate of this drug combination was significantly higher in patients with abnormal liver function tests (LFTs) compared with patients without liver function test (LFT) elevations (56.1% vs. 25%, $p = 0.009$). In this study, 47.3% of the discharged patients exhibited elevated liver function tests (LFTs) at baseline, and 23.7% progressed abnormalities during hospitalization, supposing arising liver injury from medications or during the course of the infection. Notably, liver function test (LFT) elevation during the hospital stay was associated with prolonged length of hospitalization. Chloroquine, an old drug with a possibility of repositioning for new management indications, has been tried in patients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). After a profound success in inhibiting viral replication *in vitro*, concurrent clinical trials (>20) on chloroquine conducted at 10 hospitals across China have revealed superior efficiency in viral control. The pharmacodynamic activity of this drug in coronavirus disease 2019 (COVID-19) may include the arresting of cytokine storms or the activation of CD8⁺ cells or by preventing endocytosis mediated uptake of the virus. Importantly, hepatotoxicity related to chloroquine or hydroxychloroquine has scarcely been reported. In severe cases of coronavirus disease 2019 (COVID-19) with cytokine release, tocilizumab, an interleukin-6 (IL-6) antagonist, which is humanized immunoglobulin G1 (IgG1) monoclonal antibody to the interleukin-6 (IL-6) receptor, has been used as a possible therapy for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In previous clinical trials for

other indications tocilizumab was reported to cause mild elevations of liver function tests (LFTs) which were often transient and commonly resolved within 2–6 weeks from exposure. Remdesivir is an antiviral nucleotide analog with broad activity against coronaviruses (CoVs) that is currently being trialed for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease. However, no reports of liver toxicity concerning use of this drug have emerged.

Scarcely data has been published for coronavirus disease 2019 (COVID-19) infection in patients with pre-existing liver disease. Experience from previous episodes of coronavirus (CoV) infection can guide on the extent of hepatic involvement and on the management of patients with pre-existing liver disease. In severe acute respiratory syndrome (SARS), the highest mortality rates were seen in the elderly and adults with underlying liver disease. Therefore, it has to be anticipated that the individuals with coronavirus disease 2019 (COVID-19) are also more vulnerable to liver injury. In a case series from the Zhejiang province, a prevalence of 11% of underlying liver disease was observed. About half of them suffered from symptoms for more than 10 days after the disease onset. In another study from Wuhan, 9% of patients had the underlying liver disease of cirrhosis (a chronic disease of the liver marked by degeneration of cells, inflammation, and fibrous thickening of tissue. It is typically a result of alcoholism or hepatitis) or hepatitis (inflammation of the liver that results from a variety of causes, both infectious and noninfectious. The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer) . Li *et al.* (2020), who investigated risk factors involved with liver injury, stated that two patients had presented with alcoholic liver disease [ALD, also called alcohol-related liver disease (ARLD), is a term that encompasses the liver manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis] at baseline. One of them had a moderate elevation of alanine aminotransferase (ALT) (120 U/L) within a week of hospitalization, while the other showed no such abnormalities. In the initial cohort described from China, 2.7% exhibited hepatitis B virus infection (a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is most commonly transmitted from mother to child during birth and delivery, as well as through contact with blood or other body fluids) with no description of worsening outcomes.

It is interesting to know the pattern of liver injury in coronavirus disease 2019 (COVID-19). Hepatic involvement in coronavirus disease 2019 (COVID-19) could be multifactorial related to the direct cytopathic effect of the virus, uncontrolled immune reaction, sepsis or drug induced liver injury. Given the higher expression of angiotensin-converting enzyme 2 (ACE2) receptors in cholangiocytes, the liver is a possible target for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Further, coronavirus disease 2019 (COVID-19) may lead to worsening of underlying chronic liver disease (CLD) causing hepatic decompensation and acute or chronic liver failure resulting in mortality. Here it is worthy to refer that the liver is critical to survival. When injury from viral infection, chemical toxicity, ischemia or autoimmune inflammation damage or kill liver cells, the remaining cells can compensate by doubling their metabolic function. If liver injury or cell loss outstrips its ability to compensate, the liver functions of biotransformation, glycogenolysis, gluconeogenesis, protein synthesis, filtration, etc., will diminish. As the liver fails, the body will exhibit signs of hepatic insufficiency. Minor signs including: nausea, diarrhea, anorexia and fatigue. More serious liver decompensation is associated systemic signs and symptoms. Overall, 2-11% of patients with coronavirus disease 2019 (COVID-19) were mentioned to have underlying chronic liver disease (CLD) and 14-53% with coronavirus disease 2019 (COVID-19) progressed liver dysfunction especially in severe coronavirus disease 2019 (COVID-19). Liver dysfunction was noticeably higher in critically ill patients and was related to poor outcome. In the series from Wuhan, by Wang and colleagues in (2020), 4 patients (2.9%) with coronavirus disease 2019 (COVID-19) had underlying chronic liver disease (CLD). Another study from China Medical Treatment Expert group for coronavirus disease 2019 (COVID-19) by Guan and colleagues in (2020) revealed 23 (2.1%) patients were positive for Hepatitis B infection (Hepatitis B surface antigen, HBsAg, also called Australia antigen) , of which only one had severe coronavirus disease 2019 (COVID-19). Of interest, a study from outside Wuhan by Xu and colleagues in (2020) described 26 patients with coronavirus disease 2019 (COVID-19) in whom 11% had underlying chronic liver disease (CLD). In another study, comparing 113 deceased and 161 recovered coronavirus disease 2019 (COVID-19) patients showed 4% had underlying chronic Hepatitis B. Individuals with acute liver injury (ALI) has been mentioned in 13 (5%) out of 274 patients of whom 10 (76.9%) died.

Patients with underlying cancer are immunosuppressed by nature of the disease and due to chemotherapy. A preliminary report from China, coronavirus disease 2019 (COVID-19) patients with underlying cancer were investigated. In a nationwide study of 1590 cancer patients with coronavirus disease 2019 (COVID-19) across 575 hospitals in China, it was documented that patients with cancer had higher risk of contracting severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and progress severe illness. These individuals with underlying cancer had poorer outcomes than those without cancer. Most patients with hepatocellular carcinoma (HCC) have underlying chronic liver disease (CLD) and therefore, they fall under this high-risk category and probably develop worse outcome. Alcohol-Associated Liver Disease (AASLD) currently recommends to possibly delay hepatocellular carcinoma (HCC) surveillance by 2 months; however, hepatocellular carcinoma (HCC) related treatments should be carried out without much delay. European Association for the Study of the Liver (EASL) recommends to avoid hepatocellular carcinoma (HCC) surveillance in coronavirus disease 2019 (COVID-19) positive patients, also to postpone locoregional therapy and to temporarily prevent immune check point inhibitor therapy. Here, it is interesting to say that the use of immunotherapy for cancer has become widespread in recent decades and is used to treat both solid and hematological malignances. Immune checkpoint inhibitors, particularly, have demonstrated recognizable promise in their approval for the treatment of melanoma, non-small cell lung cancer, and other cancers. The immune checkpoint proteins, cytotoxic T lymphocyte-associated 4 (CTLA-4), and programmed cell death protein 1 (PD-1), are receptors expressed on the surface of cytotoxic T-cells that interact with their ligands cluster differential 80 (CD80)/cluster differential 86 (CD86) and programmed death ligand-1 (PDL-1) on antigen presenting cells (APCs), which helps the cancer cell evade T-cell-mediated death. Immune checkpoint inhibitors prevent the receptors and ligands from binding to each other, thereby disrupting signaling. These agents have demonstrated improved survival outcomes for adults with solid tumors in clinical trials and have subsequently been approved to treat several disease types, including melanoma. Immunological adverse effects may be caused by checkpoint inhibitors. Altering checkpoint inhibition can have diverse effects on most organ systems of the body.

Management of post liver transplant recipients during the coronavirus disease 2019 (COVID-19) pandemic presents a particular challenge for clinicians because of the limited data available and

the urgent need to continue immunosuppressive drugs in these patients, which puts them at risk for more severe courses of coronavirus disease 2019 (COVID-19) infection and probable prolonged viral shedding. Case reports from China did not show an increased mortality in organ transplant recipients. Qin *et al.* (2020) reported the first case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in a patient with hepatocellular carcinoma (HCC) who subjected to liver transplantation. Lowering immunosuppression to the most acceptable level appears reasonable in infected liver transplant patients, in particular, in the setting of lymphopenia or clinical worsening of infection. Moreover, clinicians have to be aware of drug-drug interactions in the transplant setting. Immunosuppressive drugs and ritonavir-boosted antiviral therapies particularly reveal relevant interactions through cytochrome P34A (CYP34A) (cytochrome is a protein that can transfer electrons with a chemical group called a heme group) which result in increased levels of calcineurin and mammalian target of rapamycin (mTOR) inhibitors. However, it is worthy to refer that mTOR inhibitors are a class of drugs that inhibit the mammalian target of rapamycin (mTOR), which is a serine/threonine-specific protein kinase that belongs to the family of phosphatidylinositol-3 kinase (PI3K) related kinases (PIKKs). mTOR regulates cellular metabolism, growth, and proliferation by forming and signaling through two protein complexes, mTORC1 and mTORC2. Chloroquine-based regimes or remdesivir (compassionate use program only) seem to be safe, while supported protease inhibitors should be avoided. In addition, preventive strategies in those vulnerable patients involve early and prolonged screening with polymerase chain reaction (PCR)-based testing for patients with early symptoms, a contact history or infection. Personal protective equipment in high risk settings can help to protect this vulnerable patient group.

Coronavirus disease 2019 (COVID-19) leaves no stone unturned, including liver transplant recipients. An important case report from Wuhan described a 37-year-old gentleman with Hepatitis B and hepatocellular carcinoma (HCC), who underwent fever on 3rd day post trans arterial chemoembolization. He was treated initially with antibiotics and subsequently liver transplantation on day 7. His fever continued on day 9, and a computed tomography (CT) chest scan showed hypostatic changes in both lung fields. A repeat computed tomography (CT) chest on the third week showed bilateral ground glass appearance. His nasopharyngeal swab confirmed coronavirus disease 2019 (COVID-19). His tacrolimus was dose reduced to maintain under 10 ng/ml. His liver enzymes increased by 4th week but settled gradually. His polymerase chain

reaction (PCR) remained positive for nearly 2 months and subsequently cleared. Another case of post-transplant coronavirus disease 2019 (COVID-19) was also described. The patient underwent cadaver liver transplantation in July 2017. He presented with high fever and developed severe coronavirus disease 2019 (COVID-19). His tacrolimus was discontinued for a month but received corticosteroids (CSs) therapy. His allograft function remained normal.

Some immunosuppressive drugs possess antiviral activity by virtue of their mechanism of actions. Studies from severe acute respiratory syndrome (SARS), described interaction of severe acute respiratory syndrome coronavirus (SARS-CoV) non-structural proteins with cyclophilins, resulting in modulation of T cell immune response. In vitro studies demonstrated that cyclosporine inhibit severe acute respiratory syndrome coronavirus (SARS-CoV) at higher doses. However, clinical utility was restricted by its profound immunosuppressive effects. Similarly, Mycophenolic acid, an active component of mycophenolate mofetil (MMF) showed strong antiviral properties against Middle East respiratory syndrome coronavirus (MERS-CoV) in vitro. Interestingly, mammalian target of rapamycin (mTOR) inhibitors (Everolimus) exhibited effectiveness against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV) viral infections by preventing early viral entry and post-entry consequences. Although in vitro studies, the antiviral properties of these therapies may present some protection against coronavirus disease 2019 (COVID-19) in transplant recipients, especially to ameliorate disease severity. Literature from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) reveal that post liver transplant patients on immunosuppression were not at risk for high mortality. The data for the same with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is very limited.

The rapid clinical deterioration in coronavirus disease 2019 (COVID-19) is due to cytokine storm associated with elevated interleukins interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF- α) concentrations. The effects of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in immunosuppression is not well established. However, stopping immunosuppressive medications in transplant patients may lead to rejection. In coronavirus disease 2019 (COVID-19) patients on high dose steroids the dose requires to be brought down and maintained at 10 mg/day. When there is lymphopenia, fever and worsening lung condition, azathioprine and mycophenolate and calcineurin inhibitors dose requires to be

reduced but not stopped. Caution needs to be exercised when considering initiation of steroids or other immunosuppressive therapy in liver disease patients e.g.; severe alcoholic hepatitis, autoimmune hepatitis, etc. Patients on immunosuppression may be more infectious as they have higher viral titres.

The American Society of Transplantation has provided few recommendations for coronavirus disease 2019 (COVID-19) specifically for those awaiting liver transplantation and transplant recipients. The recommendations include patient education, hand hygiene and social distancing, provision for patients to contact the transplant centre via telephone if they develop fever, cough or flu like symptoms. Each hospital should provide layout protocols for managing these high-risk patients. Careful monitoring of allograft function and drug interactions should be exercised in transplant recipients with coronavirus disease 2019 (COVID-19), because Ritonavir can potentially inhibit cytochrome P34A (CYP34A) enzyme leading to increasing trough levels of mammalian target of rapamycin (mTOR) and calcineurin inhibitors, and drug toxicity. In addition, they have recommended postponing elective surgeries including living donor transplantation and non-urgent deceased donor transplantations in areas of high coronavirus disease 2019 (COVID-19). In addition, potential deceased donors should be adequately tested for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) with nucleic acid assay.

14. Negative Impact of COVID-19 on Female Reproductive System

14.1 Angiotensin-Converting Enzyme 2 in Ovary

Pereira et al (2009) revealed that angiotensin-converting enzyme 2 (ACE2) is present in immature ovaries including stroma and granulosa cells as well as oocytes, the expression of which is enhanced in antral and preovulatory follicles subjected to eCG (equine chorionic gonadotropin) therapy. Angiotensin-converting enzyme 2 (ACE2) is recorded to be expressed in the theca cells and granulosa cells of cattle. Recognizably, angiotensin-converting enzyme 2 messenger ribonucleic acid (ACE2 mRNA) transcripts were detected in ovaries from reproductive-age females and postmenopausal females. It was found that angiotensin-converting enzyme 2 (ACE2) is most abundantly expressed in ovary. It was shown that the expressional concentration of angiotensin-converting enzyme 2 (ACE2) in oocyte is relatively elevated. It is therefore concluded that from the distributions of angiotensin-converting enzyme 2 (ACE2) that the ovary and oocyte are potent targets for coronavirus disease 2019 (COVID-19). Angiotensin-converting

enzyme 2 (ACE2), as the key converzyme in the axis, plays a synergistic role in balancing the concentrations of angiotensin II (Ang II) and angiotensin (1-7) [Ang-(1-7)]. Angiotensin II (Ang II) stimulates steroid secretion, facilitates follicle development and oocyte maturation, contributes to follicular atresia, affects ovulatory process and maintains corpus luteum development. Angiotensin (1-7) [Ang-(1-7)] triggers the synthesis and release of estradiol₂ (E₂) and progesterone (P), enhances ovulatory process and the resumption of meiosis in oocytes. A valuable study demonstrated that the concentration of angiotensin (1-7) [Ang-(1-7)] is also correlated with human oocyte maturation.

14.2 Angiotensin-Converting Enzyme₂ in Uterus and Vagina

Vaz-Silva *et al.* (2009) claimed that angiotensin-converting enzyme₂ (ACE₂) expression is more abundant in epithelial cells than in stromal cells, in the secretory phase than proliferative phase of the uterine cycle. It was presented the presence of angiotensin-converting enzyme₂ (ACE₂) in uterus and vagina. A study performed by Cui *et al.* (2020) found that despite of the high infection rate for 35 female coronavirus disease 2019 (COVID-19)-patients' sexual partners, the confirmation of sexual transmission still needs extensive investigations and search findings. Angiotensin II (Ang II) has a dual role in vascular beds and endometrium regeneration, and initiates the menstruation through spiral artery vasoconstriction. The balance between angiotensin II (Ang II) and angiotensin (1-7) [Ang-(1-7)] can regulate the endometrium regeneration process and myometrium activity. In addition, angiotensin II (Ang II) increases the proliferation of uterus epithelial and stroma cells and enhances endometrial fibrosis, an effect of which is blocked by angiotensin (1-7) [Ang-(1-7)]. It is noted that the normal function of angiotensin II (Ang II) in endometrium is necessary to the regular menstrual cycle (RMC), alteration in its distribution and the level of the receptors may be correlated with dysfunctional uterine bleeding related to hyperplastic endometria. Moreover, sets of evidence exhibit that the aberrant expression of angiotensin-converting enzyme₂ (ACE₂) and angiotensin II (Ang II) associates with the metastasis and prognosis of endometrial carcinoma.

14.3 Angiotensin-Converting Enzyme₂ in Pregnancy

Angiotensin-converting enzyme₂ (ACE₂) is widely expressed in human placenta and mainly in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle (VSM) of

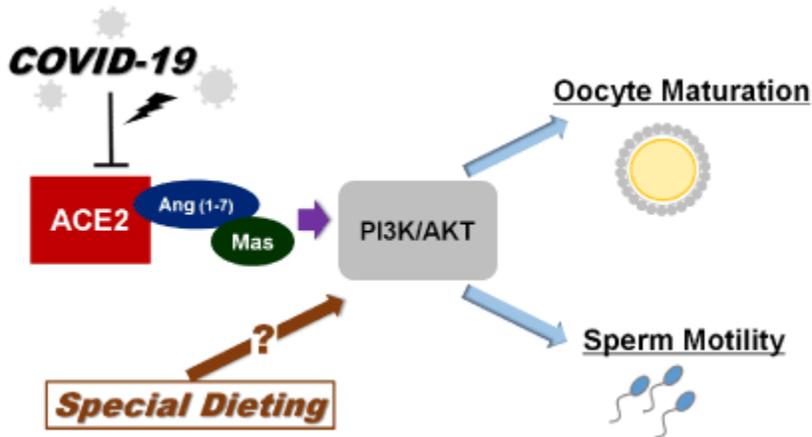
primary and secondary villi. In the maternal stroma, angiotensin-converting enzyme2 (ACE2) is expressed in the invading and intravascular trophoblast and in decidual cells. Angiotensin-converting enzyme2 (ACE2) is also present in arterial and venous endothelium and smooth muscle (SM) of the umbilical cord (UC). It is noticed that angiotensin-converting enzyme2 (ACE2) reaches the highest level in early gestation. During early gestation, angiotensin-converting enzyme2 (ACE2) is expressed in the primary and secondary decidual zone and luminal and glandular epithelial cells (GEC). During late gestation, angiotensin-converting enzyme2 (ACE2) staining was visualized in the labyrinth placenta and amniotic and yolk sac (YS) epithelium. In addition, the increase of angiotensin-converting enzyme2 (ACE2) in placenta of rat begins in the mid-gestation. It is regarded that the expression of angiotensin-converting enzyme2 (ACE2) in placenta is far more than that in lung, indicating the possible infection of placenta. Proof for intrauterine infection has yet appeared, but confirmed cases of newborns were reported. Given that the identification of coronavirus disease 2019 (COVID-19) in cultured human airway epithelial cells requires at least 96 hours, it is believed that it is possible of intrauterine infection with coronavirus disease 2019 (COVID-19) and suppose that the fetus may have already been infected during the gestation. Furthermore, It is shown the presence of angiotensin-converting enzyme2 (ACE2) in breast. Although no reports of coronavirus disease 2019 (COVID-19) in milk has appeared, the chance of transmission of breast feeding still can occur. Even if there is no virus in milk, contact transmission during breast feeding should be considered significantly. Given the weaker immune system of newborns it is strongly advised that these confirmed pregnant patients should avoid breast-fed way.

The major functions of angiotensin II (Ang II), angiotensin-converting enzyme2 (ACE2), and angiotensin (1-7) [Ang-(1-7)] during pregnancy are focusing on the regulation of blood pressure and fetus development as well as the engagement of whole pregnancy period. A study mentioned that angiotensin II (Ang II) induced trophoblast invasion in rat and human cells. Angiotensin (1-7) [Ang-(1-7)] and angiotensin-converting enzyme2 (ACE2) can act as a local autocrine/paracrine regulator throughout pregnancy, taking part in the early(angiogenesis, apoptosis, and growth) and late(uteroplacental blood flow) events of pregnancy. Angiotensin-converting enzyme2 (ACE2) hydrolyzes angiotensin II (Ang II) into angiotensin (1-7) [Ang-(1-7)] and thereby controlling the blood pressure and hydro-salinity balance of pregnant women. The aberrant expression of angiotensin II (Ang II), angiotensin-converting enzyme2 (ACE2), and

angiotensin (1-7) [Ang-(1-7)] can be included in hypertension of pregnancy, preeclampsia (a pregnancy complication characterized by high blood pressure and signs of damage to another organ system, most often the liver and kidneys), and eclampsia (the onset of seizures (convulsions) in a woman with preeclampsia). High expression of angiotensin II (Ang II) in placental villus during preeclampsia causes decreased blood flow and nutrition concentrations in fetus. Meanwhile, low levels of angiotensin-converting enzyme2 (ACE2) and angiotensin (1-7) [Ang-(1-7)] in placenta correlate with intrauterine growth restriction (IUGR). Angiotensin-converting enzyme2 (ACE2) deficient mice show high blood pressure in gestation stage, decreased angiotensin (1-7) [Ang-(1-7)] in plasma and increased angiotensin II (Ang II) within placenta, leading to the abnormal placental functions involving placental hypoxia and uterine artery dysfunction, finally developing to fetal growth retardation. Chen et.al (2014) considered that the maternal angiotensin (1-7)/angiotensin II [Ang (1-7)/Ang II] ratio is independently correlated with gestational hypertension or preeclampsia factors causing preterm birth. The up-regulation of angiotensin-converting enzyme2-angiotensin (1-7)-Mas [ACE2-Ang-(1-7)-Mas] inhibits premature birth. It is noteworthy that the involvement of premature birth and intrauterine growth restriction with adult cardiovascular risk has already been well documented. Bessa et.al(2019) recorded that induction of the angiotensin-converting enzyme2/angiotensin (1-7)/Mas [ACE2/Ang-(1-7)/Mas] axis in hypertensive pregnant rats could attenuate the cardiovascular (CV) dysfunction in adult offspring, confirming the engagement of angiotensin-converting enzyme2 (ACE2) axis in pregnancy. A study puts into account that coronavirus disease 2019 (COVID-19) infection makes a great hazard to pregnant women and babies and causes premature birth(50.0 %, 16/32) and fetal distress (39.3 %, 11/28) as well as premature rupture of fetal membranes (21.4 %, 6/28) , but whether it is angiotensin-converting enzyme2 (ACE2) that causes the dysfunction of placenta remains elusive and needs further evaluation and investigation. Furthermore, just like severe acute respiratory syndrome-coronavirus (SARS-CoV) patients, coronavirus disease 2019 (COVID-19) patients also have complicated acute renal impairment, renal dysfunction (RD) and renal failure (RF). Pacciarini et.al(2008) has found that severe acute respiratory syndrome-coronavirus (SARS-CoV) infects human tubular kidney cell. It is noteworthy that angiotensin-converting enzyme2 (ACE2) level in the renal tubules of pregnant mice increases by 117%, which may contribute to the maintenance of blood pressure. It

is proposed that pregnant women with coronavirus disease 2019 (COVID-19) can be susceptible to renal injuries.

Coronavirus disease 2019 (COVID-19) may infect ovary, uterus, vagina and placenta through the ubiquitous expression of angiotensin-converting enzyme2 (ACE2) within the female reproductive system. Therefore, it is believed that apart from droplets and contact transmission the possibility of mother-to-child tract and sexual transmission also exist. In addition, angiotensin II (Ang II), angiotensin-converting enzyme2 (ACE2), and angiotensin (1-7) [Ang-(1-7)] regulate follicle development and ovulation, modulate luteal angiogenesis and degeneration, influences the endometrial tissues' regular changes and the embryo growth. Taking these functions into consideration, the regulation of coronavirus disease 2019 (COVID-19) to angiotensin-converting enzyme2 (ACE2) may disturb the female reproductive functions and induce infertility, menstrual disorder and fetal distress. Therefore, it is advisable a following-up and evaluation of fertility after the healing, especially for the young female patients. Moreover, it must be persistently pay close attention to the situation of pregnant patients and fetus and take timely and necessary measures. What's more, to decrease the incident of coronavirus disease 2019 (COVID-19) infection, special nursing must be conducted for healthy pregnant women, puerperants and newborn infants.



Figure(85):COVID-19 an infertility risk [Tsuji A.; Ikeda Y.; Murakami M.; Matsuda S. (2020). COVID-19, an infertility risk?. Clinical Obstetrics, Gynecology and Reproductive Medicine]

In general, the angiotensin-converting enzyme²/angiotensin (1-7)/Mas [ACE²/ Ang (1–7)/Mas] activates PI3K/AKT signaling pathway. PI3K/AKT signaling pathway is an intracellular signal transduction pathway that promotes metabolism, proliferation, cell survival, growth and angiogenesis in response to extracellular signals. The PI3K/AKT signaling is thought to correlate with host-protection in several diseases by ameliorating oxidative stress (OS) and inflammatory process.

For fear that coronavirus disease 2019 (COVID-19) virus terminates the the angiotensin-converting enzyme²/angiotensin (1-7)/Mas/PI3K/AKT [ACE²/ Ang (1–7)/Mas/PI3K/AKT] pathway, a host protection and fertility-system, it is highly significant to define appropriate strategies to activate the PI3K/AKT pathway. As the efficiency of pharmacological and/or vaccinal managements against coronavirus disease 2019 (COVID-19) has been unsatisfactory at present, dietary choices may indicate a certain role via the PI3K/AKT signaling-activation. Lifestyle factors such as the special diets can play certain roles against possible infertility of coronavirus disease 2019 (COVID-19).

15.Male Infertility in COVID-19 Infection

The testes are mainly composed of seminiferous tubules and intertubular tissue. The seminiferous tubules generate sperms, and consist of sperm-producing cells (spermatogonia) and the supporting Sertoli cells. The principal functions of testes are spermatogenesis and androgens secretion. The interstitial Leydig cells produce testosterone (T) under regulation of luteinizing hormone (LH).

Molecular studies on mechanisms of coronavirus infection have shown that coronaviruses depend on the binding of viral spike proteins to cellular receptors and on spike protein priming by host cell proteases to enter a cell. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) binds to the angiotensin- converting enzyme 2 (ACE2) receptor for entry and the serine protease transmembrane serine protease 2 (TMPRSS2) for spike protein priming. Angiotensin-converting enzyme 2 (ACE2), a negative regulator in the renin–angiotensin system (RAS), is highly expressed in the epithelial cells of renal tubules, seminiferous ducts of testis, adult Leydig cells, the adrenal gland and the prostate. Serine protease transmembrane serine protease 2 (TMPRSS2) is highly expressed in the kidney, prostate, seminal vesicles and epididymis. In

addition, it is found that serine protease transmembrane serine protease 2 (TMPRSS2) mainly exists in spermatogonia and spermatids. Both of the key factors that mediate severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) pathogenicity are highly expressed in urogenital organs, supposing that these organs might be vulnerable to be destructed by this viral infection.

Findings presume the potent risk of male gonad to be susceptible to severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) invasion. In case of viremia, virus may seed into the male reproductive tract because the blood-testis barrier (BTB) is not perfect enough to completely isolate virus. Virus circulating in the blood mainly invade the testis. The deleterious impacts of viruses include the direct damage of spermatozoon, abnormal sex-hormone secretion, and dysregulation of inflammatory cytokines. It is supposed that testes may run high risk of damage and dysregulation under coronavirus disease 2019 (COVID-19). Ma *et al.* (2020) compared the sex-related hormones between reproductive-aged men with severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) disease and age-matched healthy men. Coronavirus disease 2019 (COVID-19) infected patients showed a significant increase in serum luteinizing hormone (LH) level and a dramatic decrease in serum testosterone:luteinizing hormone (T: LH) in comparison with healthy control group and to interpret these results, the following points should be considered:

(1) There is a subtle negative feedback between testosterone (T) in testes and luteinizing hormone (LH) in pituitary gland. In the early stage of hypogonadism, impaired testosterone (T) synthesis and release may induce the release of luteinizing hormone (LH) which can maintain testosterone (T) concentration temporarily.

(2) The basal testosterone (T) concentration in the males varies recognizably, thus the ratio between hormones, such as testosterone to luteinizing hormone (T/LH) or testosterone to estradiol₂ (T/E₂), was regarded better parameters for male gonad function evaluation and assessing.

In addition, in this study the serum prolactin (PRL) concentration was significantly high in coronavirus disease 2019 (COVID-19) individuals. Since serum prolactin (PRL) can be affected by multiple factors, such as diet, stress, drugs, etc., the elevation was not astonishing. But it must

shed light to the fact high prolactin (PRL) concentration can lead to pituitary suppression and decreased gonadotropins. The results found in this study, the elevated luteinizing hormone (LH) and decreased testosterone to luteinizing hormone (T:LH) ratio, were interpreted to be caused by testes dysfunction, such as the possible damage of Leydig cells. Unlike serum luteinizing hormone (LH) concentration, serum follicle-stimulating hormone (FSH), serum estradiol₂ (E₂) and the ratio of testosterone to estradiol₂ (T: E₂) were not significantly different between the coronavirus disease 2019 (COVID-19) group and the age-matched healthy control group. In men, follicle-stimulating hormone (FSH) is mainly suppressed by inhibin B secreted by Sertoli cells, and estradiol₂ (E₂) normally comes from peripheral aromatization of androgens. Therefore, it is argued that Sertoli cells were less disturbed than Leydig cells under coronavirus disease 2019 (COVID-19) infection.

C-reactive protein (CRP) is an acute-phase protein (APP) produced by the liver which rises in acute inflammation throughout the body. In coronavirus disease 2019 (COVID-19), rapid and significant increase of C-reactive protein (CRP) was recognized frequently in severe cases than in non-severe cases. In acute inflammation, elevated C-reactive protein (CRP) are also accompanied with abnormal cytokines. Some cytokines, such as interferon (IFN), may impact testes function and spermatogenesis process.

As mentioned, testis shows nearly the high concentration of angiotensin-converting enzyme 2 messenger ribonucleic acid (ACE2 mRNA) and protein expression. At the level of testicular cells, four main cell types; seminiferous duct cells, spermatogonia, Leydig cells and Sertoli cells, reveal higher percent of angiotensin-converting enzyme 2 messenger ribonucleic acid (ACE2 mRNA) expression. If the virus destroy these cells, the process of spermatogenesis could be influenced which might pose risk to male fertility. The testicular expression of angiotensin-converting enzyme₂ (ACE2) is age related. The highest expression recorded in patients aged 30 years, which is higher than those in their twenties, whereas 60-year-old patients show the lowest level of expression. This can indicate that young men patients with coronavirus disease 2019 (COVID-19) are at higher risk of testicular damage than older men with this disease. In one study, examination of autopsy specimen of testis of six patients who died due to severe acute respiratory syndrome-coronavirus (SARS-CoV) infection in 2002 documented an evidence of orchitis. Histopathological examination presented inflammatory infiltrates, mainly in

seminiferous tubules. Immunohistochemistry revealed immunoglobulin-G (IgG) deposition mainly in seminiferous epithelium, interstitium, degenerated germ cells and Sertoli cells. These are the same cell types that show high angiotensin-converting enzyme2 (ACE2) expression. Interestingly, in-situ hybridization does not detect viral genomic materials in the testicular tissue specimens. This exhibits that testicular damage is due to inflammatory and immunological response rather than direct damage by the virus. The possibility of testicular damage is caused by either direct viral invasion through binding of severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) virus to angiotensin-converting enzyme2 (ACE2) receptors or secondary to immunological and inflammatory immune response.

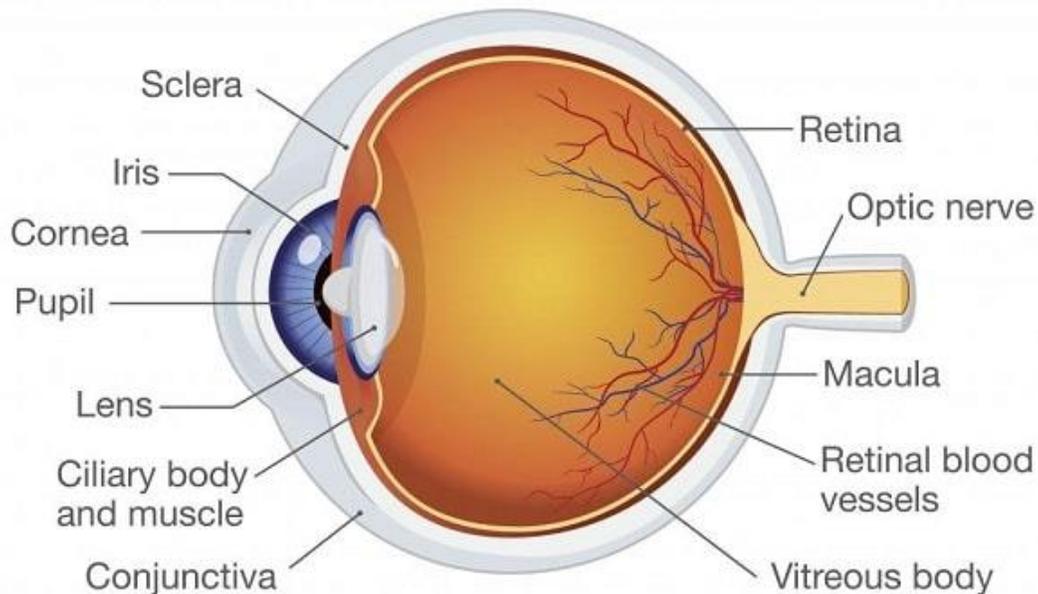
As proven, the testis, in spite of its immune privileged status, cannot be isolated from the immune system. The key factors that mediate severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) pathogenicity are highly expressed in urogenital organs. Leukocyte infiltration and CD3+ T lymphocytes and CD68+ macrophages in the interstitial tissue of the testes can produce interferons (IFNs) that obstacle steroidogenesis and production of testosterone (T). Inflammatory cytokines that are locally or systematically produced by these cells can activate the autoimmune response, destroying the seminiferous epithelium, which develops to autoimmune orchitis.

A notable testosterone (T) concentration reducing hit can be the trigger of cytokine storm as reported in H7N9 influenza infected individuals. Avian H7N9 influenza also exhibits a strong male bias and is a known potent inducer of inflammatory cytokines called as cytokine storm comparable to severe acute respiratory syndrome-coronavirus-2 (SARS- CoV-2) infection. In both diseases, elevated interleukin-6 (IL-6) concentrations admit a poor prognostic marker. Cytokine storm, involving high tumor necrosis factor-alpha (TNF- α) concentrations may suppresses steroidogenesis in the testis by blocking known pathways. Conversely, gonadal steroids are shown to inhibit interleukin-6 (IL-6) secretion in turn. This is in line with the findings that low testosterone (T) concentrations associate with elevated concentrations of inflammatory cytokines. It was found that low testosterone concentrations in male H7N9 cases were strongly combined with lethal outcome.

High concentrations of cytokines following viral or bacterial infection, illness or injury can result in deterioration in spermatogenesis and steroidogenesis, adversely affecting fertility. There is a

theoretical possibility of testicular damage and subsequent infertility following coronavirus disease 2019 (COVID-19) infection.

16.Ocular Complications



Figure(86):Eye structure (www.google.com)

Conjunctiva is a thin, translucent membrane lining the anterior part of the sclera and inside of the eyelids. It has 2 parts, bulbar and palpebral. The bulbar portion begins at the edge of the cornea and covers the visible part of the sclera; the palpebral part lines the inside of the eyelids. Inflammation or infection of the conjunctiva is known as conjunctivitis and is represented by dilatation of the conjunctival vessels, leading to hyperemia (an excess of blood in the vessels supplying an organ or other part of the body) and edema of the conjunctiva, typically with associated discharge. Conjunctivitis can be divided into infectious and noninfectious causes. Viruses and bacteria are the most common infectious agents. Noninfectious conjunctivitis involves allergic, toxic, and cicatricial conjunctivitis, as well as inflammation secondary to immunemediated diseases and neoplastic processes. The disease can also be classified into acute, hyperacute, and chronic according to the mode of onset and the severity of the clinical response. Moreover, it can be either primary or secondary to systemic diseases such as gonorrhea,

chlamydia trachomatis, graft-vs-host disease, and Reiter syndrome, in which case systemic treatment is warranted.

Viral conjunctivitis secondary to adenoviruses is highly contagious, and the risk of transmission has been estimated to be 10% to 50%.The virus spreads through direct contact via contaminated fingers, medical instruments, swimming poolwater, or personal items; in one study, 46% of infected people had positive cultures grown from swabs of their hands. Because of the high rates of transmission, hand washing, strict instrument disinfection, and isolation of the infected patients from the rest of the clinic has been advocated. Incubation and communicability are estimated to be 5 to 12 days and 10 to 14 days, respectively. Although no effective management is present, artificial tears, topical antihistamines, or cold compresses may be useful in alleviating some of the symptoms. Available antiviral medications are not useful and topical antibiotics are not indicated. Topical antibiotics do not protect against secondary infections, and their use may complicate the clinical presentation by resulting in allergy and toxicity, causing delay in diagnosis of other possible ocular diseases. Use of antibiotic eyedrops can increase the risk of spreading the infection to the other eye from contaminated droppers. Increased resistance is also of interest with frequent use of antibiotics. Patients consult an ophthalmologist if symptoms do not resolve after 7 to 10 days because of the risk of complications.



Figure(87):Photograph of eye with viral conjunctivitis (eye redness with tearing) (www.google.com)

Subconjunctival hemorrhage (SCH) is a common benign condition of the eye that has characteristic features, such as the painless acute appearance of a sharply circumscribed redness of bleeding underneath the conjunctiva in the absence of discharge, and inflammation in

contagious areas. Reduction in visual acuity is not expected. It can vary from dot-blot hemorrhages to extensive areas of bleeding that render the underlying sclera invisible. Histologically, subconjunctival hemorrhage (SCH) can be described as hemorrhage between the conjunctiva and episclera, and the blood elements are present in the substantia propria of the conjunctiva when a subconjunctival vessel breaks. The incidence of subconjunctival hemorrhage (SCH) was reported as 2.9% in a study with 8726 patients, and increase with age was observed, particularly over 50 years of age. It is thought that this considerable increase depends on the increase of prevalence of systemic hypertension (HTN) after the age of 50 years; also, diabetes mellitus (DM), hyperlipidemia, and the use of anticoagulation drugs becomes more frequent with aging. In general, subconjunctival hemorrhage (SCH) is often observed in the inferior and temporal areas of the conjunctiva, but trauma causes localized hemorrhage at the site of injury, particularly in the temporal areas. The fibrous connections under the conjunctiva, involving elastic and connective tissues (CT), become more fragile with age, and this can be the reason for easy spread of hemorrhage in older patients. Traumatic subconjunctival hemorrhage (SCH) is more likely to remain localized around the site of impact in comparison with diffuse subconjunctival hemorrhage (SCH)-associated systemic vascular disorders. Subconjunctival hemorrhages (SCHs) are seen frequently in summer, and this is in relation with the high frequency of local traumas in this season. The majority of cases are mostly regarded as idiopathic, since it is usually impossible and impractical to describe the major cause of subconjunctival hemorrhage (SCH). However, the clinician must have a systematic review scheme in mind, and major causes can be classified under ocular and systemic conditions, respectively. The first study on the risk factors was reported by Fukuyama *et al.* in 1990, who demonstrated that local trauma, systemic hypertension (HTN), acute conjunctivitis, and diabetes mellitus (DM) were the principal causes or associated conditions of subconjunctival hemorrhage (SCH). On the other hand, the cause of subconjunctival hemorrhage (SCH) was undetermined in about half of the patients. The relationship between age, local trauma, and systemic hypertension (HTN) was estimated, and it was indicated that hypertension (HTN) was observed frequently in patients older than 50 years; however, local trauma was an important cause in all age-groups. Since the 1980s, the order of the risk factors of subconjunctival hemorrhage (SCH) has changed, and the number of patients with acute hemorrhagic conjunctivitis has decreased, whereas contact lens usage and ocular surgery have

become more common as underlying causes. A study showed that the major risk factors for subconjunctival hemorrhage (SCH) were trauma and contact lens usage in younger patients, and among older patients it was mostly associated with systemic vascular disorders, such as systemic hypertension (HTN), diabetes mellitus (DM), and arteriosclerosis, which caused the walls of the blood vessels to become fragile. Ocular causes include local trauma to the globe, injuries to the orbit, acute inflammation of the conjunctiva, conjunctival tumors, conjunctivochalasis, ocular amyloidosis, contact lens usage, ocular surgery, and ocular adnexal tumors.

There is not any approved management to accelerate the resolution and absorption of subconjunctival hemorrhage (SCH). The first management mentioned in the literature was air therapy . A patient with a severe subconjunctival hemorrhage (SCH) resulted from acute hemorrhagic conjunctivitis was managed with nasal and temporal subconjunctival injection of tissue plasminogen activator (abbreviated tPA or PLAT, it is a protein involved in the breakdown of blood clots). Subconjunctival hemorrhage (SCH) was a new area of usage for tissue plasminogen activator alongside its use in vitreous, anterior chamber, and glaucoma filter bleb to trigger the clearance of fibrin clots. It was assessed the impact of subconjunctival injection of liposome-bound, low-molecular-weight heparin (LMWH) on the absorption rate of subconjunctival hemorrhages (SCHs) in rabbits. The report reached to a conclusion that the subconjunctival injection of liposome-bound low-molecular-weight heparin (LMWH) had a remarkable influence on facilitating subconjunctival hemorrhage (SCH) absorption in rabbits compared to only liposome and liposome-free form of low-molecular-weight heparin (LMWH). Another study used two forms of the same molecule–liposome-encapsulated streptokinase and free-form streptokinase which were injected into the subconjunctival area to enhance the rate of subconjunctival hemorrhage (SCH) absorption in rabbits, and authors revealed that subconjunctival hemorrhage (SCH) absorption rate in the liposome-capsulated form was faster than the free-form streptokinase injection group, especially in the early phases, which were defined as 24–48 hours after subconjunctival hemorrhage (SCH) stimulation.

Failure to resolve hemorrhage in persistent or recurrent cases supposes a serious underlying cause. A careful history is the most important step in identifying whether there is a serious underlying cause that may need more detailed testing and management. A detailed history may offer clues to the underlying conditions. It is crucial to obtain a thorough medication, medical,

and ocular history from patients presenting with subconjunctival hemorrhage (SCH), comprising any possible trauma, ocular surgery, contact lens wear, therapies, and heritable conditions. First, a careful slit-lamp examination is crucial to specify if there has been any trauma to the eye, and also to rule out any local ocular condition that can develop subconjunctival hemorrhage (SCH). After excluding ocular factors, further systemic evaluation is required. Blood pressure should be checked routinely in all patients with subconjunctival hemorrhage (SCH), especially in older patients. In recurrent cases, a workup for bleeding disorders and hypocoagulable states is needed. The international normalized ratio (INR) should be checked if the patient is taking warfarin. In summary, no treatment is required for subconjunctival hemorrhage (SCH) unless it is associated with certain serious conditions.



Figure(88):Subconjunctival hemorrhage (www.google.com)

Retinal vasculitis is a sight-threatening inflammatory eye illness that includes the retinal vessels. It may be incident as an isolated idiopathic condition, as a complication of infective or neoplastic disorders, or in association with systemic inflammatory disease. Retinal vasculitis may be either symptomatic or asymptomatic. If the retinal vascular changes are in the periphery of the fundus without vitreous involvement, patients may have minimal or no symptoms. Patients with inflammation of the posterior retinal blood vessels and/or vitreous cells, however, may experience a decrease in vision or may notice floaters. Visual field scotomata may progress and are usually in relation with the areas of ischemia. Active vascular disease is characterized by sheathing or cuffing of blood vessels, and vitreous cells. Inflammation of macular blood vessels can cause macular edema. Occlusive retinal vasculitis may cause cotton-wool spots representing microinfarcts, retinal edema, and intraretinal hemorrhage. Late changes secondary to vascular occlusion and remodelling involve telangiectasis, microaneurysms, and ischemia-induced neovascularization. These clinical signs may be proved by fluorescein angiography, which demonstrates leakage of the dye due to breakdown of the inner blood-retinal barrier (BRB), and staining of the blood vessel wall with fluorescein. Fluorescein angiography is a more sensitive technique and will frequently show that the vasculitis is more extensive than the clinical examination proposes. Optical coherence tomography is a highly effective method for the diagnosis of macular edema in uveitis as it provides highly reproducible measurements of retinal thickness in micrometers. In addition, it is of great value in evaluating the outcomes of management for uveitic cystoid macular edema. The two main causes of visual loss are cystoid macular edema (CME) and new blood vessel formation resulting from retinal ischemia that can result in vitreous hemorrhage and traction retinal detachment. Retinal vasculitis affecting predominantly the veins has been defined in relation with Behçet's disease, tuberculosis, sarcoidosis, multiple sclerosis (MS), pars planitis, retinal vasculitis associated with tuberculo-protein hypersensitivity (Eales' disease), and human immunodeficiency virus (HIV) infection. In certain diseases with predominantly arterial involvement [e.g., systemic lupus erythematosus (SLE) and polyarteritis nodosa (PAN)], the retinal arteries bear the brunt of the disease. Intraretinal infiltrates are characteristic of infectious processes; however, in the absence of these, they are pathognomonic of Behçet's disease. Cotton-wool spots are most often found in association with a systemic vasculitis. Swelling of the optic nerve head is a common

nonspecific finding related to intraocular inflammation, but may also represent infiltrative disease of the nerve itself or optic nerve head vasculitis as in patients with Behçet's disease.

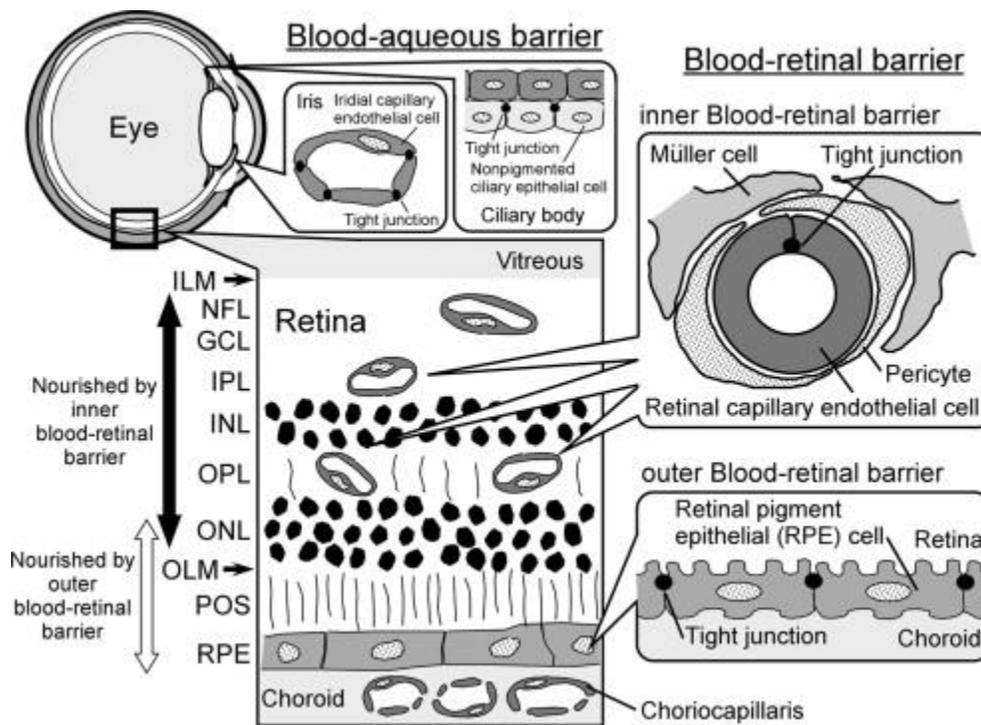


Figure(89):Ophthalmoscopy of eye showing retinal vasculitis (www.google.com)

The blood-brain-barrier (BBB) provides noticeable protection against microbial invasion of the brain. The blood-retinal barrier (BRB) and blood-brain-barrier (BBB) are derived from the same embryonic primordium. The blood-retinal barrier (BRB), which maintains eye homeostasis, has a similar nature to the blood-brain-barrier (BBB). The blood-retinal barrier (BRB) is composed of retinal capillary endothelial cells [inner blood-retinal barrier (BRB)] and retinal pigment epithelium (RPE) cells [outer blood-retinal barrier (BRB)]. These two cell types develop tight junctions that confer a high degree of control of solute and fluid permeability between the circulating blood and the neural retina.

The transmembrane proteins of tight junctions include occludin, junction adhesion molecules and claudins. These proteins extend into the paracellular space, functioning in concert to affect

barrier properties. Occludin and claudins have external loops that mediate intercellular adhesion by interaction with occludin and claudins of neighboring cells. Moreover, claudins and occludin interact with zonula occludens (ZOs) -1, -2 and -3, which in turn correlate with the actin cytoskeleton. The 220-kDa phosphoprotein ZO-1, in particular, is capable of binding to a wide variety of protein partners and allow for the control of tight junction assembly. During viral infections and other pathological conditions, altering the localization or cleavage of the tight junction proteins is the main pathological change, which leads to the increasing permeability of the barrier.



Figure(90):Blood retinal barrier [Preedy V. (2014). Handbook of nutrition, diet and the eye. Elsevier. Academic Press. ISBN:978-0-12-401717-7. <https://doi.org/10.1016/C2012-0-00367-5>]

Retinal diseases are the main causes of blindness in the Western world. Diabetic retinopathy is the leading cause of blindness in the working-age population.

Recent progress in the management of retinal disease using intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) drugs or steroids has, however, completely changed expectations considering successful vision recovery. The translational work that

established intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment for retinal illnesses was recognized as a landmark in the management of vision loss.

It is notable to recognize that intravitreal anti-vascular endothelial growth factor (anti-VEGF) and steroid injections function by stabilizing the blood-retinal barrier (BRB) and correct abnormal permeability in retinal illness.

Blood-retinal barrier (BRB) should be referred as consisting of 2 major components, the endothelium of the retinal blood vessels (inner BRB) and the retinal pigment epithelium (RPE) (outer BRB).

Morphological studies, using electron microscopy, were extremely rewarding, demonstrating the presence of zonulae occludentes in the retinal vessels between the endothelial cells, thereby showing that the retinal endothelial layer has an epithelium-like structure and offering an interpretation for the permeability behavior of the retinal vessels. The term blood-retinal barrier (BRB) system is most useful for clinical purposes and better signifies its major role, that is, regulating the microenvironment of the retina. The blood-retinal barrier (BRB) system must be viewed as whole, and as regulating both the extracellular fluid of the retina and the vitreous. The blood-retinal barrier (BRB) is considered to play a crucial role in retinal function in both health and disease. The major diseases that affect visual function, i.e., diabetic macular edema (DME) and wet age-related macular degeneration, are characterized by breakdown of the inner and outer blood-retinal barrier (BRB), respectively. Macular edema is identified by swelling of the central portion of the human retina and is associated with increased retinal thickness. It can be simply described as excess of fluid within the retinal tissue.

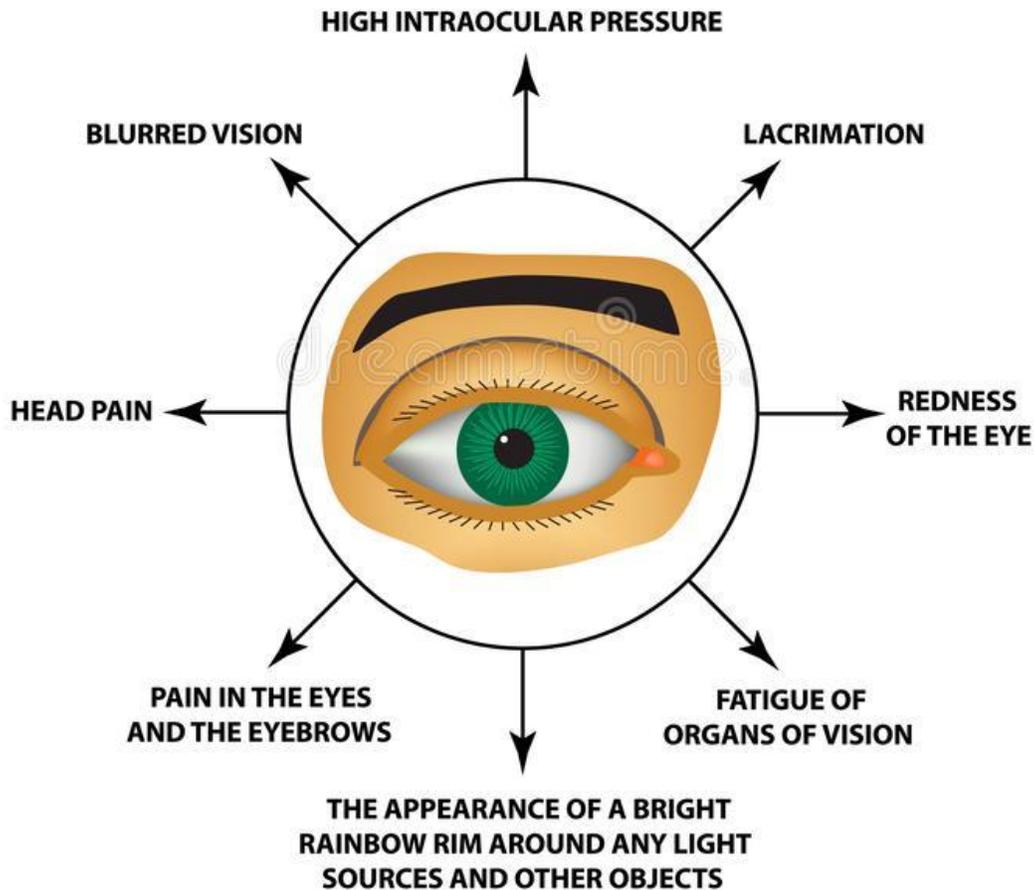
It is generally agreed that the most frequent proximate cause of macular edema, related to any systemic or ocular disease or drug, is breakdown of the inner blood-retinal barrier (BRB). Although the contents of the vascular lumina can reach the extravascular space by transcellular mechanisms directly through the endothelial cell cytoplasm, most data regard that the most often pathologic mechanism is breakdown of the interendothelial junctional complexes. The accumulation of fluid in edemas may be extracellular, intracellular, or a combination of both.

Cytotoxic edemas are those in which the primary lesion is initiated in cells, neurons, or glia. Intracellular swelling of the retina may occur primarily with certain kinds of intoxication and in

the margins of hypoxic/ischemic damage, where breakdown of the blood-retinal barrier (BRB) is a secondary event. Vasogenic edemas, which are by far the most often, are those in which the primary defect is in the blood-retinal barrier (BRB), developing abnormal accumulation of extracellular fluid. In this condition, a secondary cellular response may occur in an effort to deal with the excess fluid in the extracellular space. Müller cells and aquaporin 4 channels may indeed be included in the reabsorption of abnormal fluid entering the retina due to alterations of the blood-retinal barrier (BRB).

When there is a breakdown of the blood-retinal barrier (BRB) in vasogenic edema, it is possible to explain retinal edema in terms of the basic principles of capillary filtration. In 1896 Starling originally proposed that edema occurs in a tissue when the rate of capillary filtration exceeds the rate of fluid removal from the perivascular interstitium. Lymphatics remove fluid from peripheral tissues, but fluid from retinal capillaries must percolate through the retina to reach the vitreous or return into the circulation.

Symptoms Glaucoma

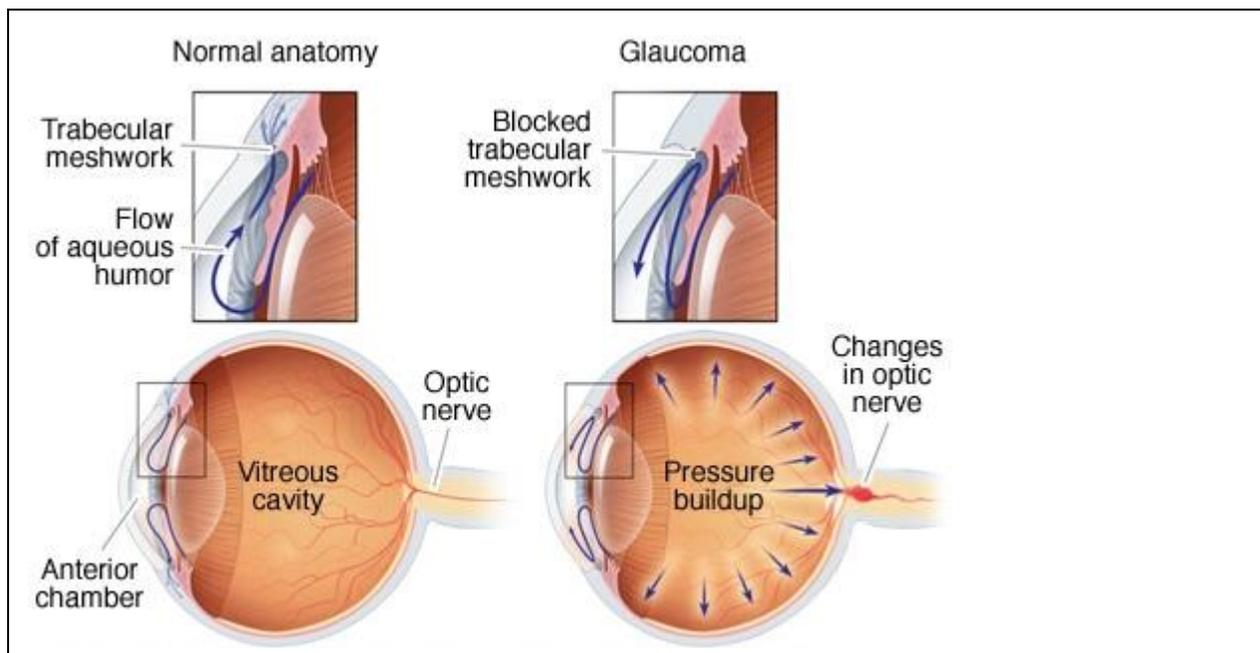


Figure(91):Symptoms of glaucoma (www.google.com)

The glaucomas are a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells. These are central nervous system (CNS) neurons that have their cell bodies in the inner retina and axons in the optic nerve. Degeneration of these nerves leads to cupping, a characteristic appearance of the optic disc and visual loss.

Glaucoma can remain asymptomatic until it is severe, causing a high probability that the number of affected persons is much higher than the number known to have it. Population-level surveys

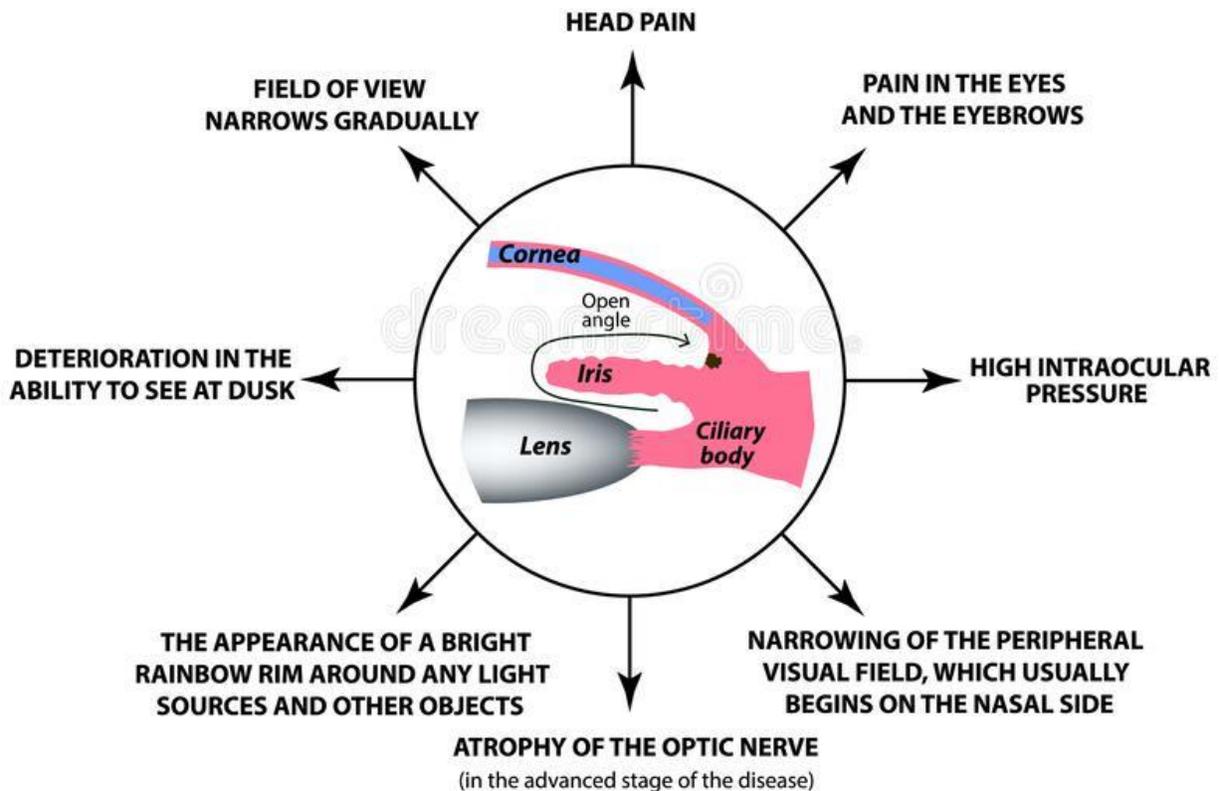
suggest that only 10% to 50% of people with glaucoma are aware they have it. Glaucomas can be classified into 2 broad categories: open-angle glaucoma and angle-closure glaucoma. In the United States, more than 80% of cases are open-angle glaucoma; however, angle-closure glaucoma is responsible for a disproportionate number of patients with severe vision loss. Both open-angle and angle-closure glaucoma can be primary diseases. Secondary glaucoma can result from trauma, certain medications such as corticosteroids (CSs), inflammation, tumor, or conditions such as pigment dispersion syndrome or pseudo-exfoliation syndrome.



Figure(92):Open-angle glaucoma (www.google.com)

For figure (92): open-angle glaucoma, normally, fluid (aqueous humor) in the eye flows freely through the anterior chamber and exits through the drainage system (trabecular meshwork). If that system is blocked or isn't functioning well, the pressure inside the eye (intraocular pressure) builds, which in turn damages the optic nerve. With the most common type of glaucoma, this leads to gradual vision loss.

Symptoms of open-angle glaucoma



Figure(93):Open-angle glaucoma symptoms (www.google.com)

For condition with primary open-angle glaucoma: although the pathogenesis of glaucoma is not fully understood, the level of intraocular pressure is related to retinal ganglion cell death. The balance between secretion of aqueous humor by the ciliary body and its drainage through 2 independent pathways-the trabecular meshwork and uveoscleral outflow pathway-determines the intra-ocular pressure. In patients with open-angle glaucoma, there is increased resistance to aqueous outflow through the trabecular meshwork. In contrast, the access to the drainage pathways is obstructed typically by their is in patients with angle-closure glaucoma.

Intraocular pressure can cause mechanical stress and strain on the posterior structures of the eye, noticeably the lamina cribrosa and adjacent tissues. The sclera is perforated at the lamina where the optic nerve fibers (retinal ganglion cell axons) exit the eye. The lamina is the weakest point in the wall of the pressurized eye. Intraocular pressure–induced stress and strain may lead to compression, deformation, and remodeling of the lamina cribrosa with consequent mechanical axonal damage and disruption of axonal transport that interrupts retrograde delivery of essential trophic factors to retinal ganglion cells from their brainstem target (relay neurons of the lateral geniculate nucleus). Research including cats and monkeys with experimentally induced ocular hypertension have shown blockade of both orthograde and retrograde axonal transport at the level of the lamina cribrosa. Disrupted axonal transport occurs early in the pathogenesis of glaucoma in experimental systems resulting in collections of vesicles and disorganization of microtubules and neurofilaments in the prelaminar and postlaminar regions. Similar ultrastructural changes in optic nerve fibers are observed in postmortem human eyes that have glaucoma. Because there also may be mitochondrial dysfunction in retinal ganglion cells and astrocytes, high levels of energy demand may be difficult to meet during periods of intraocular pressure-induced metabolic stress.

Glaucomatous optic neuropathy can occur in persons with intraocular pressures within the normal range. In such individuals, there may be an abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space resulting in a large pressure gradient across the lamina. Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress (OS) may also cause glaucoma. Primary neural pathological processes may cause secondary neurodegeneration of other retinal neurons and cells in the central visual pathway by altering their environment and increasing susceptibility to damage.

Several genes-including myocilin (*MYOC*, *GLCIA*) (CCDS1297.1), optineurin (*OPTN*, *GLC1E*) (CCDS7094.1), and WD repeat domain 36 (*GLC1G*) (CCDS4102.1)-are associated with a monogenic, autosomal dominant trait; however, these genes account for less than 10% of all glaucoma cases.

Although elevated intraocular pressure is a very consistent risk factor for the presence of glaucoma, several population-based studies revealed that intraocular pressure was lower than 22 mm Hg in 25% to 50% of patients with glaucoma. Despite the strong association between

elevated intraocular pressure and glaucoma, substantial numbers of individuals with elevated intraocular pressure never progress glaucoma even during lengthy follow-up. Glaucoma progresses without causing symptoms until the disease is advanced with substantial amounts of neural damage. When symptoms do occur, the disease causes vision loss with concomitant reduction in quality of life and the ability to perform daily activities. Early intervention is fundamental to slow the progression of the disease. Referral to an eye care practitioner should happen for patients at risk of glaucoma.

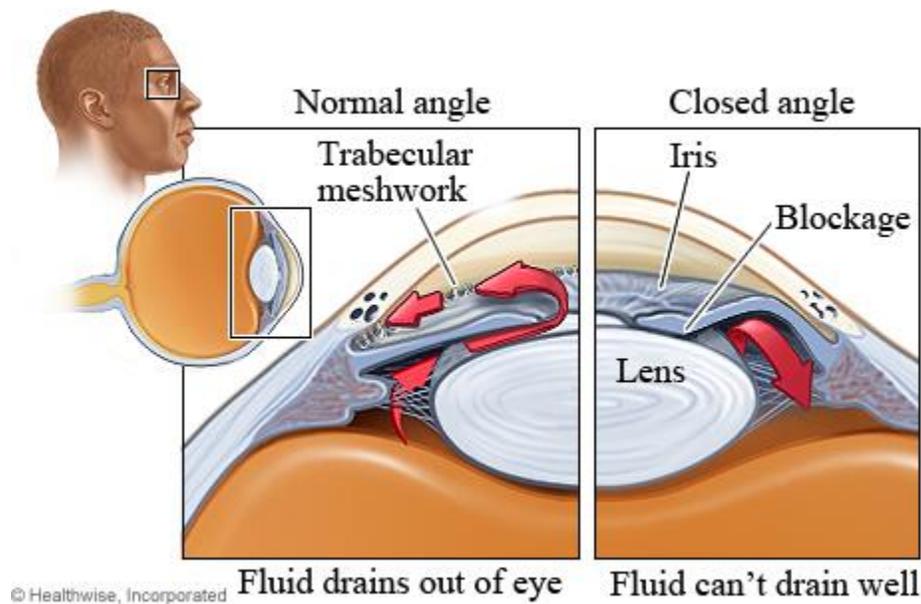
With retinal ganglion cell death and optic nerve fiber loss in glaucoma, characteristic changes in the appearance of the optic nerve head and retinal nerve fiber layer occur. These changes are the most important aspect of a glaucoma diagnosis and can be identified during ophthalmoscopic examination of the optic nerve head. The importance of conducting an appropriate ophthalmologic examination of the eye cannot be overstated with respect to early detection of glaucoma. Retinal ganglion cell loss causes progressive deterioration of visual fields, which usually begins in the midperiphery and may progress in a centripetal manner until there remains only a central or peripheral island of vision. Because there is no single perfect reference standard for establishing the diagnosis of glaucoma, early diagnosis can be challenging. Although examination of the optic nerve head can reveal signs of neuronal loss, wide variability of its appearance in the healthy individuals makes identification of early damage challenging. Presence of characteristic visual field defects can assure the diagnosis, but as many as 30% to 50% of retinal ganglion cells may be lost before defects are detectable by standard visual field testing. Longitudinal evaluation and documentation of structural damage to the optic nerve is, therefore, a critical component of the diagnosis of the illness. Such an evaluation may be performed by observing the optic nerve head using an ophthalmoscope or by obtaining optic nerve head photographs. However, subjective identification of optic disc damage from glaucoma can be challenging, with large disagreement in grading observed even among glaucoma specialists. Several recently developed laser scanning imaging techniques provide more objective and quantitative information about the amount of optic nerve fiber (retinal ganglion cell axon) loss. These techniques, including confocal scanning laser ophthalmoscopy, scanning laser polarimetry, and optical coherence tomography, have improved the identification of early disease and also enhanced the observation of progressive optic nerve fiber loss over time.

Primary care physicians have an important role in the diagnosis of glaucoma by referring patients with a family history of glaucoma to undergo a complete ophthalmologic testing. Anyone with a family history of the disease and who has not had a dilated funduscopy examination of the optic nerve head in the past 2 years should be referred for examination. In addition, evaluation of the optic nerve with direct ophthalmoscopy performed by primary care physicians during a routine clinical visit, may exhibit signs suspicious for optic nerve damage that should prompt referral to an ophthalmologist.

The decrease in quality of life associated with glaucoma may occur earlier than previously thought, underscoring the importance of early diagnosis and management. Reduction of intraocular pressure is the only proven method to manage glaucoma. Results from several multicenter clinical trials have demonstrated the benefit of lowering intraocular pressure in preventing the development and slowing the disease's progression. The Ocular Hypertension Treatment Study randomized patients with ocular hypertension to treatment vs no treatment. At the end of 5 years of follow-up, 4.4% of patients in the medication group vs 9.5% in the untreated group developed signs of glaucoma. The Early Manifest Glaucoma Trial also randomized patients to treatment vs no treatment; however, all patients had a clear diagnosis of glaucoma at the baseline visit. After a median follow-up of 6 years, progression was less frequent in the treatment group (45%) than in the control group (62%). Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern recommend lowering the intraocular pressure toward a target level, which is a value or range of values at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease. Target intraocular pressure levels for a particular eye are established from pretreatment pressure levels that were associated with retinal damage, the severity of damage, risk factors for progression, life expectancy, and potential for adverse effects from treatment. In general, the initial target aims for a 20% to 50% reduction in pressure; however, the target pressure requires to be continuously reassessed during patient follow-up, depending on the evolution of the illness. For example, if there is continued disease progression (optic nerve changes or visual field loss) despite pressure levels at the initial target value, the target will need to be lowered. The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects. Several different classes of pressure-lowering medications are available. Medication choice may be influenced by cost,

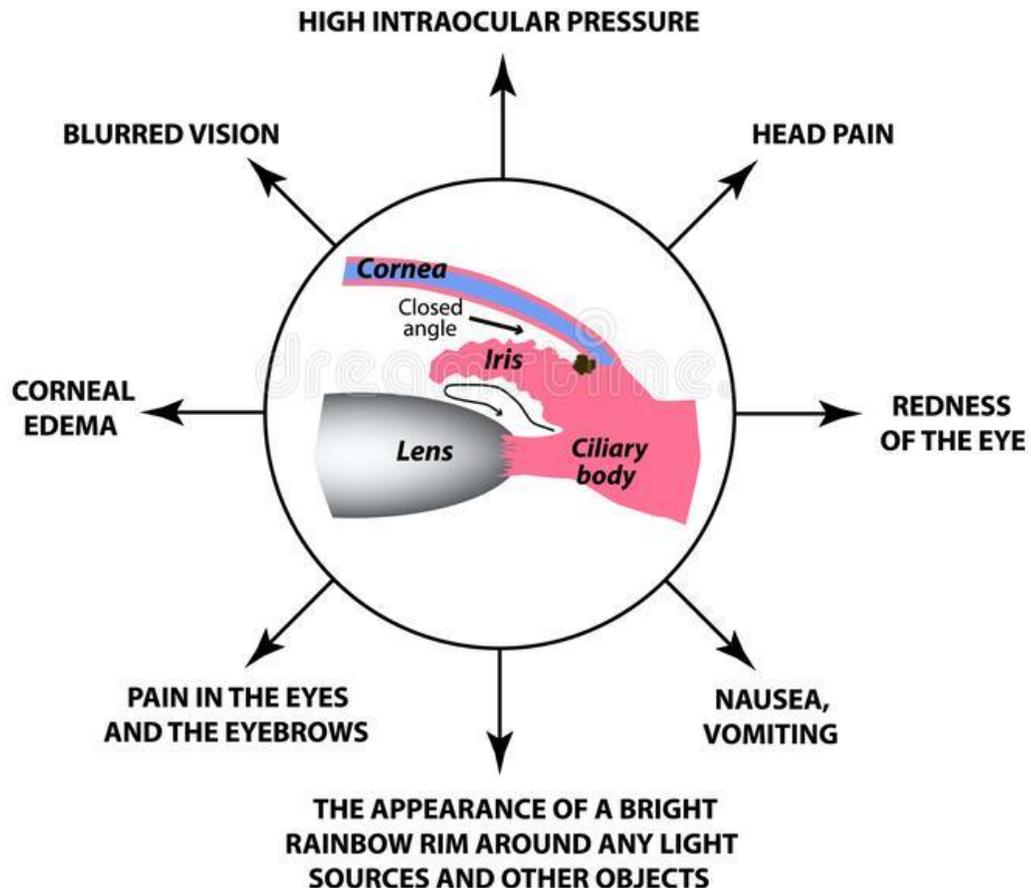
adverse effects, and dosing schedules. Generally, prostaglandin analogues are the first-line of medical management. These therapies reduce intraocular pressure by reducing outflow resistance causing increased aqueous humor flow through the uveoscleral pathway. These drugs are administered once nightly and have few, if any, systemic adverse effects. However, they can cause local adverse effects such as conjunctival hyperemia, elongation and darkening of eyelashes, loss of orbital fat (so-called prostaglandin-associated periorbitopathy), induced iris darkening, and periocular skin pigmentation. Other classes of topical medications are less effective in lowering intraocular pressure than prostaglandin analogues. They are used as second-line agents or when there is a contraindication or intolerance to the use of prostaglandin analogues. Prostaglandin analogues and carbonic anhydrase inhibitors lower intraocular pressure during both the day and night. Other therapies such as the β -adrenergic blockers and α -adrenergic agonists are efficient only during the day and not at night. Some of these agents, such as β -adrenergic blockers, may have recognizable systemic adverse effects and are contraindicated in patients with history of chronic obstructive pulmonary disease (COPD), asthma, or bradycardia. To decrease systemic absorption of topical treatments, it is advisable for patients to use gentle punctal occlusion or eyelid closure for 2 minutes after drug instillation. General practitioners and internists should be aware that topical treatments used by patients with glaucoma, including topical β -blockers, for example, may incur noticeable or even life-threatening adverse effects. Success of management can be enhanced by reinforcing the importance of compliance to the management regimen. When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or incisional surgeries are indicated. In poorly adherent patients or in those with severe disease, surgery may sometimes be offered as a first-line therapy. Laser trabeculoplasty lowers intraocular pressure by inducing biological changes in the trabecular meshwork leading to increased aqueous outflow. The procedure has an excellent safety profile and is performed during an office visit. Although substantial intraocular pressure reductions can be achieved in the majority of patients, the effect decreases gradually over time with a failure rate of about 10% per year. Trabeculectomy is the most commonly performed incisional surgical procedure to lower intraocular pressure. It consists of excision of a small portion of the trabecular meshwork and adjacent corneoscleral tissue to provide a drainage route for aqueous humor from within the eye to underneath the conjunctiva where it is absorbed. Antiscarring agents are frequently applied to

the surgical site to decrease fibroproliferative response and increase success rates of the surgery, but may increase the rate of complications such as infection and damage from very low intraocular pressure. Devices that drain aqueous humor to an external reservoir are an alternative to trabeculectomy that are similarly effective in lowering intraocular pressure. Several alternatives to these procedures have been proposed and are being investigated. These so-called minimally invasive glaucoma surgeries probably incur less risk of sight-threatening complications. These procedures have not had the same intraocular pressure-lowering efficacy as trabeculectomy; however, they may be described for selected cases for which risk-benefit considerations are more favorable than those with trabeculectomy. A recent meta-analysis comparing trabeculectomy with nonpenetrating surgeries (deep sclerectomy, viscocanalostomy, and canaloplasty) concluded that while trabeculectomy was more effective in reducing the pressure, it carried a higher risk of complications.



Figure(94):Closed-angle glaucoma explanation (www.google.com)

Symptoms of Angle-Closure Glaucoma



Figure(95):Closed-angle glaucoma symptoms (www.google.com)

For condition of primary closed-angle glaucoma the major characteristic distinguishing primary closed-angle glaucoma from primary open-angle glaucoma is that the angle, the site of aqueous outflow in the eye, is obstructed by apposition of the iris, resulting in an anatomically closed angle (defined if at least 270° of the angle is occluded). Like open-angle glaucoma, closed-angle

glaucoma is predominantly an asymptomatic disease with patients frequently unaware they have the disorder until advanced visual loss has occurred. In less than a third of cases, patients may present with acute primary angle closure, a clinical condition characterized by notable conjunctival hyperemia, corneal edema, a midsized unreactive pupil, a shallow anterior chamber, and very high intraocular pressure, usually greater than 30 mm Hg. Such individuals usually complain of ocular pain, nausea, vomiting, and intermittent blurring of vision with haloes noticed around lights.

Primary closed-angle glaucoma is caused by disorders of the iris, the lens, and retrolenticular structures. Pupillary block is the most common mechanism of angle closure and is caused by resistance to aqueous humor flow from the posterior to anterior chambers at the pupil. Aqueous humor accumulates behind the iris increasing its convexity causing angle closure. Nonpupil block mechanisms such as a plateau-like iris configuration may be responsible for a realizable proportion of angle closure in Asian patients. Closed-angle glaucoma may also be caused by dynamic physiological factors, such as an increase in iris volume with pupil dilation and choroidal effusion.

Risk factors for angle closure include female sex, older age, and Asian ethnicity (eg, Chinese). Eyes with angle closure tend to share certain biometric features. The major ocular risk factor for angle closure includes having a crowded anterior segment in a small eye, with a shallow central anterior chamber depth, a thicker and more anteriorly positioned lens, and short axial length of the eye. With anterior segment optical coherence tomography, other anatomical risk factors for angle closure have been described such as smaller anterior chamber width, area and volume, thicker irides with greater iris curvature, and a greater lens vault.

A genetic etiology for angle closure is proved by epidemiological findings: first-degree relatives of individuals with it are at greater risk than the general population, the high heritability of anatomical risk factors (such as anterior chamber depth), and ethnic variations in the prevalence.

The distinctive clinical characteristics of angle closure are seen in the angle of the eye by gonioscopy. A simple, handheld, mirrored instrument is placed on the patient's eye, followed by examination of the angle using a slit-lamp biomicroscope. With indentation, the examiner is also able to determine if peripheral anterior synechiae (adhesions between the iris and trabecular meshwork) are found. Gonioscopy is highly subjective, with poor reproducibility, and

gonioscopic findings may vary with the amount of light used during the examination or mechanical compression of the eye.

The treatment of individuals with angle closure depends on the stage of disease and on correctly identifying the underlying mechanism. The first-line treatment of angle closure is laser peripheral iridotomy, a procedure in which a full thickness hole is created in the iris to eliminate pupillary block. This procedure is generally easily performed in the office without adverse events. Rare complications of iridotomy comprise transient increases of intraocular pressure, cornea decompensation, posterior synechiae (adhesions of iris to lens) formation, and optically induced visual disturbances. Eyes managed with iridotomy may still develop increased pressure over time; thus, it is fundamental to have periodic follow-up after the procedure. Studies propose that iridotomy is most efficient in decreasing pressure in the early stages of illness, but once extensive synechial angle closure and glaucomatous optic neuropathy have developed, its effect is more subdued. If pressure remains high after iridotomy, long-term medical treatment (including topical β -blockers, α_2 -agonists, carbonic anhydrase inhibitors, and prostaglandin analogues) can be instituted, similar to the treatment of open-angle glaucoma.

Acute primary angle closure is an ocular emergency and requires immediate treatment to avoid blindness. Patients usually present with a painful red eye associated with blurring of vision, headache, nausea and vomiting. The cornea is usually hazy due to the very high intraocular pressure, and the pupil is often middilated and poorly reactive to light. The targets of the management are to achieve rapid pressure control with topical and systemic medications to limit optic nerve damage. This is followed by iridotomy to alleviate pupillary block. Iridotomy successfully aborts the attack in 42% to 72% of cases, and many patients recover without optic disc or visual field damage if the pressure is promptly and adequately controlled. Laser iridoplasty (contraction of the peripheral iris) can be performed if conventional medical management is not tolerated or does not abort the attack. If iridotomy is unsuccessful or difficult to perform because of a cloudy cornea, surgical iridectomy is indicated. Prophylactic iridotomy should be carried out for the fellow eye, which is at high risk of acute angle closure.

Treatment of patients suspected of having angle closure and who do not have glaucoma (ie, anatomically narrow angles but normal intraocular pressure and optic discs) is aimed at modifying the anterior segment configuration, before development of irreversible trabecular

meshwork damage and glaucomatous optic neuropathy. The current practice is to provide prophylactic iridotomy to such patients, particularly in the presence of risk factors such as a family history of angle closure, and those with symptoms or signs suggestive of intermittent acute angle closure, those who require repeated dilatation (such as diabetics), or for patients who lack access to medical care or are available for limited follow-up care. Cataract extraction with intraocular lens implant is an alternative to iridotomy in those with visually significant cataract because the surgery can decrease intraocular pressure and also widens the angles, thereby improving vision.

As in primary open-angle glaucoma, surgical management is indicated when there is inadequate intraocular pressure lowering or is indicated for those with progression of optic nerve or visual field damage despite medical and laser treatment. Trabeculectomy, either alone or in combination with lens extraction should be referred to if the pressure control remains too high despite laser and medical management, particularly in more advanced cases of open-angle glaucoma. Lens extraction is also performed when lens-related mechanisms predominate, especially in cases in which a significant cataract impairs vision. Finally, glaucoma drainage implants may be used in patients with chronic angle closure similarly to open-angle glaucoma when trabeculectomy has failed to control pressure, or in eyes that are deemed to be at high risk of failure with trabeculectomy.

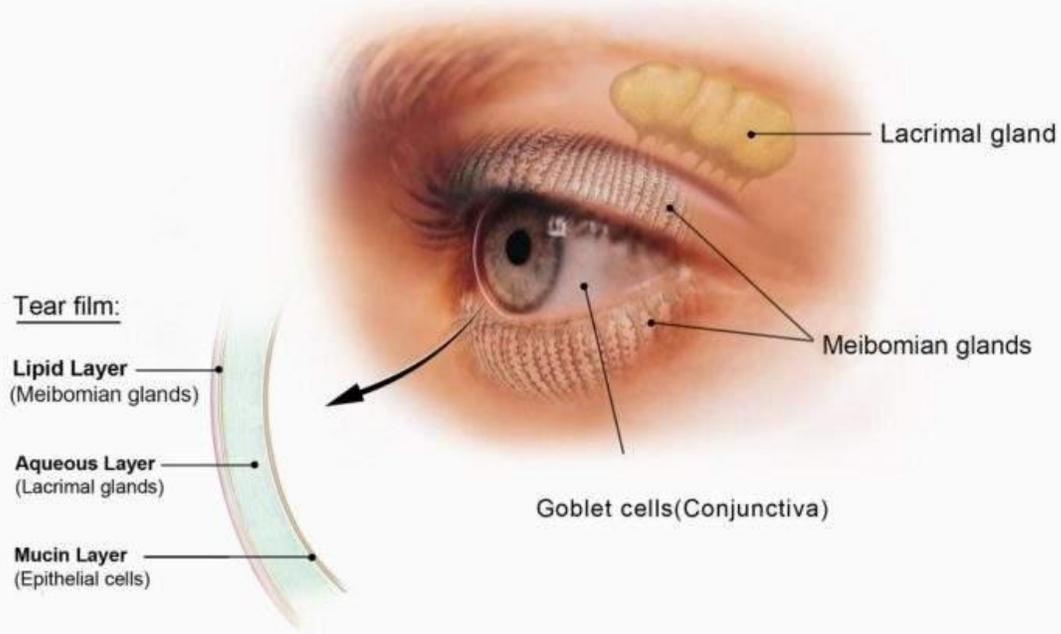
Retinal degeneration is a retinopathy which consists in the deterioration of the retina caused by the progressive death of its cells. There are several reasons for retinal degeneration, including artery or vein occlusion, diabetic retinopathy, retrolental fibroplasia/ retinopathy of prematurity (R.L.F./R.O.P.), or disease (usually hereditary). These may present in many different ways such as impaired vision, night blindness, retinal detachment, light sensitivity, tunnel vision, and loss of peripheral vision to total loss of vision. Of the retinal degenerative diseases retinitis pigmentosa (RP) is a very important example.

Photoreceptor cell death is the eventual outcome of retinal degeneration. Without proper function of the photoreceptor cells, vision is not possible. Irreversible loss of these cells has been attributed as a cause of blindness in many retinal degenerative disorders, including retinitis pigmentosa (RP). The exact mechanism of photoreceptor cell death is not clearly understood. Among potential causes is the endocytosis of stable complexes formed between

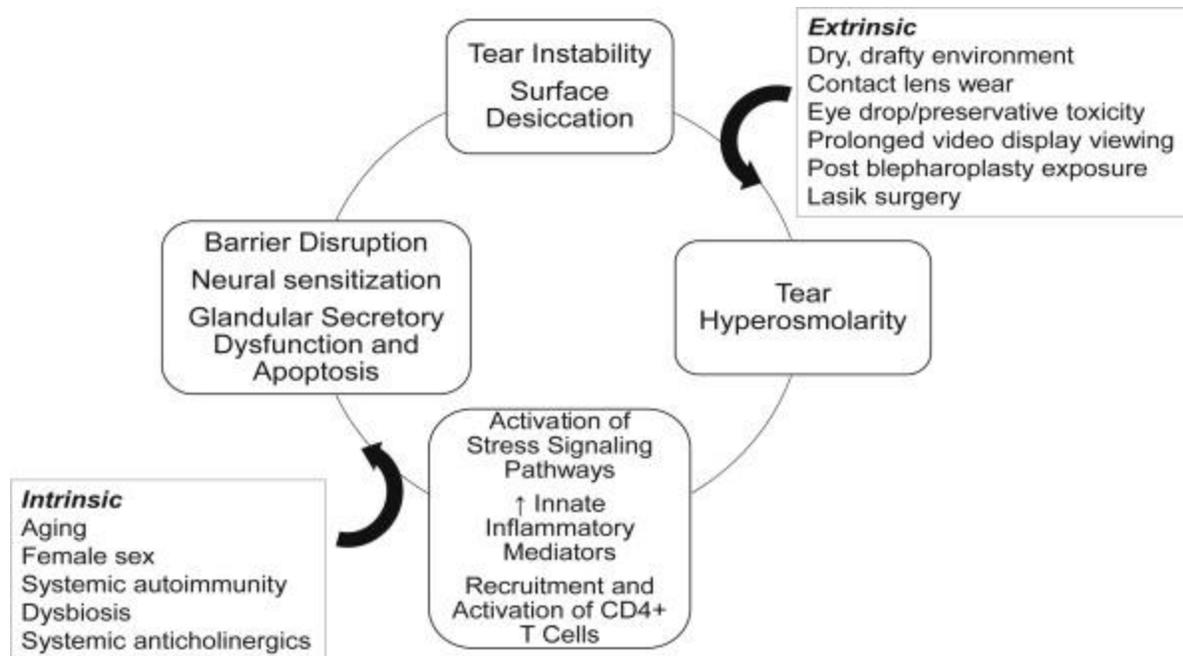
rhodopsin and its regulatory protein arrestin in certain mutants. Various studies have also recorded that over-expression of rhodopsin itself causes photoreceptor cell death and may induce photoreceptor cell loss in transgenic animals expressing truncated rhodopsin. Yet another mechanism may be prolonged photoreceptor responses and also abnormal rhodopsin deactivation may induce outer segment shortening and eventual photoreceptor death. In retinitis pigmentosa (RP) photoreceptor cell death is believed to occur by programmed cell death or apoptosis. Retinitis pigmentosa is a progressive neurodegenerative disorder. Retinitis pigmentosa (RP) begins with death of rod photoreceptor cells, which are the only cells in the retina to express rhodopsin and which express it as their most abundant protein. Eventually, loss of rod cells leads to loss of cone cells (cone photoreceptors), the mainstay of human vision. Symptoms of retinitis pigmentosa (RP) include loss of sensitivity to dim light, abnormal visual function, and characteristic bone spicule deposits of pigment in the retina. Affected patients progressively lose visual field and visual acuity, and photoreceptor cell death can ultimately lead to blindness. A prominent early clinical characteristic of retinitis pigmentosa (RP) is the loss of night vision as a result of death of rod photoreceptor cells. Proper expression of the wild-type rhodopsin gene is essential for the development and sustained function of photoreceptor cells.

Mutations in the human rhodopsin that affect its folding, trafficking and activity are the most commonly encountered causes of retinal degeneration in afflicted patients. Autosomal dominant retinitis pigmentosa (ADRP) due to rhodopsin mutations has a wide range of clinical presentation and severity.

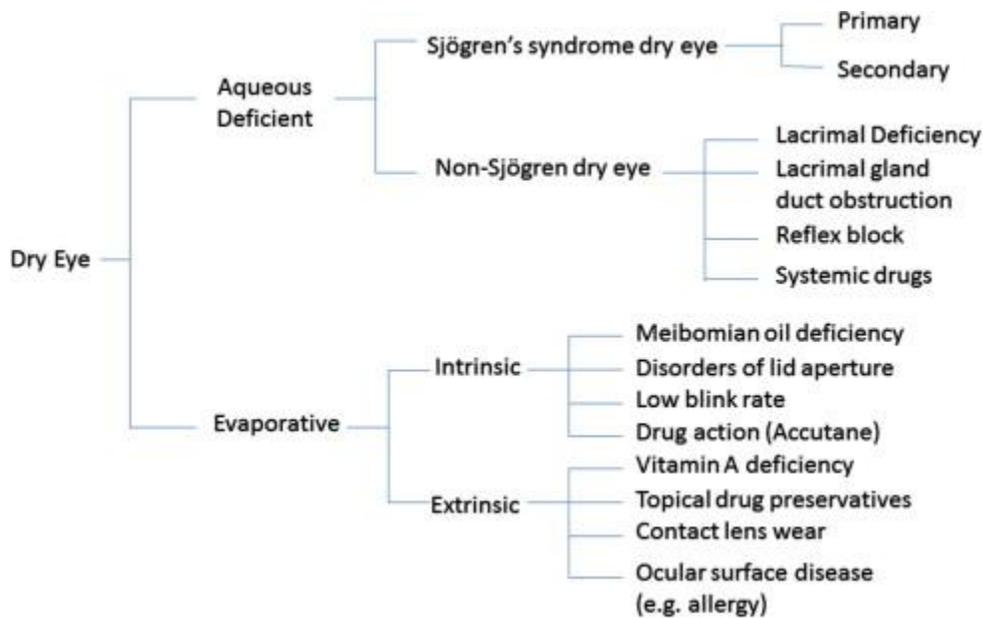
Structures Involved in Tear Production:



Figure(96):Tear production structures (www.google.com)



Figure(97):Pathophysiology of dry eye disease [Pflugfelder S.; Paiva C. (2017). The pathophysiology of dry eye disease:what we know and future directions for research. Elsevier. Ophthalmology, 124(11):S4-S13. <https://doi.org/10.1016/j.ophtha.2017.07.010>]



Figure(98):Dry eye disease [Lin H.; Yiu S. (2014). Dry eye disease: a review of diagnostic approaches and treatments. Saudi Journal of Ophthalmology, 28(3):173-181. <https://doi.org/10.1016/j.sjopt.2014.o6.002>]

Dry eye syndrome (DES) is a disorder of the pre-ocular tear film that results in damage to the ocular surface and is associated with symptoms of ocular discomfort. Dry eye syndrome (DES) is also called as keratoconjunctivitis sicca (KCS), keratitis sicca, sicca syndrome, xerophthalmia, dry eye disease (DED), ocular surface disease (OSD), or dysfunctional tear syndrome (DTS) or simply dry eyes. Keratoconjunctivitis sicca (KCS) is a latin word and its literal translation is dryness of the cornea and conjunctiva. It may be helpful to know that sicca is part of the english word desiccate. The dry eye syndrome (DES) in which the eyes do not produce enough tears is also known as Sjogrens syndrome. Dry eye disease is characterized by instability of the tear film that can be due to insufficient amount of tear production or due to poor quality of tear film, which leads increased evaporation of the tears. Dry eye therefore can mainly be divided in two groups viz:

1-Aqueous production deficient dry eye disease

2-Evaporative dry eye disease.

Insufficient tears cause damage to the inter palpebral ocular surface and is correlated with symptoms of discomfort. The International Dry Eye Workshop (2007) defined dry eye as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Dry eye syndrome (DES) is associated with decreased ability to perform certain activities such as reading, driving, computer related work etc., which require visual attention. Patients experience dry eyes symptoms constantly and severely, affecting their quality of life.

Dry eye is recognized as a consequence of disruption of lachrymal functional unit. The lachrymal functional unit consists of lachrymal glands, ocular surface comprising cornea, conjunctiva, eyelids, meibomian glands, ocular nerves, and goblet cells. The tear film is composed of three main layers. The innermost mucin or mucus layer is the thinnest, produced by cells of conjunctiva. The mucus helps the overlying watery layer to spread evenly over the eye. The middle or aqueous layer is the largest, thickest layer produced by the glands of upper lids and the accessory tear glands and contains essentially a very dilute saltwater solution. This layer keeps the eye moist and helps in removal of any dust, debris, or foreign particles. Defects of

this layer cause dry eye syndrome (DES) in most cases. The uppermost layer of tear film is a very thin layer of lipids. These lipids are produced by the meibomian glands and the glands of Zeis (oil glands in the eyelids). This layer helps to decrease evaporation of the watery layer beneath it. The mucus also reduces the surface tension between the lipid layer of the tear film and the water layer, thus contributing to the stability of the tear film. The tear fluid also consists of a complex mixture of proteins, immunoglobulins, mucins, electrolytes, cytokines, lysozymes, lactoferrin and growth factors. Lysozyme may act synergistically with immunoglobulin A (IgA) in lysis of bacteria. Tears also contain lactoferrin, which has some antibacterial effect.

Causes for dry eye syndrome (DES) include decreased tear production, excessive tear evaporation, abnormality in the production of mucus or lipids of tear layer. A report by Lemp *et al.* in 1995, classified Keratoconjunctivitis sicca (KCS) into tear deficient and evaporative dry eyes. Tear deficient dry eyes due to poor production of tears by the tear glands is found in older patients, in postmenopausal women and in individuals with autoimmune diseases like primary Sjogren syndrome, and rheumatoid arthritis (RA). Dysfunction of lacrimal functional unit causes changes in composition of the tear fluid and tear film stability leading to inflammation of ocular surface. Eye does not produce adequate tears as anti-inflammatory component of eye lacks and irritation of eye is not controlled. This causes activation of inflammatory cells including T-lymphocytes by immune system of body. T-cells release cytokines which causes inflammation of ocular surface and glands, thereby resulting in abnormal tears and dry eye symptoms. An increase in osmolarity of the aqueous layer is suggested as a global feature of dry eye syndrome (DES) and is known to trigger inflammation, damaging the ocular surface.

Sjögren syndrome (SS) is characterized by the combination of aqueous tear deficiency (ATD) and dry mouth (xerostomia). All cases of Sjögren syndrome (SS) are characterized by a progressive infiltration of the lacrimal and salivary glands by lymphocytes, leading to disorganization of the normal gland architecture and consequent loss of function. Patients with NonSjögren syndrome are associated with disease of the tear gland such as vitamin A deficiency, trachoma, sarcoidosis, lymphoma etc. In case of evaporative dry eyes, eyes dry out because of greater tear evaporation as in case of reduced blinking and lid surface anomalies. Environmental factors such as central heating, dry climate, air pollution, wind, chemical burns, contact lens wear, or reduced blinking because of driving, watching television (TV), computer work can

affect the tear film and proceed up to infection, corneal ulcer and blindness. Evaporative loss of tear fluid and dry eyes is usually associated with inadequate lipid layer. The lipid layer stabilizes and retards evaporation of the underlying aqueous layer. Rosacea, blepharitis and Meibomian gland dysfunction (MGD) are major cause of evaporative dry eyes. In case of ocular disease rosacea, there is abnormal production of lipids due to meibomian gland dysfunction.

The main symptom of dry eyes is dry and gritty feeling in the eyes. The additional symptoms involve burning or itching in the eyes, foreign body sensation, excess tearing, pain and redness of the eyes and photophobia (i.e., extreme sensitivity to light) in some cases. Sometimes it is also associated with a stringy discharge and blurred, changing vision. Symptoms are found to worsen in dry weathers, with low humidity and higher temperatures.

Treatment of keratoconjunctivitis may range from education, environmental or dietary modifications, artificial tear substitutes, punctal plugs, topical and/or systemic anti-inflammatory medications, and surgery.

Artificial tears are lubricant eye drops used to treat the dryness and irritation associated with deficient tear production in keratoconjunctivitis sicca (KCS). The lubricant tears are present as over the counter (OTC) products and often are the first line of treatment. Mild disease conditions require the application of lubricant drops four times a day while severe cases need greater frequency (10-12 times a day) of administration. These over the counter (OTC) products mainly vary in their ingredients, indications and availability of preservatives. Ingredients such as cellulose and polyvinyl derivatives, chondroitin sulfate and sodium hyaluronate determine their viscosity, retention time and adhesion to ocular surface. The increase in viscosity of tear drops prolongs the duration of action, however results in temporary blurred vision. Preservatives are added to multidose containers of artificial tears to reduce the risk of bacterial contamination, and to prolong shelf life. Many ophthalmic products contain preservatives and risk of adverse effects increases with frequency of their administration per day and also duration of their use. The clinician should consider the sensitivity of patient to preservatives, frequency of use, severity of disease, contamination risk with preservative free product and cost while recommending artificial tear product. Many ophthalmologists use other treatments such as cyclosporin, corticosteroids (CSs) and Tetracycline in conjunction with artificial tears, in moderate to severe forms of dry eyes, to reduce signs and symptoms. Lubricating tear ointments can be used during

the day, but they generally are used at bedtime due to poor vision after application. An artificial tear insert such as Lacrisert which contains hydroxyl propyl cellulose can also be used every morning.

Autologous serum eye drops contain different particular tear components such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), vitamin A, and fibronectin that are notable for maintaining healthy ocular surface. All these components are not available in the commercial products and use of these eye drops for treatment of keratoconjunctivitis sicca (KCS) is controversial.

Nonsteroidal anti-inflammatory (NSAID) drops containing drugs such as Diclofenac sodium, Ketorolac reduce the inflammation associated with dry eye syndrome (DES). Ophthalmic ointments containing antibiotics such as erythromycin and bacitracin are used for treatment of meibomian gland dysfunction. Topical ophthalmic aqueous solution of tetracycline has been developed for chronic dry eye syndrome (DES). Tetracyclines are used in dry eye syndrome (DES) primarily for their anti-inflammatory effects rather than antibacterial actions.

A small medical device called punctal plug is inserted into puncta of an eye to block the duct so as to prevent nasolacrimal drainage of tears from eye and thereby dry eyes. Clinical studies have shown that the punctal plugs as means of occlusion, improve dry eye disease (DED) symptoms and signs. Punctal plugs are usually reserved for individuals with moderate to severe keratoconjunctivitis sicca (KCS) and use of artificial tears are necessary after punctal plug insertion. Patient education and close follow up is recommended to detect plug loss and ensure adequate control of the disease.

Topical corticosteroids (CSs) such as, loteprednol etabonate, dexamethasone, prednisolone, fluomethalone are found to be efficient in inflammatory conditions correlated with keratoconjunctivitis sicca (KCS) and these are approved by the Food and Drug Administration (FDA) for treating inflammatory conditions of the conjunctiva, cornea, and anterior globe. They are generally recommended for short-term use as prolonged use may cause adverse effects such as ocular infection, glaucoma, and cataracts.

Cyclosporin A is effective in a number of ocular immune pathologies. Systemic administration of therapy is used in management of local ophthalmic conditions involving cytokines, such as

corneal graft rejection, autoimmune uveitis and dry eye syndrome (DES), however it induces severe renal and cardiovascular (CV) complications. Local administration avoids the various side effects associated with systemic delivery giving this drug a wide safety profile. Topical cyclosporine A is first Food and Drug Administration (FDA) approved drug indicated for management of individuals with aqueous production deficient dry eye and is better for long term treatment. It is a highly specific immunomodulator that prevents activation of T lymphocytes and significantly decreases levels of inflammatory cytokines in the conjunctival epithelium with an increase in goblet cells. It also inhibits mitochondrial-mediated pathways of apoptosis. The clinical study demonstrating the use of topical cyclosporine for the treatment of mild, moderate, and severe dry eye disease unresponsive to artificial tears therapy, reached to a conclusion that topical cyclosporine has shown beneficial effects in all categories of dry eye disease. Multiple studies have boosted the use of topical cyclosporine to manage dry eye disease (DED) resulted from insufficient tear production.

Vitamin A is an essential nutrient present naturally in tear film of healthy eyes. Vitamin A plays an important role in production of the mucin layer, most innermost lubricating layer of tear film that is crucial for a healthy tear film. Vitamin A deficiency causes loss of mucin layer and goblet cell atrophy. Vitamin A drops protect the eyes from free radicals, toxins, allergens and inflammation. Topical retinoic acid remedy in conjunction with systemic administration of vitamin A has been investigated to manage xerophthalmia. Effective amount of one or more retinoids alone may be dispersed in a pharmaceutically acceptable ophthalmic vehicle and topically applied for effective treatment of dry eye disorders.

Oral supplementation with essential fatty acids (EFAs) is suggested nowadays by Ophthalmologists. Essential fatty acids (EFAs) are the precursors of eicosanoids, locally acting hormones involved in mediating inflammatory processes. Essential fatty acids (EFAs) may benefit dry eye disease (DED) patients by reducing inflammation and by altering the composition of meibomian lipids. Clinicians may propose dietary intake of n-3 fatty acid to help relieve dry eye disease (DES). Some examples of omega 3 gel caps marketed specifically for dry eyes include Thera Tears and BioTears. Topical alpha-linolenic acid (ALA) treatment has been found to decrease signs of dry eye and inflammatory changes significantly at both cellular and

molecular levels. Thus topical application of alpha-linolenic acid (ALA) may be a medication to manage the clinical signs and inflammatory changes in keratoconjunctivitis sicca (KCS).

The uvea is made up of three parts: the iris, the ciliary body, and the choroid. An inflammation of any one of these is called uveitis.

The iris is the colored part of the eye and controls movement of the pupil.

The ciliary body is a muscle attached to the lens of the eye.

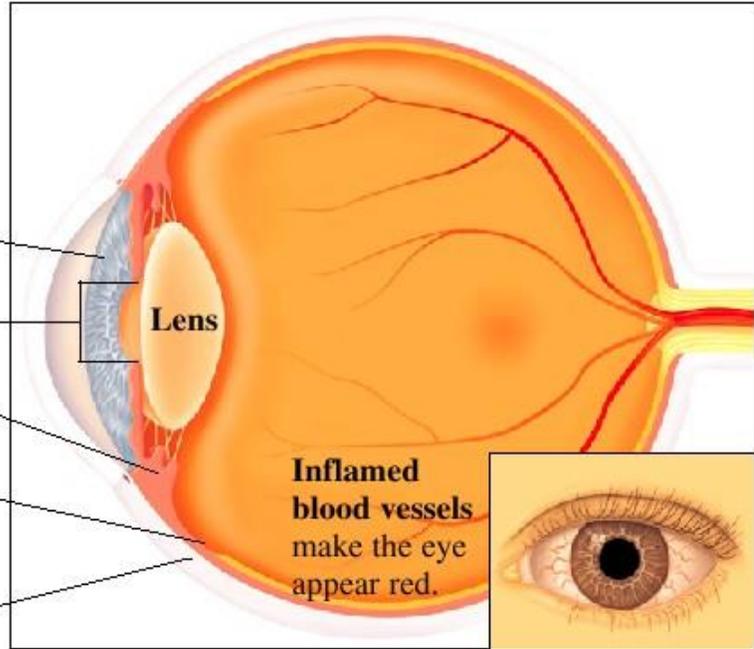
The choroid lies just behind the sclera and contains blood vessels to nourish the eye.

Sclera

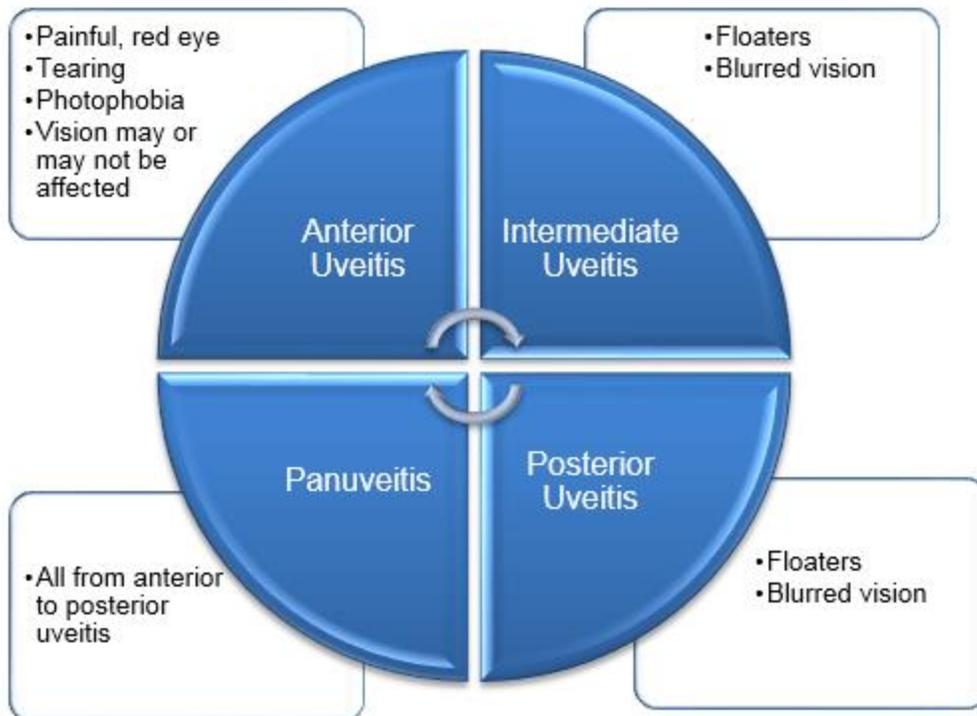
Pupil

Lens

Inflamed blood vessels make the eye appear red.



Figure(99):Uveitis [Beardsley R. (2020). Onward with uveitis. Oregon Eye Consultants. Internet]



Figure(100):Ocular inflammation (uveitis) (www.google.com)

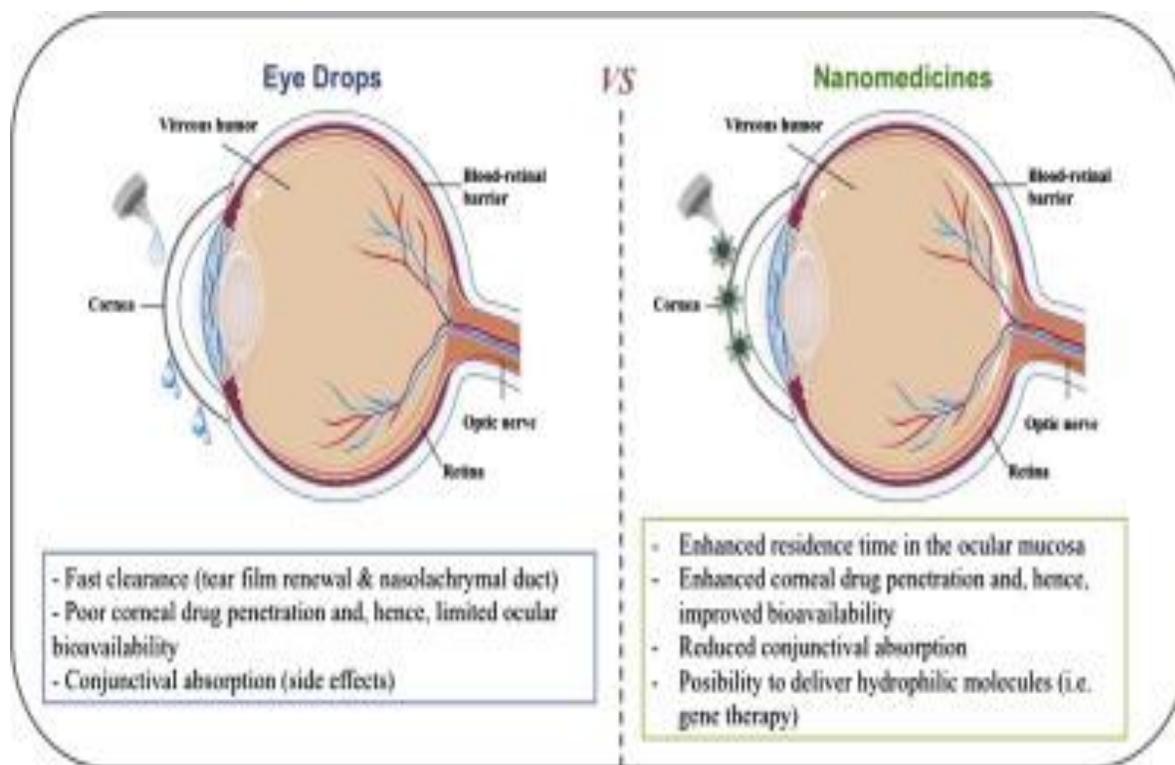
Uveitis, or inflammation of the uvea (which consists of the iris, ciliary body, and choroid), may be caused by a number of different etiologies. Anterior uveitis is defined by the presence of cells or cellular aggregates that are visible in the anterior chamber during examination. Anterior uveitis is one of the most common types of ocular inflammation that eye care practitioners will encounter. It may present as acute, subacute, or chronic. Uveitis may affect all ages, although it is most common in persons in the third and fourth decades. Under certain circumstances, the body produces a normal inflammatory response as a protective mechanism to heal itself. In chronic or uncontrolled cases, excessive infiltration of neutrophils, macrophages (MΦ), and lymphocytes may develop permanent damage to the ocular tissue. Anterior uveitis may be caused by infectious, noninfectious, and masquerade diseases. Diagnosis and treatment of the underlying disease are imperative not only to treat the disease but also to preserve vision and potentially uncover underlying systemic diseases. If untreated or not appropriately treated, acute inflammation can develop into chronic, sight-threatening inflammation, emphasizing the role of the primary eye care practitioner in appropriately and effectively treating these patients.

The pathology of an anterior uveitis can be either granulomatous or nongranulomatous. Granulomatous inflammation is associated with large, mutton-fat keratic precipitates (KPs) composed mainly of epithelioid cells on the corneal endothelium. Granulomatous uveitis tends to be chronic and is often associated with systemic conditions and autoimmune reactions. It may also be associated with infectious etiologies such as syphilis, Lyme disease, tuberculosis (TB), and herpetic viral infections. Nongranulomatous inflammation, by contrast, tends to be associated with smaller lymphocytic cells in the anterior chamber. It is most often acute and idiopathic or associated with human leukocyte antigen B27 (HLA-B27) conditions. While this distinction is useful in directing management and targeting a systemic workup, a granulomatous uveitis may initially present as nongranulomatous, as may the reverse.

Viral infections are the most common infectious underlying etiology of anterior uveitis. Increased intraocular pressure (IOP), iris atrophy, and unilateral presentations are common with viral etiologies.

Once an etiology has been established, adequate management may commence. Initial management of anterior uveitis includes topical corticosteroids (CSs). The most common topical corticosteroid (CS) prescribed for the management of anterior uveitis is prednisolone acetate 1%, followed by dexamethasone 0.1% and prednisolone sodium phosphate 1%. When a patient presents with an acute anterior uveitis, the eye care practitioner should prescribe corticosteroids (CSs) hourly while the patient is awake for at least 1 week in duration. Difluprednate 0.05% emulsion is a difluorinated prednisolone derivative that may be dosed four times daily and has been found to be similar in efficacy as compared to prednisolone acetate 1% when dosed eight times daily. The proper tapering schedule of topical corticosteroids (CSs) is one drop every 2 hours for 2 weeks, one drop four times per day for 2 weeks, one drop three times per day for 2 weeks, one drop two times per day for 2 weeks, one drop one time per day for 2 weeks, and then topical therapy should be discontinued. If the disease flares at any time during the follow-up process or the inflammation begins to increase, the primary eye care practitioner should consider either a slower taper or a referral for periocular corticosteroid injections. Cycloplegia, typically homatropine 5%, is also commonly prescribed one drop twice daily until there are fewer than five cells/HPF in the anterior chamber and then it is discontinued. Cycloplegia helps to lessen the pain a patient may experience that results from increased ciliary spasm. Cycloplegia also reduces the risk of posterior synechia development. In certain cases, additional therapies may be needed

in conjunction with topical corticosteroid (CS) and cycloplegic therapies. In all cases of anterior uveitis, it is imperative to determine whether the inflammation also includes posterior involvement, and for this reason, all patients who present with an anterior uveitis should have a dilated fundus examination. Patients who are HLA-B27 positive may have a hypopyon present along with their inflammation and usually require many weeks of hourly corticosteroids (CSs) before a taper is started. In addition to hourly topical corticosteroids (CSs), these patients may also be prescribed oral corticosteroids (CSs), which is equivalent to prednisone 1 mg/kg/d for the first 7 days or periocular injections (dexamethasone 2 mg, 0.5 mL). Patients who present with a hypopyon need to have the steroids tapered by one increment each month as it can recur rapidly without the slow taper. Antiviral coverage can be reduced to two times per day for acyclovir or one time per day for valacyclovir or famciclovir once the ocular inflammation is showing signs of reduction and once the patient's corticosteroid (CS) therapy has been tapered to one drop, three times per day. Long-term control can be extremely difficult in patients with anterior uveitis. The aim of long-term therapy is to keep the eye free of inflammation, which is the most challenging aspect in managing uveitis. In many cases of anterior uveitis, long-term therapy is not necessary, and the inflammatory process will not recur. However, in some instances, the iritis may recur during the initial corticosteroid (CS) taper or within 3 months of stopping it. Corticosteroids (CSs) are an acceptable option of maintaining long-term control of the inflammation if the dose required is low (three times per day or lower) and likely to be well tolerated, and the patient's iritis is not believed to be associated with a systemic disease. Intraocular pressure (IOP) in corticosteroid (CS) responders should be identified and closely monitored. Immunomodulatory treatment may be used for the long-term control of uveitis when patients cannot tolerate corticosteroids (CSs) either because of increased intraocular pressure (IOP) or early cataract formation or in the setting of systemic disease.



Figure(101):Treatment of ocular diseases [Reimondez-Troitino S.; Csaba N.; Alonso M.; de la Fuente M. (2015). Nanotherapies for the treatment of ocular diseases. Elsevier. European Journal of Pharmaceutics and Biopharmaceutics, Volume 95, Part B:279-293. <https://doi.org/10.1016/j.ejpb.2015.02.019>]

16.1Ocular Complications in COVID-19 Infection

There are reports of ocular infection in the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic. On the 22nd of January 2020, Guangfa Wang, a member of the national expert on pneumonia had developed conjunctivitis during an inspection of Wuhan, the epicenter of the outbreak. He was subsequently tested positive for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) but he ultimately recovered from the infection. This led to a call for research into ocular infection as a possible alternative route of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission. From genomic and structural analyses, it has been reported that the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has a similar receptor-binding motif as severe acute respiratory syndrome coronavirus (SARS-CoV), which allows it to infect host cells via the angiotensin-converting enzyme-2 (ACE2). The renin-angiotensin system (RAS), apart from its well-known endocrine role in blood pressure regulation, also has complicated autocrine functions within specific tissues. The human

eye has its own intraocular renin-angiotensin system (RAS), a system that has been the interest of many projects focusing on developing anti-glaucomatous drugs. Angiotensin-converting enzyme-2 (ACE2) is found in the aqueous humor.

Angiotensin-converting enzyme-2 (ACE2) is a cellular receptor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Angiotensin-converting enzyme-2 (ACE2) has been detected in the human retina, vascularised retinal pigment epithelium choroid and conjunctival epithelia. In a study, severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) was detected in conjunctival sac specimens obtained from the patient on days 13, 14 and 17 of illness. The conjunctiva may be a locus of direct inoculation as a result of severe acute respiratory syndrome coronavirus (SARS-CoV) droplet from the infected patients via aerosol route or migration from upper respiratory tract through naso lacrimal duct (NLD) or via hematogenous spread. In-vitro and in-vivo studies confirmed that the eye can function dual intent for establishment of an infection. On one hand it acts as a portal of entry and on the other hand it also functions as a primary virus replication site. In the case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), few cases reported ocular symptoms first, which was followed by systemic symptoms, which sheds light on the importance of this hypothesis and importance of this route in establishment of the infection. Infected tear can be taken up by cornea or conjunctiva, epithelium of lacrimal duct or drained to nasopharynx through the nasolacrimal duct (NLD). The epithelial lining of nasolacrimal duct (NLD) with presence of microvilli additionally allows both secretion and reabsorption of tear fluid components. Beyond these anatomical connections, the molecular associate at the level of receptors may play a main role in ocular tropism of respiratory viruses. Many cellular proteins line human epithelial cell glycoproteins such as angiotensin-converting enzyme-2 (ACE2) and CD147. These receptor mediated entry and subsequent replication in those cells may pave way for further replication and spread of the virus. In case of severe acute respiratory syndrome coronavirus (SARS-CoV), the initial interaction between the S1 domain of the virus interacts with either angiotensin-converting enzyme-2 (ACE2) or CD147, which is followed by S2 domain of spike (S) protein mediated entry of the virus inside the cell, which is followed by replication of the same intracellularly and subsequent budding and release of virion progenies.

As early as 1988, angiotensin-converting enzyme (ACE) activity was demonstrated in human eye. Later on an independent ocular renin-angiotensin system (RAS) system was detected. Presence of angiotensinogen and angiotensin-converting enzyme (ACE) gene expression can be detected by reverse transcription polymerase chain reaction (RT-PCR) in retinal pigment epithelium (RPE), choroid and neural retina and sclera individually. Immuno histo chemistry (IHC) studies shows, angiotensin-converting enzyme-2 (ACE2) and angiotensin II (Ang-II) were localized to non-pigmented epithelium of ciliary body, corneal epithelium and endothelium, conjunctival epithelium and trabecular meshwork lining. In the posterior segment, angiotensin-converting enzyme (ACE) and angiotensin II (Ang-II) were localized to retinal ganglion cells, some cells in inner nuclear layer and retinal photoreceptor cells, endothelium lining of choroidal and retinal vessels. Angiotensin-converting enzyme-2 (ACE2) receptor is also located in aqueous humor and the level was elevated in glaucomatous eyes. In in-vitro studies also expression of angiotensin-converting enzyme-2 (ACE2) is positive in cornea and conjunctiva; the conjunctival and corneal cells can bind to the spike proteins (S240) of severe acute respiratory syndrome coronavirus (SARS-CoV). Also it is to be noted that location of angiotensin-converting enzyme-2 (ACE2), cellular receptor for severe acute respiratory syndrome coronavirus (SARS-CoV) on cardiac and lung tissue likely contributes to severe acute respiratory syndrome (SARS) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus. One of the novel route of severe acute respiratory syndrome coronavirus (SARS-CoV) entry to human host is through its interactions with CD147. Localization studies using immuno histo chemistry (IHC) assured the presence of CD147 in tear, different human ocular tissues comprising corneal epithelium and endothelium, stromal keratocytes, conjunctiva and retinal pigment epithelium (RPE). The expression of CD147 is increased in tear samples of patients with dry eye disease (DED).

Coronavirus (CoV) had been previously reported to be associated with conjunctivitis in humans. Additionally, retinal disorders, such as retinal vasculitis, retinal degeneration and blood–retinal barrier (BRB) breakdown, had been demonstrated in experimental animal models of coronavirus (CoV) infection.

A study documented the ocular complications of a patient with confirmed coronavirus disease 2019 (COVID-19) after 13 days of disease onset. The clinical presentation of this case met the

criteria of acute viral conjunctivitis. It is possible that ribavirin eye- drops helped to manage the symptoms of illness. The conjunctival swabs tested positive for severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) for at least 5 days with the cycle threshold (Ct) values gradually increasing. However, the detection was much lower in conjunctival swabs than in respiratory specimens. This case explains several aspects of ocular complications of coronavirus disease 2019 (COVID-19), involving the full clinical course of ocular manifestations and the dynamic changes of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral detection in conjunctival swab samples. A retrospective study tested conjunctival samples for severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV-2 RNA) in 30 infected patients, and the conjunctival samples from one patient were positive for the viral RNA on 3 days after onset. The fact that the patient developed acute viral conjunctivitis with positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) tests in conjunctival swab samples showed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could really lead to ocular complications but not necessarily in the early stage of disease. This report determined the presence of the viral ribonucleic acid (vRNA) in the conjunctival specimens of a patient with coronavirus disease 2019 (COVID-19). Viral ribonucleic acid (vRNA) was present in the patient's conjunctival sacs for at least 5 days. The viral ribonucleic acid (vRNA) levels in conjunctival specimens were dramatically lower than those in respiratory samples. More viral ribonucleic acid (vRNA) in conjunctival sacs [inversely related to threshold cycle (Ct) value] was detected 13 days after onset, soon after the symptom onset of acute conjunctivitis. Conjunctival samples taken on illness days 13, 14, 17 and 19 revealed a tendency toward decreasing levels of viral ribonucleic acid (vRNA). The result presumed that viral loads in conjunctival specimens gradually decrease over time with less probable for transmissibility accompanied by improvement of the ocular symptoms. Authors in this study defined the clinical features of acute conjunctivitis occurring 13 days after onset in a patient with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. This case confirmed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) led to ocular complications, but not in the early stage of infection. On the one hand, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in conjunctival samples might represent a source of spread, especially with higher viral loads at the acute stage of ocular complications. On the other hand, the conjunctiva might not function as an ideal site for

sampling for early diagnostic tests of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

However, a report in the scientific literature revealed the presence of severe acute respiratory syndrome coronavirus (SARS-CoV) in patients' tears early in the course of the coronavirus disease 2019 (COVID-19).

A total of 6 studies (total 854 patients) reported incidence of ocular symptoms in coronavirus disease 2019 (COVID-19). The pooled prevalence of conjunctivitis was 3.175%.

Chen *et al.* (2020) described in their research the other ocular symptoms of coronavirus disease 2019 (COVID-19) infected patients as different ocular discomfort apart from conjunctivitis as 3.8% conjunctival congestion, increase conjunctival secretion 10.6%, ocular pain 5.7%, foreign body sensation 19% and increased tearing 13.3% among total 534 patients of Mobile cabin hospital. Of interest about 31.2% patients suffers from co-existing dry eye and few individuals have past history of ocular disease [conjunctivitis 7.6%, keratitis (inflammation of the cornea of the eye) 4.2%, and xerophthalmia (abnormal dryness of the conjunctiva and cornea of the eye, with inflammation and ridge formation, typically associated with vitamin A deficiency) 8%]. Similarly in a different hospital, out of 271 patients in Tongji hospital, 5.5% had conjunctival congestion, 8.9% had increased conjunctival secretion, 2.6% had ocular pain and 4.8 % had foreign body sensation. On taking the detail history, 4.8% had keratitis, 1.1% had xerophthalmia, 2.6% had cataract, 0.4% had macular disease, 1.5% had diabetic retinopathy, and 0.7% had other retinal disease.

In a considered meta-analysis study in 2020 regarding patients suffering from coronavirus disease 2019 (COVID-19) the proportion of patients reporting conjunctivitis/red eye was 3.175%, however only 0.703% patients reported conjunctivitis as the first symptom of the disease. Other characteristics that are reported by a single study are increase conjunctival secretion 10.6%, ocular pain 5.7%, and foreign body sensation 19% and increased tearing 13.3%, however in that study, patients also had history of other ocular co-morbidities (e.g. dry eye) and past history of ocular disease (e.g. keratitis, xerophthalmia, retinal and macular disease). None of the included study reported any ocular complication following conjunctival sampling. So, ocular manifestations are not so common analysis or are under-reported in case of coronavirus disease

2019 (COVID-19) as evidenced by this meta- analysis study. Two of the included studies has reported pattern of conjunctival secretion in conjunctivitis case. It was reported that the discharge is first watery which may become thin mucoid discharge along with occasional small piece of conjunctival haemorrhage. On looking back to the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) epidemic, similar lower incidence of ocular complication was also seen in case of severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1). Yuen *et al.* (2003) mentioned that out of 90 eyes of diagnosed severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) patients (45 patients) during the epidemic outbreak with not a single case of conjunctivitis. However insights from the animal model (rhesus macao) highlights the importance of the oculoconjunctival route in establishing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. In this study, for the macaos infected by conjunctival route, distinct pattern of viral localization was found which included primarily the nasolacrimal duct (NLD) and ocular structure, nasal cavity and lungs. However, in case of intratracheal instillation, the primarily affected region was lung and viral load was relatively high. However gastrointestinal (GI) localization was recognized in case of both the routes. Animal models provide authors further insight about the different possible ocular manifestation/complication, which involve anterior uveitis, choroiditis with retinal detachment, retinal vasculitis, and optic neuritis. Similarly virus induced retinal vasculitis, retinopathy, inflammation induced retinal pigment degeneration and subsequent loss of photoreceptor, ganglion cells and thinning neuroretinal tissue as a delayed response after resolution of viremia (delayed sequelae) also has to be taken into account. Another notable point is that animal models of coronavirus (CoV) infection generally exhibit poor visual and systemic prognosis. So direct clinical transability of these animal data to human is a matter of question, however it should not be overlooked. As the drug hydroxychloroquine (HCQ) and chloroquine are being used in the treatment of coronavirus disease 2019 (COVID-19) as recommended, the next generation patients may present with different ocular toxicities of these agents and this may change the ophthalmologic scenario in case of coronavirus disease 2019 (COVID-19) treatment and ophthalmologist should be aware of it. In this study and among all coronavirus disease 2019 (COVID-19) patients, the proportion of conjunctival/tear sample that was positive for the virus [reverse transcription-polymerase chain reaction (RT-PCR) detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)] was found to be 1.949%. Among patients with coronavirus disease 2019 (COVID-19)

associated conjunctivitis (n=7), however only 28.6% cases were found to contain the virus in tear or conjunctival swab as evidenced by reverse transcription-polymerase chain reaction (RT-PCR). Again amongst all patients positive for the virus in tear/conjunctival samples (n=6), only 33.3% patients showed red eye/conjunctivitis. In this study, polymerase chain reaction (PCR) positivity among coronavirus disease 2019 (COVID-19) cases was low (1.949%). Therefore, sampling by trained manpower (ophthalmologist/optometrist) plays a very important role more specifically in case of tear sampling, which needs a definite grade of expertise. Among studies included in this meta-analysis study, the person taking the sample and details of sampling technique, number of times same sample analyzed (duplicate/triplicate) timing of sampling with reference to onset of disease (which is likely to reflect the viral load) is not clearly mentioned, which may be a cause of lesser number of positive cases in the conjunctival sample. It was recommended the use of micro capillary pipettes or Shirmer's filter paper strips for getting good quantity and quality of sample which is performed in only a few followed studies. However the agents for treating the ocular shredding of virus are a matter of concern. Although there is Gancyclovir, acyclovir as antiviral agent, however efficacy of the agents in coronavirus disease 2019 (COVID-19) is unknown. Povidone iodine 1% eye drop is already in use against viral conjunctivitis and the same solution has shown excellent anti- severe acute respiratory syndrome coronavirus (SARS-CoV)activity, however it is not established against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and there is a need of clinical data on this.

17.Kidney Injury

Traditionally, emphasis on acute renal failure (ARF) was focused on the most severe acute decrease in kidney function, as manifested by severe azotaemia and frequently by oliguria or anuria. Azotemia is a biochemical abnormality, described as elevation, or buildup of, nitrogenous products [blood urea nitrogen (BUN)-usually ranging 7 to 21 mg/dL], serum creatinine (SCr), and other secondary waste products within the body. Raising the level of nitrogenous waste is attributed to the inability of the renal system to filter[decreased glomerular filtration rate,(GFR)] such as waste products appropriately. Azotaemia is a typical characteristic of both acute kidney injury (AKI) and chronic kidney injury (CKI). Oligouria is described by consensus opinion as a urine output of < 0.5 ml/kg/h for more than 6 h. Anuria or anuresis happens when the kidneys are

not producing urine. A person may first suffer from oliguria, or low output of urine, and then develop anuria.

Currently, evidence presumes that even relatively mild injury or impairment of kidney function manifested by small changes in serum creatinine (sCr) and/or urine output (UO), is a predictor of serious clinical consequences to kidney.

Acute kidney injury (AKI) is the term that replaced the term acute renal failure (ARF). Acute kidney injury (AKI) is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that scarcely has a solo and distinguished pathophysiology. Many individuals with acute kidney injury (AKI) have a mixed aetiology where the presence of sepsis, ischaemia, and nephrotoxicity often co-exist and complicate recognition and management.

Classification of acute kidney injury (AKI) involves pre-renal acute kidney injury (AKI), acute post-renal obstructive nephropathy, and intrinsic acute kidney diseases. Of these, only intrinsic acute kidney injury (AKI) represents true kidney disease, while pre-renal and post-renal acute kidney injury (AKI) are the consequence of extra-renal diseases leading to the decreased glomerular filtration rate (GFR). If these pre- and/or post-renal conditions persist, they will lastly develop to renal cellular damage and hence intrinsic renal disease.

The current diagnostic approach of acute kidney injury (AKI) is relied on an acute decrease of glomerular filtration rate (GFR), as reflected by an acute elevation in serum creatinine (sCr) concentrations and/or a fall in urine output (UO) over a given time interval.

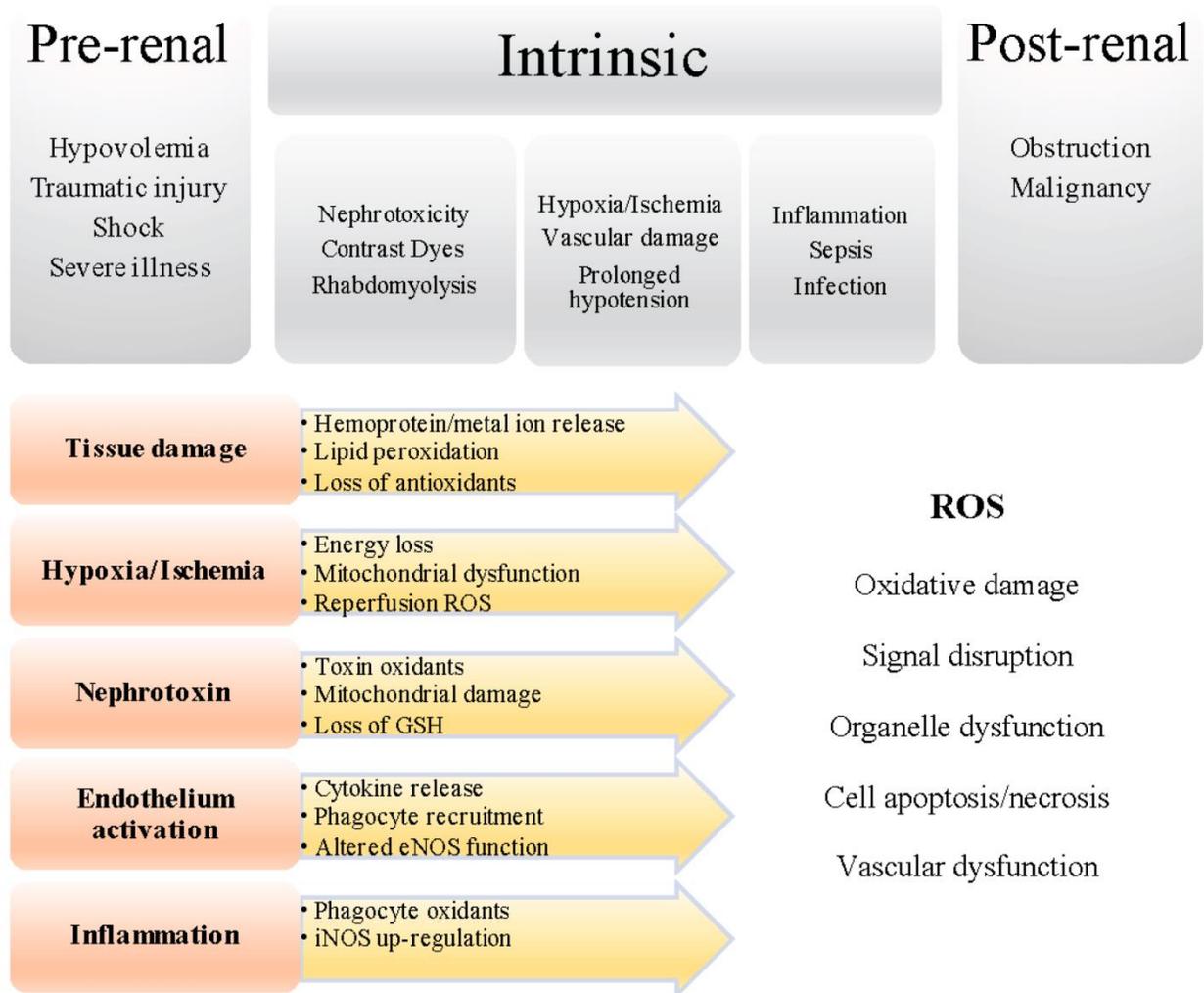
Acute kidney injury (AKI) is particularly a term used to define the clinical syndrome that happens when renal function is acutely decreased to a point that the body accumulates waste products and becomes unable to maintain electrolyte, acid-base and water balance.

The pathophysiology of acute kidney injury (AKI) is multifactorial and complicated. The most common cause of acute kidney injury (AKI) is ischaemia, which can occur for a number of causes. Physiological adaptations, in response to the decrease in blood flow can compensate to a particular degree, but when delivery of oxygen and metabolic substrates becomes inappropriate, the resulting cellular injury progresses to organ dysfunction. The kidney is highly susceptible to injury related to ischaemia, causing vasoconstriction, endothelial injury, and activation

inflammatory immune responses. This susceptibility can be interpreted partly from structural associations between renal tubules and blood vessels in the outer medulla of the kidney, with ischaemia compromising blood flow to critical nephron structures present therein. Following the decrease in efficient kidney perfusion, the epithelial cells are unable to maintain appropriate intracellular adenosine triphosphate (ATP) for particular processes. This adenosine triphosphate (ATP)-depletion develops cell injury and if it is severe enough can result in cell death by necrosis or apoptosis. During an ischaemic insult all segments of the nephrons can be affected but proximal tubular cells are the most commonly injured. Furthermore, the nephron's natural function is to filter, concentrate and reabsorb many substances from tubular lumen, and the level of these substances may reach toxic concentrations for the surrounding epithelial cells.

Acute kidney injury (AKI) is also very common in the setting of sepsis. In sepsis the circulation is hyperdynamic and blood flow is altered, albeit not requisitely in the ischaemic range, and glomerular filtration rate (GFR) drops rapidly. The pathophysiology of septic-acute kidney injury (AKI) is very complicated and includes inflammation, oxidative stress (OS), microvascular dysfunction, and amplification of injury via release of cytokines by tubular cells. The traditional classification of acute kidney injury (AKI) into pre-renal, intrinsic-renal, and post-renal has been challenged since histological diagnosis is performed very scarcely and distinguishing between pre-renal azotaemia and tubular damage cannot be assured and only hypothesised retrospectively. The knowledge is mostly taken from animal studies where the ischaemia-reperfusion model has been extensively researched. Other models (toxic injury, septic model) are less researched. However, these latter models are quite extreme and are not representative of the clinical manifestations of acute kidney injury (AKI) in humans, where renal blood flow never fully stops (except in certain surgical procedures i.e. abdominal aortic aneurysm repair) but less severe forms of low blood flow followed by reperfusion generally happen. Controversy also exists regarding the extent of damage as well as the cell types affected by this damage (proximal vs distal tubular cells).

Pathophysiology of Acute Kidney Injury



Figure(102):Acute kidney injury pathophysiology [Dennis J.; Witting P. (2017). Protective role for antioxidants in acute kidney disease. *Nutrients*, 9(7), 718. <https://doi.org/10.3390/nu9070718>]

AKI - Diagnostic criteria

RIFLE ^a and Acute Kidney Injury Network (AKIN) staging criteria for acute kidney injury			
RIFLE stage	AKIN stage	Serum creatinine criteria	Urine output criteria
Risk	1	Increase in serum creatinine of 1.5- to two-fold from baseline (RIFLE and AKIN) or increase in serum creatinine of ≥ 0.3 mg/dL (AKIN)	< 0.5 mL/kg/h for 6 h
Injury	2	Increase in serum creatinine of two- to threefold from baseline	< 0.5 mL/kg/h for 12 h
Failure	3	Increase in serum creatinine of more than threefold from baseline or a serum creatinine of > 4 mg/dL with an acute rise of ≥ 0.5 mg/dL	< 0.3 mL/kg/h for 24 h or anuria for 12 h
Loss		Persistent renal failure for > 4 wk	
End-stage renal disease		Persistent renal failure for > 3 mo	

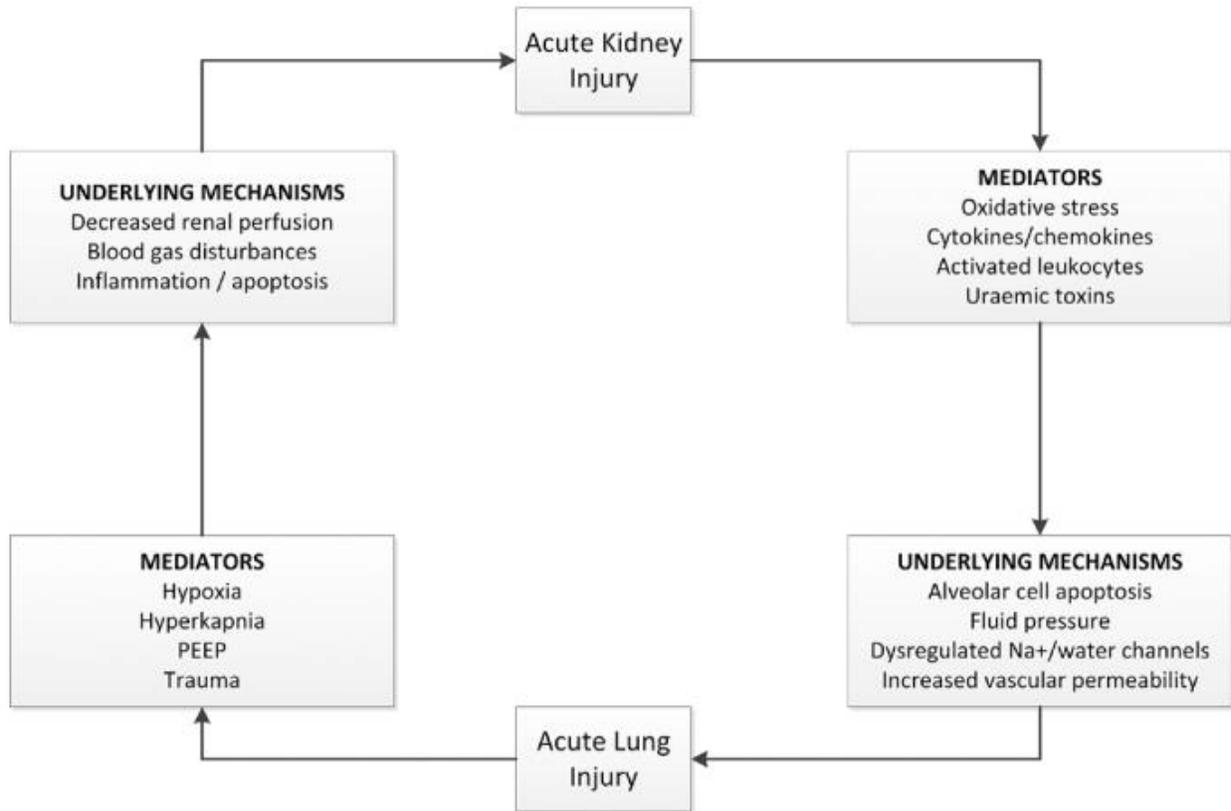
^a RIFLE defines three grades of increasing severity of acute renal dysfunction (risk, injury, and failure; respectively R, I, and F) on the basis of graded changes in serum creatinine or urine output and two outcomes variables (loss and end-stage kidney disease, L and E, respectively) based on the duration of loss of kidney function.

www.MedicHemco.com

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Figure(103):Acute kidney injury diagnostic criteria (www.google.com)

The kidney and the lung are the two most commonly included organs in multi-organ failure. Acute lung injury (ALI) and acute kidney injury (AKI) are common complications of sepsis and the development of either increases mortality. Currently there is growing interest in the probable cross-talk that is found between these organs when injured, with one organ causing or contributing to injury to the other. Animal studies have demonstrated that acute kidney injury (AKI) can lead to acute lung injury (ALI) and vice versa. The mechanism of acute kidney injury (AKI) associated lung injury remains incompletely understood. Several studies have indicated the involvement of pro-inflammatory and proapoptotic factors [leukocyte trafficking, cytokines activation of caspases, oxidative stress (OS) and uraemic toxins]. Acute kidney injury (AKI) causes lung injury and inflammation and acute lung injury (ALI) in turn facilitates and exacerbates kidney dysfunction via metabolic and biochemical derangements.



Figure(104): Kidney-lung interaction and acute kidney injury [Makris K.; Spanou L. (2016). Acute kidney injury: definition, pathophysiology and clinical phenotypes. The Clinical Biochemist Reviews, 37(2):85-98]

Management & Treatment

- Treat underlying disorder, ? steroids if AIN.
- Avoid nephrotoxic insults; review dosing of renally cleared drugs.
- Optimize hemodynamics (both MAP & CO); may take 1–2 wks to recover from ATN
- Watch for and correct volume overload, electrolyte (\uparrow K, \uparrow PO₄), & acid/base status
- If obstruction is diagnosed and relieved, watch for:
 - Hypotonic diuresis (2° buildup of BUN, tubular damage); Rx w/ IVF (e.g. 1/2 NS).
 - Hemorrhagic cystitis (rapid Δ in size of bladder vessels); avoid by decompressing slowly.
- Indications for urgent dialysis (when condition refractory to conventional therapy)
 - ✓ Acid-base disturbance: **acidemia**
 - ✓ Electrolyte disorder: generally **hyperkalemia**; occasionally hypercalcemia, tumor lysis
 - ✓ **Intoxication**: methanol, ethylene glycol, lithium, salicylates
 - ✓ **Overload of volume** (CHF)
 - ✓ **Uremia**: pericarditis, encephalopathy, bleeding

Figure(105): Acute kidney injury management and treatment (www.google.com)

17.1 Kidney Injury in COVID-19 Infection

A study of 59 patients with coronavirus disease 2019 (COVID-19) showed that 34% of patients developed massive albuminuria on the first day of admission, and 63% developed proteinuria during their stay in hospital. Albuminuria is a sign of kidney disease and indicates that there is too much albumin in urine. Albumin is a protein found in the blood. A healthy kidney doesn't let albumin pass from the blood into the urine. A damaged kidney lets some albumin pass into the urine. Proteinuria is described as urinary protein excretion of greater than 150 mg per day. Urinary protein excretion in healthy persons varies considerably and may reach proteinuric concentrations under several circumstances. In the study, blood urea nitrogen (BUN) was elevated in 27% overall and in two-thirds of patients who died. Computed tomography (CT) scan of the kidneys showed reduced density, suggestive of inflammation and edema. Cheng *et al.* (2020) mentioned that amongst 710 consecutive hospitalized patients with coronavirus disease 2019 (COVID-19), 44% had proteinuria and hematuria, i.e. blood in the urine, and 26.7% had hematuria on admission. The prevalence of elevated serum creatinine (SCr) and blood urea nitrogen (BUN) was 15.5% and 14.1%, respectively. Acute kidney injury (AKI) was an

independent risk factor for patients' in-hospital mortality. Authors in this study interpreted that the exact mechanism of kidney involvement is unclear: postulated mechanisms include sepsis leading to cytokine storm syndrome or direct cellular injury due to the virus. Angiotensin-converting enzyme and dipeptidyl peptidase-4, both expressed on renal tubular cells, were identified as binding partners for severe acute respiratory syndrome coronavirus (SARS-CoV) and MERS-CoV, respectively. Viral ribonucleic acid (vRNA) has been identified in kidney tissue and urine in both infections. Zhong's lab in Guangzhou successfully isolated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) from the urine sample of an infected patient, supposing the kidney as the target of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

A retrospective study of coronavirus disease 2019 (COVID-19) patients revealed a specific mortality risk factor: kidney dysfunctions, which generally appeared at first as mild abnormalities and could later progress as clinically-diagnosed acute kidney injury (AKI) in a recognizable fraction of severely ill patients. The development of Acute kidney injury (AKI) in coronavirus disease 2019 (COVID-19) patients is a critical negative prognostic factor for survival, which, unlike other known negative prognostic factors, is possibly curable by interventions.

Severe case of coronavirus disease 2019 (COVID-19) was defined as either:

1-Respiratory rate $> 30/\text{min}$; or

2-Oxygen saturation $\leq 93\%$; or

3-Partial pressure of arterial oxygen/percentage of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio ≤ 300 mmHg.

Lung imaging showed that the lesions progressed more than 50% within 24-48 hours, and these patients were also treated as severe cases. Critical severe case was described as that involving one criterion as follows: shock; respiratory failure requiring mechanical ventilation; combined with the other organ failure admission to intensive care unit (ICU).

According to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria , acute kidney injury (AKI) was defined as any of the following (not graded):

1-Increase in serum creatinine (SCr) by ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/l}$) within 48 hours; or

2-Increase in serum creatinine (SCr) to ≥ 1.5 times of baseline, which is known or presumed to have occurred within the prior 7 days; or

3-Urine volume < 0.5 ml/kg/hour for 6 hours.

Although the lung was considered as the primary target organ of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as observed by the early autopsy reports, authors found that coronavirus disease 2019 (COVID-19) patients also generally exhibited kidney dysfunctions as characterized by the presence of proteinuria and hematuria and also by the elevated concentrations of blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA), and D-dimer (DD). Blood urea nitrogen (BUN) and serum creatinine (SCr) [the relevant indicator of acute kidney injury (AKI)] concentrations were especially higher in non-severe coronavirus disease 2019 (COVID-19) patients than in patients of other commonly known pneumonia, although the respiratory symptoms were broadly indifferent at this stage. This result was further boosted by the analysis of kidney computed tomography (CT) images that the group of non-severe coronavirus disease 2019 (COVID-19) patients were significantly distinguishable from either the group of other pneumonia or the healthy control group. These results together demonstrated the general presence of kidney dysfunctions in coronavirus disease 2019 (COVID-19) patients, which for most non-severe patients were mild and not diagnosed as acute kidney injury (AKI) [9%, 12 of 128 with acute kidney injury (AKI)]. In contrast, acute kidney injury (AKI) was found in a significant fraction of severe patients [66%, 43 of 65 with acute kidney injury (AKI)]. Further, the factors for assessing kidney functions involving blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA), and D-dimer (DD) had considerably elevated concentrations in severe patients including dead patients than those in non-severe ones. All these factors were recognizably associated with the death of coronavirus disease 2019 (COVID-19) patients. Remarkably, authors mentioned that elevated concentration of D-dimer (DD) as a probable risk factor had been also reported in coronavirus disease 2019 (COVID-19) patients. In addition, the survival analysis exhibited a striking contrast that coronavirus disease 2019

(COVID-19) patients with acute kidney injury (AKI) had ~ 5.3 times mortality risk higher than those without acute kidney injury (AKI). In contrast, patients with the above-mentioned chronic diseases had only on average ~ 1.5 times mortality risk. Therefore, the presence of kidney dysfunctions in coronavirus disease 2019 (COVID-19) patients is a remarkable negative prognostic factor for survival. The occurrence of kidney dysfunctions in coronavirus disease 2019 (COVID-19) patients might be interpreted by the kidney-lung crosstalk theory because of the following reasons: first, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor, which was not exclusively expressed in the respiratory organs in humans but also in the kidney with a much higher level than that in the lung and thus, it is possible that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) could also attack renal tubular epithelial cells in addition to attacking lung epithelial cells. Consistent with this possibility, a report analyzed the histology of renal tissues from autopsies and found acute renal tubular damage in six coronavirus disease 2019 (COVID-19) cases; second, kidney dysfunctions could accelerate the inflammation progress started at the lung, not just as a collateral damage of lung-derived inflammation and that on the one hand, inflammatory reactions following lung impairments could damage the kidney; and on the other hand, the injury and death of renal tubular epithelial cells could also cause severe damage of the lung and other organs through a large amount of inflammatory substances. Authors added that over a certain critical point, the kidney-lung crosstalk could lead to an irreversible self-amplifying cytokine storm that rapidly induces multi-organ failure and death.

Another study documented an association of coronavirus disease 2019 (COVID-19) with acute kidney injury. During infection, the virus circulates in the blood to reach kidney and cause damage to renal resident cells which are manifested by proteinuria, hematuria, and elevated concentrations of blood urea nitrogen (BUN), serum creatinine (SCr), uric acid (UA), and D-dimer. Coronavirus disease 2019 (COVID-19) causes kidney involvement in about 3-9% of the patients and several studies reported that in-hospital mortality of coronavirus disease 2019 (COVID-19) patients who developed acute kidney injury (AKI) is significantly higher [5.3 times higher in acute kidney injury (AKI) than 1.5 times in chronic illnesses]. Currently, studies have begun to investigate influence of coronavirus disease 2019 (COVID-19) on kidney function while several mechanisms have been identified. Firstly, coronavirus disease 2019 (COVID-19) exploits the angiotensin-converting enzyme 2 (ACE2) as a receptor to entry the cells which is

present much higher in kidney than lungs, as reported previously. Hence, lungs contamination with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may be paralleled in kidneys. Consistent with this possibility, studies informed the presence of virus in kidney tissues. Using immunohistochemistry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nucleocapsid protein antigen in kidney specimens of six death cases, authors revealed that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can be detected in distal convoluted renal tubules and proximal straight tubular cells. Moreover, the potent presence of viral ribonucleic acid (vRNA) in urine samples proved that kidneys are also a target of this virus. These results explain that renal cells are targeted and infected by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Organ involvement by this virus is a noticeable way to elaborate a new strategy for the prevention and the management of this disease. Secondary, the patient's immune system response to this virus consists of an exaggerated and usually uncontrolled surge of plasma pro-inflammatory factors [interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-10 (IL-10), granulocyte colony-stimulating factor (G-CSF or GCSF), interferon gamma-induced protein 10 (IP-10, also called C-X-C motif chemokine 10, CXCL10), monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein 1alpha (MIP-1 α , also called chemokine (C-C motif) ligand 3, CCL3), and tumor necrosis factor-alpha (TNF- α)] known as cytokines storm. The cytokines storm might lead to damage to lungs and multi-organs failure including kidneys. Really, a valuable study reported a reduced density of kidney and showed inflammation and edema of the renal parenchyma using computed tomography (CT) scan. The precise mechanism of cytokines storm leading to acute kidney injury (AKI) is not well understood. Additionally, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) might cause tubular damage through infiltrating renal parenchyma by proinflammatory cells. It has been seen that inflammatory cells like CD68⁺ macrophages (M Φ), CD4⁺ T cells, and CD56⁺ natural killer (NK) cells can be present in tubulointerstitium of affected individuals. The hyperactivation of these immune cells may ultimately stimulate fibrosis, promote epithelial cell apoptosis, and lead to microvasculature change. Moreover, C5b-9 expression, known also as membrane attack complex (MAC), is absent in normal kidney. The final product of the complement pathway is the membrane attack complex (MAC) comprising C5b-C59, which then punctures holes in the cell membrane thereby facilitating killing of foreign pathogens. However, C5b-9 complexes activation has been shown to trigger renal parenchymal cells to release pro-

inflammatory cytokines, reactive oxygen species (ROS) and profibrotic factors causing kidney damage. Developing acute kidney injury (AKI) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can also act through triggering C5b-9 expression. In this context, It was confirmed a potent C5b-9 deposition on tubular cells compared to glomeruli and capillaries. This deposition causes renal interstitial damage. In brief, cytokines release might exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis. As it is known, kidney is the most sensitive organ to hypoxia. Insufficient blood flow from afferent arterioles may develop acute kidney injury (AKI) [ischemic acute tubular necrosis (ATN)] and ischemia can induce HIF-1 (hypoxia-inducible factor 1) and then reactive oxygen species (ROS) generation of mitochondrial dysfunction. Hypoxia-inducible factor 1 (HIF-1) activates genes that stimulate the synthesis of fibrous connective tissue which interferes with the kidney's normal function and enhances effector T cell function, involving promotion of cytolytic activity and inflammatory cytokine production while reactive oxygen species (ROS) destroys the molecular components of nephron inducing a cells damage and/or death. In addition, hypoxia-inducible factor 1(HIF-1) up-regulates the adenosine A2B receptor (ADORA2B, a G-protein coupled adenosine receptor) on alternatively activated macrophages (M Φ) which contribute to the development and progression of pulmonary fibrosis (a lung disease that occurs when lung tissue becomes damaged and scarred. This thickened, stiff tissue makes it more difficult for the lungs to work properly. As pulmonary fibrosis worsens, one becomes progressively more short of breath). This crosstalk between lungs and kidneys may complicate coronavirus disease 2019 (COVID-19) patients. The increased incidence of acute kidney injury (AKI) in coronavirus disease 2019 (COVID-19) patients could be due to the synergistic effect of all of these factors and also by state of dehydration, toxic tubular damage, and drug-induced nephrotoxicity.

Several studies showed the influence of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in urine analysis. Therefore, it would be very interesting to introduce urine tests as a diagnostic guideline for coronavirus disease 2019 (COVID-19) and also predict disease severity, particularly for developing countries where resources are limited. Moreover, kidney injury was correlated with an increased risk of death in patients. There should be alert to medical staff to observe kidney function of coronavirus disease 2019 (COVID-19) patients by avoiding

nephrotoxic drugs and precisely note and monitor kidneys function of affected patients and prevent additional nephrotoxic insult to them.

A study was conducted in Wuhan concerning incidence of acute kidney injury (AKI) and in-hospital death. During hospitalization, acute kidney injury (AKI) occurred in 5.1% of patients. The incidence of acute kidney injury (AKI) was noticeably higher in patients with elevated baseline serum creatinine (SCr) (11.9%) than in patients with normal baseline values (4.0%). In-hospital death occurred in 16.1% of patients. The median time to death was 6 days (interquartile range, 3–12 days). The incidence of in-hospital death in the patients with elevated baseline serum creatinine (SCr) was 33.7%, which was significantly higher than in those with normal baseline serum creatinine (SCr) (13.2%). The authors of this study discussed that multiple organ involvement including the liver, gastrointestinal tract (GIT), and kidney have been reported during the course of severe acute respiratory syndrome (SARS) in 2003 and very recently in patients with coronavirus disease 2019 (COVID-19). One possible interpretation of the high prevalence of kidney involvement at hospital admission is that some the patients with coronavirus disease 2019 (COVID-19) had a past history of chronic kidney disease (CKD). Such patients have a proinflammatory state with functional defects in innate and adaptive immune cell populations and are known to have a higher risk for upper respiratory tract infection and pneumonia. The median time period between the first symptoms and signs of coronavirus disease 2019 (COVID-19) and hospital admission was notably slightly more than a week in this study. An alternative interpretation is that many patients with coronavirus disease 2019 (COVID-19) could not be admitted in the very early stage of disease outbreak because of the acutely increasing, large number of patients and limited availability of hospital beds in Wuhan. Earlier admission to hospital might have helped to prevent disease spread and deterioration. Authors found that patients with elevated baseline serum creatinine (SCr) were more likely to be admitted to the intensive care unit (ICU) and to undergo mechanical ventilation, supposing that kidney disease on admission represented a higher risk of deterioration. In this study indicators of kidney involvement at admission were associated with a higher risk of in-hospital death even after adjustment for potential confounders. This observation indicated poor prognosis regardless of initial coronavirus disease 2019 (COVID-19) severity and general physical condition. Monitoring kidney function must therefore be emphasized even in patients with mild respiratory

symptoms, and altered kidney function should be given special attention after admission in clinical practice. Early detection and management of renal abnormalities, involving adequate hemodynamic support and avoidance of nephrotoxic medications, may help to improve the vital prognosis of coronavirus disease 2019 (COVID-19). Acute kidney injury (AKI) results from an abrupt loss of kidney function and is potently associated with increased mortality and morbidity. This study recorded that patients with elevated serum creatinine (SCr) were more probably to develop acute kidney injury (AKI) during hospitalization. It is therefore important to increase the awareness of acute kidney injury (AKI) in those who entered the hospital with an elevated serum creatinine (SCr). In this cohort study, the detection rate of acute kidney injury (AKI) in patients with coronavirus disease 2019 (COVID-19) was 5.1%, which is in keeping with other reports of small sample size and much higher than the 0.5% of a large observational study. This may be explained by an extremely high proportion of severely sick patients in a previous case series and only 15.7% in the large observational study. In this cohort study, 42.7% of patients were severely ill, and this may explain the higher detection rate of acute kidney injury (AKI) in clinic practice in Wuhan. Importantly, the present method of detecting acute kidney injury (AKI) is mainly based on acute changes in serum creatinine (SCr) and the frequency of serum creatinine (SCr) tests has a substantial impact on detection rate. To improve early detection of kidney injury, more frequent serum creatinine (SCr) measurements should be performed in patients with coronavirus disease 2019 (COVID-19). The etiology of kidney disease involvement in patients with coronavirus disease 2019 (COVID-19) is likely to be multifactorial. First, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may exert direct cytopathic effects on kidney tissue. This is supported by the detection of polymerase chain reaction fragments of coronavirus (CoV) in blood and urine in both the patients with the 2003 severe acute respiratory syndrome (SARS) virus and those with coronavirus disease 2019 (COVID-19). It has been seen that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor, which is identical to that of the severe acute respiratory syndrome coronavirus (SARS-CoV) as reported in 2003. Human tissue ribonucleic acid (RNA)-sequencing data demonstrated that angiotensin-converting enzyme 2 (ACE2) expression in urinary organs (kidney) was nearly 100-fold higher than in respiratory organs (lung). Therefore, the kidney disease may be caused by coronavirus (CoV) entering kidney cells through an angiotensin-converting enzyme 2 (ACE2)-dependent pathway. Second,

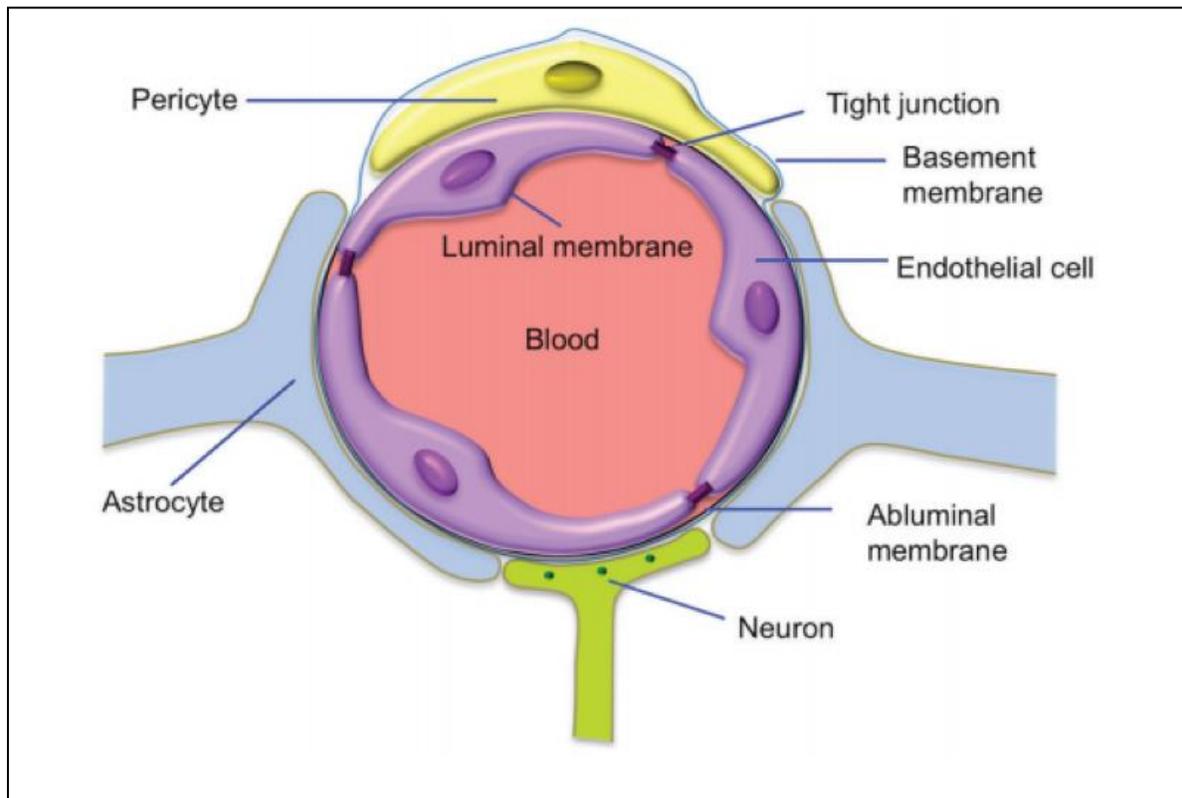
deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T-cell lymphocyte or antibody) may destruct the kidney. However, kidney microscopy samples from patients with severe acute respiratory syndrome (SARS) were reported to exhibit a normal glomerular aspect and absence of electron-dense deposits. This is not in support of an active immune-mediated glomerulonephritis. Clearly, potential pathological kidney changes in patients with coronavirus disease 2019 (COVID-19) require further study. Third, virus-induced cytokines or mediators might exert indirect effects on renal tissue, such as hypoxia, shock, and rhabdomyolysis. In fact, some of the patients with the 2009 H1N1 virus had mild to moderate elevations of serum creatine kinase (CK). In keeping with this observation, 138 patients with coronavirus disease 2019 (COVID-19), who were admitted to an intensive care unit (ICU), exhibited a tendency toward increased creatine kinase (CK) levels, and the patients with kidney involvement in this study tended to have increased creatine kinase (CK) levels as well. Authors compared the therapies on the first day of admission and during the hospitalization in patients with acute kidney injury (AKI) and non-acute kidney injury (AKI). Authors found that patients with acute kidney injury (AKI) were more likely to have higher proportion of glucocorticoid and lower proportion of antiviral drugs and renin-angiotensin-aldosterone system inhibitors management on admission. The difference in the use of glucocorticoids may be explained by the condition of patients with acute kidney injury (AKI) that was more severe, thus physicians tended to use glucocorticoids in the most critically ill patients, even if there is a controversy on the use of glucocorticoids in patients with coronavirus disease 2019 (COVID-19). However, the oral antiviral drugs, including umifenovir, oseltamivir, and lopinavir with ritonavir, were preferred in moderate patients on admission. Given that angiotensin-converting enzyme 2 (ACE2) is a functional receptor for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the safety and probable effects of renin-angiotensin-aldosterone system (RAAS) inhibitors in patients with coronavirus disease 2019 (COVID-19) should be carefully taken into account. These potentially harmful effects may consider for the low proportion of renin-angiotensin-aldosterone system (RAAS) inhibitors used by physicians in this cohort study, particularly in patients with acute kidney injury (AKI) who had higher concentration of serum creatinine (SCr) on admission. Due to the small number of patients with acute kidney injury (AKI) and the bias in different medication of patients with coronavirus disease 2019 (COVID-19), causal relationship between drug and acute kidney injury (AKI) in

patients with coronavirus disease 2019 (COVID-19) remains undetermined. However, this study concluded that the prevalence of kidney disease in patients with coronavirus disease 2019 (COVID-19) hospitalized in Wuhan, China, was high. After adjustment for confounders, kidney disease on admission and acute kidney injury (AKI) during hospitalization were associated with an increased risk of in-hospital death. Clinicians should increase their awareness of kidney disease in hospitalized patients with coronavirus disease 2019 (COVID-19). Early detection and effective intervention of kidney involvement may help to reduce deaths of patients with coronavirus disease 2019 (COVID-19).

18. Neurological Manifestations

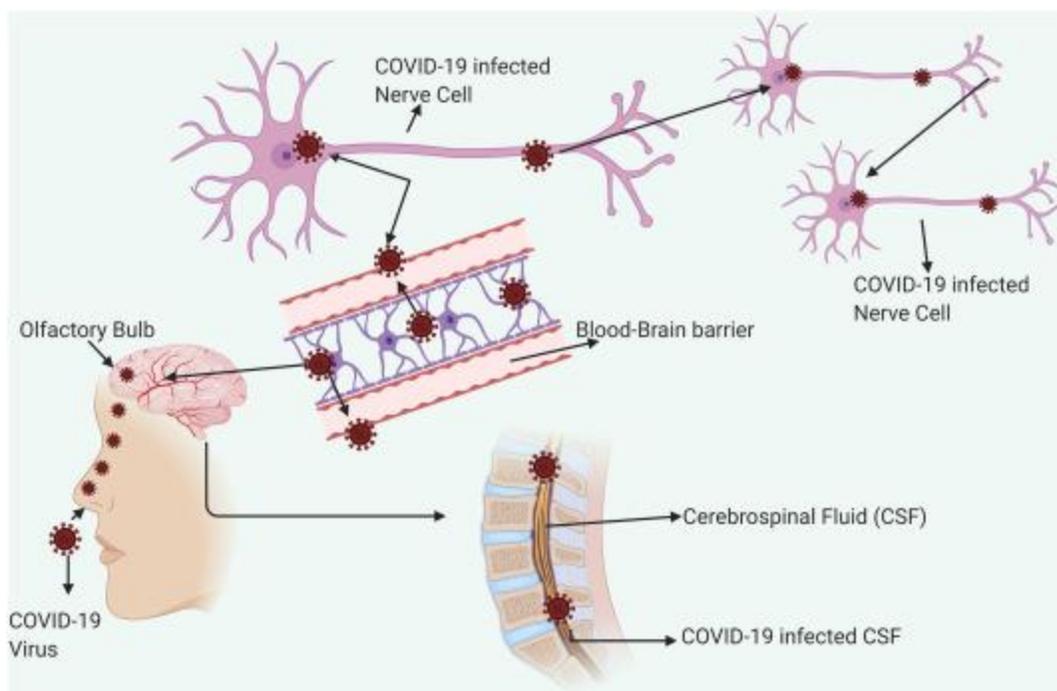
Neurotropism is the ability of a pathogen to invade and survive in the nervous system (NS). Coronaviruses (CoVs) are neurotropic in several hosts, involving human beings. The blood brain barrier (BBB), the anatomical gateway crucial for the maintenance of homeostasis and physiological environment of the central nervous system (CNS), plays an important role in the protection against pathogenic agents. Endothelial cells of the capillaries, pericytes, and astrocyte end-feet constitute the blood brain barrier (BBB). Inflammation and vascular damage can increase blood brain barrier (BBB) permeability and potentially leads to unwanted central nervous system (CNS) effects. Viruses can cross the blood brain barrier (BBB) through several ways involving transcellular, paracellular, and retrograde axonal transport along sensory and olfactory nerves. Viremia is the viral mechanism for migration. Viral transcellular migration happens when the virus invades the host cells or macrophages to overcome the blood brain barrier (BBB). Paracellular migration occurs when the virus attacks the tight junctions in blood brain barrier (BBB). Axonal transport is provided via adherence of the virus to proteins of peripheral or cranial nerves, which permits retrograde neuronal transport. Considerable studies propose axonal transport of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) via the cribriform plate, adjacent to the olfactory bulb, to the brain. The loss of smell, which can be an early symptom of coronavirus disease 2019 (COVID-19), favors this mechanism. Further, it has been found that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can cause viremia reaching the cerebral circulation via systemic spread. The slow microcirculation at the capillary level can also facilitate the interaction of the spike (S) glycoprotein of severe acute respiratory

syndrome coronavirus-2 (SARS-CoV-2) with the angiotensin converting enzyme2 (ACE2) expressed on endothelial cells.



Figure(106):The blood brain barrier (www.google.com)

It is important to mention that the blood brain barrier (BBB) is a highly specialized structure formed by a tight monolayer of brain endothelial cells, which maintain bloodstream cells, neurotoxic compounds, and microorganisms outside of the central nervous system (CNS). This barrier has also the ability to orchestrate the flow of some solutes from in and out of the brain. In addition, the blood brain barrier (BBB) constitutes a key component of the neurovascular unit (NVU). The neurovascular unit (NVU) is a functional unit composed of a complex cellular system formed by neurons, interneurons, astrocytic endfeet, microglia, oligodendrocytes, basal lamina covered with smooth muscular cells and pericytes, endothelial cells and extracellular matrix, and circulating blood components.

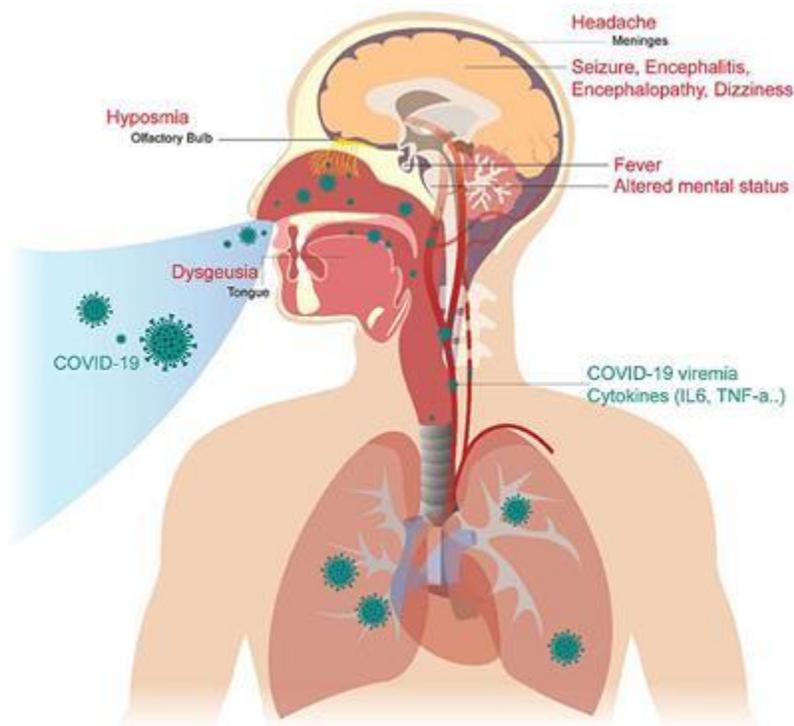


Figure(107):COVID-19 infection and blood brain barrier [Vellingiri B.; Jayaramayya K.; Lyer M.; Narayanasamy A.; Govindasamy V.; Giridharan B.; Ganesan S.; Venugopal A.; Venkatesan D.; Ganesan H.; Rajagopalan K.; Rahman P.; Cho SG.; Kumar N.; Subramaniam M. (2020). COVID-19: a promising cure for the global panic. *Science of The Total Environment*, 725. <https://doi.org/10.1016/j.scitotenv.2020.138277>]

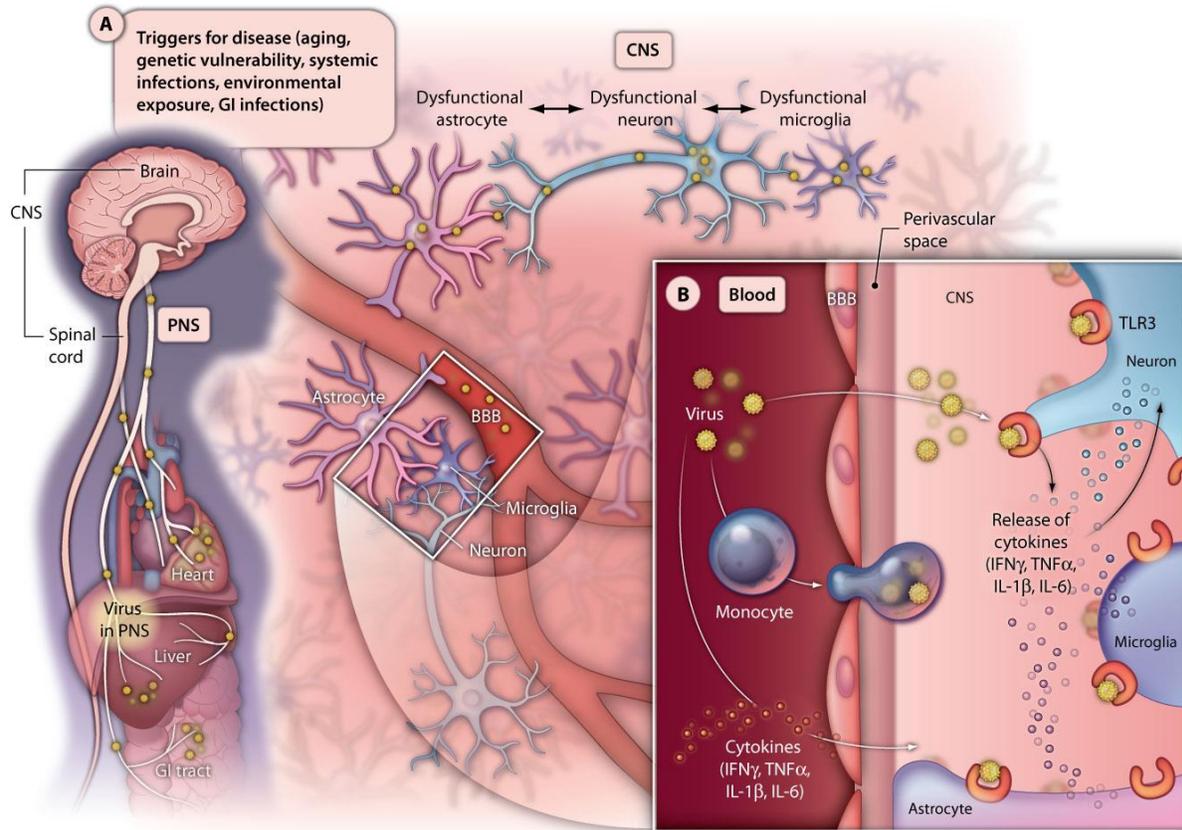
A report of 217 hospitalized patients in Wuhan, China, demonstrated neurologic manifestations in nearly half of those with severe coronavirus disease 2019 (COVID-19) infection (40 of 88), including cerebrovascular complications (e.g., stroke), encephalopathies, and muscle injuries. Total blood lymphocyte counts were considerably lower in patients with central nervous system (CNS)-associated (e.g. headache, dizziness, ataxia) or muscular (e.g., myalgia) symptoms, and the latter group also presented high plasma C-reactive protein (CRP) relative to patients without muscular involvement. Immunologic results in coronavirus disease 2019 (COVID-19) patients with neurologic symptoms are in line with prior coronavirus (CoV)-related results, describing considerably decreased blood lymphocyte counts in coronavirus (CoV)-positive children with encephalitis (CoV-CNS) in comparison with those with acute respiratory coronavirus (CoV)-associated infection, and when taken in conjunction with circulating C-reactive protein (CRP) concentrations or neutrophil counts can be prognostic of poorer coronavirus disease 2019 (COVID-19) outcomes. It is unknown if decreased lymphocytes in circulation reflect margination or target tissue migration, although probable. Plasma granulocyte macrophage

colony-stimulating factor (GM-CSF) concentrations were significantly elevated in coronavirus-central nervous system (CoV-CNS) patients, which can lead to the expansion of central nervous system (CNS)-invading phagocytes [e.g., inflammatory monocyte-derived cells (M_dC) such as dendritic cells (DCs)]. granulocyte macrophage colony-stimulating factor (GM-CSF) has arisen as a potential biological target in treating severe coronavirus disease 2019 (COVID-19); this may mitigate neuropsychiatric sequelae by limiting monocyte-derived cells (M_dC) neuroinvasion.

As will be explained, central nervous system (CNS) features include headache, dizziness, ataxia, alteration of sensorium, encephalitis, stroke, and seizures. Headache can be a symptom of viral infection and usually remains associated with fever. Studies have revealed an incidence of headaches ranging from 6 to 13% in coronavirus disease 2019 (COVID-19) patients. However, attention has already been raised in recent correspondence if this particular symptom is a manifestation of viral meningitis or, for that matter, encephalitis, which may exhibit itself subsequently in the form of drowsiness and seizures.



Figure(108):Neurological manifestations in COVID-19[Tsai ST.; Lu MK.; San S.; Tsai CH. (2020). The neurologic manifestations of coronavirus disease 2019 pandemic: a systemic review. *Front. Neurol.* <https://doi.org/10.3389/fneur.2020.00498>.



Figure(109):Viral and inflammatory triggers of neurodegenerative diseases [Deleidi M.; Isacson O. (2012). Viral and inflammatory triggers of neurodegenerative diseases. Science Translational Medicine, 4(121).

18.1 Mechanisms of SARS-CoV-2 Infections on The Nervous System Damage

1-Direct infection injury

The genetic material and even proteins of various viruses can often be detected in nervous system (NS) tissue samples [such as cerebrospinal fluid (CSF) or brain], supposing that viruses may directly invade the nervous system (NS) and lead to nerve damage.

a-Blood circulation pathway

Although there is scarce evidence that severe acute respiratory syndrome coronavirus-2 (SARSCoV-2), invade the nervous system (NS) via the blood circulation pathway, subsequent studies are expected.

b-Neuronal pathway

Neuronal pathway is important vehicles for neurotropic viruses to enter the central nervous system (CNS). Viruses can migrate by infecting sensory or motor nerve endings, achieving retrograde or anterograde neuronal transport through the motor proteins, dynein and kinesins. An example of a neuronal pathway is that of olfactory neuron transport. The unique anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and forebrain effectively makes it a channel between the nasal epithelium and the central nervous system (CNS). Consequently, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can enter the brain through the olfactory tract in the early stages of infection or nasal vaccination. For example, after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infects nasal cells, it can reach the entire brain and cerebrospinal fluid (CSF) through the olfactory nerve and olfactory bulb within days and cause inflammation and demyelinating reaction. Gu *et al.* (2005) also detected severe acute respiratory syndrome coronavirus (SARS-CoV) particles and genome sequences in brain neurons. Findings indicate that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can invade the central nervous system (CNS) from the periphery through neural pathways.

2-Hypoxia injury

When a virus proliferates in lung tissue cells, it causes diffuse alveolar and interstitial inflammatory exudation, edema, and the formation of transparent membranes. This, in turn, develops alveolar gas exchange disorders causing hypoxia in the central nervous system (CNS), increasing anaerobic metabolism in the mitochondria of brain cells. The accumulation of acid can cause cerebral vasodilation, swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, and even headache due to ischemia and congestion. If the hypoxia (deficiency in the amount of oxygen reaching the tissues) continues unabated, cerebral edema and the cerebral circulation disorder may worsen sharply. With intracranial hypertension, the brain function gradually deteriorates, and drowsiness, bulbar conjunctival edema, and even coma can be seen. In addition, for patients at particular risk of progressing cerebrovascular disease, hypoxia may also stimulate the occurrence of acute cerebrovascular disease such as acute ischemic stroke. According to the fact that the patients with coronavirus disease 2019 (COVID-19) frequently experience severe hypoxia, hypoxia injury may lead to subsequent nervous system damage.

3-Immune injury

Nervous system damage resulted from viral infection may be mediated by the immune system. The pathology of severe viral infections is closely bound to the development of a systemic inflammatory response syndrome (SIRS). Systemic inflammatory response syndrome (SIRS) could be abnormally initiated in severe pneumonia caused by coronavirus (CoV) infection, while early anti-inflammatory intervention effectively prevent immune damage and reduce the risk of injury in the nervous system (NS). In addition, severe acute respiratory syndrome (SARS) and coronavirus disease 2019 (COVID-19) have caused a large number of fatalities, most of which have been due to multiple organs failure (MOF) resulted from virus-induced systemic inflammatory response syndrome (SIRS) or systemic inflammatory response syndrome (SIRS)-like immune disorders. The persistence of coronavirus (CoV) infections and its ability to infect macrophages, microglia, and astrocytes in the central nervous system (CNS) are really significant. A neurotropic virus can activate glial cells and induce a pro-inflammatory state. Interleukin-6 (IL-6), an important member of the cytokine storm, is positively associated with the severity of coronavirus disease 2019 (COVID-19) symptoms. Furthermore, experiments have confirmed that primary glial cells cultured in vitro secrete a large amount of inflammatory factors such as interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-15 (IL-15), and tumor necrosis factor-alpha (TNF- α) after being infected with coronavirus (CoV). Activation of immune cells in the brain will lead to chronic inflammation and brain damage.

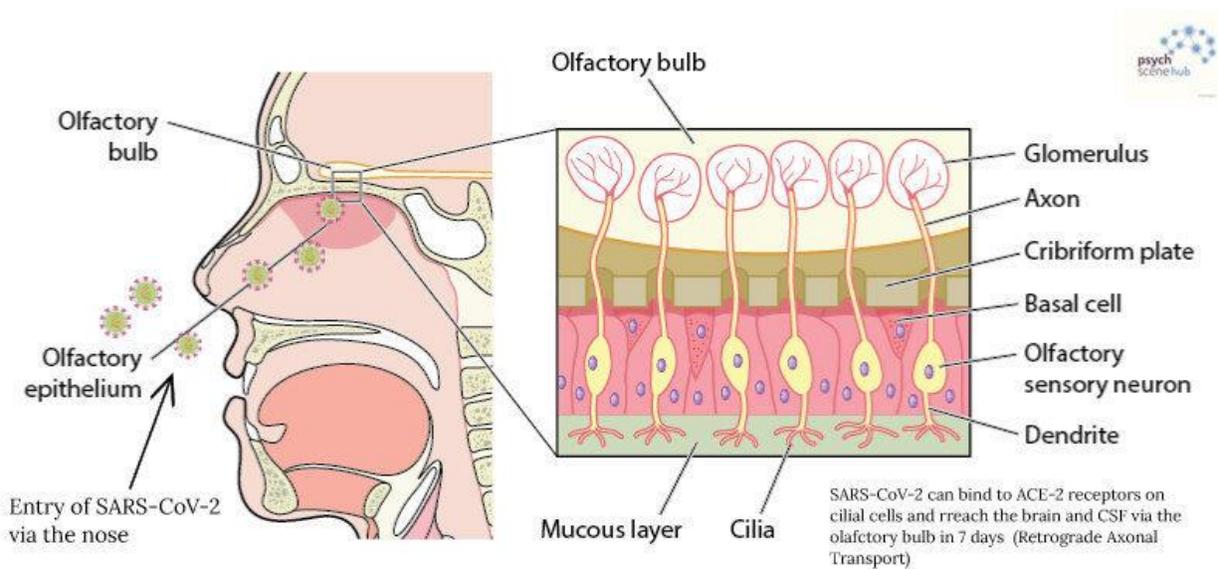
4-Angiotensin-converting enzyme 2

Angiotensin-converting enzyme 2 (ACE2) is a cardio-cerebral vascular protection factor found in a variety of organs, including the nervous system (NS) and skeletal muscles, playing a significant role in regulating blood pressure and anti-atherosclerosis mechanisms. Meanwhile, angiotensin-converting enzyme 2 (ACE2) is also a crucial target for coronavirus (CoV) infection. Binding to angiotensin-converting enzyme 2 (ACE2) receptors, coronavirus (CoV) may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage. Finding that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike (S) protein could interact with angiotensin-converting enzyme 2 (ACE2) expressed in the capillary endothelium, the virus can also damage the blood brain barrier (BBB) and enter the central nervous system (CNS) by attacking the vascular system.

5-Others

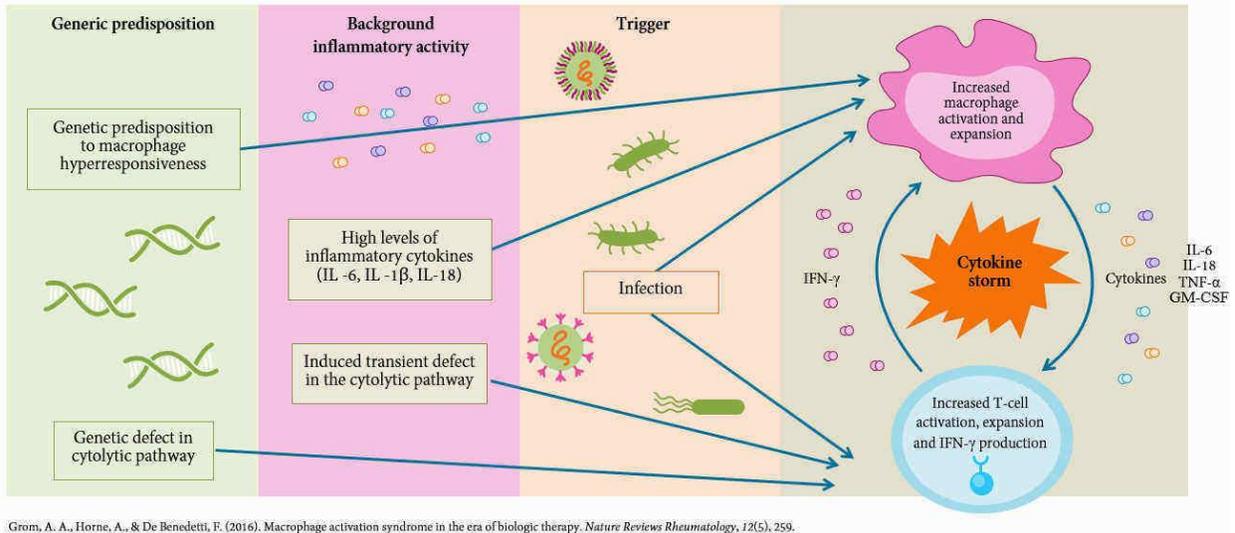
The biological characteristics of the central nervous system (CNS) may facilitate exacerbation of the neurological damage caused by coronavirus (CoV) infections. The central nervous system (CNS) has a dense parenchymal structure and the usual lack of permeability of its blood vessels is a barrier to virus invasion. However, if a virus gains access to the central nervous system (CNS), it is difficult to remove. Due to the lack of major histocompatibility complex antigens in nerve cells, the elimination of viruses in nerve cells depends solely on the role of cytotoxic T cells; however, the apoptosis of mature neurons after virus infection also has somehow protective influences. Moreover, the homeostasis characteristics of the cells in the central nervous system (CNS) also contribute to the continued existence of the virus.

18.2 Central Nervous System Manifestations



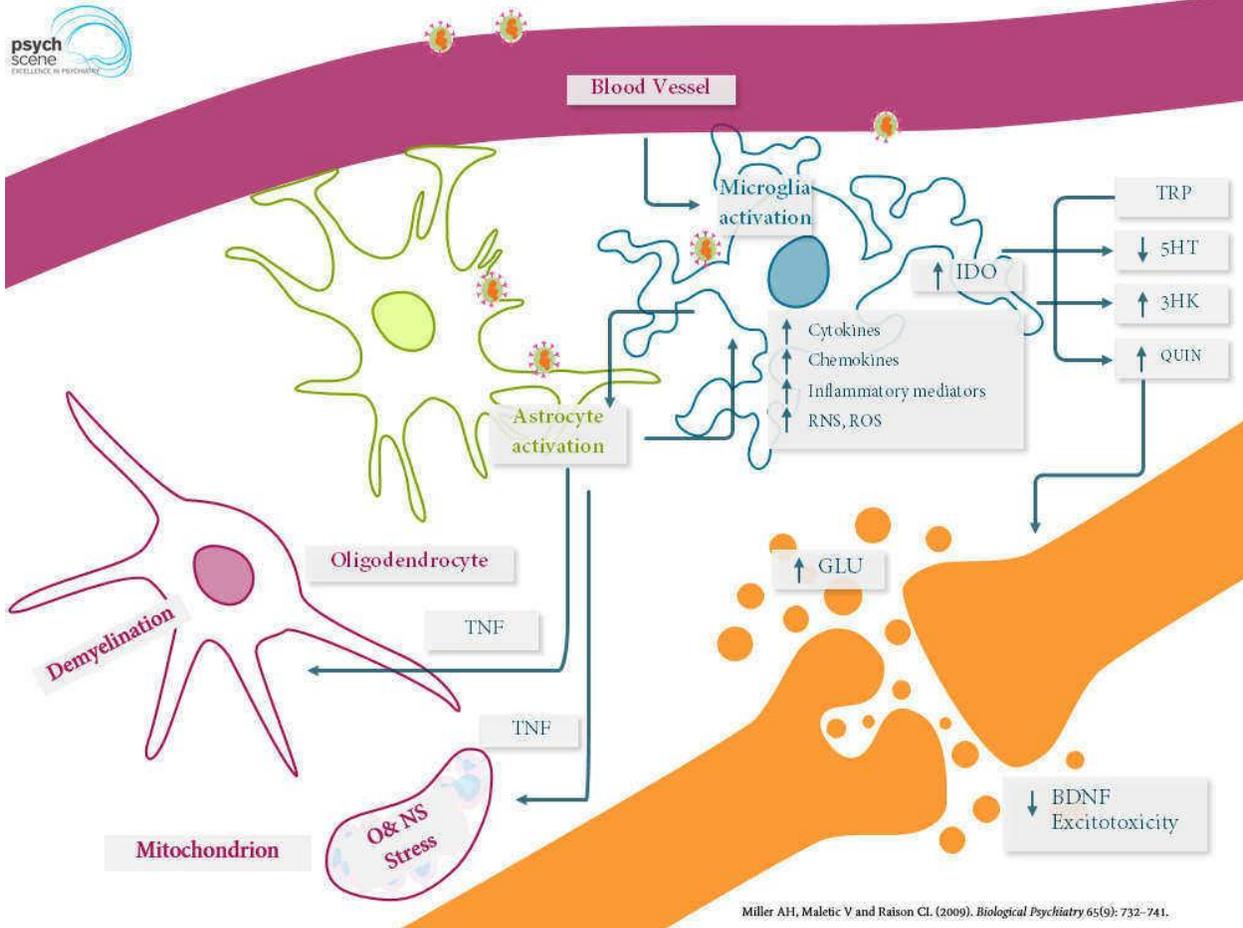
Figure(110):Neuropsychiatry of SARS-CoV-2 central nervous system infection [Troyer E.; Kohn J.; Hong S. (2020). Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav Immun*. doi:10.1016/j.bbi.2020.04.027]

Cytokine Storm



Figure(111):Cytokine storm in COVID-19 infection [Rege S. (2020). COVID-19 and the brain-pathogenesis and neuropsychiatric manifestations of SARS-CoV-2 CNS involvement]

Cytokine dysregulation in coronavirus disease 2019 (COVID-19) characterized by significantly higher pro-inflammatory cytokines (e.g., IL-6 and TNF- α) which has been linked to cytokine storm syndrome-related encephalitis.



Figure(112):Neuroinflammation in COVID-19 [Rege S. (2020). COVID-19 and the brain-pathogenesis and neuropsychiatric manifestations of SARS-CoV-2 CNS involvement]

Neuroinflammation in coronavirus disease 2019 is characterized by:

1-Cytokines released through peripheral inflammation may increase the permeability of the blood brain barrier (BBB) providing a pathway for the virus to enter the brain.

2-Once in the central nervous system (CNS), it can infect of astrocytes and microglia activating the cascade of neuroinflammation and neurodegeneration through the release of tumor necrosis factor (TNF), cytokines, reactive oxygen species (ROS), and other inflammatory mediators.

18.2.1 Intracranial Infection

Intracranial infections comprise a wide range of different processes, each with unique clinical characteristics. Many intracranial infections develop rapidly and result in considerable morbidity and mortality if appropriate remedies are not initiated promptly. Clinical presentations of intracranial infection vary considerably. Common manifestations involve altered mental status, seizures, and subtle focal deficits, such as cranial nerve palsies (i.e., a decreased or complete loss of function of one or more cranial nerves).

The radiologist plays a crucial role in the diagnosis and management of patients with intracranial infections. Different imaging modalities offer different advantages in the diagnostic paradigm. Computed tomography (CT) is important in rapidly excluding a focal mass lesion in the acute setting, prior to lumbar puncture. Magnetic resonance imaging (MRI) is much more sensitive for defining the extent of disease, and for identifying infection-related complications, such as infected subdural effusions and venous sinus thrombosis. Many investigators have demonstrated the value of magnetic resonance (MR) spectroscopy to aid in the differentiation of abscesses and neoplasms.

18.2.1.1 Symptoms Related to Intracranial Infection in COVID-19 Infection

Coronavirus (CoV) may invade the central nervous system (CNS). Authors have detected severe acute respiratory syndrome coronavirus (SARS-CoV) nucleic acid in patients' cerebrospinal fluid (CSF), and severe acute respiratory syndrome coronavirus (SARS-CoV) was also verified in brain tissue on autopsy. Attributed to this, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak, some patients have experienced symptoms similar to those with intracranial infections such as headache, seizure and disturbance of consciousness. Few patients had central nervous system symptoms before having pulmonary symptoms. Therefore, neurologists should be vigilant when seeing coronavirus disease 2019 (COVID-19) infected patients and look for any signs suspicious for intracranial infection, and if possible, magnetic resonance imaging (MRI) of head with and without contrast should be done. A lumbar puncture to look for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) nucleic acid by using polymerase chain reaction (PCR) assay is advised. As a result, coronavirus disease 2019 (COVID-19) patients with intracranial infection, therapy strategies such as controlling cerebral oedema, treating and preventing seizures and treating psychotic symptoms should be taken into account and the guidelines should be followed and pursued.

18.2.2 Seizures and Epilepsy

Epilepsy is a common chronic neurological disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability and featured by recurrent unprovoked seizures. It is now clear that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures. Epilepsy is a collection of many different types of seizures that vary widely in severity, appearance, cause, consequence and management. The seizures are correlated with characteristic signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. Epileptic seizures frequently lead to transient impairment of consciousness leaving the person at risk of bodily harm and frequently interfering with education and employment. It is universal, with no age, sex, geographical, social class or racial boundaries. Epilepsy is occurring more in young children or people above 65 years of age; however it can occur at any time. Epilepsy is not a single disorder but a syndrome with vastly divergent symptoms, including episodic abnormal electrical activity in the brain. All epilepsy syndromes are not life-long-some forms are confined to particular stages of childhood. Conventional treatment of epilepsy consists primarily of anticonvulsant medications. It is found that over 30% of patients with epilepsy do not have seizure control even with the best available medications. Although these drugs often control or reduce the frequency of seizures, some cases exhibit little or no improvement and therefore surgery may be considered in difficult cases. Therapy is symptomatic in that available drugs inhibit seizure but neither effective prophylaxis nor cure is available. Compliance with remedy is a principal problem because of the long term therapy together with unwanted effects of many drugs.

The cause of epilepsy is completely unknown. The word epilepsy does not indicate anything about the cause or severity of the person's seizures, some cases of epilepsy are triggered by genetic factors, but it can be caused by brain injuries resulted from blows to the head, stroke, infections, high fever or tumors. It has been recognized that heredity (genetics) play an important role in many causes of epilepsy in very young children, but it can be a factor for individuals of any age. Not everyone who has a serious head injury (a clear cause of seizures) will experience epilepsy. Certain epilepsy syndromes termed as reflex epilepsy need specific precipitants or trigger for seizures to occur like reading, flashing lights and precipitants like emotional stress, sleep deprivation sleep itself, heat stress, alcohol and febrile illness are examples of precipitants

cited by patients with epilepsy. It is noticed that the impact of various precipitants varies with the epilepsy syndrome. The menstrual cycle (MC) in epileptic females can affect patterns of seizure recurrence, catamenial epilepsy in the seizure related to the menstrual cycle (MC).

Seizures are paroxysmal manifestations of the cerebral cortex. A seizure results when a sudden imbalance is incident between the excitatory and inhibitory forces within the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates from the gray matter of any cortical or subcortical area. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and excess excitability spread either locally to produce a focal seizure or more widely to produce a generalized seizure. This onset propagates by physiologic pathways to involve adjacent to remote areas. As abnormality of potassium conductance, a defect in the voltage activated ion channels, or a deficiency in the membrane ATPases bound to ion transport may cause neuronal membrane unstable and result in a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotropin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas gamma aminobutyric acid (GABA) and dopamine (DA, a catecholamine neurotransmitter) block neuronal activity and propagation. During a seizure, the demand for blood flow to the brain increases to carry off carbon monoxide and to bring substrate for metabolic activity of the neurons, as the seizure prolongs, the brain experiences more from ischemia that may result in neuronal destruction and brain damage.

Antiepileptic drugs may act primarily by one of three main mechanisms:

1-Reducing electrical excitability of cell membranes, particularly (by blocking) the voltage dependent sodium channels which are responsible for the inward current that generates an action potential;

2-Enhancing gamma aminobutyric acid (GABA) mediated synaptic inhibition, by inhibiting gamma aminobutyric acid (GABA) transaminase or by drugs with direct gamma aminobutyric acid (GABA) agonist properties; the result is increased membranes permeability to chloride ion, which reduces cell excitability;

3-Inhibiting T-type calcium channels (important in controlling absence seizures) or by inhibiting excitatory neurotransmitters. e.g. glutamate.

18.2.2.1 Seizures and Epilepsy in COVID-19 Infection

Karimi *et al.* (2020) reported a case with coronavirus disease 2019 (COVID-19) and frequent seizures, with no past medical history. There are many different viruses that play a role in the development of seizures and convulsions. The causes of seizure may be due to a primary infection or due to reactivation of the latent virus. There are several mechanisms for the etiology of seizure in the patients who suffer from viral infections, comprising direct infiltration of brain tissue and production of toxins by the virus or production of inflammatory mediators by the brain. It was reported that coronavirus disease 2019 (COVID-19) induces the inflammatory cascade and consequently, secretes inflammatory cytokines, including interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-7 (IL-7), and interleukin-10 (IL-10), tumor necrosis factor- α (TNF- α) and the granulocyte colony-stimulating factor (G-CSF). Previous studies reported that tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) and C3 of the complement system are the major factors of stimulating the immune system. Consecutively, these cytokines can drive neuronal hyper-excitability via activation of glutamate receptors and lead to the development of acute seizures. To the best of authors' knowledge, this is the first case study that reports a relation between frequent seizures and coronavirus disease 2019 (COVID-19). Authors hypothesized about this subject that the etiology of seizure might be encephalitis and the invasion of the virus to the brain or toxic effect of inflammatory cytokines.

A valuable study specifically investigated the neurological manifestations of coronavirus disease 2019 (COVID-19) and documented central nervous system (CNS) manifestations in 25% of the patients [headache (13%), dizziness (17%), impaired consciousness (8%), acute cerebrovascular problems (3%), ataxia (0.5), and seizures (0.5%)]. A report of meningitis/encephalitis was correlated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) accompanied by seizures [severe acute respiratory syndrome coronavirus-2 ribonucleic acid (SARS-CoV2 RNA) was detected in the cerebrospinal fluid (CSF)]. Another study reported a patient affected by coronavirus disease 2019 (COVID-19) whose primary presentation was a focal status epilepticus. Therefore, it is worthy to hypothesize that some patients with coronavirus disease 2019 (COVID-

19) develop seizures as a consequence of hypoxia, metabolic derangements, organ failure, or even cerebral damage that can occur in patients with coronavirus disease 2019 (COVID-19).

Seizures can occur as a result of an acute systemic illness, a primary neurological pathology, or a medication adverse-effect in critically ill cases and can present in a wide array of symptoms from convulsive activity, subtle twitching, to lethargy. In critically ill cases, untreated isolated seizures (as one or more epileptic seizure(s) occurring within a 24-hour period, without later recurrence) can quickly escalate to generalized convulsive status epilepticus (the range of seizure continuum extending from isolated seizure to repetitive seizures to status epilepticus) or, more often, nonconvulsive status epilepticus (NCSE), which is associated with a high morbidity and mortality.

When visiting a patient who is in a critical medical condition and has a change in mental status, it is suggested to make sure that nonconvulsive status epilepticus (NCSE) is not a part of the clinical scenario. Salzburg Consensus Criteria for Non-Convulsive Status Epilepticus is a helpful guide to make a diagnosis of nonconvulsive status epilepticus (NCSE) in critically ill patients. If a case with coronavirus disease 2019 (COVID-19) develops a clinical or subclinical seizure or status epilepticus, it is very important to administer the therapy urgently. In such circumstances, one should try to determine the cause of the seizure and manage the cause [e.g., hypoxia, fever (in children), metabolic derangements, etc.] soon. It is often crucial to start antiseizure medication (ASM) therapy as well; this is to abort prolonged seizures and also to prevent further seizures from occurring.

When an antiseizure medication (ASM) is initiated, drug factors, such as the onset of action, drug interactions, and adverse effects, and also patient factors, such as age, respiratory, renal, hepatic, and cardiac functions, should be taken into consideration.

In case of a single seizure less than 5 minutes long, there is no need for rescue treatment with benzodiazepines (these drugs should be used with caution in patients with compromised respiratory function), but an antiseizure medication (ASM) should be initiated to prevent further seizures from occurring. Since these cases are critically ill, a drug with intravenous (IV) formulation is more preferred. However, because these cases experience severe respiratory and/or cardiac problems, drugs with significant respiratory/cardiac adverse effects (e.g., Phenytoin, Phenobarbital, etc.) should be prescribed cautiously, with clinical monitoring as appropriate.

Moreover, drugs with significant drug interactions (e.g., Carbamazepine, Phenytoin, Phenobarbital, and Valproic acid) should be prescribed cautiously. Furthermore, extracorporeal membrane oxygenation (ECMO), which may become necessary in the management of cases with coronavirus disease 2019 (COVID-19) and severe pneumonia, can affect the pharmacokinetics of highly protein-bound drugs (e.g., Phenytoin and Valproic acid). Lacosamide should be administered with caution in cases with cardiac conduction problems (e.g., marked first-degree AV block, second-degree or higher AV block), on concomitant medications that prolong PR interval, or with severe cardiac disease such as myocardial ischemia or heart failure (HF). Lacosamide use is not recommended in cases with severe hepatic impairment. However, if cardiac impairment or severe hepatic impairment does not exist in a patient with coronavirus disease 2019 (COVID-19), it is a reasonable antiseizure medication (ASM). Brivaracetam is a safe treatment option in these patients. Dosage adjustment is recommended for all stages of hepatic impairment. On the same, levetiracetam is an optimal antiseizure medication (ASM) in critically ill cases with a reasonable adverse effect profile and minimal interactions with other drugs. Dosage adjustment is necessary in patients with renal impairment.

In case more than one seizures (either shorter or longer than 5 minutes) or status epilepticus (convulsive or nonconvulsive) general management principals of serial seizures and status epilepticus should be applied. Rescue treatment (with benzodiazepines) and an antiseizure medication (ASM) should be started to abort the seizure and also prevent further seizures from occurring.

New-onset seizures in these patients could be considered as acute symptomatic seizures. Patients with acute symptomatic seizures do not need long-term antiseizure medication (ASM) remedy after the period of acute illness, unless a subsequent seizure occurs. Since the period from the onset of coronavirus disease 2019 (COVID-19) symptoms to death may range from 6 to 41 days, it is worthy to continue the antiseizure medication (ASM) for about 6 weeks and then taper and discontinue the drug rapidly in 1-2 weeks.

Another important issue is the potential risks associated with coronavirus disease 2019 (COVID-19) in people with epilepsy (PWE). Drug-drug interactions between antiseizure medications (ASMs) and anti-coronavirus disease 2019 (COVID-19) remedies may pose significant challenges. Furthermore, cardiac, hepatic or renal impairments, which may be incident in

patients with severe coronavirus disease 2019 (COVID-19), may require adjustment to antiseizure medications (ASMs). Finally, adverse effects of both groups of therapies [antiseizure medications (ASMs) and anti- coronavirus disease 2019 (COVID-19) treatments] should be taken into account. For example, lacosamide prolongs the PR interval and hydroxychloroquine (HCQ) prolongs the QT interval in electrocardiogram (ECG). Therefore, administering hydroxychloroquine to a patient with epilepsy, who is already taking lacosamide, may carry an added risk and should be done with precaution and electrocardiogram (ECG) monitoring. Also, QT prolongations may occur with azithromycin and chloroquine and some antiseizure medications (ASMs) (e.g., carbamazepine, lacosamide, phenytoin, and rufinamide) may cause cardiac conduction abnormalities. Co-administration of these two groups of drugs should be done cautiously, with electrocardiogram (ECG) monitoring as appropriate.

18.2.3 Acute Myelitis

Acute transverse myelitis (ATM), an inflammatory myelitis, is one of the causes of acute transverse myelopathy. The three principal categories in the differential diagnosis of acute transverse myelitis (ATM) are demyelination, including multiple sclerosis (MS), neuromyelitis optica (NMO), and idiopathic transverse myelitis; infections such as herpes zoster (HZ) and herpes simplex virus (HSV); and other inflammatory disorders such as systemic lupus erythematosus (SLE) and neurosarcoidosis.

Acute transverse myelitis (ATM) is an acute inflammatory process of the spinal cord that can be classified in three distinct groups according to its etiology: myelitis due to a direct infection of the spinal cord; myelitis in the context of a systemic disease, such as leukemia or a connective tissue disorder; and myelitis with a suspected autoimmune basis. The last group is the most common form of acute transverse myelitis (ATM) and may happen as a post- or parainfectious condition. Respiratory and intestinal infections are important potential triggers of acute transverse myelitis (ATM), but some postvaccinal cases have also been mentioned. Direct infection of the spinal cord is a common cause of acute transverse myelitis (ATM) in developing countries.

Viral, bacterial, fungal, and parasitic agents can cause acute myelitis. Patients are systemically ill with fever and meningismus. Prominent cerebrospinal fluid (CSF) inflammation (pleocytosis,

frequently neutrophilic and elevated protein level) must prompt investigation for a causative agent, especially a treatable one. This is in contrast to parainfectious or idiopathic inflammatory myelitis where patients have recovered from a recent infection, usually viral.

The clinical picture of acute transverse myelitis (ATM) involves partial or complete paraplegia or quadriplegia, decrease or loss of deep reflexes, sensory impairment and varying degrees of bladder and bowel disturbance. Usually the full-blown disease is reached four weeks after onset, but in most patients the peak occurs in the first week with the level of involvement set at the onset. In a few patients, the disease has an ascending course with risk of asphyxia when upper cervical segments (C3-C5) are included.

Treatment of acute transverse myelitis (ATM) is still a matter of controversy in the studies. The efficacy of intravenous methylprednisolone in immune-mediated neurological disorders such as optic neuritis and multiple sclerosis (MS), led some authors to use it in children with acute transverse myelitis (ATM). Studies have confirmed its efficacy shortening motor recovery and considerably increasing the percent of patients have the ability to walk independently at follow-up when compared to a historical control group. A study case showed that a patient was with fair outcome in spite of the very acute course of the disease and the presence of a cervical sensory level, and might be well ascribed to the early use of methylprednisolone.

18.2.3.1 Acute Myelitis in COVID-19 Infection

Zhao *et al.* (2020) reported acute myelitis in a 66-year-old man from Wuhan city who presented with fever and body aches. During the admission he progressed acute flaccid paralysis (AFP) of bilateral lower limbs, sensory level at T-10 with urinary and bowel incontinence. Computed tomography (CT) scan chest confirmed patchy pneumonia and polymerase chain reaction (PCR) assay for nasopharyngeal secretion was positive for coronavirus disease 2019 (COVID-19) infection. His serology for all other organisms was negative. He was treated empirically with intravenous immunoglobulin (IVIG), steroids, antibiotics and antiviral drugs. The response to therapy was good and he was discharged to an isolation facility for further rehabilitation. The authors attributed acute myelitis to the cytokine storm and overactive inflammatory response as evident by high levels of serum ferritin, C-reactive protein (CRP), serum Amyloid- A and interleukin-6 (IL-6) concentrations. A principal limitation of this case report is the lack of

cerebrospinal fluid polymerase chain reaction (CSF PCR) test for coronavirus (CoV) and magnetic resonance imaging (MRI) of spine due to epidemic in Wuhan city. Although the literature is scarce at this point in time, the idea that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can cause para-/post-infective complications affecting the neuroaxis at different levels seems realistic, and supposedly patients with the inflammatory storm will be more likely to manifest this.

18.2.4 Cerebrovascular Disease

Cerebrovascular disease is defined as neurological deficits due to arterial insufficiency or occlusion, venous occlusive disease, or haemorrhage with usually focal deficits that may be multifocal in recurrent disease. Cerebrovascular disease is a complication of a variety of infections impacting the central nervous system (CNS). Infection may cause vasculitis affecting mainly the vessels at the base of the brain in the setting of meningitis; an immune-mediated parainfectious process developing to vasospasm or thrombosis; or a hypercoagulable state in combination with endothelial dysfunction resulting from activation of inflammatory and procoagulant cascades. Although systemic signs and symptoms may be present to aid in the diagnosis, cerebral infarction secondary to infection may be indistinguishable from more typical causes of stroke. Confirmation of an infectious vasculitis may also be challenging, as brain biopsy, the ideal for diagnosis, is scarcely pursued. In many central nervous infections (CNS) infections, vascular complications portend a poor prognosis as they are often associated with devastating neurologic outcomes, including death.

The nervous system manifestations were significantly more common in patients with severe coronavirus disease 2019 (COVID-19) infection, manifested as ischaemic stroke and cerebral haemorrhage diagnosed by clinical symptoms and head computed tomography (CT), impaired consciousness and skeletal muscle injury. Rapid clinical deterioration or worsening could be from a neurological event such as stroke, which may have contributed to its high mortality rate. The main reason of clinical deterioration is the hyperactivation of inflammatory factors that eventually causes a fatal inflammatory storm as the disease progresses. Moreover, coagulation system is damaged causing the D-dimer (DD) and platelet abnormalities, which elevates the risk of cerebrovascular disease. During the epidemic period of coronavirus disease 2019 (COVID-19), when observing cases with above neurological manifestations specifically more progress to

nervous system (NS) manifestations, doctors should consider severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection as a differential diagnosis so to avoid misdiagnosis and seize the opportunity of stopping it from infecting other individuals.

Among cases with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, middle-aged and elderly people are vulnerable for the majority of strokes, especially in critically ill cases. Serum D-dimer (DD) concentration is generally elevated, which might be the source of embolic vascular events. Many of these patients may already have other cerebrovascular risk factors, such as hypertension (HTN), diabetes mellitus (DM), hyperlipidaemia, smoking or previous stroke history. Some may progress to their first-ever acute ischaemic stroke. Therefore, medical staff should obviously follow the manifestation of neurological symptoms. If an acute ischaemic stroke patient with suspected or confirmed diagnosis of coronavirus disease 2019 (COVID-19) are admitted, emergency therapy should be jointly administered by neurologists and infectious disease specialists. For ischaemic stroke patients with a high D-dimer (DD) concentration, preventive anticoagulation is recommended potently. These cases should be transferred to the isolation ward, and neurologists would assist in the management.

It is indicated that respiratory-related infection as an independent risk factor for acute cerebrovascular disease. Data from the use of experimental mouse models supposes that influenza virus can aggravate ischemic brain injury by provoking a cytokine cascade and elevate the risk of cerebral hemorrhage after management with tissue-type plasminogen activator. The infection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been broadly reported to cause cytokine storm syndromes, which can be considered as one of the factors that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cause acute cerebrobasilar disease. Further, critically ill patients with severe severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections frequently present increased concentrations of D-dimer (DD) and severe platelet reduction, which can make these patients vulnerable to acute cerebrovascular events.

Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) specifically binds to angiotensin-converting enzyme2 (ACE2) receptors, patients with hypertension may encounter blood pressure fluctuations following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which may increase the risk of intracranial haemorrhage. Furthermore, some

critically ill patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection have severe thrombocytopenia, another high-risk factor for cerebral haemorrhage. For hypertensive patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, it is recommended to stop using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) as antihypertensive drugs, and consider calcium channel blockers, diuretics and other classes of antihypertensive therapies.

Cerebrovascular disease is a heterogeneous disorder. It consists of a number of distinct pathologies, comprising transient ischemic attack, stroke pathological types (ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage) and etiological subtypes (e.g., cardioembolic, atherothrombotic, lacunar ischemic strokes, and aneurysmal subarachnoid hemorrhage), and other intracranial vascular disorders (e.g., vascular malformations and unruptured aneurysms), each of which has different epidemiological and management features. Stroke is the significant and devastating clinical manifestation of all the cerebrovascular disorders. It is worthy to identify each of the disorders mentioned above and as following: ischemic stroke occurring when a blood vessel supplying blood to the brain is obstructed; intracerebral hemorrhage (ICH) is when blood suddenly bursts into brain tissue, causing damage to brain; subarachnoid hemorrhage (SAH) is a life-threatening type of stroke caused by bleeding into the space surrounding the brain, can be caused by a ruptured aneurysm, arteriovenous malformation (AVM), or head injury; cardioembolic stroke is presence of a potential intracardiac source of embolism in the absence of cerebrovascular disease in a patient with nonlacunar stroke; atherothrombotic stroke occurs when a blood clot forms on an atherosclerotic plaque within a blood vessel in the brain and blocks blood flow to that part of the brain; lacunar ischemic stroke or lacunar infarct (LACI) is the most common type of ischaemic stroke, resulting from the occlusion of small penetrating arteries that provide blood to the brain's deep structures; aneurysmal subarachnoid hemorrhage (SAH) or basal acute subarachnoid hemorrhage (SAH) is a ruptured cerebral aneurysm, and basal means that the blood is most prominently observed in the basal cisterns; vascular malformations is a type of birthmark or a growth, often present at birth and composed of blood vessels that can cause functional or cosmetic problems, and congenital or acquired blood vessel abnormalities can include arteries, veins, capillaries, lymphatics, and combinations of these blood vessel; unruptured aneurysms is where aneurysm referring to a bulge or ballooning in a blood vessel in the brain and is often seems like a berry

hanging on a stem, and this brain aneurysm can leak or rupture, leading bleeding into the brain (hemorrhagic stroke).

18.2.4.1 Cerebrovascular Disease in COVID-19 Infection

Sharifi *et al.* (2020) from Iran recorded a patient of intracranial bleed resulting in cerebrovascular accident (CVA) in a 79 years old coronavirus disease 2019 (COVID-19) positive man. He was admitted in the emergency in a semi-conscious state (Glasgow Coma Scale 7/15) with history of fever and cough. On examination there was, bilateral extensor planter response with coarse crepitation in left lower zones. Polymerase chain reaction (PCR) assay from nasopharyngeal secretion was positive for coronavirus disease 2019 (COVID-19). Computed tomography (CT) scan chest presented ground glass opacity suggestive of viral pneumonia. Computed tomography (CT) scan brain showed a massive bleed within the right hemisphere with intraventricular and subarachnoid extension. This man was neither a known hypertensive nor on any anticoagulants that could have caused this event. The platelets and prothrombin time/international normalized ratio (PT/INR) on admission were normal. The authors explained that probably dysregulation in the angiotensin-converting enzyme2 (ACE2) receptors cause cerebral auto regulation, sympatho-adrenal system and cerebral blood flow could have resulted in the bleed. Another aspect that is difficult to explain is the near normal blood pressure in this man at the time of admission. Mao and colleagues reported six case of cerebrovascular accident (CVA) in their cohort study of 214. There were five ischemic and one patient of hemorrhagic stroke. The French cohort had three patients of ischemic strokes which were detected on neuroimaging when the patients underwent imaging for encephalopathy. The patients did not have focal neurological signs. Probably the symptoms were masked due to presence of encephalopathy, but it sheds light to the significance of neuroimaging in assessing of such cases. However more evidence is needed to establish a causal relationship between stroke and coronavirus disease 2019 (COVID-19).

18.2.4.2 Stroke in COVID-19 Infection

A stroke is a medical condition in which poor blood flow to the brain causes cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. Both cause parts of the brain not functioning properly. Signs and symptoms of a

stroke may involve an inability to move or feel on one side of the body, problems understanding or speaking, dizziness, or loss of vision to one side. Signs and symptoms frequently appear soon after the stroke has occurred.

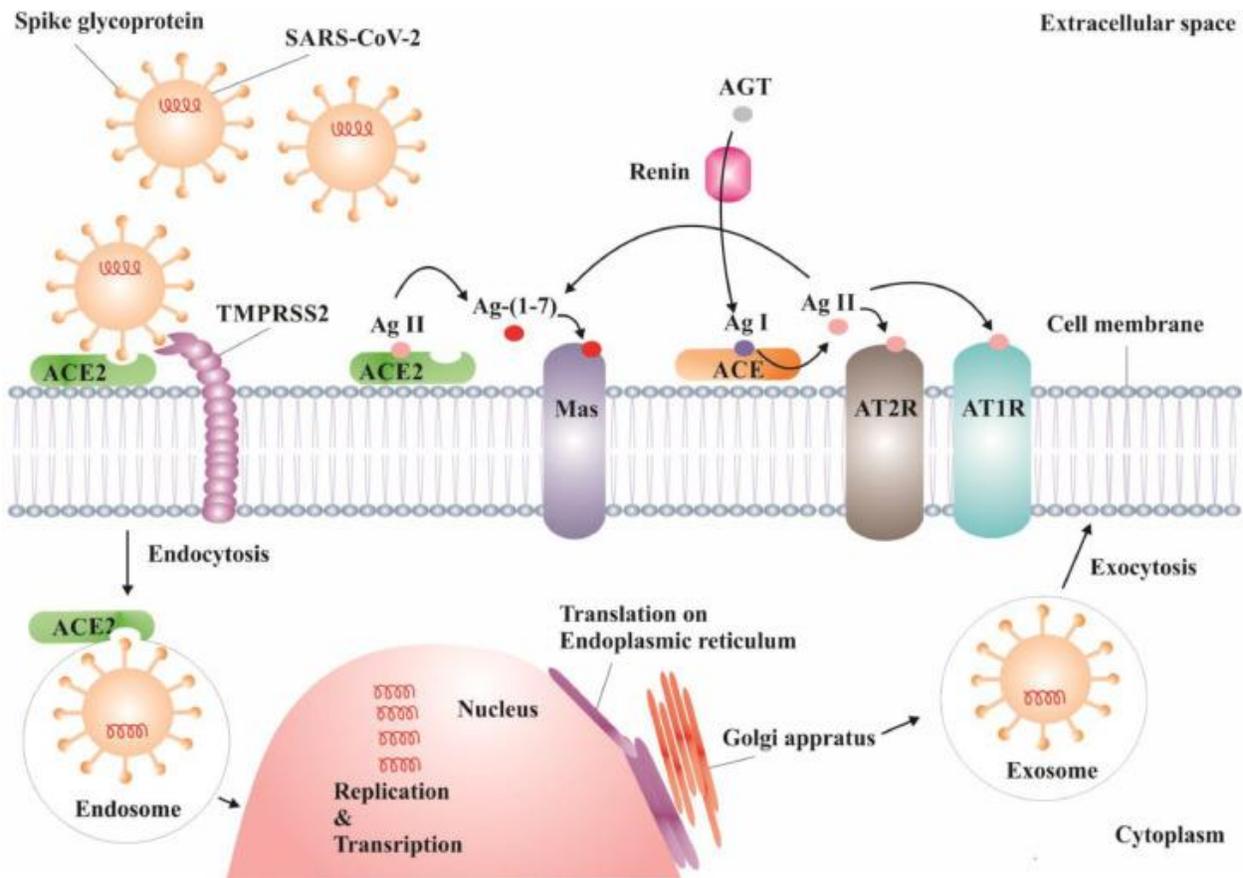
Previously, acute infections have been linked to stroke mainly among younger adult individuals. Therefore, it is probably that also in instances of coronavirus disease 2019 (COVID-19) infection, the systemic inflammatory response in the host rather than the viral invasion per se could be responsible for elevated stroke risk incidence. There is preliminary evidence for an association between coronavirus disease 2019 (COVID-19) and stroke, but causality has not been established. The immune response to acute cerebral ischemia plays an important role in the pathophysiology and outcomes of strokes. The inflammatory cascade, heightening the risk of stroke, can be activated by acute infections. Systemic inflammation and inflammatory biomarkers are associated with ischemic stroke risk. Serum interleukin-6 (IL-6) concentration has been seen to be a reliable prognostic factor of ischemic stroke. Therefore, together with the appropriate blood coagulation markers (including antiphospholipid antibodies) and inflammatory biomarker panel including C-reactive protein (CRP), pro-inflammatory cytokines [i.e., interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α)], circulating complement proteins (C3, C4, C5b-9), and Bb should be part of routine laboratory tests.

The renin-angiotensin system (RAS) plays several physiological roles, involving electrolyte homeostasis, cardiovascular (CV) control, and regulation of body fluid volume. Renin-angiotensin system (RAS) includes angiotensinogen (AGT), renin, angiotensin I (Ang I), angiotensin II (Ang II), angiotensin-converting enzyme (ACE), angiotensin-converting enzyme2 (ACE2), angiotensin type-1 receptor (AT1R), angiotensin type-2 receptor (AT2R), and Mas receptor (MAS). Brain renin-angiotensin system (RAS) has similar components to that of the peripheral renin-angiotensin system (RAS). The blood brain barrier (BBB) insulates the brain from the peripheral renin-angiotensin system (RAS) preventing the diffusion of angiotensin II (Ang II) from blood circulation into the brain. The brain also has the ability to synthesize its own angiotensin II (Ang II), which is involved in central brain renin-angiotensin system (RAS) activities. However, peripheral angiotensins may interact with brain renin-angiotensin system (RAS) at the circumventricular organs that lack blood brain barrier (BBB). In many areas of the brain, angiotensinogen (AGT) and renin are co-expressed. Most of angiotensinogen (AGT) is

expressed in the astrocytes. Angiotensin-converting enzyme (ACE) is expressed in the endothelium of cerebral vasculature; it is also highly expressed in choroid plexus (CP), organum vasculosum of the lamina terminalis, area postrema, and subfornical organ. In the classical axis (ACE-Ang II-AT1R), renin first cleaves angiotensinogen (AGT) to angiotensin I (Ang I). Having been hydrolyzed by angiotensin-converting enzyme (ACE), angiotensin I (Ang I) is converted to angiotensin II (Ang II) that in turns simulate angiotensin type-1 receptor (AT1R) and angiotensin type-2 receptor (AT2R). angiotensin II (Ang II) has a higher affinity to angiotensin type-1 receptor (AT1R) where it exhibits its main physiological impacts by mediating vasoconstriction, neuroinflammation, oxidative stress (OS), apoptosis, and cellular proliferation. In the alternative axis (ACE2-Ang (1–7)-Mas), angiotensin-converting enzyme2 (ACE2) cleaves angiotensin II (Ang II) to Ang (1–7), which is a ligand for the Mas receptor. Activation of this axis results in vasodilation, angiogenesis, anti-inflammatory, antioxidant, and anti-apoptotic responses. Over-activation of the ACE/Ang II/AT1R axis can serve an important role in the pathogenesis of acute ischemic stroke through its vasoconstrictor effects upon cerebral vessels, in addition to pro-fibrotic, proinflammatory, and elevated oxidative stress (OS) effect upon the brain parenchyma. Conversely, brain ACE2-Ang-(1-7)-MAS axis is an important regulator of blood pressure that counteracts the pressor effect of ACE-Ang II-AT1R axis in the brain. A larger metabolic penumbra volume and higher cerebral blood flow (CBF) in the core and penumbra were observed in angiotensin type-1 receptor (AT1R) knockout mice with a permanent middle cerebral artery (MCA) occlusion, compared to wild-type controls; mice with overexpression of human renin and angiotensinogen (AGT) genes had large infarcts. Angiotensin II (Ang II) has been shown to increase contractile response in isolated middle cerebral arteries (MCAs) subsequent to middle cerebral artery (MCA) occlusion through angiotensin type-1 receptor (AT1R) and impair cerebral perfusion post occlusion.

Some coronavirus disease 2019 (COVID-19) cases experience strokes, seizures, confusion, and brain inflammation. Early case reports described a Chinese patient with coronavirus disease 2019 (COVID-19) with left hemiparesis due to acute cerebral infarction and large blood vessel occlusion, as well as a case with coronavirus disease 2019 (COVID-19) with massive intracerebral hemorrhage (ICH) without prior history of arterial hypertension or anticoagulant use. Guan *et al.* (2020) revealed that cerebrovascular morbidity was seen in 1.4% and headache in 13.6% of cases with coronavirus disease 2019 (COVID-19). In another study, cerebrovascular

morbidity, dizziness, and headache have been recognized in 5.1%, 9.4%, and 6.5%, respectively, among coronavirus disease 2019 (COVID-19) patients. In a further study, among 214 patients with coronavirus disease 2019 (COVID-19), acute cerebrovascular disease was found in 6 (2.8%). Comparing severe and moderate coronavirus disease 2019 (COVID-19) patients, neurologic symptoms (45.5% vs 30.2%) such as acute cerebrovascular diseases (5.7% vs 0.8%) and impaired consciousness (14.8% vs 2.4%) were seen more frequently among severe coronavirus disease 2019 (COVID-19) cases. Helms *et al.*(2020) studied 58 patients with coronavirus disease 2019 (COVID-19) of which 13 had brain magnetic resonance imaging (MRI). The researchers reported ischemic strokes in 3 of the 13 cases (23%). Li *et al.* (2020) reported that out of 221 patients with coronavirus disease 2019 (COVID-19), 11 (5%) had an acute ischemic stroke, 1 (0.5%) a cerebral venous sinus thrombosis (CVST), and 1 (0.5%) an intracerebral hemorrhage (ICH).



Figure(113):Stroke and COVID-19 [Divani A.; Andalib S.; Napoli M.; Lattanzi S.; Hussain M.; Biller J.; McCullough L.; Azarpazhooh M.; Seletskaya A.; Mayer S.; Torbey M. (2020). Coronavirus disease and stroke: clinical manifestations and pathophysiological insights. *Journal of Stroke and Cerebrovascular Diseases*. <https://doi.org/10.1016/j.strokecerebrovasdis.2020.104941>]

Figure (113): Abbreviations: SARS-COV-2: severe acute respiratory syndrome coronavirus-2, RAS: renin-angiotensin system, ACE2: angiotensin-converting enzyme 2, TMPRSS2: Transmembrane protease, serine 2, Ang: angiotensin, Mas: Mas receptor, AT1R: angiotensin 1 receptor

Figure (113) shows schematic process of endocytosis of severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), proliferation of the virus inside the cell, and effect of virus upon renin-angiotensin system (RAS). Having been primed by transmembrane protease serine2 (TMPRSS2), severe acute respiratory syndrome coronavirus-2 (SARS-COV-2)'s spike glycoprotein binds to angiotensin-converting enzyme2 (ACE2). The virus enters the cell and is proliferated. Severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) downregulates angiotensin-converting enzyme2 (ACE2), which in turn under-activates the renin-angiotensin

system (RAS) alternative axis (ACE2-Ang-(1-7)-Mas). Under-activation of the alternative axis gives rise to over-activation of the classical renin-angiotensin system (RAS) axis (ACE-Ang II-AT1R). The consequent imbalance in vasodilation, neuroinflammation, oxidative stress (OS), and thrombotic response can contribute to the pathophysiology of stroke during severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) infection.

18.2.5 Encephalopathy

Encephalopathy means any disorder or disease of the brain, especially chronic degenerative conditions. Encephalopathy refers to a syndrome of overall brain dysfunction; this syndrome has many possible organic and inorganic causes. The principal character of encephalopathy is an altered mental state or delirium. Characteristic of the altered mental state is impairment of the cognition, attention, orientation, sleep-wake cycle and consciousness. An altered state of consciousness varies from failure of selective attention to drowsiness. Hypervigilance, which can be present in encephalopathy, is a state of heightened alertness accompanied by behavior that aims to prevent danger. Hypervigilance can be found with or without: cognitive deficits, headache, epileptic seizures, myoclonus or asterixis . According to the type and severity of encephalopathy, common neurological symptoms are loss of cognitive function, subtle personality changes, and an inability to concentrate. The other neurological symptoms include dysarthria, hypomimia, problems with movements (they can be clumsy or slow), ataxia, and tremor. Other neurological symptoms may include involuntary grasping and sucking motions, nystagmus , jactitation , and respiratory abnormalities such as Cheyne-Stokes respiration , apneustic respirations, and hypercapnic apnea. Focal neurological deficits are less common. Focal neurological deficit is a problem with nerve, spinal cord, or brain function. It affects a specific location, such as the left side of the face, right arm, or even a small area such as the tongue. Speech, vision, and hearing problems are also considered focal neurological deficits.

Treatment differs according to the type and severity of the encephalopathy. Anticonvulsants may be prescribed to reduce or halt any seizures. Changes to diet and nutritional supplements can help some patients. In severe cases, dialysis or organ replacement surgery may be considered necessary. Sympathomimetic drugs can increase motivation, cognition, motor performance and alertness in persons with encephalopathy caused by brain injury, chronic infections, strokes, and

brain tumors. When the encephalopathy is caused by untreated celiac disease or non-celiac gluten sensitivity (NCGS), the gluten-free diet stops the progression of brain damage and improves the headaches.

18.2.5.1 Encephalopathy in COVID-19 Infection

Filatove *et al.* (2020) reported a patient of a 74-year-old male with past medical history of atrial fibrillation (AF or Afib), stroke, Parkinson disease (PD), chronic obstructive pulmonary disease (COPD), and recent cellulitis, who admitted to the emergency department (ED) with fever and cough. Initial diagnostic work up did not suggest any serious issue and he was discharged to home. He reported back with worsening symptoms, including headache, altered mental status, fever, and cough. Chest X ray was suggestive of pneumonia, while computed tomography (CT) scan brain was unremarkable except for signs of previous stroke. Polymerase chain reaction (PCR) assay of cerebrospinal fluid (CSF) was negative for infection. He tested positive for coronavirus disease 2019 (COVID-19) and was intubated after developing respiratory failure (RF). He was started on hydroxychloroquine (HCQ), lopinavir/ritonavir, and was continued on broadspectrum antibiotics.

A retrospective report of coronavirus disease 2019 (COVID-19) patients from Wuhan described encephalopathy, or persistent (>24 hr) alterations in consciousness, in roughly one-fifth of patients succumbing to the disease. Notably, blood plasma concentrations of pro-inflammatory cytokines [e.g., interleukin (IL)-6, tumor necrosis factor-alpha (TNF- α), interleukin-8 (IL-8), interleukin-10 (IL-10), and interleukin-2 receptor (IL-2R)] were considerably elevated among fatal coronavirus diseases 2019 (COVID-19) patients, indicative of hypercytokinemia, or cytokine storm syndrome, which was also recorded in severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), and may underlie encephalopathy. Beyond the acute effects of cytokine storm, a recent meta-analysis of delirium among intensive care patients of mixed conditions reported evidence of persistent neurocognitive deficits up to 18 months post-discharge, including mild cognitive impairment. Given other emerging evidence of hypercytokinemia in hospitalized coronavirus disease 2019 (COVID-19) cases, the burden of long-term post-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) delirium may be urgent, especially for elderly cases who are more susceptible to post-infectious neurocognitive complications.

18.2.5.2 Acute Necrotizing Encephalopathy

Acute necrotizing encephalopathy (ANE) is a rare type of acute encephalopathy (AE) with global distribution. It is regarded as a parainfectious disease that is induced primarily by viral diseases.

Prodromal viral infections seem to play a critical role in the initiation of acute necrotizing encephalopathy (ANE). Despite the various antecedent infections, acute necrotizing encephalopathy (ANE) is not considered to be an inflammatory encephalitis.

Although the exact pathogenesis of acute necrotizing encephalopathy (ANE) is still not clear, the most prevalent hypothesis is the hypercytokinemia, that is, cytokine storm. Patients suffering from acute necrotizing encephalopathy (ANE) frequently have an exaggerated immune response to various viral infections by releasing high levels pro-inflammatory cytokines resembling systemic inflammatory response syndrome (SIRS). The cytokine storm leads to systemic symptoms, such as liver dysfunction (LD), acute renal failure (ARF), shock, and disseminated intravascular coagulation (DIC). In the nervous system, it leads to brain injury through alteration of vessel wall permeability without vessel wall disruption. Based on this hypothesis, acute necrotizing encephalopathy (ANE) is an encephalopathy concomitant with systemic immune imbalance. Flow cytometric analysis (FCA) on peripheral blood lymphocytes of patients with acute necrotizing encephalopathy (ANE) showed high proportion of CD56⁺ natural killer (NK) cells during the recovery phase. These cells released a high concentration of cytokines, proposing that natural killer (NK) cells could be correlated with the pathogenesis of acute necrotizing encephalopathy (ANE). Several lines of evidence revealed that concentrations of cytokines were highly increased in the serum and/or cerebrospinal fluid (CSF) in different virus-associated acute necrotizing encephalopathy (ANE) including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), interleukin-10 (IL-10), interleukin-15 (IL-15), interleukin-1beta (IL-1 β), soluble tumor necrosis factor receptor (sTNFR), and interferon-gamma (IFN- γ). Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) were critical among these cytokines, because the former was neurotoxic at elevated levels, whereas the latter might damage the endothelium of the central nervous system (CNS). Hypercytokinemia engenders proteolytic destruction of the blood-brain barrier (BBB) through the action of trypsin and the activation of matrix metalloproteinase-9 (MMP-9), which subsequently increases vascular permeability and

leads to brain edema (fluid builds up around the brain), petechial hemorrhage (areas of pericapillary bleeding), and necrosis. Genetic background might contribute to the pathogenesis of acute necrotizing encephalopathy (ANE). The impaired mitochondrial β -oxidation and the generation of adenosine triphosphate (ATP) in the cerebral microvascular endothelial cells (ECs) engendered the increasing permeability of the vascular wall and the development of brain edema. The increasing permeability of the vascular wall could be resulted from genetic factors of susceptibility to energy failure in addition to pathophysiologic factors of hypercytokinemia. Another interesting finding was the ephrin type B receptor 2 (EphB2), a novel cell-surface autoantigen which had critical functions to neuronal and endothelial cells (ECs). Ephrin type B receptor 2 (EphB2) was expressed by human brain microvascular endothelial cells (ECs), which was presented as a target of autoantibody from a patient with acute necrotizing encephalopathy (ANE) complicated with systemic lupus erythematosus (SLE). Anti- ephrin type B receptor 2 (anti-EphB2) antibody, however, was not detectable in any systemic lupus erythematosus (SLE) patients without acute necrotizing encephalopathy (ANE), indicating it as a potent a biomarker of acute necrotizing encephalopathy (ANE). The proposed mechanisms are as follows:

1-Anti- ephrin type B receptor 2 (anti-EphB2) antibodies destruct vascular endothelial cells (ECs) which causes breakdown and increased permeability of blood brain barrier (BBB);

2-When blood brain barrier (BBB) is breached, anti- ephrin type B receptor 2 (anti-EphB2) antibodies exudate into brain tissue and bind neurons and neuroglia causing neuronal dysfunction and cell death.

Patients with acute necrotizing encephalopathy (ANE) have neither specified symptoms nor typical neurological signs. In addition to prodromal symptoms due to different viral infections, which include fever, signs of upper respiratory tract infections and gastroenteritis, and erythema, patients with acute necrotizing encephalopathy (ANE) often have signs of systemic inflammatory response syndrome (SIRS) like shock, multiple organ failure (MOF), and disseminated intravascular coagulation (DIC). With the incidence of acute necrotizing encephalopathy (ANE), brain dysfunctions may present as seizures, disturbance of consciousness, and focal neurological deficits. None of the above manifestations are specific to acute necrotizing encephalopathy (ANE). Laboratory results vary from patient to patient, while some could be indicated as differential diagnosis, such as abnormalities of liver function without

hyperammonemia (HA), hypoglycemia, or lactic acidosis. In addition, protein concentrations of cerebrospinal fluid (CSF) and platelet count could be a predictor of the prognosis of acute necrotizing encephalopathy (ANE). The clinical course of acute necrotizing encephalopathy (ANE) is fulminant and diverse, from a mild form with completely recovery or mild sequelae to a severe form with a high mortality. Survivors of acute necrotizing encephalopathy (ANE) undergo three phases during the clinical course comprising prodromal stage, period of acute encephalopathy, and recovery stage. Due to the decreased incidence of autopsies, the diagnosis of acute necrotizing encephalopathy (ANE) was mainly based on characteristic neuroradiologic findings. Diagnosis can only be established pending the exclusion of other resembling diseases.

Diagnostic Criteria for acute necrotizing encephalopathy (ANE) as proposed by Mizuguchi *et al.* (1997) are as follows:

-Mediators of Inflammation:

1-Acute encephalopathy (AE) preceded by viral febrile disease (a sudden fever or elevation in body temperature); rapid deterioration in the level of consciousness, and convulsion;

2-Increased cerebrospinal fluid (CSF) protein without pleocytosis, i.e., without the presence of an abnormally large number of lymphocytes in the cerebrospinal fluid (CSF);

3-Neuroradiologic findings for symmetric, multifocal brain lesions including bilateral thalami, cerebral periventricular white matter, internal capsule, putamen, upper brain stem tegmentum, and cerebellar medulla without involvement of other central nervous system (CNS) regions;

4-Elevation of serum aminotransferase level to a variable degree without hyperammonemia (an excess of ammonia in the blood);

5-Exclusion of other resembling diseases:

(a)-Clinical differential diagnosis; toxic shock syndrome (TSS), hemolytic uremic syndrome (HUS), Reye syndrome, hemorrhagic shock and encephalopathy syndrome, and heat stroke;

b-Radiological (or pathological) differential diagnosis; Leigh encephalopathy, glutaric acidemia (GA), methyl malonic aciduria, infantile bilateral strial necrosis (IBSN), Wernicke encephalopathy (WE), acute disseminated encephalomyelitis (ADEM), acute hemorrhagic

leukoencephalitis (AHLE), arterial or venous infarct, severe hypoxia or traumatic injury, toxins resulting in symmetric bilateral basal ganglia necrosis [such as carbon monoxide, methanol, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), cyanide, manganese, carbon disulfide, and tegretol], and some other diseases causing symmetric bilateral basal ganglia necrosis such as osmotic myelinolysis, prolonged hypotension, Canavan disease, methylmalonic acidemia, Wilson disease, Juvenile Huntington disease (JHD), striatonigral degeneration, and Hallervorden-Spatz syndrome.

Diagnostic Criteria for acute necrotizing encephalopathy (ANE) as proposed by Neilson (2010). Except for the above diagnostic criteria for acute necrotizing encephalopathy (ANE), simultaneously meet any of the following criteria:

1-Familial history of neurological symptoms which could be parainfectious;

2-Recurrent encephalopathy following fever;

3-Additional magnetic resonance imaging (MRI) changes in one of the following: medial temporal lobes, insular cortices, claustrum, external capsule, amygdale, hippocampi, mammillary, and spinal cord.

The hallmark of neuroradiologic manifestations of acute necrotizing encephalopathy (ANE) is multifocal, symmetric brain lesions involving both the gray matter and the white matter that are demonstrated by computed tomography (CT) or magnetic resonance imaging (MRI), consistent with histopathologic findings via autopsy. The topographic distributions are remarkably similar among patients with acute necrotizing encephalopathy (ANE), comprising thalami, brain stem, cerebral white matter, and cerebellum. Bilateral thalami are typically involved in all cases with acute necrotizing encephalopathy (ANE), serving as a distinctive feature of acute necrotizing encephalopathy (ANE). Spinal cord (SC) may occasionally be involved as well. Neuroradiologic manifestations are characterized by dynamic changes during the clinical course corresponding to pathophysiological changes from edema to petechial hemorrhage and then to necrosis. Regression or recovery of the brain lesions is possible for survivors. Lesions in the brain are edematous and combined with mass effect at the onset of acute necrotizing encephalopathy (ANE).

It is significant to say that the typical lesions appear predominantly in the gray matter, especially in the bilateral thalami. Finding suggests that alteration of the blood brain barrier (BBB) permeability might be the first step in the development of brain lesions.

There have been no recommended treatments for acute necrotizing encephalopathy (ANE). Intensive care, symptomatic treatment and empirical treatment (antiviral therapy), and immunomodulatory agents were tested in majority of patients. Due to the pathogenesis of acute necrotizing encephalopathy (ANE), mainly the hypercytokinemia secondary to variable viral infections through immune-mediated mechanism, the immunomodulatory therapy, particularly the therapy that suppressed the cytokine production, has potent role in improving the outcome of acute necrotizing encephalopathy (ANE). Intravenous (IV) glucocorticoids (GCs), immunoglobulin, and plasmapheresis should be effective on the basis of the pathogenesis of acute necrotizing encephalopathy (ANE). Among these therapies, intravenous (IV) glucocorticoids (GCs), involving methylprednisolone and dexamethasone, were the most presented and investigated, although empirically without systematically determined. However, findings from different literature were conflicting. Some authors mentioned that administration of steroids within 24 hours after onset or at the early stage of the disease was related to a better prognosis in those without brain stem involvement. However, in spite of the severity of presentation and the late administration of steroids, good outcome was still found in some patients, and some researchers suggested that a trail of steroids should be given to all cases experiencing acute necrotizing encephalopathy (ANE). Another study, on the contrary, found that acute necrotizing encephalopathy (ANE) cases administered steroids showed poor outcomes. Thus, there has been no consensus on whether steroids should be prescribed to patients with acute necrotizing encephalopathy (ANE), as well as the dosage, timing, and the duration. Therapeutic hypothermia, another method of anticytokine therapy, has been used for treating brain swelling caused by trauma and encephalopathy. Therapeutic hypothermia has proven neuroprotective effects in global cerebral ischemia. Indications for hypothermia induction include cardiac arrest and neonatal asphyxia. The two general methods of induced hypothermia are either surface cooling or endovascular cooling. Hypothermia should be induced as early as possible to attain maximum neuroprotection and edema blocking effect. Endovascular cooling has the benefit of shorter time to reach target temperature but catheter insertion requires expertise and training, which may be a barrier to widespread availability. The optimum method of cooling

is yet to be determined but a multimodal approach is necessary to address three phases of cooling: induction, maintenance, and re-warm. Specifying core practitioners who are well-versed in established guidelines can help integrate the multidisciplinary team that is needed to successfully implement cooling protocols. Reducing shivering to make heat exchange more efficient with tighter temperature control enables quicker time to target temperature and avoids re-warming which can lead to inadvertent increase in intracranial pressure and cerebral edema. Promising applications but yet to be determined is whether hypothermia treatment can improve outcomes in acute ischemic stroke or traumatic brain injury. Therapeutic hypothermia is pivotal to the outcome of the children with acute necrotizing encephalopathy (ANE), especially if it is initiated within 12 hours after onset.

18.2.5.2.1 Acute Necrotizing Encephalopathy in COVID-19 Infection

Acute necrotizing encephalopathy (ANE) is a rare complication of viral infections like influenza. The supposed mechanism is due to cytokine storm which causes disruption of blood brain barrier (BBB) and damage to the brain parenchyma. Health care providers should be cautious that patients with coronavirus disease 2019 (COVID-19) can have encephalopathy during hospitalization.

Poyiadji and colleagues (2020) recorded the first incidence of coronavirus disease 2019 (COVID-19)-associated acute necrotizing encephalopathy (ANE) from United States of America. A woman in her late fifties presented with a 3-day history of cough, fever, and altered mental status. Polymerase chain reaction (PCR) assay was positive for coronavirus disease 2019 (COVID-19) and negative for Herpes Simplex Virus 1 and 2 (HSV-1 and HSV-2), West Nile Virus (WNV) and Varicella Zoster Virus (VZV). Non contrast head computed tomography (CT) images revealed symmetric hypoattenuation within the bilateral medial thalami with a normal computed tomography (CT) angiogram and computed tomography (CT) venogram. Magnetic resonance imaging (MRI) brain showed hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and sub insular regions. She was administered intravenous Immunoglobulin (IVIG), but the outcome was not mentioned.

Desforges *et al.* (2020) reported a woman airline worker with coronavirus disease 2019 (COVID-19) diagnosed with acute necrotizing encephalopathy (ANE). Head tomographs

confirmed symmetric hypoattenuation within the two-medial thalamus with standard computed tomography angiography (CTA) and computed tomography (CT) venogram tomography. This encephalitis should be accompanied by the detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in cerebrospinal fluid (CSF) by Real-Time Polymerase Chain Reaction (RT-PCR) assay.

18.2.5.3Viral Encephalitis

Encephalitis stands for inflammation of the brain. To be more precise, it refers to inflammation of brain parenchyma and is usually associated with a spectrum of signs and symptoms including fever, headache, clouding of consciousness, seizures, personality change, focal neurological deficits, and coma. Sometimes it can also be associated with brain dysfunction and noteworthy morbidity and mortality.

Although viral encephalitis (VE) is an unusual complication of viral infection, viral infection is one of the prime causes of encephalitis. Around 100 viruses are believed to cause encephalitis. Viral infection can strike any part of central nervous system (CNS), but it frequently causes meningitis and encephalitis. The ambit of vital findings includes fever, headache, altered mental status, sometimes accompanied by seizures and focal neurologic abnormalities.

Based on etiology and pathogenesis, viral encephalitis (VE) can be divided into four classes:

- 1-Acute viral encephalitis (AVE);
- 2-Postinfectious encephalomyelitis (PIEM);
- 3-Slow viral infections of central nervous system (CNS); and
- 4-Chronic degenerative diseases of central nervous system (CNS).

The severity of viral encephalitis is affected by the following factors:

1-Age and gender variation: the highest incidence of viral encephalitis (VE) is observed among younger age group patients and elderly individuals. Studies have reported that number of male patients diagnosed with viral encephalitis (VE) is more in comparison with the number of female patients.

2-Role of immune status: Patients who have compromised immune system are at greater risk of acquiring disseminated disease with the incidence up to 36%.⁶⁵.

3-Seasonal distribution of viral encephalitis (VE): Certain viruses have specific favorable set of atmospheric conditions for its growth and proliferation. Therefore, it blooms out in certain seasons and causes more damage.

The onset of viral encephalitis (VE) starts with breach in central nervous system (CNS) protective barriers. There are essentially two pathways mentioned below through which viruses can gain access to the central nervous system (CNS) and result in infection:

1-Through blood supply:

a-By directly damaging endothelial cells and creating passage through the junctions.

b-Through anatomic structures that are less secured and have low strength defense such as the choroid plexus (CP) and circumventricular organs (CVOs).

c-Or with the assistance of infected hematopoietic cells (Trojan horses).

2-By infecting peripheral sensory or motor nerves. Following viral invasion in central nervous system (CNS), monocytes sneak into the infected central nervous system (CNS) area and get transformed into required cell forms, for example, dendritic cell (DC, antigen-presenting cell), macrophage (MΦ, a type of phagocyte), and microglial cells. Presence of Ly6Chi monocyte in inflamed area of central nervous system (CNS) is considered as pathognomonic finding of viral encephalitis (VE). These transformed cells aim at limitation and depopulation of viral components by assisting in antigen presentation and T cell stimulation. It also aids in releasing numerous proinflammatory mediators and reactive oxygen species (ROS). Pathogenic component that has reached central nervous system (CNS) destructs the nerve cells that causes disease and thus development of clinical symptoms.

Onset of clinical signs and symptoms of viral encephalitis mostly hinges upon type of viral infection, immune status, and age of the infected person. Younger and elder individuals manifest more severe form of encephalitis in comparison with the others. Cardinal signs and symptoms are fever, headache, altered level of consciousness, changed mental status, nausea, and vomiting.

When cortex is included, seizures are one of the prominent findings. Findings associated with viral encephalitis can be divided into following groups:

1-Cognitive dysfunction: acute memory loss, speech, and orientation disturbance.

2-Behavioral changes: disorientation, hallucinations, psychosis, personality changes, and agitation.

3-Focal neurological abnormalities: ataxia, anomia, dysphasia, and hemiparesis.

4-Pyramidal signs: brisk tendon reflexes and extensor plantar responses.

5-Cranial nerve abnormalities: oculomotor and facial nerves are mainly involved.

6-Involuntary movements: myoclonus and tremors.

7-Seizures (may or may not be associated with the disease).

Patients experiencing viral encephalitis (VE) generally need intensive care. Essentially, while dealing with viral encephalitis (VE), following three parameters are to be taken into account:

1-The need of antiviral or immune modifier drugs to arrest the infection;

2-To keep a check on symptoms and sufferings of patients; for example, to manage seizures, phenytoin and low dosage of benzodiazepines can be administered;

3-To prevent any late deleterious outcome of the disease; for example, certain drugs can result in nephrotoxicity and raise serum liver enzymes.

There has been a notable improvement in prognosis of this disease in the past decades. Acyclovir intravenous (IV) drug has decreased the mortality risk from 70 to 20%. But still the satisfactory level of results has not been attained. Approximately, up to 10% of the cases suffer from reactivation of the disease after completion of antiviral therapy. A large section of patients, who manages to recover from viral encephalitis (VE), frequently complains of symptoms suggestive of permanent neurologic damage. Prognosis of this disease also relies on age and immune status of the patient, etiology, and severity of the disease. Patients of younger and older age groups are at greater risk to sustain permanent neuronal damage.

18.2.5.3.1 Viral Encephalitis in COVID-19 Infection

Early diagnosis of viral encephalitis (VE) is urgent. In the ongoing pneumonia epidemic, the treatment team of Beijing Ditan Hospital affirmed the presence of severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) in the cerebrospinal fluid (CSF) of patients with coronavirus disease 2019 (COVID-19) by genome sequencing, thereby clinically verifying viral encephalitis (VE). This offered a solid basis for severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) developing the encephalitis.

Moriguchi *et al.* (2020) reported first confirmed case of coronavirus disease 2019 (COVID-19) associated viral encephalitis from Japan. A 24 years old man presented with fever followed by seizure and unconsciousness. He had neck stiffness and subjected to computed tomography (CT) scan brain which was normal. There was patchy pneumonia on computed tomography (CT) chest. Polymerase chain reaction (PCR) assay from nasopharyngeal swab was negative but cerebrospinal fluid (CSF) sample was positive for coronavirus disease 2019 (COVID-19). The Diffusion weighted Images (DWI) showed hyperintensity along the wall of inferior horn of right lateral ventricle. Fluid-attenuated inversion recovery (FLAIR) images showed hyperintense signal changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy mainly on right mesial lobe and hippocampus. There was no post contrast enhancement. The authors concluded that imaging findings were suggestive of right lateral ventriculitis and encephalitis.

Two studies reported a possible complication of the presence of severe acute respiratory syndrome coronavirus-2 (SARSCoV-2) within the human nervous system (NS), mainly encephalopathy. Physical examination and medical history can be used to diagnose encephalopathy, such as brain imaging [magnetic resonance imaging (MRI) or computed tomography (CT) images], which can show any swelling of the brain, cerebrospinal fluid (CSF), in which any changes in this fluid can refer to infection and tenderness in the brain. Electroencephalogram (EEG) records the brain's electrical activity, in which certain abnormal patterns may indicate a diagnosis of encephalitis. In addition, biomedical tests such as blood tests, urine tests, or swab from the throat can be shown for viruses or other infectious causes.

18.2.5.4 Infectious Toxic Encephalopathy and COVID-19 Infection

The term toxic encephalopathy refers to brain dysfunction caused by toxic exposure. Toxic encephalopathy comprises a spectrum of symptomatology ranging from subclinical deficits to overt clinical disorders. The clinical manifestations of toxic encephalopathy are related to the affected brain regions and cell types. Toxic encephalopathy typically manifests as a non-focal or symmetrical neurological syndrome.

Many viral infections can lead to serious damage to the structure and function of the nervous system (NS), involving severe encephalitis due to viral infections in the central nervous system (CNS), toxic encephalopathy caused by severe systemic viral infections, and severe acute demyelinating lesions developing after viral infections. Some viruses are neurotropic and can invade nervous tissues and cause infections of immune-functioning macrophages, microglia, or astrocytes in the central nervous system (CNS).

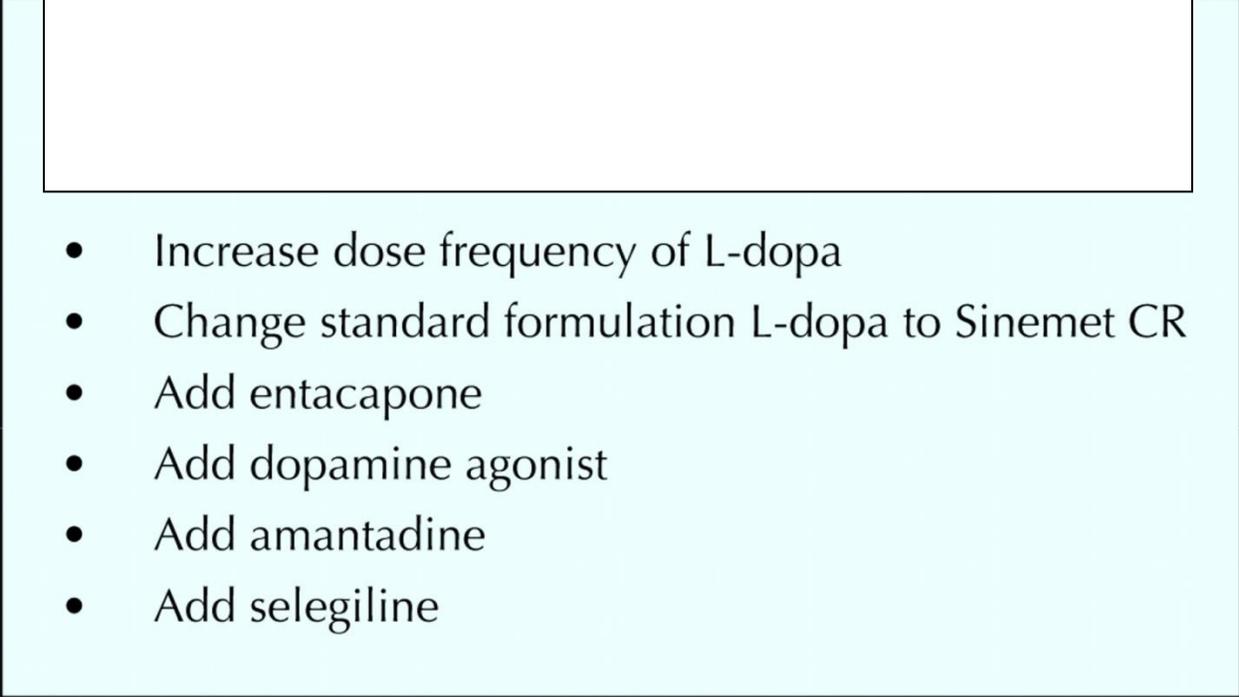
Infectious toxic encephalopathy, also known as acute toxic encephalitis, indicates a type of reversible brain dysfunction syndrome caused by factors such as systemic toxemia, metabolic disorders, and hypoxia during the process of acute infection. The basic pathological changes in this disease include cerebral edema, with no evidence of inflammation on cerebrospinal fluid (CSF) analysis. Its clinical symptoms are complex and diverse. Patients with a mild course of the disease may develop headache, dysphoria, mental disorder, and delirium. Seriously affected patients may experience disorientation, loss of consciousness, coma, and paralysis. Acute viral infection is also an important cause of this disease, exemplified by a respiratory infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) patients with coronavirus disease 2019 (COVID-19) frequently experience severe hypoxia and viremia, which has the potential to cause toxic encephalopathy. Moreover, almost 40% of patients with coronavirus disease 2019 (COVID-19) suffer from headache, disturbed consciousness, and other brain dysfunction symptoms, and that an autopsy study reported that edema has been detected in brain tissue of coronavirus disease 2019 (COVID-19) patients. These findings present the evidence that coronavirus disease 2019 (COVID-19) can cause infectious toxic encephalopathy, although detailed studies are greatly required.

18.2.6 Postencephalitic Parkinsonism

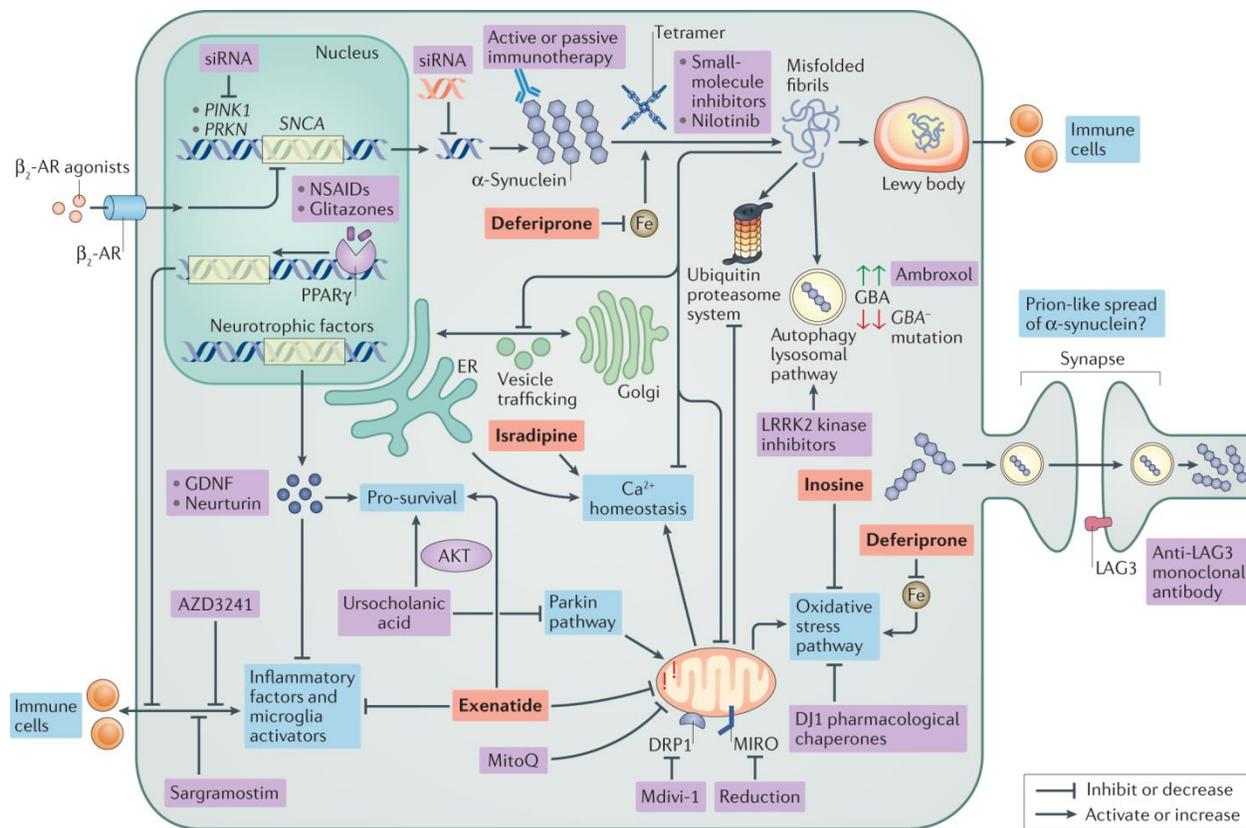
It is still to be investigated if severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can develop parkinsonism following an episode of encephalitis. The issue of a viral etiology of encephalitis lethargica and postencephalitic parkinsonism remains a matter of debate. A strong linkage of parkinsonism with influenza virus (IV) and many other viruses stem from an outbreak of encephalitis lethargica (EL), and postencephalitic parkinsonism that occurred subsequent to the 1918 pandemic influenza outbreak resulted from a type A H1N1 influenza virus. The cause of encephalitis lethargica (EL) and the link to subsequent postencephalitic parkinsonism (PEP) remains controversial with clinical features showing both similarities and distinct symptomatology to Parkinson disease (PD). Following an acute episode, the chronic phase of postencephalitic parkinsonism (PEP) developed after one to five years, but it could also follow immediately, or could follow more than a decade, with typical clinical presentations involving upper limb bradykinesia (i.e., slowness of movement) and stiffness correlated with frequent episodes of kinesia paradoxical, oculogyric crisis (OGC), and psychiatric disturbances. Perhaps, encephalitis lethargica (EL) is not necessarily a prerequisite to progressing to postencephalitic parkinsonism, but just a contributing factor. Although direct evidence for influenza virus has never been substantiated in these cases, proving a negative is also difficult. Despite the etiological controversy, people born during the time of the pandemic influenza outbreak of 1918 have a two-to-three fold-increased risk of Parkinson's disease (PD) than those born prior to 1888 or after 1924 . While encephalitis lethargica (EL) and coronavirus disease 2019 (COVID-19) comprise different primary organs for their clinical manifestations, they are both pandemics influencing more than one million people with a link to neurotrophic viruses. In addition to parkinsonism, there is a theoretical possibility that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) can contribute to accelerated central nervous system (CNS) aging in survivors, which could manifest months or years after the infection. Therefore, the medical community should be cautious of neurological comorbidities of coronavirus disease 2019 (COVID-19) that can develop after an outbreak.

Parkinson disease (PD) therapy choices have conventionally focused on dopamine (DA) replacement and provision of symptomatic relief. Current therapies develop undesirable adverse effects, and a large unmet clinical need remains for treatments that offer disease modification

and that address symptoms resistant to levodopa. Search contributed to the emergence of novel compounds, repurposed drugs and new technologies. Emerging therapies for Parkinson disease (PD) have focused largely on disease modification and on dopamine (DA) resistance symptoms, which are both important unmet needs. Some new disease-modifying therapies target α -synuclein and its pathways, whereas others target different genes and proteins implicated in Parkinson's disease (PD) pathogenesis, including leucine-rich repeat kinase 2 (LRRK2), parkin and glucocerebrosidase (GCase). Disease-modifying pharmacotherapies (such as nilotinib, inosine and isradipine) are being repurposed to treat Parkinson's disease (PD); antibody therapies, vaccines and immune-mediated therapies that aim to clear abnormal proteins have also emerged as promising approaches. Cellular therapies can be divided into rescue and restoration therapies; rescue therapy aims to salvage neurons and slow the progression of the disease whereas restoration therapy focuses on replacing neurons. Adaptive deep brain stimulation is an alternative symptomatic therapy that can be used to target dopamine-responsive and dopamine-resistant symptoms.

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- Increase dose frequency of L-dopa
 - Change standard formulation L-dopa to Sinemet CR
 - Add entacapone
 - Add dopamine agonist
 - Add amantadine
 - Add selegiline

Figure(114):Current management of Parkinson disease (www.google.com)



Figure(115):Emerging therapies in Parkinson disease [Elkouzi A.; Vedam-Mai V.; Eisinger R.; Okun M. (2019). Emerging therapies in Parkinson disease-repurposed drugs and new approaches. Nature Reviews Neurology, 15:204-223]

Parkinson's disease (PD) patients experience a subacute worsening of their condition, particularly motor symptoms, during systemic infections, mainly as a result of altered medication intake and changes in the pharmacodynamics of dopaminergic therapies. For those with mild symptoms of coronavirus disease 2019 (COVID-19), patients must be advised to observe their symptoms closely and to seek consultation if their condition, particularly respiratory symptoms, considerably worsen. While most dopaminergic therapies can be continued during a period of systemic infections without any absolute contraindications, alert should be taken into account with the use of cough syrup containing dextromethorphan and cyclobenzaprine or nasal decongestants containing pseudoephedrine, phenylephrine, and phenylpropanolamine with a monoamine oxidase inhibitor (e.g., selegiline and rasagiline) for potent drug interactions that can intensify sympathomimetic activities. Antiviral (e.g., favipiravir, atazanavir, iopinavir/ritonavir) and anti-malarial (chloroquine and hydroxychloroquine) remedies are being tested for

coronavirus disease 2019 (COVID-19) without any specific interactions with dopaminergic medications recorded. Therapeutic implications of amantadine, an agent that can block a pore in the envelope protein of severe acute respiratory syndrome coronavirus (SARS-CoV) and is no longer used as an antiinfluenza agent due to its high resistance, remain unexplored as a potential treatment of coronavirus disease 2019 (COVID-19). Patients with device-aided remedies, involving deep brain stimulation (DBS), apomorphine and levodopa-carbidopa intestinal gel infusions may encounter problems related to hardware, acute adverse events, or severe symptom fluctuations during this outbreak. While the recommendations are to postpone device-aided therapies for all new cases, acute problems may emerge among those who are already on one of these treatments where immediate interventions may be urgent. For example, if the battery for a deep brain stimulation (DBS) system stops working completely and the deep brain stimulation (DBS) is no longer effective, patients may experience a significant return of Parkinson's disease (PD) symptoms. Although most deep brain stimulation (DBS) procedures are considered elective, it is not an elective procedure if it is the end of battery life. In these conditions, decisions should be made individually by taking into account the risk of complications, exposure risk to coronavirus disease 2019 (COVID-19) for both patients and health care workers, and the availability of all resources to treat that particular complication during this outbreak. In places where there are no limitations of resources, elective procedures can be resumed but full consultations with various experts and appropriate health authorities should be undertaken to ensure that it is safe to do so.

18.3 Peripheral Nervous System Manifestations and Complications:

18.3.1 Anosmia and Chemosensory Dysfunction

Chemosensory deficits can be classified in three broad types as either transport, sensory, or neural dysfunctions. Transport dysfunctions interfere with the interaction of a taste or olfactory stimulus with peripheral receptor sites. Taste pore blockage by food, bacteria, or debris can limit the access of gustatory stimulants. Adenoids, chronic inflammation, septum deviation, or polyps will also limit access of volatile stimulants to the olfactory neuroepithelium. It is worthy to mention that the olfactory neuroepithelium is located at the upper area of each nasal chamber adjacent to the cribriform plate, superior nasal septum, and superior-lateral nasal wall. It is a specialized pseudostratified neuroepithelium containing the primary olfactory receptors. Sensory

dysfunctions affect the peripheral receptor system. For example, radiation, drugs, endocrine diseases, viral infections, airborne pollutants, and toxic chemicals will impact either cell turnover, the receptors, signal transduction, or processing mechanisms, resulting in chemosensory impairment. Neural dysfunction is the consequence of damage to the peripheral or central nervous pathways. Viral infections, neoplasm, head trauma, and surgery are common causes that progress to chemosensory dysfunction. From a diagnostic point of view, it is noteworthy to make a distinction between chemosensory disorders that manifest as a deficit in perception, transport, or integration of sensory information and chemosensory disorders that may be due to a normally functioning chemosensory system in contact with real and persistent stimuli.

Anosmia and hyposmia is the inability or decreased ability to smell. Risk of olfactory dysfunction increases with old age and may also result from chronic sinonasal diseases, severe head trauma, and upper respiratory infections, or neurodegenerative diseases.

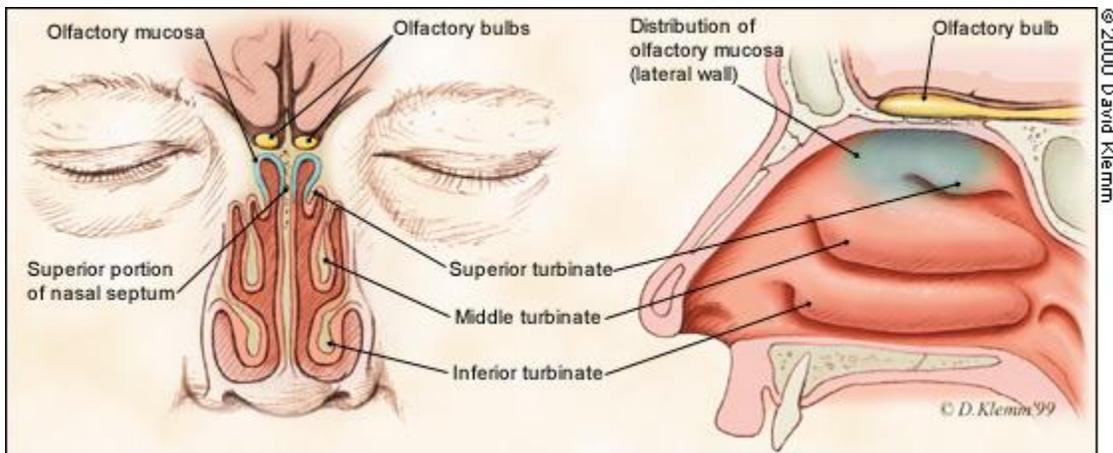
Olfactory functioning can be categorized as a range of normal (normosmic) to diminished (hyposmic) and absent (anosmic) ability to detect and correctly label odors. Anosmia can be specific, emerging from a genetic variation, such as the inability to detect the musky smell of androstenone, which is illustrated by polymorphisms in the OR7D4 gene. Altered olfactory perception or dysosmia also exists. Dysosmia can be the distortion of perceived odor quality (parosmia, e.g., smelling burnt paper instead of baby powder) or a phantom olfactory sensation with no apparent olfactory stimulus (olfactory hallucinations, phantosmia).

Impairment of olfactory function impacts negatively the quality of life of patients. Persons with olfactory dysfunction report difficulties with cooking, decreased appetite and enjoyment of eating, challenges with maintaining personal hygiene and social relationships, fear of hazardous events or feeling less safe, and greater depressive symptoms and loneliness. Females are more prone to report depression and anxiety related to the olfactory impairment than do males.

Anosmia can result from many underlying diseases. The most common causes are sinonasal diseases, postinfectious disorder, and post-traumatic disorder. Other etiologies (e.g., congenital, idiopathic, toxic disorders, or disorders caused by a neurodegenerative disease) are less common but important to be taken into account.

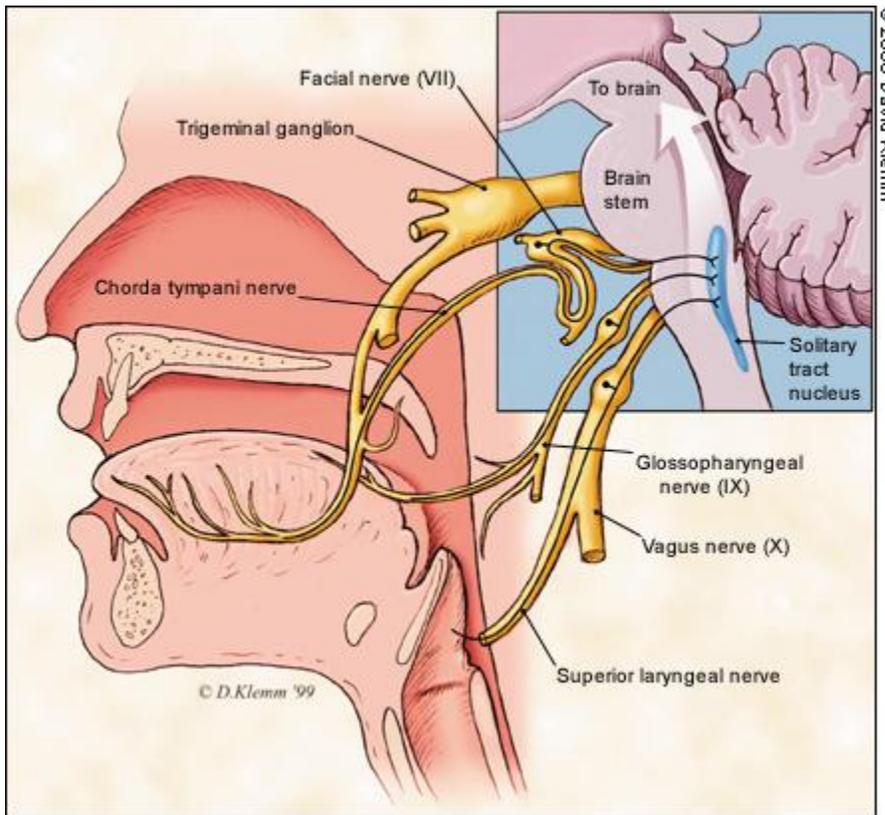
Patients with anosmia are by definition not able to perceive olfactory stimuli consciously. Therefore, the common way to investigate function by using stimulation is impossible, as no functional brain activation in response to pure odorants can be expected. Most investigations therefore employ stimulation of the trigeminal system, which is closely connected and interacts with the olfactory system to create a uniform flavor experience. Central processing of trigeminal stimuli after olfactory loss reflects the strong relationship between these sensory systems. Besides the effect on global functional connections of the brain due to smell loss, a regain of olfactory function correlated with olfactory training can develop to re-established functional connections. The training, combined with improvements of olfactory threshold scores, resulted in an increase of functional connections in networks involved in chemosensory processing. Moreover, before training, piriform cortex showed a multitude of connections to nonolfactory regions, which declined after training.

Olfactory loss requires medical evaluation. It can be an early marker for progressing neurodegenerative disorders such as Parkinson's disease (PD) or Alzheimer's disease (AD), increases the risk of malnutrition, safety problems, and has been related to increased mortality among older adults. From a public health perspective, continued monitoring of the prevalence of olfactory impairment is paramount to increase knowledge of risk factors and track changes with prevention and treatment efforts.



Figure(116): Anatomy of the olfactory neural pathways [Bromley S. (2000). Smell and taste disorders: a primary care approach. American Family Physician, 61(2):427-436]

Figure(116) shows the anatomy of the olfactory neural pathways, revealing the distribution of olfactory receptors in the roof of the nasal cavity. The human sense of smell depends on the functioning of not only cranial nerve I (olfactory nerve) but also portions of cranial nerve V (trigeminal nerve). Qualitative odor sensations (e.g., the smell of a rose, lemon or grass) are mediated by cranial nerve I, whereas somatosensory overtones of odorants (e.g., warmth, coolness, sharpness and irritation) are mediated by the ophthalmic and maxillary divisions of cranial nerve V.



Figure(117):Anatomy of peripheral taste pathways [Bromley S. (2000). Smell and taste disorders: a primary care approach. American Family Physician, 61(2):427-436]

Figure (117) shows anatomy of peripheral taste pathways. Multiple nerves, including cranial nerves VII, IX and X, transmit taste information from the mouth and pharynx to the brain via the brain stem. Taste receptors are found within taste buds located not only on the tongue but also on the soft palate, pharynx, larynx, epiglottis, uvula and first one third of the esophagus. Taste buds

are continually bathed in secretions from the salivary glands, and excessive dryness can distort taste perception.

18.3.1.1 Anosmia and Chemosensory Dysfunction in COVID-19 Infection

Yan *et al.* (2020) from United States of America, recorded chemosensory dysfunction in 59 coronavirus disease 2019 (COVID-19) positive and 203 coronavirus disease 2019 (COVID-19) negative patients from a single center using an internet based cross sectional survey. They showed that the smell and taste dysfunction was higher in the coronavirus disease 2019 (COVID-19) positive cases in comparison with the negative tested patients. (smell loss: 68% Vs. 16% and taste loss: 71% Vs. 17%). Most of the cases in this study were ambulatory, did not need hospitalization and none required mechanical ventilation. They theorized that probably in ambulatory coronavirus disease 2019 (COVID-19) patients virus spreads via the nasal route as compared to the seriously ill patients in which the spread is most likely pulmonary. Bagheri *et al.* (2020) reported results of a large Iranian cohort of 10069 cases by employing an online questionnaire-based survey. Participants were cases with problems in decreased sense of smell recently. Anosmia and hyposmia was reported by 48.23% of the respondents while 83.38% also had a decreased taste sensation. The onset of anosmia was sudden in 76.24%. Other clinical features reported by the participants were flu or cold symptoms before anosmia (75.5%), headaches (48.6%), nasal stiffness (43.7%) and fever (37.3%). In contrast the study by Mao *et al.* (2020) in their cohort of 214 Chinese cases recorded impairment of taste in 12 (5.6%) and impairment of smell in 11 (5.1%) patients. Anosmia and taste dysfunction were not mentioned in the French cohort of coronavirus disease 2019 (COVID-19) patients.

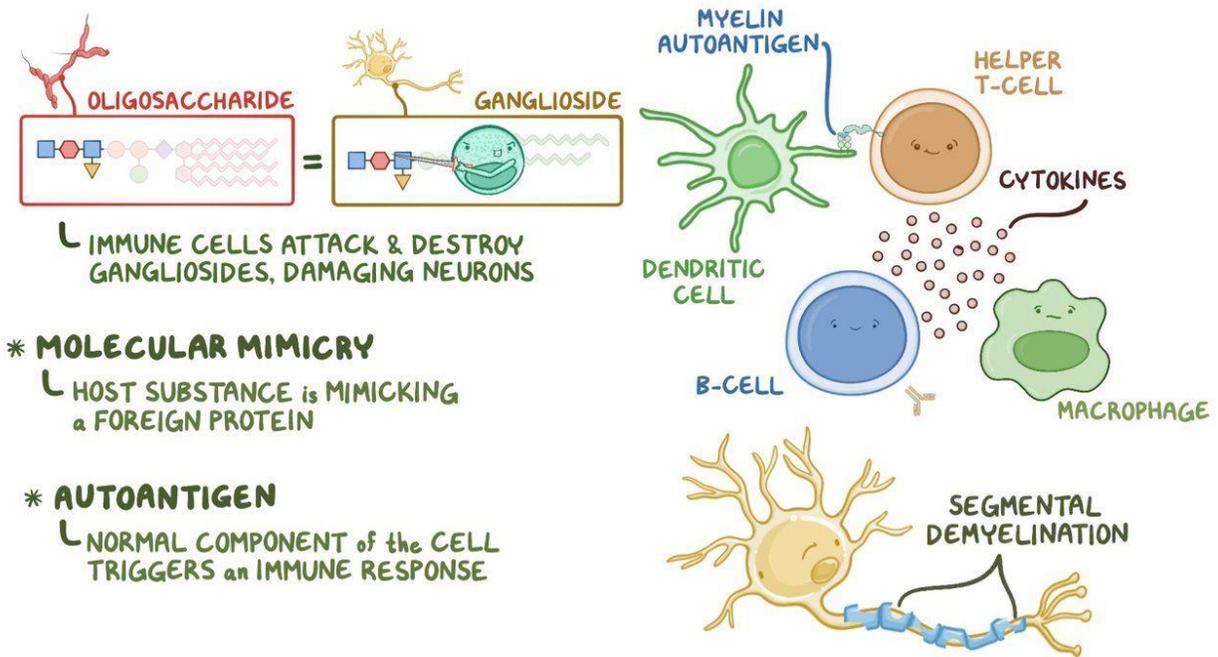
It is valuable to mention that olfactory epithelial cells express the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) receptor, angiotensin-converting enzyme 2 (ACE2), but the precise cellular subtype that may mediate anosmia in coronavirus disease 2019 (COVID-19) is still not clear. For both olfactory and gustatory perception, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infiltration of higher-order structures within the central nervous system (CNS), or cranial nerves such as the vagus nerve (VN), included in signal transduction and chemosensory processing, may underlie their dysfunction.

18.3.2 Guillain Barre Syndrome

Guillain-Barré syndrome (GBS) is a very rare immune mediated disorder which is related to demyelination of peripheral nervous system (PNS) and development of muscle weakness that happens mainly in previously healthy persons. Guillain-Barré syndrome (GBS) is an acute/subacute immune-mediated polyradiculoneuropathy characterized by varying degrees of limbs or cranial-nerves weakness, loss of deep tendon reflexes, sensory and dysautonomic symptoms due to peripheral nerves and roots demyelination and/or axonal damage. Dysautonomia refers to a disorder of autonomic nervous system (ANS) function including failure of the sympathetic or parasympathetic components of the autonomic nervous system (ANS), but dysautonomia comprising excessive or overactive autonomic nervous system (ANS) actions also can be incident. Guillain-Barré syndrome (GBS) usually exhibits with ascending paralysis and is severe enough to warrant hospital admission for its management. The occurrence of Guillain-Barré syndrome (GBS) is 1.1-1.8 patients in 100,000 per year and the incidences increases with age. Recent studies reveal that Guillain-Barré syndrome (GBS) can be classified into at least 4 principal clinical and electrophysiological subtypes such as acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN) and miller fisher syndrome (MSF). Acute inflammatory demyelinating polyneuropathy (AIDP) is characterized by demyelination, acute motor axonal neuropathy (AMAN) is limited to pure motor involvement, acute motor sensory axonal neuropathy (AMSAN) is a more severe disease with motor-sensory involvement, and Miller Fisher syndrome (MFS) presents with ataxia, areflexia, and ophthalmoplegia. On clinical examination of Guillain-Barré syndrome (GBS), a flaccid areflexic paralysis is found. Muscle wasting usually occurs within two weeks of the onset of symptoms and can be severe. Autonomic dysfunction is common and may cause arrhythmias, swings in blood pressure, urinary retention, paralytic ileus, and hyperhidrosis. If the condition is severe this can lead to sudden death.

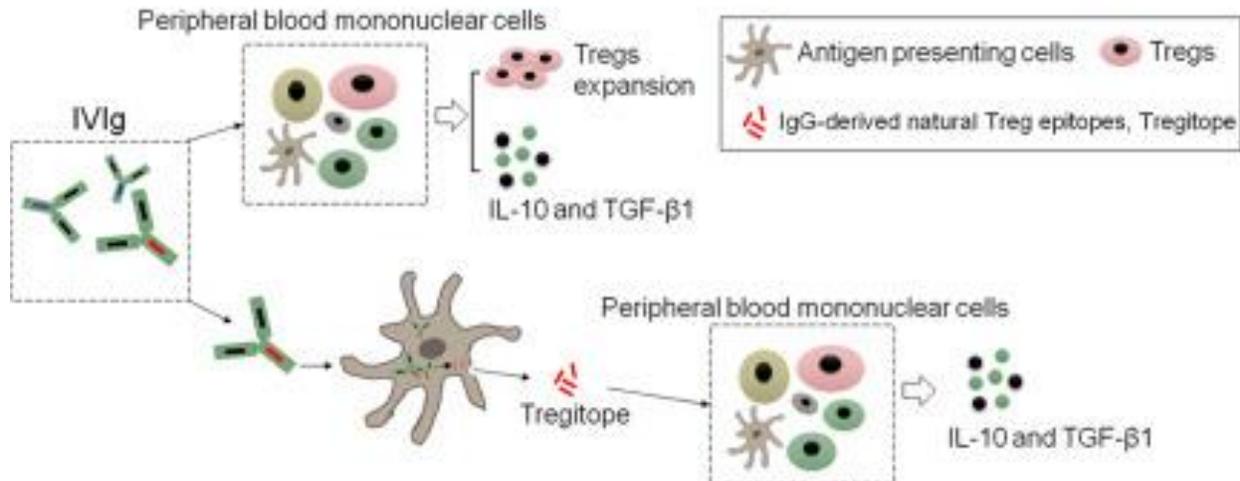
The disease is typically characterized by a rapid onset of symmetrical limb weakness, which progresses over days to 4 weeks, and happens in patients of all ages. Most patients also have sensory disturbances such as tingling or dull feelings (weak and not intense). In developed countries Guillain-Barré syndrome (GBS) has become the most common cause of acute flaccid paralysis (AFP). Despite improved recognition and treatment, Guillain-Barré syndrome (GBS) is

still a severe disease. Efficacious treatments comprise intravenous immunoglobulin (IVIg) and plasma exchange but supportive care during and following the hospitalization is also very much necessary.



Figure(118): Immune response in Guillain-Barre syndrome (www.google.com)

Action mechanism of IVIg on GBS *in vitro*



Figure(119):Mechanism of intravenous immunoglobulin on Guillain-Barre syndrome *in vitro*. [Zhang G.; Wang Q.; Song Y.; Cheng P.; Xu R.; Feng X.; Li X. (2019). Intravenous immunoglobulin promotes the proliferation of CD4⁺ CD25⁺Foxp3⁺ regulatory T cells and the cytokine secretion in patients with Guillain-Barre syndrome in vitro. Elsevier. Journal of Neuroimmunology, 336. <https://doi.org/10.1016/j.jneuroim.2019>]

A study performed by Zhang *et al.* (2019) stimulated peripheral blood mononuclear cells (PBMCs) from patients with Guillain-Barré syndrome (GBS) and healthy controls using intravenous immunoglobulin (IVIg) and an immunoglobulin-G (IgG)-derived natural T regulatory (Treg) epitopes, namely Tregitopes. This research findings demonstrated that intravenous immunoglobulin (IVIg) considerably stimulated both the expansion of CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Tregs) and secretion of interleukin-10 (IL-10) and transforming growth factor beta 1 (TGF-β1) while Tregitopes promoted secretion of interleukin-10 (IL-10) and transforming growth factor beta 1 (TGF-β1) only.

18.3.2.1 Guillain-Barre Syndrome in COVID-19 Infection

Eight patients of coronavirus disease 2019 (COVID-19) associated Guillain-Barré syndrome (GBS) have been recorded from China, Iran and Italy. It was reported the first case of Guillain-Barré syndrome (GBS) in a 61 years old woman who had travelled to Wuhan City, China. She presented with acute weakness in both legs and severe fatigue, progressing within 1 day. Nerve Conduction Studies (NCS) and Electromyography (EMG) were supposing of demyelinating polyneuropathy. She was treated with intravenous immunoglobulin (IVIg) and later on

developed respiratory symptoms. She tested positive for coronavirus disease 2019 (COVID-19). She infected two of her relatives and eight other people including two neurologist and six nurses who were isolated but were tested negative for coronavirus disease 2019 (COVID-19). It was found that based on the travel history, lymphopenia, and thrombocytopenia at the time of admission were consistent with a para-infectious pattern of Guillain-Barré syndrome (GBS) due to coronavirus disease 2019 (COVID-19). She made a good motor recovery after isolation and administration of antiviral drugs. Another study reported a 61 -Years old man with diabetes mellitus (DM) from Iran. He suffered from cough, fever and sometimes dyspnea two weeks before presenting with ascending paralysis progressing to quadriplegia (paralysis of all four limbs; tetraplegia) and bilateral facial paralysis (or AKA Facial Diplegia). Nerve conduction studies and electromyogram (NCS/EMG) was suggesting acute motor sensory axonal neuropathy (AMSAN). He was managed with intravenous immunoglobulin (IVIg). Authors have proposed that Guillain-Barré syndrome (GBS) should be regarded as a neurological complication of coronavirus disease 2019 (COVID-19) since respiratory involvement is common in coronavirus disease 2019 (COVID-19) and can be a risk factor for the progression of Guillain-Barré syndrome (GBS). A recognizable research reported Guillain-Barré syndrome (GBS) in a 54-Years man from United States of America. He presented with rapidly progressing ascending paralysis leading to respiratory difficulty. There was no bladder or bowel dysfunction. Reflexes were absent and magnetic resonance imaging (MRI) of the spine was normal. He had history of diarrhea preceding the acute attack of weakness. He tested positive for coronavirus disease 2019 (COVID-19). He was treated with intravenous immunoglobulin (IVIg) and anti-malarial therapy. He responded well and was weaned off from the ventilator. He was discharged to a rehabilitation facility for physical therapy. Toscano *et al.* (2020) reported five patients with Guillain-Barré syndrome (GBS) from Northern Italy. Lower-limb weakness and paresthesia were the main presenting features in four patients, followed by facial weakness, ataxia, and paresthesia in one patient. Four had positive polymerase chain reaction (PCR) from the nasopharyngeal swab on initial visit and fifth one was initially negative but later turned positive. On nerve conduction studies and electromyogram (NCS/EMG), 2 patients had features of demyelinating polyneuropathy while three had axonal polyneuropathy. All the patients were treated with intravenous immunoglobulin (IVIg). It was repeated in 2 patients and one patient

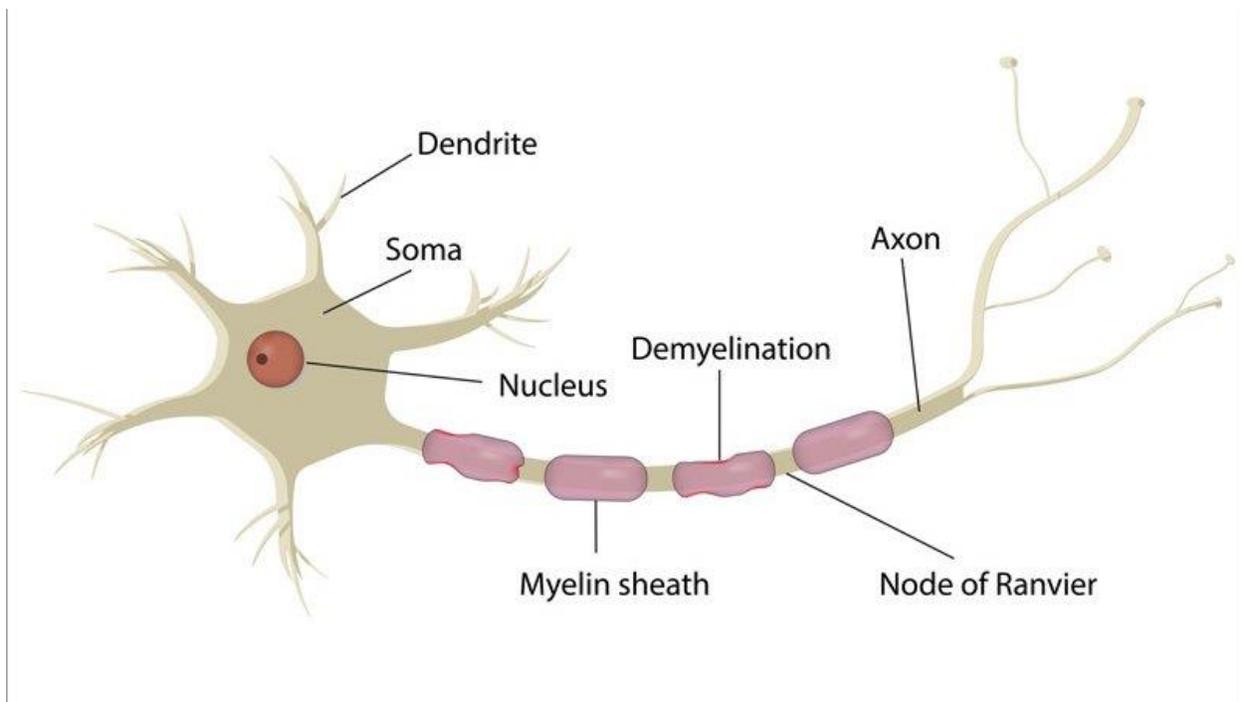
had plasma exchange. After one week, only one patient was able to ambulate independently and discharged from the hospital.

A 71-year-old man patient was referred to the emergency department for subacute onset of paresthesia at limb extremities, followed by distal weakness rapidly developing to a severe, flaccid tetraparesis over the previous 3 days. In the previous week, he had low grade fever for a few days. Relevant conditions at his medical history involved hypertension (HTN), abdominal aortic aneurysm (AAA) treated with endovascular repair in 2017, and lung cancer treated with surgery only (without additional chemotherapy or radiotherapy) in 2017 with negative oncological follow-up; no previous neurologic history was recorded. Neurologic examination showed normal consciousness and language, no cranial nerve deficit, symmetric limb weakness (Medical Research Council score 3/5 at upper limbs and 2/5 at lower limbs), symmetric and extensive stocking-and-glove hypesthesia at the 4 limbs (more pronounced at lower limbs), absent deep tendon reflexes, and normal plantar response. The patient complained of severe paresthesia in both hands and feet. Moderate dyspnea and moderate low back pain were present at the time of the first assessment. He showed hemodynamic disturbances (edema hyperemia & congestion hemorrhage thrombosis infarction shock) with severe drug-resistant hypertension. Arterial blood gases indicated severe hypoxia (paO₂ 65 mm Hg without supplemental oxygen). Brain computerized tomography (CT) scan was normal, whereas chest computerized tomography (CT) scan showed multiple bilateral ground glass opacities and consolidations, typical of coronavirus disease 2019 (COVID-19) pneumonia. Nasopharyngeal swab tested positive for severe acute respiratory syndrome coronavirus-2 (SARSCoV-2). Lumbar puncture was performed urgently and showed a mild increase in the protein content (54 mg/dL) and mild leukocytosis (9 cells/ μ L); Cerebrospinal fluid (CSF) was negative for severe acute respiratory syndrome coronavirus-2 (SARSCoV-2). Electroneurography (ENoG) showed the absence of both the sural nerve sensory nerve action potential (SAP) and the tibial nerve compound muscle action potential (CMAP), markedly increased common peroneal compound muscle action potential (CMAP) distal latency, markedly decreased velocity, moderately decreased compound muscle action potential (CMAP) amplitude (with spatial and temporal dispersion) for the same nerve, and decreased ulnar sensory nerve action potential (SAP) amplitude. F waves were not performed at lower limbs for the reduced amplitude of the evocable compound muscle action potential (CMAP) and not performed at upper limbs for intolerance at the stimulation. Overall,

these findings were interpreted as a severe form of acute polyradiculoneuritis with prominent demyelinating features. Diagnosis of Guillain-Barre´ syndrome (GBS) associated with coronavirus disease 2019 (COVID-19) was done. High-dose intravenous immunoglobulin (IVIG) (0.4g/kg/d for 5 days) were started few hours after admission, together with high-flow 60%–80% oxygen via nonrebreather mask, antiviral therapy (lopinavir + ritonavir), and hydroxychloroquine. Despite these efforts, severe respiratory failure (SRF) developed during the first 24 hours after admission, unresponsive to continuous positive airway pressure ventilation and prone positioning. The patient died a few hours later because of progressive respiratory failure (RF).

The authors report a possible correlation between acute coronavirus disease 2019 (COVID-19) infection and Guillain-Barré syndrome (GBS), a condition that in recent years has been bound to other emergent infections, such as Zika virus. It is suggested that coronavirus disease 2019 (COVID-19) can cause peripheral nervous system (PNS) involvement, even before the resolution of pneumonia. Dysregulation of the immune system due to coronavirus disease 2019 (COVID-19) is not that astonishing since it has been recently described systemic hyperinflammation in coronavirus disease 2019 (COVID-19) cases with a macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis; recognizably, Quin *et al.* (2020) also assessed a cohort of 452 patients with coronavirus disease 2019 (COVID-19) observing alterations in lymphocytes.

Early respiratory support, including intensive care unit (ICU) admission, is indicated but not always feasible during the current pandemic. The authors agree that a close attention to neurologic complications of coronavirus disease 2019 (COVID-19) is necessary, as recently proposed by Mao *et al.* (2020). The Italian Society of Neurology is currently proposing a multicenter nationwide observational study on neurologic presentations and complications of coronavirus disease 2019 (COVID-19). Similar efforts by other neurologic societies worldwide will benefit both neurologists and patients at a global level.



Figure(120):First case of COVID-19 presented as Guillain-Barre syndrome reported (www.google.com)

18.3.3Skeletal Muscle Damage

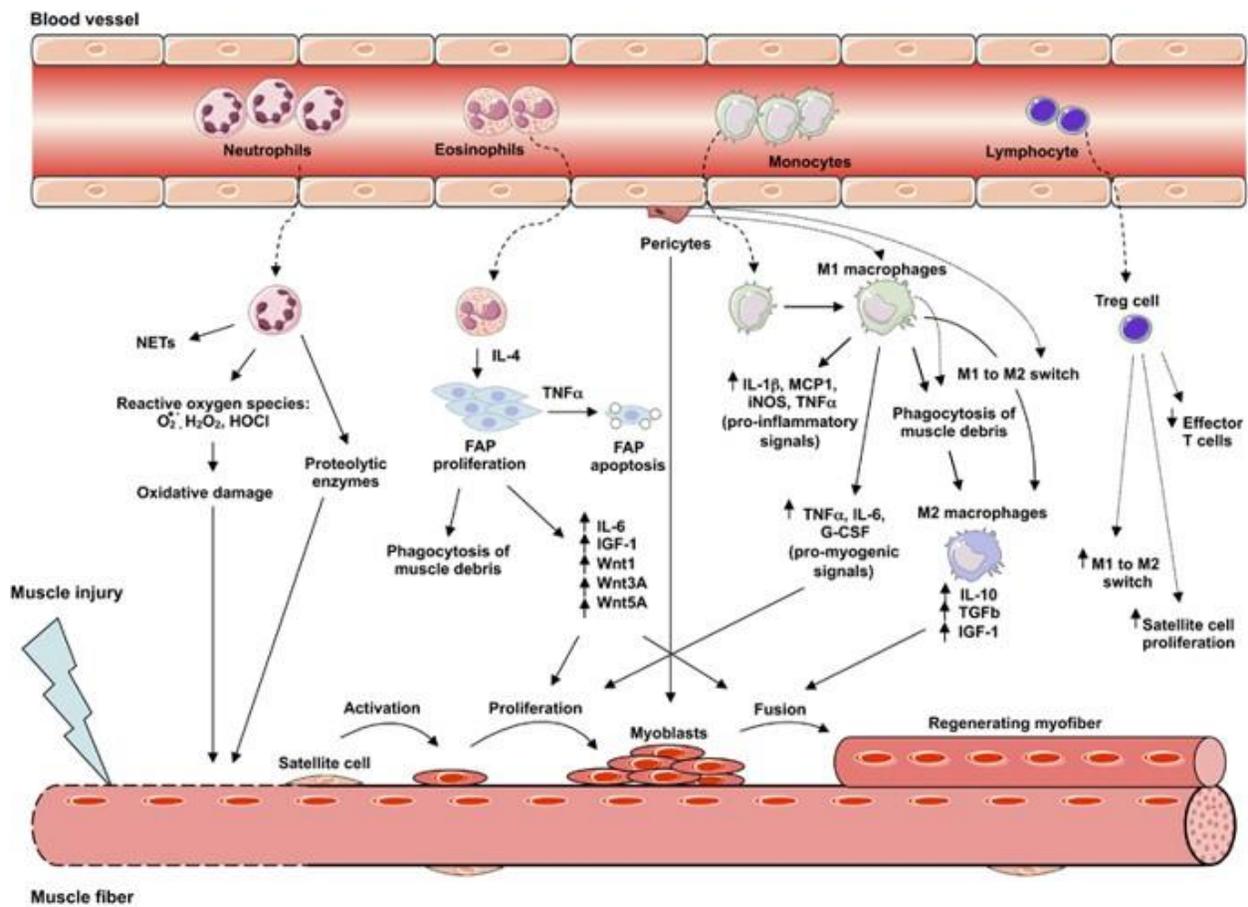
Skeletal muscle injury (SMI) is defined according to physiological or morphological indices. Injury is expressed quantitatively as decrements in force production or disruptions in normal myofibrillar structure. The most rigorous assessments of injury depend on quantitation of the loss of muscle contractile function, such as reductions in force production relative to muscle cross section (specific tension or specific force), increases in time-to-peak force production, loss of peak tetanic force, or increases in fatigability.

Acute muscle injuries (AMIs) are defined as defects in normal muscle structure or function that result from perturbations that are applied over a brief period, such as lacerations, contusions, freezing, burning, or exposure to toxins. Acute muscle injuries (AMIs) can also incident during muscle use and are attributable to the loading conditions that are applied to the muscle that exceed the load-bearing capacity of the muscle. However, stresses within the muscle can be increased several-fold when external loads are applied while a muscle is actively generating force under conditions called lengthening contractions or eccentric contractions. Eccentric

contractions are the most common cause of acute muscle injury (AMI) that is attributable to muscle use.

The general injury and repair mechanism is similar in most types of muscle injuries. Three stages are distinguished: the destruction and inflammatory phase (1 to 3 days), the repair phase (3 to 4 weeks), and the remodeling phase (3 to 6 months). The last two phases tend to overlap. When a muscle is injured, the myofibers rupture and necrotize. A haematoma is formed. At the same time during this first phase, the inflammatory cells can freely invade the injury site because the blood vessels are torn. The most abundant inflammatory cells are the polymorphonuclear leukocytes (PMNLs). These are replaced by monocytes, a few hours after the injury. These cells eventually transform into macrophages. Macrophages have 2 functions. Firstly, they remove the necrotic myofibers by phagocytosis. Secondly, they produce, together with fibroblasts, chemotactic signals such as growth factors, cytokines, and chemokines. The extracellular matrix (ECM) also contains growth factors that become active when tissue is damaged. Some of these growth factors, such as fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), insulin-like growth factor-2 (IGF-2), transforming growth factor- β (TGF- β), hepatocyte growth factor (HGF), tumor necrosis factor- α (TNF- α), and (interleukin-6 (IL-6) can activate myogenic precursors, called the satellite cell. The next phase, the repair phase, consists of 2 concomitant processes. The first is the regeneration of the disrupted myofibers. Regeneration can occur because there still is a pool of undifferentiated reserve cells, also known as myogenic precursors or satellite cells under the basal lamina of the myofiber. The satellite cells will proliferate and eventually differentiate into myoblasts. Because these new myoblasts fuse with the injured myofibers, the gap formed between the two ends of the injured myofiber is refilled. The second process of the repair phase is the formation of a connective tissue scar by fibrin and fibronectin, derived from blood of the haematoma that was formed immediately after the injury. The scar tissue gives the muscle strength to withstand contractions, and it gives the fibroblasts an anchoring site to invade the granulation tissue. However, in case of excessive proliferation of these fibroblasts, dense scar tissue is formed within the injured muscle. This not only interferes with the repair process but also interrupts the muscle regenerative process and contributes to incomplete functional recovery of the injured muscle during the third phase, the remodeling phase. In this last phase, the newly formed myofibers mature. At the same time, the scar tissue is reorganized and it contracts. Due to an injury, the intramuscular nerve branches can be damaged.

Hence, the muscle fibers may be denervated, which might affect the healing process negatively. The whole process is coordinated through different mechanisms like cell-cell and cell-matrix interactions as well as extracellular secreted factors. Hepatocyte growth factor (HGF), interleukin-1 (IL-1), and interleukin-6 (IL-6) are secreted factors that can stimulate the activity of satellite cells. Fibroblast growth factor (FGF) and insulin-like growth factor (IGF) can also activate satellite cells, but in contrast to insulin-like growth factor (IGF), fibroblast growth factor (FGF) can also inhibit their differentiation, while insulin-like growth factor (IGF) stimulates the differentiation. transforming growth factor- β 1 (TGF- β 1) stimulates collagen deposition, leading to the formation of fibrotic scar tissue.



Figure(121):Skeletal muscle healing depending on inflammation [Sciorati C.; Rigamonti E.; Manfredi A.; Rovere-Querini P. (2016). Cell death, clearance and immunity in the skeletal muscle. *Cell Death and Differentiation*, 23:927-937]

Skeletal muscle healing depends on inflammation. Efficient skeletal muscle healing happens in overlapping phases of inflammation, proliferation and remodeling. Upon muscle injury, satellite

cells activate, start proliferating and subsequently fuse and differentiate into new myotubes that later grow and replace damaged muscle. Several cell types modulate both proliferation and differentiation of satellite cells, particularly inflammatory cells that are recruited from the blood. Neutrophils and eosinophils firstly arrive in the damaged tissue. Neutrophils release reactive oxygen species (ROS) and proteolytic enzymes that further amplify the damage and local inflammation. Eosinophils induce the proliferation of fibro/adipogenic progenitors (FAPs) that in turn contribute to debris clearance and satellite cell proliferation. Shortly after, monocytes extravasate in the injured areas where they differentiate in proinflammatory M1 macrophages (i.e., macrophages that encourage inflammation) that clear cellular debris and stimulate satellite cell proliferation. This initial T helper 1 (Th1)-driven inflammation is later overcome by an anti-inflammatory response that coincides with a M1-to-M2 switch. M2 macrophages (i.e., macrophages that decrease inflammation and encourage tissue repair) and T helper2 (Th2) cytokines (IL-10, IGF-1, TGF β) reduce local inflammation and contribute to myoblast fusion and new myofiber formation. A variety of intrinsic and extrinsic factors are responsible for macrophage phenotypic polarization; pericytes and T regulatory (Treg) cells represent an additional layer of control. Pericytes sustain the ability of macrophages to clear apoptotic cells and promote the expression of genes associated with their alternative activation. T regulatory cells (Treg) cells begin to accumulate in damaged muscle within days after injury and contribute to muscle healing at several levels. They promote M1-to-M2 switch, increase satellite cell proliferation and modulate effector T cell (CD8+ or B cells).

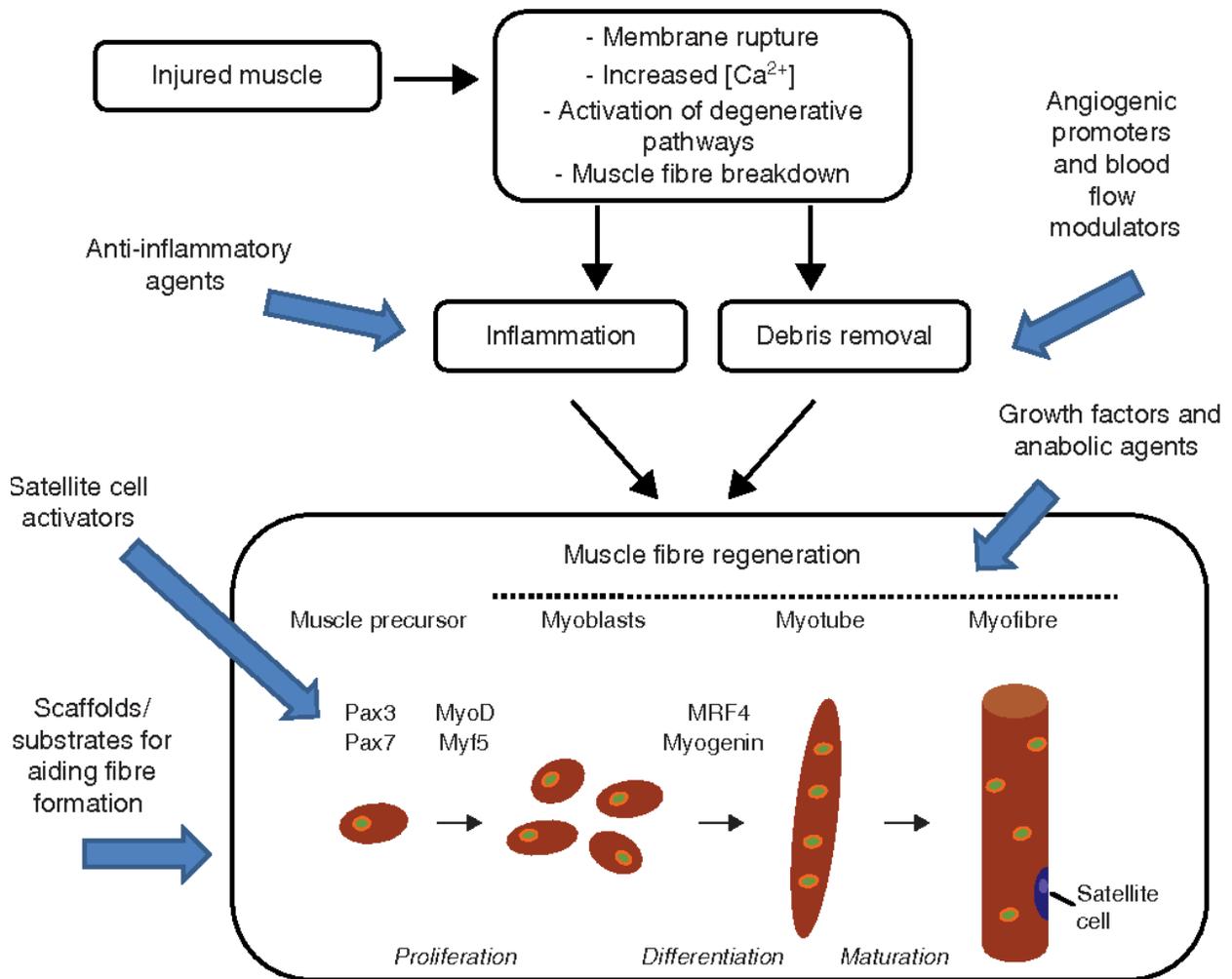
The best known treatment immediately after a muscle injury is the RICE approach. This acronym stands for rest, ice, compression and elevation. The target is to minimize the haematoma of the injured muscle and, subsequently, the size of the connective tissue scar.

The physiotherapy is the early mobilization that accelerates capillary ingrowth and triggers the regeneration of muscle fibers. The healed muscle also more rapidly regains its preinjury level of strength. However, early mobilization also has disadvantages. The scar that is formed will be larger, and reruptures will be more common. Therefore, rest is advised during the first 3 to 7 days to allow the scar tissue to gain strength. Subsequently, mobilization within the painfree limits is initiated.

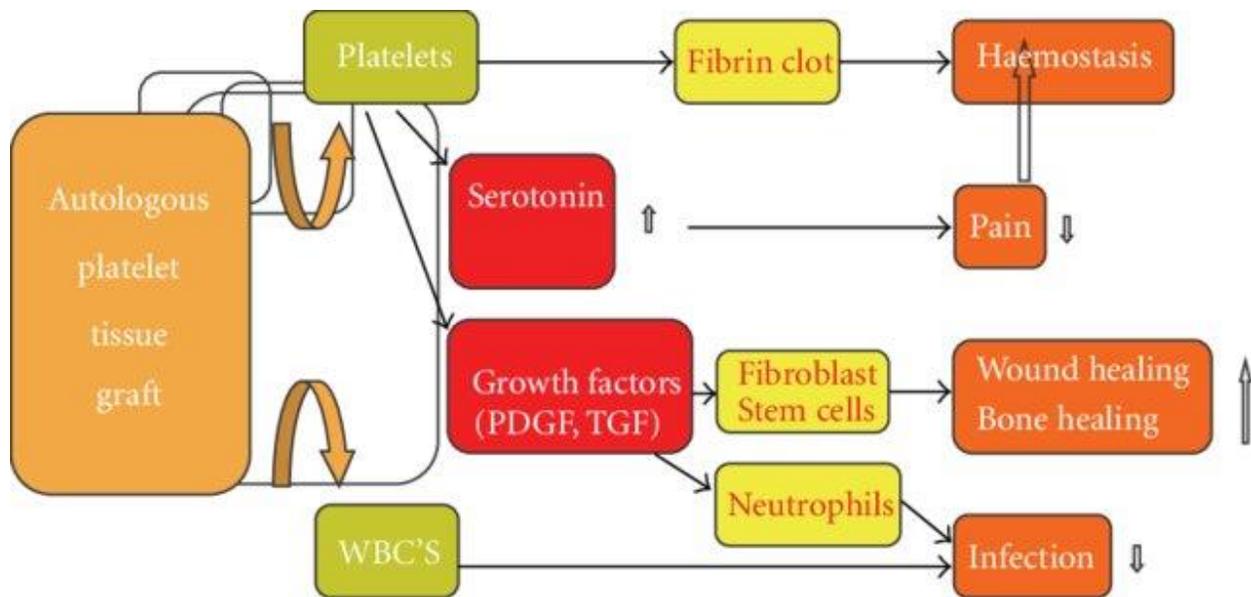
Nonsteroidal anti-inflammatory drugs (NSAIDs) are primarily used for their analgesic, anti-inflammatory, and antipyretic properties. Inflammatory cells play an important role in the healing process of an injured muscle. Therefore, the use of drugs that inhibit these cells, such as nonsteroidal anti-inflammatory drugs (NSAIDs), is questioned nowadays. Experimental studies in which nonsteroidal anti-inflammatory drugs (NSAIDs) were given immediately after the injury, have shown conflicting results. Nonsteroidal anti-inflammatory drugs (NSAIDs) would not have a greater effect on the pain of a muscle injury than paracetamol, but they have more side effects including asthma exacerbations, gastrointestinal and renal side effects, hypertension, and other. However, nonsteroidal anti-inflammatory drugs (NSAIDs) also have beneficial effects. The inflammatory process can be excessive and cause edema, resulting in anoxia (an absence of oxygen) and further cell death. This can be prevented by the administration of low-dose nonsteroidal anti-inflammatory drugs (NSAIDs).

Recently, several studies have led to the identification of growth factors that have the potential to influence the regeneration of injured muscles. Since then, multiple research groups have been trying to find drugs that work on this natural basis and can help an injured muscle to recover better and/or faster. The researchers investigated several biological growth factors, such as exogenous growth factors which would promote healing of injured muscle fibers, and transforming growth factor beta 1(TGF- β 1), the inhibition of which would block the muscle fibrosis. Several growth factors are able to promote muscle regeneration. These involve basic fibroblast growth factor (bFGF), insulin growth factor (IGF), nerve growth factor (NGF), transforming growth factor beta 1(TGF- β 1), and platelet-derived growth factor (PDGF).

Operative treatment can only be implemented in specific conditions. These include a large intramuscular haematoma, a complete strain or tear of a muscle with few or no agonist muscles or a partial strain if more than half of the muscle belly is torn and if the patient complains of persistent (>4–6 months) extension pain. After surgery, the operated limb should be placed in a cast and immobilized in a neutral position with an orthosis.



Figure(122): Treatment of skeletal muscle injury [Gehrig S.; Lynch G. (2011). Emerging drugs for treating skeletal muscle injury and promoting muscle repair. Expert Opinion on Emerging Drugs, 16(1):163-182]



Figure(123):Autologous platelet tissue graft: mechanism of action [Baoge L.; Steen E.; Rimbaut S.; Philips N.; Witvrouw E.; Almqvist K.; Vanderstraeten G.; Bossche L. (2012). Treatment of skeletal muscle injury: a review. ISRN Orthopedics. doi:[10.5402/2012/689012](https://doi.org/10.5402/2012/689012)]

18.3.3.1 Skeletal Muscle Damage in COVID-19 Infection

Mao *et al.* (2020) reported skeletal muscle injury as a consequence of coronavirus disease 2019 (COVID-19) in 17 (19.3%) patients in the severely ill and 6 (4.8%) patients in the non-severe group. They diagnosed skeletal muscle injury (SMI) as patient having myalgia and elevated serum creatine kinase (CK) level above 200 U/L. Creatine Kinase (CK) is an enzyme found in the heart, brain, skeletal muscle, and other tissues and increased amounts of creatine kinase (CK) released into the blood is indicating muscle damage. Mao *et al.* (2020) concluded that it was not clear whether this was due to the direct effect of virus on muscle tissue. The other possible mechanism proposed was the infection-mediated immune response that causing elevated pro-inflammatory cytokines in serum leading to skeletal muscle damage. It is worthy to observe that patients in the severely ill group in addition to raised muscle enzymes, also had elevated liver enzymes and deranged renal functions which could have contributed to the this clinical picture. Furthermore, no specific diagnostic workup for confirmation like nerve conduction studies and electromyogram (NCS/EMG) or muscle histopathology was done. Therefore, it is difficult to exclude that these patients might be having critical illness myopathy and neuropathy in addition to skeletal muscle damage.

A deserved study showed that symptoms of skeletal muscle damage were frequently correlated with liver and kidney involvement. They reported incidence of 10.7%, and like other neurological features, this was also combined with a severe form of the illness. It can be explained that patients with pre-existing renal or hepatic impairment will be highly vulnerable to progress to features of multi-organ failure in the backdrop of skeletal muscle injury (SMI). Muscle enzymes, including creatine kinase (CK) and lactate dehydrogenase (LDH), are found to be highly elevated in the symptomatic patients – a recognition that affirms muscle membrane damage. The exact mechanism of muscle damage, however, has not been established. Possibilities involve viral muscle invasion through angiotensin-converting enzyme2 (ACE-2) receptor tropism and immune-mediated muscle fiber damage. Further studies are needed to explain the mechanisms underlying skeletal muscle injury (SMI) in coronavirus disease 2019 (COVID-19).

Additionally, since about 10% of hospitalized patients need assistance in intensive care wards, neurological monitoring must also be aimed at verifying the onset of the so-called "critical illness neuro-myopathy" type peripheral nervous system (PNS) complications. These issues are notably recognized to delay weaning from ventilation and pose a significant burden on the health care delivery system.

18.4 Neuropsychiatric Sequelae of COVID-19 Infection

18.4.1 Depression and Anxiety

Depression and anxiety have been correlated with coronavirus (CoV) outbreaks, but it is still not clear whether the risk factors are attributed to the viral infections per se or to the host immune response. Research of healthcare workers during severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) epidemic, Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak, and the current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic propose that the frequency and severity of psychiatric symptoms are linked to proximity to coronavirus (CoV)-infected patients. But these studies did not test serology or immune markers in healthcare workers, and no studies have been done comparing psychiatric outcomes in healthcare workers who contracted coronavirus (CoV) during pandemics versus those who did not. In a separate study, seropositivity for a human coronavirus (CoV) strain

(HCoV-NL63) has been found to be related to history of mood disorder, although not with its polarity (i.e., unipolar versus bipolar depression) or with history of committing suicide attempts. Although there are very limited data available for coronavirus disease 2019 (COVID)-19-related psychiatric symptoms currently, survivors of severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) were clinically diagnosed with posttraumatic stress disorder (PTSD) (54.5%), depression (39%), pain disorder (36.4%), panic disorder (32.5%), and obsessive compulsive disorder (OCD) (15.6%) at 31 to 50 months post-infection, a dramatic increase from their pre-infection prevalence of any psychiatric diagnoses of 3%. The need for sustained follow-up of such symptoms related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, beyond documenting acute stress levels, is therefore crucial and urgent.

18.4.2 Psychotic Disorders

Exposure to viral infections in utero, during childhood development, and in adulthood have each been associated with increased risk of experiencing schizophrenia. Schizophrenia is a long-term mental disorder of a type involving a breakdown in the relation between thought, emotion, and behavior, leading to faulty perception, inappropriate actions and feelings, withdrawal from reality and personal relationships into fantasy and delusion, and a sense of mental fragmentation. While most studies have shed light and concentrated on history of influenza infection and psychosis risk, two studies have assessed presence of antibodies against several strains of coronavirus (CoV) in persons with psychosis. No association was reported between seropositivity for human coronavirus (NL63) (HCoV-NL63) and history of psychotic symptoms in mood disorder patients in one study. Another study conducted by Severance and colleagues (2011) found increased prevalence of antibodies against four human coronavirus (HCoV) strains in patients with a recent psychotic episode compared to non-psychiatric controls, supposing a possible relationship between coronavirus (CoV) infections and psychosis, which may also occur in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infections.

18.5 Long Term Impact

With the growing number in recovery from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease, rehabilitation issue is suggested to become an essential condition. Personal communication with neurologists working in the field in Italy shows that there is proof

for the need for rehabilitation, involving neurological aspects, in clinically recovered cases. It can be presumed that the psycho-social influences of long term social distancing and home isolation will require adequate psychological rehabilitation measures as the pandemic will start waning off. Since the outbreak of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), if there is one pulmonary manifestation that has received maximum attention, it is acute respiratory distress syndrome (ARDS). It is proved significant percentage of acute respiratory distress syndrome (ARDS) survivors can experience long-term cognitive impairment. Several factors, including mechanical ventilation, have been seen to lead to a decline in higher brain functions following acute respiratory distress syndrome (ARDS). Acute injury to the blood-brain barrier (BBB) has been implicated as the underlying mechanism for cognitive impairment following acute respiratory distress syndrome (ARDS). The effect of such injury may be amplified if there is a pre-existing cognitive impairment that corresponds to chronic blood brain barrier (BBB) damage. Patients with brain injury, on the other hand, have been realized to experience neurogenic pulmonary edema. Neurogenic pulmonary edema (NPE) is a clinical syndrome characterized by the acute onset of pulmonary edema following a significant central nervous system (CNS) insult. The etiology is believed to be a surge of catecholamines that results in cardiopulmonary dysfunction (CPD). Therefore, it is illustrated that the so-called brain-lung axis works both ways. These recognitions are especially relevant in the present circumstances, given the need for mechanical ventilation in the majority of the severely affected coronavirus disease 2019 (COVID-19) patients. As the pandemic continues to unfold, the number of people getting off mechanical ventilation will rise, and long-term cognitive outcomes will become viewed notably . It can be speculated that not only we shall witness cognitive decline lasting for months in this group of cases, but also some of them may develop premature onset of dementia.

18.6 Immunomodulatory Treatments

Some coronavirus disease 2019 (COVID-19) patients are associated with a hyperinflammatory response, and immunomodulatory drugs have therefore been recommended in the treatment of severe cases. The clinical efficacy of corticosteroids (CS) in treating coronavirus disease 2019 (COVID-19) is currently unclear, with some groups advising against their use. However, retrospective studies suppose corticosteroids (CS) are not uncommonly used to treat hospitalized

coronavirus disease 2019 (COVID-19) patients. Similarly, high doses of corticosteroids (CS) were administered to treat severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) infection symptoms during the acute phase, but were correlated with organic hallucinations and manic symptoms, which were treated with haloperidol. There is ample evidence of adverse neuropsychiatric effects following corticosteroid (CS) treatment, influencing about 35% of treated patients, comprising cognitive and sleep disturbances, delirium, hypomania, mania, depression, and psychosis. The neuropsychiatric effects of corticosteroid (CS) therapies are acute and resolve upon termination of treatment, suggesting that steroid-mediated neuropsychiatric symptoms among coronavirus disease 2019 (COVID-19) patients will be acute, but necessitate close monitoring and intervention as needed, nonetheless. Moreover, other immunomodulatory treatments have been advised for treating severe coronavirus disease 2019 (COVID-19), involving intravenous immunoglobulin (IVIG), cytokine blocking medications, and Janus kinase (JAK) inhibitors. The degree to which these therapies have been used clinically, and the neuropsychiatric outcomes in infected persons who have been exposed versus not exposed to such treatments, are unknown, highlighting the need for further investigation going forward.

19. Malnutrition in COVID-19 Infection

Malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. The term malnutrition addresses 3 broad groups of conditions:

1- undernutrition, which includes wasting (low weight-for-height), stunting (low height-for-age) and underweight (low weight-for-age);

2- micronutrient-related malnutrition, which includes micronutrient deficiencies (a lack of important vitamins and minerals) or micronutrient excess; and

3- overweight, obesity and diet-related noncommunicable diseases (such as heart disease, stroke, diabetes and some cancers).

A study done by Li *et al.* (2020) showed the prevalence of malnutrition in elderly patients with coronavirus disease 2019 (COVID-19) was high, Elderly patients' prognosis was worse than that of young and middle-aged patients. This may be attributed to the poor nutritional status of

elderly patients. This cross-sectional study found that 27.5% of patients aged more than 65 years old were at risk of malnutrition and 52.7% were malnourished, which was in general higher than that of elderly patients with other diseases. Li *et al.* (2020) explained the higher incidence of malnutrition in elderly patients with COVID-19 according to the following reasons:

1-The protein that made up muscles was consumed by the acute inflammatory response of neo-coronavirus disease. Patients' inflammation indicators elevated mostly, such as C-reactive protein (CRP), ferritin, tumor necrosis factor alpha (TNF- α), interleukin family factors, etc. The synthesis of these acute-phase proteins required the consumption of albumin (alb) and even muscle protein. The patient's albumin (alb) concentration and calf circumference (CC) were considerably lower. Similarly, hypoalbuminemia and low calf circumference (CC) were generally used as notable indicators for assessing malnutrition condition.

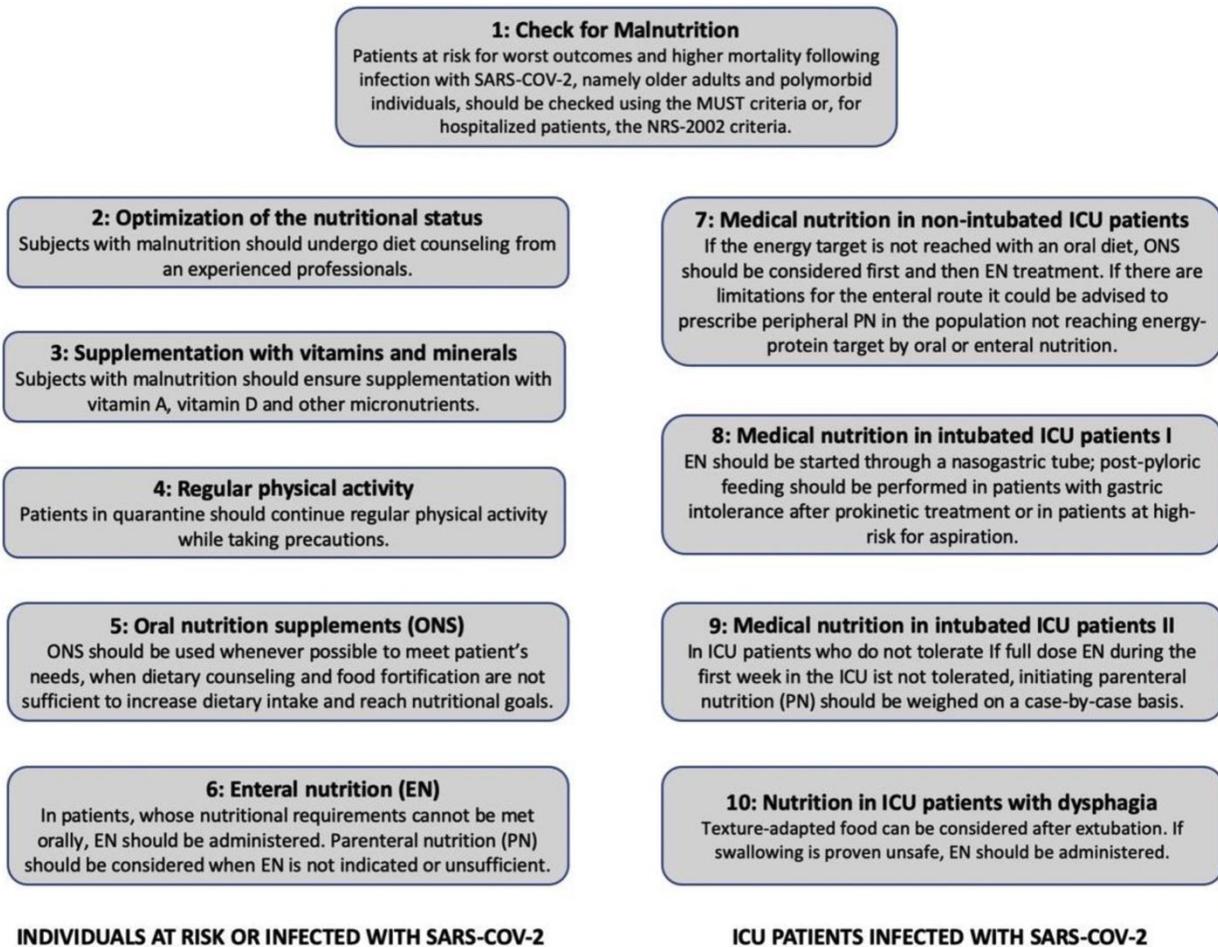
2-Among elderly patients with coronavirus disease 2019 (COVID-19), comorbidity in diabetes mellitus (DM) was higher than general population. This means high rates of comorbid diabetes mellitus (DM) caused elevated rates of malnutrition in elderly patients with coronavirus disease 2019 (COVID-19). Diabetes mellitus (DM) patients due to their own internal glandular dysfunction, suffer from anomalies in metabolism, which was the internal cause of malnutrition. Moreover, diabetic patients' diet control, improper nutrient ratio and other factors were external causes of malnutrition. Furthermore, the inflammatory response caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the use of glucocorticoids (GCs) caused fluctuations in blood glucose (Glc), which was related to pathogenesis.

3-Gastrointestinal (GI) symptoms caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) exacerbated malnutrition in elderly cases. Angiotensin-converting enzyme 2 (ACE2) was also highly expressed in the gastrointestinal (GI) track. So the gastrointestinal tract (GIT) was also the principal target of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) attack. Clinically, in addition to respiratory symptoms, gastrointestinal (GI) symptoms were the most in elderly patients with coronavirus disease 2019 (COVID-19). Diarrhea, mild abdominal pain, nausea, vomiting, poor appetite, and other symptoms were very common. The involvement of the digestive tract had accelerated the incidence of malnutrition in elderly patients with coronavirus disease 2019 (COVID-19).

4-The poor appetite of the patients was also associated to the patient's anxiety. Patients' fear of their own illness, worrying about long-term isolation, and desire for normal social communication, resulted in anxiety, which more decreased the appetite of the patient and more aggravated malnutrition. Anxiety disrupted homeostasis, which was also a contributing factor to malnutrition.

Clinical observations have revealed that many elderly patients with coronavirus disease 2019 (COVID-19) are at risk of malnutrition or co-malnutrition. Moreover, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) may attack the mucosal epithelium and cause gastrointestinal (GI) symptoms, which further destroy the nutritional status of elderly patients. Malnutrition is a nutritional disorder that cause adverse reactions to normal human functioning and is more common in elderly patients. In elderly patients with coronavirus disease 2019 (COVID-19), nutritional support should be boosted, specifically for elderly patients with diabetes mellitus (DM), low calf circumference (CC), or low albumin (alb).

Regarding undernourished subjects, coronavirus disease 2019 (COVID-19) infection is associated to a high risk of malnutrition development, mostly combined with increased requirements and the presence of a severe acute inflammatory status. These patients show also a hyporexix state, thus contributing to a negative nutritional balance. Estimated nutritional requirements are 25–30kcal/kg of weight and 1.5g protein/kg/day. A nutrient dense diet is recommended in hospitalized cases including high protein supplements (2–3 intakes per day) containing at least 18g of protein per intake. Adequate supplementation of vitamin D is recommended particularly in areas with large known prevalence of hypovitaminosis D and due to the decreased sun exposure. If nutritional requirements are not met, complementary or complete enteral feeding are required, and if enteral feeding is not possible because of inadequate gastrointestinal (GI) tolerance, the patient must be put on parenteral nutrition. Coronavirus disease 2019 (COVID-19) patients' outcome is supposed to be better with nutritional support.

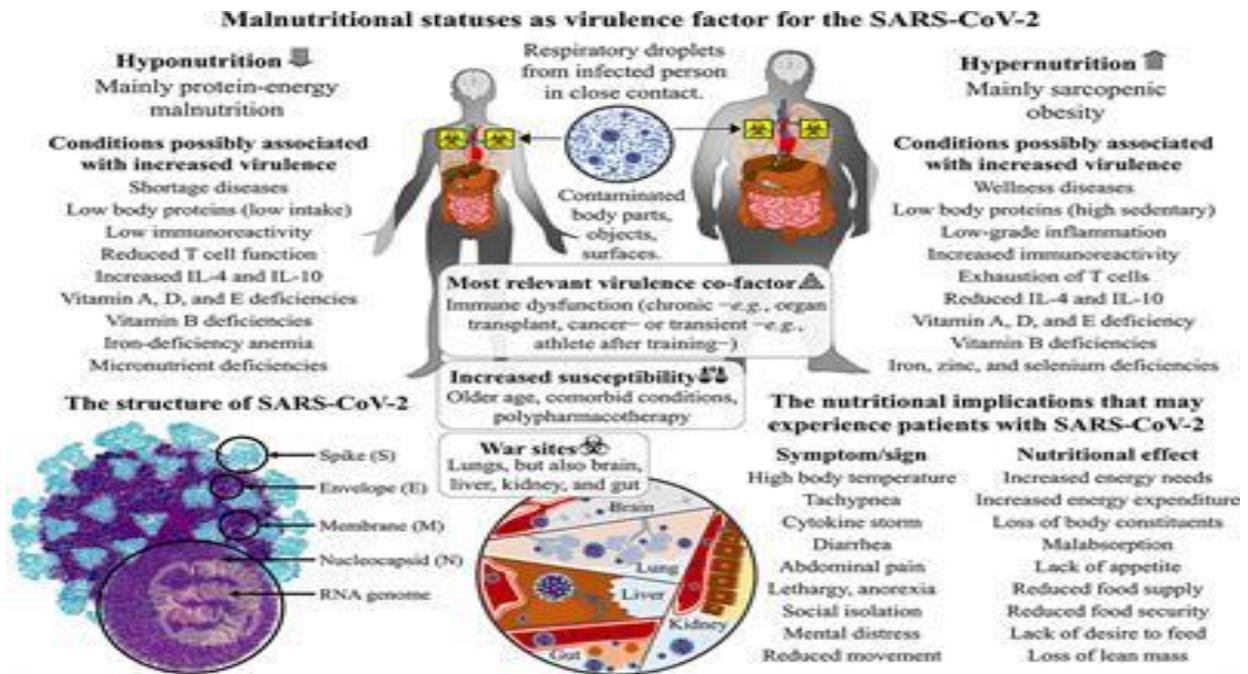


Figure(124):Nutrition for COVID-19 patients with malnutrition (www.google.com)

Chronic diseases, which are demonstrated as virulence factors for severe coronavirus disease 2019 (COVID-19), are frequently comorbid with protein-energy malnutrition (also called disease-related malnutrition), which is found to impair immune cell activation, thus allowing longer viral persistence and increased trafficking of inflammatory cells to lungs. The basal immuno-incompetence can be further aggravated upon infection. Insufficient protein intakes can cause nutrition-related sarcopenia. The concomitant excess of adiposity is defined as sarcopenic obesity and associates with issues of both conditions. Increased body fat sustains a systemic low-grade inflammation, mainly because of the leptin-induced CD4 T-cell function that increases autoimmunity. Basal T cells are more vulnerable to exhaustion in obese individuals who are more exposed to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) proliferation. Exhausted T cells show poor effector function, proliferation, and cytotoxic effects. In the 2009

pandemic happened by the influenza A (H1N1)pdm09 virus, obesity was considered a virulence factor for a more severe outcome much like for respiratory infectious diseases. Micronutrient deficiencies are regarded a considerable issue among malnourished individuals. Vitamins have a role in the proper functioning of both the innate and adaptive immune responses, with vitamin D and A being the main actor players. Vitamin D is important for the proper functioning of antibody-secreting cells and vitamin A sustains T-cell proliferation. The immune dysfunction in hyponutritional statuses may be bound to these deficiencies alike the excess of feeding, which is frequently correlated with a monotonous diet and therefore low in vitamins' sources. A plethora of other micronutrients is known to have a role in the immunocompetence of the host against infections, including B vitamins, vitamin C, vitamin E, iron, selenium, and zinc, with malnourished individuals often suffering from the most. Malnutritional statuses carry less endurance to survive from severe coronavirus disease 2019 (COVID-19). Hypermetabolism and excessive nitrogen loss are factors recognized to be related to infective states, and malnourished subjects are therefore disadvantaged because of the lesser body reserves.

The basal immune dysfunction that exists in protein-energy malnutrition and sarcopenic obesity can lead subjects to be more susceptible to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) contraction and affections. Other than the collapse of alveoli and respiratory failure, the coronavirus replication results in systemic consequences in the brain, liver, kidneys, and gut. Once affected, malnourished subjects will have fewer body reservoirs and immune boost to fight for recovery from illness.



Figure(125):The SARS-CoV-2 virulence and the malnutritional status of the human host: immune based dysfunction in hypo-and hyper-nutrition [Briguglio M.; Pregliasco F.; Lombardi G.; Perazzo P.; Banfi G. (2020). The malnutritional status of the host as a virulence factor for a new coronavirus SARS-CoV-2. *Front. Med.* <https://doi.org/10.3389/fmed.2020.00146>.]

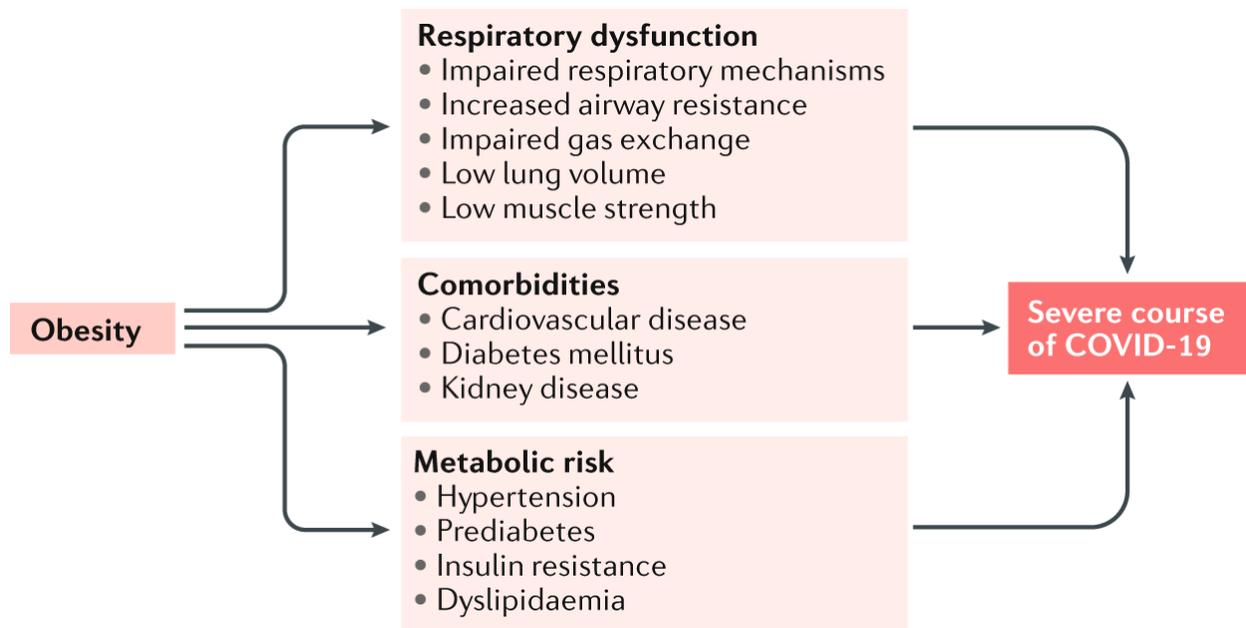
20. Complications of COVID-19 Infection in Obese Patients

It was mentioned that in some hospitals in Spain, there were cases of young people suffering from coronavirus disease 2019 (COVID-19) in which severe obesity was present and these patients developed towards destructive alveolitis with respiratory failure and death. There is no current illustration for this clinical finding, although it is found that severe obesity is correlated with sleep-apnea syndrome (SAS) and also to surfactant dysfunction (SD), which can lead to worse outcomes in the case of coronavirus disease 2019 (COVID-19). In addition, deterioration of glycemic control was considered with an impairment of ventilatory function and therefore contributed to a worse prognosis in these suffering individuals. Moreover, type 2 diabetes mellitus (T2DM) and obesity were concurrent in a given suffering case, which was accompanied by an age >65 years.

Stefan *et al.* (2020) reveals that coronavirus 2019 (COVID-19) patients with obesity frequently have respiratory dysfunction, which is characterized by alterations in respiratory mechanisms,

increased airway resistance, impaired gas exchange and low lung volume and muscle strength. Obese patients are prone to hypoventilation-associated pneumonia, pulmonary hypertension (PH) and cardiac stress. Obesity is also associated with an increased risk of diabetes mellitus (DM), cardiovascular disease (CVD) and kidney disease (KD), comorbidities that are regarded as leaders to increased vulnerability to pneumonia-associated organ dysfunctions. However, even in the absence of comorbidities of obesity, the presence of hypertension (HTN), dyslipidemia, prediabetes and insulin resistance (IR) can make individuals susceptible to cardiovascular (CV) events and increased vulnerability to infection via atherosclerosis, cardiac dysfunction (CD) and impaired immune response. In brief, obese patients are at a recognizable higher risk of impaired outcomes in coronavirus disease 2019 (COVID-19).

Adipose tissue, besides its role in energy storage, is a notable source of hormones, peptides, procoagulant microparticles (MPs), and cytokines, known as adipokines, and was regarded as an important reservoir of angiotensin-converting enzyme2 (ACE2). Adipose tissue is included in the regulation of inflammation [e.g., tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), macrophage chemo attractant protein-1 (MCP-1/CCL2)] and thrombosis [e.g., plasminogen activator inhibitor-1 (PAI-1)]. Since adipose tissue is observed to promote an inflammatory state, the potent binding between obesity and coronavirus disease 2019 (COVID-19) coagulopathy deserves further insights. Really, metabolic syndrome on a broader scale is a hallmark of a pre-existing inflammatory state that may be a required condition and/or amplified by coronavirus disease 2019 (COVID-19) in the progression of a pro-thrombotic condition.



Figure(126):Impaired metabolic health in obese COVID-19 patients[Stefan N.; Birkenfeld A.; Schulze M.; Ludwig D. (2020). Obesity and impaired metabolic health in patients with COVID-19. Endocrinology. <https://doi.org/10.1038/s41574.020.0364.6>]

• GLOSSARY

-Abdominal aortic aneurysm: AAA or triple A, this is a localized expansion of the abdominal aorta where the diameter is more than 3 cm or more than 50% greater than normal.

-Acidosis: it refers to excessive acid in the body, a distinguished anomaly state caused by collection of acid or from the exhaustion of alkaline counters. In acidosis, pH of blood is anomalically low. Acidosis is correlated with diabetic ketoacidosis, lung illness, and severe kidney illness.

-Acral ischemia: it is the black discoloration of skin of peripheries attributed to lowered blood feeding to influenced locations.

-Acrocyanosis: this is a condition characterized by bluish or purple colouring of hands and feet, resulted from cumbersome blood circulation.

-Activated partial thromboplastin time (aPTT or APTT): this is a blood lab exam that describes coagulation of blood.

-Acute coagulopathy: acute traumatic coagulopathy (ATC) is a precocious endogenous activity, helmed by combination of tissue lesion and shock that is correlated with elevated deaths and adverse results in polytrauma case. Endothelial stimulation of protein C is a prime mechanism of acute traumatic coagulopathy (ATC), which leads to haste anticoagulation and fibrinolysis following serious harm. Persistent blood wastage, hypothermia, acidosis, and hemodilution enhance acute traumatic coagulopathy (ATC) and result in a thorough derangement in whole ingredients of hemostasis.

-Acute coronary syndrome (ACS): the term acute coronary syndrome (ACS) includes ST-elevation myocardial infarction (STEMI) and non-ST elevation acute coronary syndrome (NSTE-ACS), which comprises non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). Nearly two thirds of acute coronary syndrome (ACS) manifestations are with non-ST elevation acute coronary syndrome (NSTE-ACS) and the rest are ST-elevation myocardial infarction (STEMI). Further, with coming of high sensitivity troponin (Tn) procedures, many patients already classified as unstable angina (UA) are now diagnosed with non-ST elevation myocardial infarction (NSTEMI). This led to that occurrence of unstable angina (UA) is falling

while non-ST elevation myocardial infarction (NSTEMI) is rising. It is substantial to indicate that normal ST-segment in electrocardiogram (ECG) must not be quite flat, it must be upward concave, or it must be as take-off shape. ST-segment which no longer has its upward concavity and becomes straight or upward convex, it is a symptom of acute myocardial infarction (MI).

-Acute crisis of a chronic haemolytic anaemia: this is a hemolytic crisis, body is not manufacturing sufficient red blood cells (RBCs) to substitute those damaged. This is leading to acute and frequently severe anemia; hemoglobin is liberated into bloodstream resulting in kidney lesion.

-Acute decompensated heart failure (ADHF): it is a syndrome described by exacerbating fatigue, dyspnea, or edema coming from breaking down heart function and frequently leading to hospital admission or unscheduled medical intervention. It is not a homogenous syndrome, but has many features and different appearances.

-Acute disseminated encephalomyelitis (ADEM): this is described by a brief but huge attack of inflammation in brain and spinal cord leading to destruction of myelin – the protective covering of nerve fibers.

-Acute flaccid paralysis (AFP): this is a neurological state described by weakness or paralysis and decreased muscle contraction without other clear reason.

-Acute (fulminant) hepatic failure (AHF): this is characterized by beginning of hepatic encephalopathy within eight weeks of commencement of symptoms contributing to severe hepatocellular dysfunction in ill individuals without former recognized liver illness.

-Acute hemorrhagic leukoencephalitis (AHLE): this is a very seldom form of acute disseminated encephalomyelitis (ADEM), described by a brief but strong attack of inflammation in brain and spinal cord causing destructions of myelin, often leading to mortality.

-Acute kidney injury (AKI): this is an abrupt event of kidney failure or kidney damage that incides within a few hours or a few days. Acute kidney injury (AKI) causes an accumulation of waste substituents in blood and creates a difficult condition for kidneys to continue appropriate balance of fluid in body.

-Acute lung injury (ALI): it is described as a syndrome of inflammation and elevating permeability associated with a constellation of clinical, radiologic, and physiologic anomalies coexist with left atrial or pulmonary capillary hypertension.

-Acute motor sensory axonal neuropathy (AMSAN): this is defined as a subtype of Guillain-Barré syndrome (GBS) featured by acute beginning of distal weakness, loss of deep tendon reflexes and sensory presentations.

-Acute myocardial injury: this is described by higher cardiac troponin (cTn) level, often faced clinically and related disadvantageous disease prediction.

-Acute phase proteins (APPs): these are a class of proteins whose plasma levels increase [positive acute-phase proteins (positive APPs)] or lower [negative acute-phase proteins (negative APPs)] a reaction to inflammation. This reaction is known as acute-phase reaction [also called acute-phase response (APR)]. The acute-phase reaction obviously includes fever, acceleration of peripheral leukocytes, circulating neutrophils and their precursors. Positive acute-phase proteins (positive APPs) function [as part of innate immune system (IIS)] various physiological activities within immune system. Some serve to destruct or block growth of microbial agents, e.g., C-reactive protein (CRP), mannose-binding protein [MBP, or mannose-binding lectin (MBL)], complement factors, ferritin, ceruloplasmin, serum amyloid A (SAA) and haptoglobin (Hp). Others develop negative feedback (or balancing feedback) on inflammatory immune response, e.g. serpins (serine protease inhibitors or classified inhibitor family I4). Alpha 2-macroglobulin (α 2M) and coagulation factors impact coagulation, majorly inducing it. This pro-coagulant effect may restrict infectious process by catching pathogenic agents in local blood clots. Also, some outputs of coagulation system (CS) can contribute to innate immune system (IIS) by their capability of elevating vascular permeability and functioning as chemotactic factors for phagocytes. Negative acute-phase proteins (negative APPs) lessen in inflammation. Examples include albumin (alb), transferrin (an iron-binding glycoprotein), transthyretin [TTR or TBPA, a transport protein in serum and cerebrospinal fluid (CSF)], retinol-binding protein (RBP, a plasma retinol transporter), antithrombin (AT, a serine protease inhibitor blocking thrombin), and transcortin (also known as corticosteroid-binding globulin (CBG) or serpin A6). The lowered levels of these proteins may be used as signs of inflammation. The physiological role of lowered production of such proteins is in general to

scavenge amino acids (AAs) for synthesizing positive acute-phase proteins (positive APPs) more effectively. Theoretically, a lowered transferrin might be decreased by an upregulation of transferrin receptors (TfRs), but the latter does not seem to change with inflammation. While the production of C3 (a complement factor) elevates in liver, plasma concentration frequently decreases because of growing turn-over, therefore it is often seen as a negative acute-phase protein (negative APP).

-Acute polyradiculoneuritis (APRN): this refers to an inflammation progressing abruptly when body's immune system attacks nerves.

-Acute pulmonary heart disease: pulmonary heart disease (PHD) indicates change in structure or function of right ventricle happening in association with anomalous respiratory activity. Although almost usually associated with some degree of pulmonary hypertension (PH), the degree, nature, severity, and causality of pulmonary hypertension (PH) related to pulmonary heart disease (PHD) is not requisitely linear and straight. Abnormal gas exchange is a crucial underpinning of pulmonary heart disease (PHD), affecting pulmonary vascular, cardiac, renal, and neurohormonal systems. Direct and indirect effects of chronic respiratory disease (CRD) may damage right ventricular-pulmonary arterial (RV-PA) interaction and, factors such as sympathetic nervous system (SNS) stimulation, altered blood viscosity, and salt and water retention can serve in a feedback loop to more influence right ventricular-pulmonary arterial (RV-PA) action. Left heart function can also be influenced, particularly in those with pre-existing left heart disease (LHD). Thus, physiologic interactions between abnormal respiratory and cardiovascular (CV) function are complicated, with pulmonary heart disease (PHD) exemplifying a heterogeneous end organ effect of a consolidated multisystem process. It is proposed to distinguish pulmonary heart disease (PHD) into two distinct entities, type I and type II pulmonary heart disease. Type I pulmonary heart disease (Type I PHD) is most prevalent, and refers to individuals with chronic respiratory disease (CRD) where disturbances in respiratory function dominate over more mild cardiac and circulatory perturbations. In contrast, type II pulmonary heart disease (PHD) refers to smaller subset of ill individuals with more severe pulmonary vascular and right heart dysfunction (RHD), whom present in a fashion similar to sick individuals with pulmonary arterial heart (PAH). Phenotypic variations are not produced by pulmonary arterial (PA) pressure alone, but alternately by variations in thorough physiology and clinical syndrome. Therefore, crucial variations can be recognized in symptomatology, physical

signs, cardiac imaging, hemodynamics, and the cardiovascular (CV) and gas exchange responses to exercise. Such substantial baseline differences in thorough physiologic phenotype are probably definitive to estimating response to pulmonary hypertension (PH) particular medication.

-Acute renal failure (ARF) is defined as quick reduction in kidney activity as apparent by a decrease in glomerular filtration rate (GFR).

-Acute respiratory distress syndrome: it is a sort of non-cardiogenic pulmonary oedema (NCPO), attributable to alveolar injury secondary to an inflammatory process, that can be either pulmonary or systemic in emergence. This syndrome shows as acute hypoxemia with bilateral pulmonary infiltrates on chest imaging, which are not thoroughly due to heart failure (HF).

-Acute respiratory failure (ARF): this is a syndrome described by hypoxemia, with or without hypercapnia and respiratory distress. Acute respiratory failure (ARF) is when fluid develops in air sacs in lungs. When that happens, lungs cannot liberate oxygen into blood. In turn, the organs can't get sufficient oxygen-rich blood to serve.

-Adaptive immunity: it refers to antigen-specific immune response. Adaptive immune response is more complicated than innate immune response. The antigen first must be processed and recognized. Once antigen is recognized, adaptive immune system makes an army of immunocytes particularly purposed to attack that antigen. Adaptive immunity also includes a memory that creates future responses against a particular antigen more effective.

-Adenoid (pharyngeal tonsil or nasopharyngeal tonsil): this indicates a mass of enlarged lymphatic tissue between back of nose and throat, frequently handicapping speaking and breathing in young children.

-Adenovirus: the two most common organ systems affected by adenovirus are respiratory and gastrointestinal (GI) tracts. Infections can exemplified as a “common cold” upper respiratory infection. One can also develop a lower respiratory infection such as bronchitis or pneumonia. Current symptoms involve cough, fever, fast breathing, wheezing and sore throat. Adenovirus can also lead to diarrhea, eye infections (conjunctivitis or pink eye) and even urinary tract

infection (UTI). Seldomly, it can be associated with liver (hepatitis), brain (encephalitis), and/or heart (myocarditis) issues.

-Adipokines, or adipocytokines: these are cytokines (cell signaling proteins) secreted by adipose tissue.

-Adult-onset Still's disease (AOSD): adult-onset Still's disease (AOSD) is a scarce multisystemic anomaly regarded as a complex (multigenic) autoinflammatory syndrome. A genetic background would give susceptibility to development of autoinflammatory reactions to environmental excites. Macrophage (MΦ) and neutrophil activation is a note of adult-onset Still's disease (AOSD) which can lead to a reactive hemophagocytic lymphohistiocytosis (HLH). As in the latter illness, cytotoxic function of natural killer cells is reduced in ill individuals with active adult-onset Still's disease (AOSD). Interleukin-18 (IL-18) and interleukin-1beta (IL-1β), two proinflammatory cytokines processed through inflammasome machinery, are substantial agents in pathogenesis of adult-onset Still's disease (AOSD); they cause interleukin-6 (IL-6) and T helper 1 (Th1) cytokine release as well as natural killer (NK) cell dysregulation leading to macrophage (MΦ) activation. Still's disease (AOSD) features include high spiking fever with joint symptoms, evanescent skin rash, sore throat, striking neutrophilic leukocytosis, hyperferritinemia with breakdown glycosylated ferritin (<20%), and abnormal liver function lab exams.

-Advanced cardiopulmonary disease: this is medical term used to describe a range of serious disorders affecting heart (cardio-) and lungs (-pulmonary).

-Advanced heart failure: this is when sick individuals with heart failure (HF) experiencing persistent heavy symptoms interfering with daily life despite maximum medical therapy.

-Air therapy: or oxygen therapy, also known as supplemental oxygen, is the use of oxygen as a medical remedy.

-Alanine aminotransferase (ALT): it is an enzyme that is normally found in hepatic and cardiac cells. Alanine aminotransferase (ALT) is released into blood when liver or heart is destructed. Blood alanine aminotransferase (ALT) levels are thus elevated with liver lesion or

with heart harm [for example, from a heart attack (also called myocardial infarction)]. It is referred as glutamic pyruvic transaminase (SGPT).

-Albumin (alb): albumin (alb) forms more than 50% of serum proteins in sound persons. It has a fundamental role in oncotic pressure maintenance and it is known as a versatile protein carrier for transportation of various endogenous and exogenous ligands. Lowered concentrations of albumin (alb) in body will develop different diseases such as hypovolemia and hypoproteinemia. It also has various indications such as in shocks, burns, cardiopulmonary bypass (CPB), and acute liver failure (ALF).

-Alcoholic liver disease (ALD): also called alcohol-related liver disease (ARLD), is a term that comprises liver manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis.

-Aldosterone: it is a corticosteroid (CS) hormone which stimulates absorption of sodium by kidneys and so regulates water and salt equilibrium.

-Alveolar dead space fraction: it relies on difference between arterial and end-tidal carbon dioxide ($AVDSf = (PaCO_2 - P_{ET}CO_2)/PaCO_2$).

-Alveolar hypoventilation syndrome: it is caused by several disturbances that are collectively referred as hypoventilation syndromes. Alveolar hypoventilation is defined as insufficient ventilation leading to hypercapnia, which is an increase in partial pressure of carbon dioxide as measured by arterial blood gas analysis ($PaCO_2$). Sick persons who hypoventilate may progress hypoxemia, and presence of hypoxemia along with hypercapnia aggravates clinical signs seen with hypoventilation syndromes. Alveolar hypoventilation may be acute or chronic and may be caused by several mechanisms.

-Amniotic emboli: an amniotic fluid embolism (AFE), is a very uncommon childbirth emergency where amniotic fluid (AF) entering blood stream of mother to promote an adverse reaction; this reaction results in cardiorespiratory (heart and lung) failure and immense bleeding (coagulopathy).

-Amyloidosis: it is deposition of amyloid in body. It is a state where amyloid protein deposited in liver, kidneys, spleen, or other tissues in particular illnesses.

-Anemia: it is defined as a reduction in either percentage of red blood cells (hematocrit), or a reduction in concentration of hemoglobin (Hb) in a sample of venous blood when compared with reference levels. Anemia leads to pallor and weariness.

-Angina: it is a condition marked by heavy pain in chest, frequently spreading to shoulders, arms, and neck, attributable to an inappropriate blood supply to heart.

-Angiopoietin 2 (Ang2): this is a growth factor belonging to the angiopoietin/Tie [tyrosine kinase (TK) with immunoglobulin (Ig) and epidermal growth factor (EGF) homology domains] signaling pathway, one of primary pathways included in angiogenesis (i.e., the growth of blood vessels).

-Angiopoietin-like 4 (ANGPTL4): it is a secreted protein modulating triglyceride (TG) homeostasis. Its transcription is promoted by glucocorticoids (GCs), which serve to increase circulating angiopoietin-like 4 (Angptl4) concentrations during fasting.

-Angiotensin II: it is also known as angiotensin-(1-8), an active peptide causing vasoconstriction, pro-fibrosis, pro-inflammation action, inducing aldosterone secretion by binding to angiotensin II type 1 receptor (AT1 receptor).

-Anomia: this is a form of aphasia in which sick individual is not able to recall names of everyday objects.

-Anorexia: it is lack or loss of appetite for food (as a medical condition). It is an emotional anomaly exemplified by obsessive inclination to lose weight by declining eating.

-Anti- β 2-glycoprotein I IgA and IgG antibodies: antiphospholipid antibodies (aPL) are a group of autoantibodies (aAb) pointed against phospholipid-binding plasma proteins, including both those circulating in blood and/or located in plasma membrane of blood vessel cells. Antiphospholipid syndrome (APS) is an autoimmune disturbance exemplified by presence of circulating antiphospholipid antibodies (aPL) associated with vessels thrombosis or aggravate pregnancy result. Beta 2 Glycoprotein I (B2GP1) is a protein that is majorly synthesized in liver, kidney, and heart. It is located in plasma and in membrane of endothelial cells. Platelets are most frequent antigen recognized by pathogenic antiphospholipid antibodies (aPL). Prevalence of anti- β 2-glycoprotein 1 (anti-B2GP1) antibodies of immunoglobulin A (IgA) isotype (IgA-aB2GP1) is

higher in patients with chronic kidney disease (CKD) than in the general population (30 vs. 1.5%), and an association between these antibodies (Abs) in ill individuals undergoing hemodialysis and thrombotic events and death has been seen.

-Antibody (Ab): an antibody (Ab) is a Y-shaped protein constituent of the immune system that circulates in blood, recognizes foreign substances like bacteria and viruses, and neutralizes them. After exposing antibodies (Abs) to a foreign agent, called an antigen (Ag), antibodies (Abs) keep circulating in blood, offering security against exposing to that antigen (Ag) in future. Antibody (Ab) is a part of host cell's defense. It is produced by a type of white blood cell (WBC) called a B cell. Structure of antibody (Ab) is composed of two light chains and two heavy chains, and at the very tip of antibody (Ab) is a hypervariable (HV) region, and this hypervariable (HV) region makes antibody (Ab) making various types of antibodies (Abs) that will respond to thorough antigens (Ags) attacking body. An antigen (Ag) is a foreigner agent for body. It can be a virus, or bacteria, and in certain conditions own body may manifest as a foreigner. And in these conditions, where own body manifests as a foreigner, own body will make antibodies (Abs) against parts of body.

-Anticardiolipin antibodies (ACA): antibodies (Abs) that are frequently pointed against cardiolipin (CL) and found in several illnesses.

-Antiphospholipid antibodies: these are antibodies (Abs) went ahead against phosphorus-fat constituents of individual's cell membranes called phospholipids (PL), particular blood proteins binding with phospholipids (PL), and complexes are formed when proteins and phospholipids (PL) are bound.

-Anuria: it is when the kidneys stop producing urine. This condition results from illness or decay to kidneys. Anuria diagnosing is when kidneys are producing less than 500 milliliters (mL) of urine each day. A usual daily urine yield is between 1 to 2 liters for adult individual.

-Apneustic respiration: this is an anomal type of breathing exhibited by deep, gasping inspiration with a pause at full inspiration followed by a brief, insufficient release.

-Appendicitis: it refers to a grave medical situation where appendix is inflamed and painful.

-Areflexia: this is a state where muscles are not responding to stimuli or exciters.

-Arrhythmia: it is a problem with rate or rhythm of heartbeat, meaning that heart beats too hastily, too slowly, or with an irregular pattern. When heart beats faster than normal, it is called tachycardia, and when beats too slowly, it is called bradycardia.

-Arterial hypertension (AHT): it is also called arterial high blood pressure. It is a pressure acting importantly on walls of arteries (arterial pressure). It is a risk for cardiovascular (CV) events. It is managed preventively including a hygienic diet and drug therapy. Also, it is called silent disease as it is often not detected in numerous sick individuals indicating a real health catastrophe. Arterial hypertension has presentations of pressure indicators, either equal or higher than 140mmHg for systolic or 90mmHg for diastolic pressure, after repeatedly measuring arterial tension.

-Arterial or venous infarct: arterial infarcts is a pathophysiology of inflow occlusion, while venous infarcts, is a pathophysiology of outflow occlusion and cerebral edema.

-Ascending paralysis: it is paralysis where muscle weakness initiates in legs and spreads to arms.

-Aspartate aminotransferase (AST): it is also known as serum glutamic oxaloacetic transaminase (SGOT). It is an enzyme that is normally present in liver and heart cells. It is released into blood when there is liver or heart damage. Blood aspartate aminotransferase (AST) levels are thus elevated in case of liver damage or in heart insult [i.e., from a heart attack (myocardial infarction)]. In addition, some medications can raise aspartate aminotransferase (AST) levels.

-Asphyxia: this refers to a condition arising when body is deprived of oxygen, causing unconsciousness, suffocation, or decease.

-Aspiration syndromes: these include all conditions where foreign constituents are inhaled into lungs. Most commonly, aspiration syndromes involve oral or gastric contents associated with gastroesophageal reflux (GER), swallowing dysfunction, neurological disorders, and structural abnormalities. Volume of reflux can be significant, causing serious presentations

associated with penetration of gastric components into airways, or where amounts of oral or gastric reflux or saliva enter airways developing intermittent or persistent symptoms.

-Asterixis: this indicates flapping tremor of hand when wrist is extended.

-Asthma: the 1991, 1997, and 2007 National Institute of Health Guidelines on Asthma (NIH Guidelines) define asthma as follows: “Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Reversibility of airflow limitation may be incomplete in some patients with asthma.”

-Astrocytes: they are stellate cells (hence their name) with multiple fine processes. Astrocytes in white matter are complex cells with 50 to 60 long branching processes that radiate from cell body and terminate in end-feet at pial surface, on blood vessels, or freely among axons. White matter astrocytes are usually called fibrous astrocytes. Astrocytes in gray matter, called protoplasmic astrocytes, have profuse, short stubby processes that contact blood vessels and pial surface, and surround neurons. Astrocytic end-feet cover the entire surface of intraparenchymal capillaries. These end-feet express glucose transporters of the GluT 1 type and are a site of glucose (Glc) uptake. In gray matter, astrocytic processes ensheath virtually every synapse. Ensheathing membranes form about 80% of total membrane surface and are devoid of organelles. Thus, astrocytes are polarized cells with some processes contacting cells of mesodermal origin (i.e., endothelial cells of the capillary or fibroblasts of pia mater), whereas other processes are intimately intertwined with neuronal processes and synapses.

-Ataxia: persistent ataxia usually results from decay of cerebellum that controls muscle coordination. Ataxia describes a lack of muscle control or coordination of voluntary movements, such as walking or picking up objects. Ataxia can affect various movements and create difficulties with speech, eye movement and swallowing.

-Atelectasis: it indicates partial collapse or incomplete inflation of lung.

-Atheroma: it refers to degeneration of walls of the arteries caused by accumulated fatty deposits and scar tissue, and progress restriction of blood circulation and thrombosis risk.

-Atherosclerosis: it is hardening of a blood vessel coming from buildup of plaque. Plaque is made of fatty deposits, cholesterol, and calcium. Plaque buildup causes artery narrowing and hardening. Plaque buildup can slow and even stop blood flow. This means tissue supplied by the artery is cut off from its blood supply. This often leads to pain or reduced activity. This status can cause a number of grave health issues. Depending on block locus, it can cause: coronary artery disease (CAD), stroke, and peripheral vascular disease (PVD).

-ATPase: this is a class of enzymes catalyzing decomposition of adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and a free phosphate ion or the inverse reaction.

-Atrial fibrillation (AF or Afib): it is an irregular, rapid heart rate causing presentations like heart palpitations (having fast beats), fatigue, and shortness of breath (dyspnea).

-Atrial septal defect (ASD): this is a hole in the wall (septum) between the atria.

-Atrioventricular nodal reentrant tachycardia (AVNRT): this is most common type of paroxysmal supraventricular tachycardia (PSVT) encountered in clinical practice. Atrioventricular nodal reentrant tachycardia (AVNRT) is generally a narrow complex tachycardia with rates of 120 to 240 bpm.

-Autoantibody: an antibody (Ab) produced in response to a constituent of its own tissues.

-Auto-immune hepatitis: this is an illness where body's own immune system attacks liver and causes it to become inflamed. This illness is chronic, meaning it lasts many years. If untreated, it can lead to cirrhosis and liver failure.

-Autonomic neuropathy: this is a group of symptoms occurring when there is damage to nerves that manage every day body functions which comprise blood pressure, heart rate, sweating, bowel and bladder emptying, and digestion.

-Axonal neuropathy: acute motor axonal neuropathy (AMAN) is a variant of Guillain-Barré syndrome (GBS). It is characterized by acute paralysis and loss of reflexes without sensory loss.

-Axonal polyneuropathy: this is a damage affecting peripheral nerves.

-Bactericidal/permeability-increasing protein fold-containing family member A1 (BPIFA1): it is formerly known as SPLUNC1, is one of the most abundant proteins in respiratory secretions and has been identified with increasing frequency in studies of pulmonary disease. Its expression is largely restricted to the respiratory tract, being highly concentrated in the upper airways and proximal trachea. Bactericidal/permeability-increasing protein fold-containing family member A1 (BPIFA1) is highly responsive to airborne pathogens, allergens, and irritants. Bactericidal/permeability-increasing protein fold-containing family member A1 (BPIFA1) actively participates in host protection through antimicrobial, surfactant, airway surface liquid regulation, and immunomodulatory properties. Its expression is modulated in multiple lung diseases, including cystic fibrosis, chronic obstructive pulmonary disease, respiratory malignancies, and idiopathic pulmonary fibrosis.

-B cells: they, also known as B lymphocytes, are a type of white blood cell (WBC) of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies (Abs). Additionally, B cells present antigens [they are also classified as professional antigen-presenting cells (APCs)] and secrete cytokines. In mammals, B cells mature in the bone marrow, which is at the core of most bones.

-B-type natriuretic peptide: it is also called brain-type natriuretic peptide (BNP). It was first described in 1988 after isolation from porcine brain. However, it was soon found to originate mainly from the heart, representing a cardiac hormone. B-type natriuretic peptide (BNP) belongs to the natriuretic peptide family together with other structurally similar peptides, namely atrial natriuretic peptide (ANP), C-type natriuretic peptide (CNP), and urodilatin. The major source of B-type natriuretic peptide (BNP) synthesis and secretion is the ventricular myocardium. Only small amounts of B-type natriuretic peptide (BNP) are stored in granules and rapid gene expression with de novo synthesis of the peptide is the underlying mechanism for the regulation of B-type natriuretic peptide (BNP) secretion. B-type natriuretic peptide (BNP) is synthesized as

a prehormone (proBNP) comprising 108 amino acids. Upon release into the circulation it is cleaved in equal proportions into the biologically active 32 amino acid B-type natriuretic peptide (BNP), which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP). Both molecules are constantly released and can be detected in the blood. The main stimulus for increased B-type natriuretic peptide (BNP) and NT-proBNP synthesis and secretion is myocardial wall stress. Furthermore, factors such as myocardial ischemia and endocrine (paracrine) modulation by other neurohormones and cytokines are also of importance. In the systemic circulation B-type natriuretic peptide (BNP) mediates a variety of biological effects by interaction with the natriuretic peptide receptor type A (NPR-A) causing intracellular cyclic guanosine monophosphate (cGMP) production. The physiological effects of B-type natriuretic peptide (BNP) are manifold and comprise natriuresis/diuresis, peripheral vasodilatation, and inhibition of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS). B-type natriuretic peptide (BNP) is cleared from plasma by binding to the natriuretic peptide receptor type C (NPR-C) and through proteolysis by neutral endopeptidases. In contrast, NT-proBNP is mainly cleared by renal excretion. However, recent studies suggest that there might also be other important clearing mechanisms for NT-proBNP. The half-life of B-type natriuretic peptide (BNP) is 20 mins whereas NT-proBNP has a half-life of 120 mins, which explains why NT-proBNP serum values are approximately six times higher than B-type natriuretic peptide (BNP) values, even though both molecules are released in equimolar proportions.

-Behçet's disease: also called Behçet's syndrome, it is a rare disorder that causes blood vessel inflammation throughout the body.

-Beta-thalassemias: these are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Three main forms have been described: thalassemia major, thalassemia intermedia and thalassemia minor. Individuals with thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell (RBC) transfusions. Findings in untreated or poorly transfused individuals with thalassemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, development of masses from extramedullary

hematopoiesis, and skeletal changes that result from expansion of the bone marrow. Regular transfusion therapy leads to iron overload-related complications including endocrine complication (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), dilated cardiomyopathy, liver fibrosis and cirrhosis). Patients with thalassemia intermedia present later in life with moderate anemia and do not require regular transfusions. Main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and increased predisposition to thrombosis. Thalassemia minor is clinically asymptomatic but some subjects may have moderate anemia. Beta-thalassemias are caused by point mutations or, more rarely, deletions in the beta globin gene on chromosome 11, leading to reduced (beta+) or absent (beta0) synthesis of the beta chains of hemoglobin (Hb). Transmission is autosomal recessive; however, dominant mutations have also been reported.

-Bilateral facial paralysis: or AKA Facial Diplegia, it is defined as facial paralysis or paresis affecting both sides of the face.

-Biliary sludge: this is a mixture of particulate solids that have precipitated from bile. Such sediment consists of cholesterol crystals, calcium bilirubinate pigment, and other calcium salts. Sludge is usually detected on transabdominal ultrasonography.

-Bilirubin: this is an orange-yellow pigment formed in the liver by the breakdown of haemoglobin and excreted in bile.

-Blepharitis: it is a condition characterized by inflammation of the eyelid margin and is a common cause of discomfort and irritation among people of all ages, ethnicity, and sex. In general, blepharitis is not a sight-threatening condition, but if left untreated has the potential to cause keratopathy, corneal neovascularization and ulceration, and permanent alterations in eyelid morphology.

-Blood urea nitrogen (BUN) test: A blood urea nitrogen (BUN) test measures the amount of urea nitrogen found in the blood. Urea nitrogen is a waste product made when the liver breaks

down protein. It's carried in the blood, filtered out by the kidneys, and removed from the body in the urine. If the liver isn't healthy, it may not break down proteins the way it should. And if the kidneys aren't healthy, they may not properly filter urea. Either of these problems can lead to changes in the amount of urea nitrogen in the body. Blood urea nitrogen (BUN) levels help healthcare provider see how well the kidneys are working. The test may be used along with other measurements to help diagnose a kidney disorder or find out how well the treatment for kidney disease is working.

-Bradykinin: it is a compound released in the blood in some circumstances which causes contraction of smooth muscle and dilation of blood vessels. It is a peptide with nine amino acid (AA) residues.

-Brisk tendon reflexes: this is an above-average response during a reflex test.

-Bronchiectasis: it is a disease in which there is permanent enlargement of parts of the airways of the lung. Symptoms typically include a chronic cough with mucus production. Other symptoms include shortness of breath, coughing up blood, and chest pain.

-Bronchiolitis: it is a common lung infection in young children and infants. It causes inflammation and congestion in the small airways (bronchioles) of the lung. Bronchiolitis is almost always caused by a virus. Typically, the peak time for bronchiolitis is during the winter months.

-Brunt: it is the principal force, shock, or stress ,as of an attack.

-Cachexia: it indicates fat and muscle loss, anorexia, and weakness.

-Calf circumference (CC): It has been established normative data for anthropometric markers in healthy and frail elderly, and found that among other anthropometric markers, calf circumference (CC) was more significantly affected in cases of malnutrition. Calf circumference (CC) has been proposed, together with arm circumference, to be a valid nutritional screening instrument for malnutrition in the elderly. This anthropometric measurement has been found to be correlated with fat free mass, with bone mass and is also linked to exercise intolerance and altered muscle metabolism in heart failure (HF). Calf circumference (CC) is recommended by the World Health Organization (WHO) as a measurement of nutritional state in older individuals.

-Canavan disease: this is a rare inherited disorder damaging the ability of nerve cells (neurons) in the brain for sending and receiving messages.

-Cardiac arrhythmias: this is characterized by accelerated, slowed, or irregular heart rates caused by abnormalities in the electrical impulses of the myocardium.

-Cardiac dysfunction: this indicates left ventricular function depression, mitral valve regurgitation (also called mitral regurgitation, mitral insufficiency or mitral incompetence, a condition in which heart's mitral valve doesn't close tightly, allowing blood to flow backward in heart), or pericardial effusion (excess fluid between the heart and the sac surrounding the heart).

-Cardiac magnetic resonance: cardiovascular magnetic resonance imaging (CMR, also known as cardiac MRI) is a medical imaging technology for non-invasive assessment of the function and structure of the cardiovascular system. Conventional magnetic resonance imaging (MRI) sequences are adapted for cardiac imaging by using electrocardiogram (ECG) gating and high temporal resolution protocols.

-Cardiac troponins (cTn): Troponins are regulatory proteins that are part of the contractile apparatus of skeletal and cardiac muscle tissue. They are not present in smooth muscle tissue. With the proteins actin and tropomyosin, they are part of the thin filaments within the myofibrils and are essential for the calcium-mediated regulation of muscle contraction. The troponin complex consists of 3 interacting and functionally distinct proteins (troponin I, T, and C). Tissue-specific isoforms exist for each type of troponin. Within the thin filament, tropomyosin dimers form a continuous chain along the groove of the actin helix. The troponin complex lies at regular intervals along the filament. Tropomyosin acts to block the myosin binding sites on actin. Each troponin protein has specific functions that regulate muscle contraction. Troponin I and T have specificity for cardiac injury. The troponin protein exists in 2 populations within the cells. The majority of troponin is structurally bound within the thin filaments of the contractile apparatus. A small percentage of protein remains free in the cytosol. This percentage is approximately 2–4% for cardiac troponin I (cTnI) and 6–8% for cardiac troponin T (cTnT). Troponins are considered leakage markers. Damage to cardiac myocytes resulting in loss of membrane integrity causes the release of cardiac troponin (cTn) into the circulation. Apoptosis, a genetically programmed form of cell death, does not result in loss of cell membrane integrity and therefore will not cause

leakage of troponins. Cardiac troponins also have a role in establishing prognosis. With myocardial infarction (MI), any troponin level above the reference range is associated with an increased risk of adverse events in both the short- and long-term. It has also been shown that the magnitude of troponin level elevation correlates with risk of future cardiac events or death and aids the identification of patients with greater disease severity who may benefit from more aggressive therapy. In fact, the size of the infarcted area may be predicted based on peak cardiac troponin I (cTnI) levels or cardiac troponin T (cTnT) levels at 72 hours. In addition, elevations of cardiac troponin (cTn) have prognostic significance in other forms of cardiovascular disease (CVD) such as heart failure (HF) and pulmonary thromboembolism (PTE). Elevations in cardiac troponin (cTn) indicate myocardial infarction (MI) and direct trauma to the heart. Myocardial dysfunction and cardiac troponin (cTn) elevations during sepsis are common. Both cardiac troponin I (cTnI) and cardiac troponin T (cTnT) may be elevated in humans with heart failure (HF) due to left ventricular dysfunction and these patients have a worse prognosis than those with normal cardiac troponin (cTn) levels. Pericardial disease has been shown to cause elevations in troponin levels. Cardiac troponin (cTn) elevations in patients who have received chemotherapy can be predictive for the development of cardiac toxicity and decreased left ventricular function. Many studies have reported elevated cardiac troponin (cTn) levels in humans after extreme endurance exercise such as marathons and Ironman triathlons. Pulmonary thromboembolism (PTE) and pulmonary hypertension (PH) cause pressure overload of the right ventricle due to increased pulmonary arterial resistance. The resultant increase in right ventricular pressure leads to decreased myocardial perfusion and oxygen supply. These changes, in addition to hypoxemia with pulmonary thromboembolism (PTE), can cause cardiac damage and cardiac troponin (cTn) leakage. Pulmonary embolism (PE) has also been associated with right ventricular infarction, confounding the interpretation of elevated cardiac troponin (cTn) in these patients. However, patients with pulmonary thromboembolism (PTE) and elevated cardiac troponin (cTn) have a worse prognosis than those without cardiac troponin (cTn) elevation. Chronic elevations of troponins exist in approximately 50% of patients with chronic renal insufficiency (CRI). Although the exact cause is unknown, many mechanisms for these elevations have been proposed including silent myocardial necrosis, ventricular hypertrophy, and impaired renal clearance. Troponin T (TnT) is more commonly associated with elevations during

renal disease with 1 study showing 82% of patients with cardiac troponin T (cTnT) elevations compared with only 6% with elevated cardiac troponin I (cTnI).

-Cardiogenic shock: this is a common cause of mortality, and management remains challenging despite advances in therapeutic options. Cardiogenic shock is caused by severe impairment of myocardial performance that results in diminished cardiac output, end-organ hypoperfusion, and hypoxia. Clinically this presents as hypotension refractory to volume resuscitation with features of end-organ hypoperfusion requiring pharmacological or mechanical intervention. Acute myocardial infarction (MI) accounts for 81% of patient in cardiogenic shock.

-Cardiomyocytes: Cardiac muscle cells or cardiomyocytes (also known as myocardiocytes or cardiac myocytes) are the muscle cells (myocytes) that make up the cardiac muscle (heart muscle). Each myocardial cell contains myofibrils, which are specialized organelles consisting of long chains of sarcomeres, the fundamental contractile units of muscle cells. Cardiomyocytes show striations similar to those on skeletal muscle cells. Unlike multinucleated skeletal cells, the majority of cardiomyocytes contain only one nucleus, although they may have as many as four. Cardiomyocytes have a high mitochondrial density, which allows them to produce adenosine triphosphate (ATP) quickly, making them highly resistant to fatigue.

-Cardiovascular disease (CVD): Cardiovascular disease (CVD) is an abnormal functioning of the heart or blood vessels. It is the term for all types of diseases that affect the heart or blood vessels, including coronary heart disease (clogged arteries), which can cause heart attacks, stroke, congenital heart defects and peripheral artery disease.

-Caspases: they are a family of cysteine proteases that serve as primary effectors during apoptosis to proteolytically dismantle most cellular structures, including the cytoskeleton, cell junctions, mitochondria, endoplasmic reticulum (ER), Golgi, and the nucleus.

-Cataract: this is a medical condition in which the lens of the eye becomes progressively opaque, resulting in blurred vision.

-Catastrophic antiphospholipid syndrome (CAPS): it is a rare life-threatening autoimmune disease characterized by disseminated intravascular thrombosis resulting in multiorgan failure.

-CE marking: this is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA). The CE marking is also found on products sold outside the European Economic Area (EEA) that have been manufactured to European Economic Area (EEA) standards. This makes the CE marking recognizable worldwide even to people who are not familiar with the European Economic Area (EEA).

-Celiac disease: this is a digestive disorder that damages the small intestine.

-Cellular hyperpolarity: this is a change in a cell's membrane potential that makes it more negative.

-Cellular infiltration: this is the migration of cells from their sources of origin, or the direct extension of cells as a result of unusual growth and multiplication.

-Cellulitis: this is inflammation of subcutaneous connective tissue.

-Cerebral infarcts: it is the focal brain necrosis due to complete and prolonged ischemia that affects all tissue elements, neurons, glia, and vessels.

-Chemokines: they are a family of chemoattractant cytokines (small proteins secreted by cells that influence the immune system) which play a vital role in cell migration through venules from blood into tissue and vice versa, and in the induction of cell movement in response to a chemical (chemokine) gradient by a process known as chemotaxis. In addition, chemokines also regulate lymphoid organ development and T-cell differentiation, mediate tumor cell metastasis, and have recently been shown to have a function in the nervous system as neuromodulators.

-Chemotherapy-induced cardiomyopathy (CCM): the basis of the suggested definitions of chemotherapy-induced cardiomyopathy (CCM) are the development of left ventricular dysfunction (LVD) [defined as depressed left ventricular ejection fraction (LVEF)]and/or manifestations of symptomatic heart failure (HF). The definitions are supported by reports that the incidence of heart failure (HF) and left ventricular dysfunction (LVD) range between 5% and 65% depending on the diagnostic criteria adopted. Broadly, these definitions suggest chemotherapy-induced cardiomyopathy (CCM) is a functional or structural heart injury related to anti-cancer treatment. Oncologists base their definition on the Cardiac Review and Evaluation

Committee on trastuzumab associated cardiotoxicity and the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. They define chemotherapy-induced cardiomyopathy (CCM) as a decrease of left ventricular ejection fraction (LVEF) by 5% or more to less than 55% in the presence of symptoms of heart failure (HF) or an asymptomatic decrease in left ventricular ejection fraction (LVEF) by 10% or more to less than 55% and symptoms of congestive heart failure (CHF). Both the European Society of Cardiology (ESC) and European Society for Medical Oncology (ESMO) emphasize that a change in left ventricular ejection fraction (LVEF) is the basis for clinical definitions of chemotherapy-induced cardiomyopathy (CCM).

-Chemotherapy-induced cardiotoxicity: this is a major cause of morbidity and mortality in cancer survivors. It may manifest as arrhythmias, hypertension, myocardial ischemia, thromboembolism, heart failure, systolic dysfunction or other adverse events. Anthracyclines and trastuzumab are the chemotherapeutic agents with the most documented cardiac side effects; however, the array of novel molecular targeting therapies available is concerning because their side effects are not yet well understood.

-Chest radiography: it is a chest radiograph, also called a chest X-ray (CXR), or chest film. It is a projection radiograph of the chest used to diagnose conditions affecting the chest, its contents, and nearby structures. Chest radiographs are the most common film taken in medicine. Like all methods of radiography, chest radiography employs ionizing radiation in the form of X-rays to generate images of the chest. The mean radiation dose to an adult from a chest radiograph is around 0.02 mSv (2 mrem) for a front view (PA, or posteroanterior) and 0.08 mSv (8 mrem) for a side view (LL, or latero-lateral). Together, this corresponds to a background radiation equivalent time of about 10 days.

-Cheyne-Stokes respiration: this is cyclic waxing and waning of tidal volume.

-Chilblains: these indicate painful, itching swelling on a hand or foot, caused by poor circulation in the skin when exposed to cold.

-Chlamydia trachomatis: this is a gram-negative bacterium that infects the columnar epithelium of the cervix, urethra, and rectum, as well as nongenital sites such as the lungs and eyes. The bacterium is the cause of the most frequently reported sexually transmitted disease in the United

States, which is responsible for more than 1 million infections annually. Most persons with this infection are asymptomatic. Untreated infection can result in serious complications such as pelvic inflammatory disease, infertility, and ectopic pregnancy in women, and epididymitis and orchitis in men. Men and women can experience chlamydia-induced reactive arthritis.

-Cholangitis: this is inflammation of the bile duct system.

-Cholecystectomy: this indicates surgical removal of the gall bladder.

-Cholecystokinin (CCK): it is a hormone which is secreted by cells in the duodenum and induces the release of bile into the intestine and the secretion of enzymes by the pancreas.

-Chorioretinitis: this is a type of uveitis involving the posterior segment of the eye, which includes inflammation of the choroid and the retina of the eye.

-Choroid plexus (CP): this is a set of ependymal-derived structures regulating the composition of cerebrospinal fluid (CSF).

-Chronic hemolytic anemia: this is a disorder in which red blood cells (RBCs) are destroyed faster than they can be made;

-Chronic high altitude exposure: high-altitude illnesses encompass the pulmonary and cerebral syndromes that occur in non-acclimatized individuals after rapid ascent to high altitude. The most common syndrome is acute mountain sickness (AMS) which usually begins within a few hours of ascent and typically consists of headache variably accompanied by loss of appetite, nausea, vomiting, disturbed sleep, fatigue, and dizziness. With millions of travelers journeying to high altitudes every year and sleeping above 2,500 m, acute mountain sickness is a wide-spread clinical condition. Risk factors include home elevation, maximum altitude, sleeping altitude, rate of ascent, latitude, age, gender, physical condition, intensity of exercise, pre-acclimatization, genetic make-up, and pre-existing diseases. At higher altitudes, sleep disturbances may become more profound, mental performance is impaired, and weight loss may occur.

-Chronic inflammatory demyelinating polyneuropathy (CIPD): this is a rare neurological disorder in which there is inflammation of nerve roots and peripheral nerves and destruction of the fatty protective covering (myelin sheath) over the nerves.

-Chronic lung disease (CLD): it is a type of disorder that affects the lungs and other parts of the respiratory system. It generally progresses slowly and may get worse over time. Chronic lung disease may be caused by smoking tobacco or by breathing in secondhand tobacco smoke, chemical fumes, dust, or other forms of air pollution. Types of chronic lung disease include asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, asbestosis, pneumonitis, and other lung conditions.

-Chronic lymphocytic leukemia (CLL): this is the most common leukemia in adults, a type of cancer starting in cells becoming certain white blood cells (called lymphocytes) in the bone marrow. The cancer (leukemia) cells starting in the bone marrow (BM) but then going into the blood; stage A leukemia: The patient does not have anemia or low levels of platelets.

-Chronic obstructive pulmonary disease (COPD): American Thoracic Society/European Respiratory Society (ATS/ERS) Definition: chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although chronic obstructive pulmonary disease (COPD) affects the lungs, it also produces significant systemic consequences. Airflow limitation is a reduction in expiratory airflow that occurs due to increased resistance to flow and reduced lung parenchymal elastic recoil. Chronic obstructive pulmonary disease (COPD) is characterized by an inflammatory reaction within the lung to inhaled particles or gases and this response may be triggered by activation of both innate and adaptive immune responses. Inflammatory markers are present both systemically as well as within the lung. Historically, chronic obstructive pulmonary disease (COPD) has been considered an overlapping dyad of pulmonary disorders characterized by airflow obstruction and different clinical, radiographic, and physiologic manifestations: chronic bronchitis and emphysema, that are distinguished from asthma, the other major cause of airflow obstruction. Chronic bronchitis is the presence of a productive cough for at least 3 consecutive months in 2 consecutive years. Emphysema is an abnormal enlargement of the air spaces distal to the terminal bronchioles accompanied by destruction of their wall and without obvious fibrosis pathologically or radiographically.

-Chronic renal failure (CRF) or chronic kidney disease (CKD): it is defined as persistent impairment of kidney function, in other words, abnormally elevated serum creatinine for more than 3 months or calculated glomerular filtration rate (GFR) less than 60 ml per minute / 1.73m². It often involves a progressive loss of kidney function necessitating renal replacement therapy (dialysis or transplantation). When a patient needs renal replacement therapy, the condition is called end-stage renal disease (ESRD).

-Chronic thromboembolic pulmonary hypertension (CTEPH): this is a condition where there is elevated blood pressure in the pulmonary arteries caused by chronic blood clots (thromboembolic), which obstruct the free flow of blood through the lungs. become short of breath more easily. One might first become short of breath more easily. One might also be more tired (fatigued) than usual. If one experiences shortness of breath and/or fatigue several months after having a blood clot in the legs or lungs, the health care provider should look for chronic thromboembolic pulmonary hypertension (CTEPH). Some patients also may feel light headed or even pass out. Swelling (edema) of feet and ankles is common and may progress to swelling of the belly (ascites). Chest pain may also occur and can be mistaken for a heart attack. One may feel the heart racing or pounding (palpitations). The oxygen level in blood may become very low, making one's feet and/or fingers turn blue. Some people with chronic thromboembolic pulmonary hypertension (CTEPH) cough up blood.

-Chronic tubulointerstitial disease (TID): it is defined as involvement of tubular and interstitial components of the renal parenchyma.

-Chronic venous insufficiency: it is a condition occurring when the venous wall and/or valves in the leg veins not working effectively, making it difficult for blood to return to the heart from the legs. Chronic venous insufficiency causes blood to pool or collect in these veins, and this pooling is called stasis.

-Circulatory failure: it is also called cardiac circulatory collapse, affecting the vessels of the heart such as the aorta and almost always fatal.

-Circulatory shock: it is commonly known simply as shock. It is a life-threatening medical condition that occurs due to inadequate substrates for aerobic cellular respiration. In the early stages, this is generally caused by an inadequate tissue level of oxygen.

-Circumventricular organs (CVOs): these are highly vascularized structures located around the third and fourth ventricles and characterized by the lack of a blood–brain barrier (BBB). These specialized areas are points of communication between the blood, the brain parenchyma, and the cerebrospinal fluid (CSF).

-Colitis: this is inflammation of the mucosal lining of the colon which may be acute or chronic. Colitis is common and increasing in prevalence worldwide. Patients with colitis present with watery diarrhea, abdominal pain, tenesmus, urgency, fever, tiredness, and blood in the stool. However, colitis has different types and results from several mechanisms including infection, autoimmunity, ischemia, and drugs. Also, it may occur secondary to immune deficiency disorders or secondary to exposure to radiation.

-Common variable immunodeficiency (CVID): this is a disorder characterized by low levels of serum immunoglobulins (antibodies) and an increased susceptibility to infections. The exact cause of the low levels of serum immunoglobulins is usually not known. It is a relatively common form of immunodeficiency, hence, the word common. The degree and type of deficiency of serum immunoglobulins, and the clinical course, varies from patient to patient, hence, the word variable. In some patients, there is a decrease in both immunoglobulin G (IgG) and immunoglobulin A (IgA); in others, all three major types [immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin M (IgM)] of immunoglobulins may be decreased. The clinical signs and symptoms also vary from severe to mild. Frequent and unusual infections may occur first during early childhood, adolescence or adult life. In the majority of patients, the diagnosis is not made until the 3rd or 4th decade of life. However, about 20% of patients have symptoms of disease or are found to be immune deficient, under the age of 16. Due to the relatively late onset of symptoms and diagnosis, other names that have been used for this disorder include acquired agammaglobulinemia, adult onset agammaglobulinemia, or late onset hypogammaglobulinemia. The causes of common variable immunodeficiency (CVID) are largely unknown, although recent studies have shown the involvement of a small group of genes in some of the patients. Over the past few decades, studies on the cells of the immune system in patients with common variable immunodeficiency (CVID) have revealed a spectrum of lymphocyte abnormalities. Most patients appear to have normal numbers of B-lymphocytes, but

they fail to undergo normal maturation into plasma cells capable of making the different types of immunoglobulins and antibodies (Abs). Other patients lack enough function from helper T-lymphocytes necessary for a normal antibody (Ab) response. A third group of patients have excessive numbers of cytotoxic T-lymphocytes, and although the role of these cells in the disease is unclear. Both males and females may have common variable immunodeficiency (CVID). Some patients have symptoms in the first few years of life while many patients may not develop symptoms until the second or third decade, or even later. The presenting features of most patients with common variable immunodeficiency (CVID) are recurrent infections involving the ears, sinuses, nose, bronchi and lungs. When the lung infections are severe and occur repeatedly, permanent damage to the bronchial tree may occur and a chronic condition of the bronchi (breathing tubes) develops, causing widening and scarring of these structures. This condition is known as bronchiectasis.

-Compensated hemolysis: this is occurring when the rate of hemolysis is modest and the bone marrow (BM) is capable of completely compensating for the decreased red blood cell (RBC) life span, and the hemoglobin concentration is normal.

-Complement system: the complement system, also known as complement cascade, is a part of the immune system that enhances (complements) the ability of antibodies (Abs) and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane. It is part of the innate immune system, which is not adaptable and does not change during an individual's lifetime. The complement system can, however, be recruited and brought into action by antibodies (Abs) generated by the adaptive immune system. The complement system consists of a number of small proteins that are synthesized by the liver, and circulate in the blood as inactive precursors. When stimulated by one of several triggers, proteases in the system cleave specific proteins to release cytokines and initiate an amplifying cascade of further cleavages. The end result of this complement activation or complement fixation cascade is stimulation of phagocytes to clear foreign and damaged material, inflammation to attract additional phagocytes, and activation of the cell-killing membrane attack complex. Over 30 proteins and protein fragments make up the complement system, including serum proteins, and cell membrane receptors. They account for about 10% of the globulin fraction of blood serum. Three biochemical pathways activate the

complement system: the classical complement pathway, the alternative complement pathway, and the lectin pathway.

-Complete blood count (CBC)/differential: complete blood count components (CBC) involve: red blood cells (RBCs), hematocrit (Hct), hemoglobin (Hgb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cells (WBCs), platelets, and mean platelet volume (MPV).

-Computed tomography angiography (CTA): this uses an injection of contrast material into your blood vessels and CT scanning to help diagnose and evaluate blood vessel disease or related conditions, such as aneurysms or blockages. CT angiography uses a CT scanner to produce detailed images of both blood vessels and tissues in various parts of the body. During the exam, contrast material is injected through a small catheter placed in a vein of the arm. A radiologic technologist will capture high-resolution CT images while the contrast material flows through the blood vessels.

-Computed tomography (CT) pulmonary angiography: this is a test detecting how blood flowing through the lung.

-Computed tomography venography (CTV): computed tomography venography (CTV) is typically done after the patient receives contrast injection through the cubital vein; this is indirect computed tomography venography (CTV). Another option is direct computed tomography venography (CTV), wherein a contrast agent is injected in the dorsal vein of the affected foot, with a tourniquet applied to the ankle to allow preferential contrast flow into the deep veins. This allows superior visualization of the venous network and a more precise 3-dimensional reconstruction. Combined direct and indirect computed tomography venography (CTV) is highly accurate but requires a larger dose of intravenous (IV) contrast; therefore, it is recommended that this only be used in more complicated cases. Computed tomography venography (CTV) has been proposed as a method for predicting success of catheter-directed thrombolysis (CDT) in acute deep vein thrombosis (DVT) patients. Computed tomography venography (CTV) can provide excellent road map for varicose vein (VV) surgery without significant complications. It

cannot replace duplex ultrasound, but can provide powerful 3D images for designing operation as well as education and research.

-Congenital heart disease: Congenital heart disease, or a congenital heart defect, is a heart abnormality present at birth. The problem can affect:the heart walls, the heart valves, and the blood vessels. Though there are many different types of congenital heart defects, they can be divided into three main categories:first, in heart valve defects, the valves inside the heart that direct blood flow may close up or leak; this interferes with the heart's ability to pump blood correctly; second, In heart wall defects, the natural walls that exist between the left and right sides and the upper and lower chambers of the heart may not develop correctly, causing blood to back up into the heart or to build up in places where it doesn't belong; the defect puts pressure on the heart to work harder, which may result in high blood pressure; third, in blood vessel defects, the arteries and veins that carry blood to the heart and back out to the body may not function correctly. This can reduce or block blood flow, leading to various health complications.

-Congestive heart failure: sometimes it is known as heart failure (HF), occurs when the heart muscle doesn't pump blood as well as it should. Certain conditions, such as narrowed arteries in the heart (coronary artery disease, CAD) or high blood pressure, gradually leave the heart too weak or stiff to fill and pump effectively.

-Conjunctivochalasis: this is defined as a redundant, nonedematous conjunctiva that causes a wide variety of symptoms ranging from completely asymptomatic, to worsening of an unstable tear film, and when severe, a real mechanical disruption of tear flow.

-Connective tissue disorder: this is any disease affecting the parts of the body that connect the structures of the body together.

-Cor pulmonale: a condition causes the right side of the heart to fail. Long-term high blood pressure in the arteries of the lung and right ventricle of the heart lead to cor pulmonale. When the right side of the heart is not pumping blood to the lungs as well as normal, is also called cor pulmonale or pulmonary heart disease.

-Corneal ulcer: this is a painful open sore on the cornea that can cause loss of vision and even blindness. A corneal ulcer appears as a grey to white cloudy or translucent area on the normally transparent cornea. Corneal ulcers may sometimes be too small to see without sufficient magnification and lighting. Corneal ulcers are divided into infectious and non-infectious ulcers.

-Coronary artery disease (CAD): it is a disorder of the heart and the blood vessels. Coronary artery disease (CAD) begins with progressive endothelial injury, inflammatory oxidative stress, diminution of nitric oxide production, foam cell formation, and development of plaques that may rupture to cause a myocardial infarction (MI) or stroke.

-Coronary artery spasm: this is a temporary tightening (constriction) of the muscles in the wall of one of the arteries that sends blood to the heart.

-Coronary endothelial dysfunction: this is a type of non-obstructive coronary artery disease (CAD) in which there are no heart artery blockages, but the large blood vessels on the heart's surface constrict (narrow) instead of dilating (opening). This condition tends to affect more females than males and results in chronic chest pain.

-Cortical blindness: it is defined as visual loss with intact pupillary light responses in the absence of retinal or optic nerve lesions to explain the blindness; diffuse lesions of the cerebral cortex should be suspected when this combination of findings is identified.

-C-reactive protein (CRP): it is an acute-phase protein that serves as an early marker of inflammation or infection. The protein is synthesized in the liver and is normally found at concentrations of less than 10 mg/L in the blood. During infectious or inflammatory disease states, C-reactive protein (CRP) levels rise rapidly within the first 6 to 8 hours and peak at levels of up to 350–400 mg/L after 48 hours. C-reactive protein (CRP) binds to phosphocholine expressed on the surface of damaged cells, as well as to polysaccharides and peptidoglycans present on bacteria, parasites and fungi. This binding activates the classical complement cascade of the immune system and modulates the activity of phagocytic cells, supporting the role of C-reactive protein (CRP) in the opsonization (i.e. the process by which a pathogen is marked for ingestion and destruction by a phagocyte) of infectious agents and dead or dying cells. When the inflammation or tissue destruction is resolved, C-reactive protein (CRP) levels fall, making it a useful marker for monitoring disease activity. C-reactive protein (CRP) has been most widely

measured using enzyme-linked immunosorbent assays (ELISA), immunoturbidimetry, or antibody-based nephelometric assays, which are typically sensitive to concentrations of 5-20 mg/L. Recent awareness of the utility of measuring C-reactive protein (CRP) as a risk factor for cardiovascular disease (CVD) has led to the development of high-sensitivity C-reactive protein (hs-CRP) assays to detect lower levels of C-reactive protein (CRP); these assays are sensitive to 0.5–10 mg/L.

-Creatine: it is a compound formed in protein metabolism and present in much living tissue. It is involved in the supply of energy for muscular contraction.

- Creatinine: it is a compound which is produced by metabolism of creatine and excreted in the urine.

-Creatine kinase (CK): creatine phosphokinase (CPK), or simply creatine kinase (CK), is an enzyme that helps regulate the concentration of adenosine triphosphate (ATP) within a cell. Creatine kinase (CK) catalyzes the conversion of creatine and uses adenosine triphosphate (ATP) to create phosphocreatine (PCr) and adenosine diphosphate (ADP). Creatine kinase (CK), an enzyme protein found in the heart, brain, skeletal muscle, and other tissues. Increased amounts of it released into the blood when a muscle damage present.

-Creatine kinase MB: creatine kinase (CK), formerly known as creatine phosphokinase, is an intracellular enzyme present in greatest amounts in skeletal muscle, myocardium, and brain; smaller amounts occur in other visceral tissues. Creatine kinase (CK) is a dimeric molecule composed of two subunits designated M and B. Combinations of these subunits form the isoenzymes CK–MM, CK–MB, and CK–BB. A significant concentration of creatine kinase MB (CK–MB) isoenzyme is found almost exclusively in the myocardium, and the appearance of elevated creatine kinase MB (CK–MB) levels in serum is highly specific and sensitive for myocardial cell wall injury. Normal reference values for serum creatine kinase MB (CK–MB) range from 3 to 5% (percentage of total CK) or 5 to 25 IU/L.

-CURB-65: it is also known as the **CURB** criteria, is a clinical prediction rule that has been validated for predicting mortality in community-acquired pneumonia and infection of any site.

-CXCL9: or C-X-C motif chemokine 9 precursor, this is a cytokine that affects the growth, movement, or activation state of cells that participate in immune and inflammatory response. It is chemotactic for activated T-cells.

-CXCL10: or C-X-C motif chemokine 10, also known as Interferon gamma-induced protein 10 (IP-10) or small-inducible cytokine B10, it is an inflammatory chemokine and it binds to CXCR3 to mediate immune responses through the activation and recruitment of leukocytes such as T cells, eosinophils, monocytes and natural killer (NK) cells.

- CXCL11: or C-X-C motif chemokine 11, it is a small cytokine called interferon-inducible T-cell alpha chemoattractant (I-TAC) and interferon-gamma-inducible protein 9 (IP-9).

-Cyanosis: this is a condition in which the extremities-usually the hands, feet, fingers, and/or toes developing a distinctive bluish discoloration for not receiving enough oxygen-rich blood.

-Cyst: cysts usually noncancerous and having a sac-like structure can be containing fluid, pus, or gas.

-Cystoid macular edema (CME): this is a painless disorder which affects the central retina or macula. When this condition is present, multiple cyst-like (cystoid) areas of fluid appear in the macula and cause retinal swelling or edema.

-Cytochrome P450 (CYP): this is a super family of phase I enzyme in the biotransformation of xenobiotics and medications. Most medications undergo deactivation by CYP, and then are eliminated through either bile or kidneys from the body. CYP isozymes play a crucial role in drug interactions that may result in enhanced toxicity, reduced efficacy or onset of adverse reactions. On the other hand, many agents affecting CYP expression and activity may alter metabolic rate of different medications co-administered. Therefore, the molecular basis, regulation by inducers or inhibitors, and pharmacologic reaction of specific CYP isozymes are the key issue of biochemical mechanisms, pharmaceutical development and safe use of various medications.

-Cytochrome P450 family 3 subfamily A member 4 (CYP3A4): cytochromes P450 (CYPs) represent a diverse group of heme-thiolate proteins found in almost all organisms. CYPs share a

common protein fold but differ in substrate selectivity and catalyze a wide variety of monooxygenation reactions via activation of molecular oxygen. Among 57 human P450s, the 3A4 isoform (CYP3A4) is the most abundant and the most important because it metabolizes the majority of the administered drugs.

-Cytokines: they are small, non-structural proteins with low molecular weights which have a complex regulatory impact on inflammation and immunity. It has long been regarded that development of immune and inflammatory response comprises hematopoietic cells, lymphoid cell, and various pro-inflammatory and anti-inflammatory cells, and cytokines mediate the complex interactions of these cells. Cytokines are the intercellular messengers in the immune system where they integrate function of several cell types in various body compartments into a coherent immune response. According to their secretion they are classified into lymphokines (cytokines that are secreted by T cells and regulate the immune response), monokines (cytokines made by monocytes), proinflammatory cytokines (cytokines that amplify and perpetuate the inflammatory process), growth factors (cytokines that promote cell survival and result in structural changes in the airways), chemokines (cytokines that are chemotactic for inflammatory cells), and anti-inflammatory cytokines (cytokines that negatively modulate the inflammatory response). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines.

-Cytokine release syndrome (CRS): this is a systemic inflammatory response that can be induced by a variety of factors such as infections and certain drugs.

-Cytomegalovirus (CMV): Human cytomegalovirus (HCMV) is a prevalent infectious agent affecting the health of the human population. In a simple sense, human cytomegalovirus (HCMV) pathogenesis can be broken down to that observed in immunocompetent hosts and that observed in immunocompromised hosts. Human cytomegalovirus (HCMV) pathogenesis in immunologically normal individuals is usually considered less severe when compared to the morbidity and mortality seen in immunocompromised individuals. Severe complications such as pneumonia, retinitis, hepatitis, encephalitis, and disseminated human cytomegalovirus (HCMV) disease with multiorgan involvement are extremely rare in immunologically healthy people. The majority of human cytomegalovirus (HCMV) infections in the immunocompetent are asymptomatic; however, primary infection can result in a mononucleosis-like syndrome. In

addition, data from both clinical and experimental studies now define a potentially strong role for human cytomegalovirus (HCMV) infection in the development and/or severity of inflammatory cardiovascular diseases (CVDs), and human cytomegalovirus (HCMV) infection has been linked to the development of certain types of cancers. In immunocompromised individuals, human cytomegalovirus (HCMV) infection can result in severe disease. For example, in patients undergoing immunosuppressive therapies, such as in transplant and cancer patients, and in patients with acquired immunodeficiency syndrome (AIDS), human cytomegalovirus (HCMV) infection is of significant clinical concern. In addition, HCMV is one of the leading infectious agents causing congenital infection. Thus individuals with suppressed or underdeveloped immune systems are prone to severe disease following primary human cytomegalovirus (HCMV) infection or reactivation of latent virus.

-Cytopenia: it is a deficiency of cellular elements of the blood particularly deficiency of a specific element (as granulocytes in granulocytopenia).

-D-dimer (DD): it is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. D-dimer is the degradation product of crosslinked (by factor XIII) fibrin. It reflects ongoing activation of the hemostatic system. The reference concentration of D-dimer is < 250 ng/mL, or < 0.4 mcg/mL.

-Dead space ventilation (VD): dead space is the volume of gas in the airways and lung that participates in tidal breathing but does not participate in gas exchange.

-Deep vein thrombosis (DVT): it is the formation of blood clots (thrombi) in the deep veins. It commonly affects the deep leg veins (such as the calf veins, femoral vein, or popliteal vein) or the deep veins of the pelvis. It is a potentially dangerous condition that can lead to preventable morbidity and mortality.

-Delirium: this is an acutely disturbed state of mind characterized by restlessness, illusions, and incoherence, occurring in intoxication, fever, and other disorders.

-Demyelination: this is a degenerative process that erodes away the myelin sheath that normally protects nerve fibers.

-Dendritic cells (DCs): they are antigen-presenting cells (also known as accessory cells) of the mammalian immune system. Their main function is to process antigen material and present it on the cell surface to the T cells of the immune system. They act as messengers between the innate and the adaptive immune systems.

-Depression: or major depressive disorder, this is a mood disorder causing a persistent feeling of sadness and loss of interest.

-Diabetes mellitus (DM): it is also known as simply diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. This high blood sugar produces the symptoms of frequent urination, increased thirst, and increased hunger. Untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus: first, Type 1 DM results from the body's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown; second, Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise; third, Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood glucose level.

-Diabetic ketoacidosis (DKA): this disease is characterized by high blood glucose (Glc) with the presence of ketones in the urine and bloodstream, often caused by taking too little insulin or during illness.

-Diabetic macular edema (DME): it is manifested as retinal thickening caused by the accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers. It is believed to be a result of hyperpermeability of the retinal vasculature. Diabetic macular edema can be present with any level of diabetic retinopathy.

-Diabetic retinopathy: this is a diabetes complication that affects eyes. It's caused by damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina), causing blindness.

-Diffusion capacity (DL): also called transfer factor, measures the capacity to transfer gas from alveolar spaces into the alveolar capillary blood.

-Digital clubbing: it is also called nail clubbing or clubbing, a deformity of the finger or toe nails associated with a number of diseases, mostly of the heart and lungs.

-Digitalis: it is a drug prepared from the dried leaves of foxgloves and containing substances (notably digoxin and digitoxin) that stimulate the heart muscle.

-Dilated cardiomyopathy (DCM): it is defined as left ventricular (LV) dilation and systolic dysfunction in the absence of coronary artery disease (CAD) or abnormal loading conditions proportionate to the degree of left ventricular (LV) impairment.

-Diplopia: it indicates technical term for double vision.

-Direct Coombs test: it is used to test for autoimmune hemolytic anemia—that is, a condition where the immune system breaks down red blood cells (RBCs), leading to anemia. The direct Coombs test is used to detect antibodies or complement proteins attached to the surface of red blood cells (RBCs).

-Disseminated intravascular coagulation (DIC): it is a serious disorder in which the proteins that control blood clotting becoming overactive. It is a condition in which small blood clots develop throughout the bloodstream, blocking small blood vessels. The increased clotting depletes the platelets and clotting factors needed to control bleeding, causing excessive bleeding.

-Dopamine (DA): it is a contraction of 3,4-dihydroxyphenethylamine, a compound present in the body as a neurotransmitter and a precursor of other substances including adrenaline. Dopamine injection (Intropin) is used to treat certain conditions that occur when one is in shock, which may be caused by heart attack, trauma, surgery, heart failure, kidney failure, and other serious medical conditions.

-Driving pressure: it is calculated by plateau pressure minus positive end-expiratory pressure (PEEP). Driving pressure is the plateau airway pressure minus positive end-expiratory pressure

(PEEP). It can also be expressed as the ratio of tidal volume to respiratory system compliance, indicating the decreased functional size of the lung observed in patients with acute respiratory distress syndrome (ARDS).

-Dry gangrene: it is characterized by dry and shriveled skin ranging in color from brown to purplish blue or black; develop slowly and occurring most commonly in people having arterial blood vessel disease, such as atherosclerosis, or in people with diabetes.

-Dyslipidemia: it is defined as elevated total or low-density lipoprotein (LDL) cholesterol levels, or low levels of high-density lipoprotein (HDL) cholesterol, is an important risk factor for coronary heart disease (CHD) and stroke.

-Distal ischemic gangrene: symmetrical peripheral gangrene is characterized as acral (distal extremity) ischemic limb injury affecting two or more extremities, without large vessel obstruction, typically in a symmetrical fashion. Risk factors include hypotension, disseminated intravascular coagulation (DIC), and acute ischemic hepatitis (shock liver). In contrast, venous limb gangrene is characterized by acral ischemic injury occurring in a limb with deep vein thrombosis. Both symmetrical peripheral gangrene and venous limb gangrene present as acral limb ischemic necrosis despite presence of arterial pulses. The coexistence of symmetrical peripheral gangrene and venous limb gangrene is rare, with potential to provide pathophysiological insights.

-Dysarthria: it is difficult or unclear articulation of speech that is otherwise linguistically normal.

-Dysphagia: it is difficulty or discomfort in swallowing, as a symptom of disease.

-Dysphasia: this is a language disorder marked by deficiency in the generation of speech, and sometimes also in its comprehension, due to brain disease or damage.

-Dysphoria: this is a state of unease or generalized dissatisfaction with life.

-Dyspnea: Dyspnea is a sign of serious disease of the airway, lungs, or heart. It is defined as shortness of breath, often described as an intense tightening in the chest, air hunger, difficulty breathing, breathlessness or a feeling of suffocation.

-Eales Disease: this is a rare disorder of sight that appears as an inflammation and white haze around the outer coat of the veins in the retina. The disorder is most prevalent among young males and normally affects both eyes.

-Ebola: an infectious and frequently fatal disease marked by fever and severe internal bleeding, spread through contact with infected body fluids by a filovirus (*Ebola virus*), whose normal host species is unknown.

-Eccentric contractions: this is when the total length of the muscle increasing as tension produced.

-Echocardiography: echocardiography, or echo, is a painless test that uses sound waves to create moving pictures of the heart. The pictures show the size and shape of the heart. They also show how well the heart's chambers and valves are working.

-Egophony (British English, aegophony): it is an increased resonance of voice sounds heard when auscultating the lungs, often caused by lung consolidation and fibrosis. It is due to enhanced transmission of high-frequency sound across fluid, such as in abnormal lung tissue, with lower frequencies filtered out.

-Ejection fraction (EF): it is a measurement, expressed as a percentage, of how much blood the left ventricle pumps out with each contraction.

-Electrocardiogram (ECG or EKG): this records the electrical signal from the heart to check for different heart conditions. Electrodes are placed on the chest to record the heart's electrical signals, which cause the heart to beat. The signals are shown as waves on an attached computer monitor or printer.

-Electrocardiography: it is the measurement of electrical activity in the heart and its recording as a visual trace (on paper or on an oscilloscope screen), using electrodes placed on the skin of the limbs and chest.

-Electromyography (EMG): this is a test that is performed to diagnose neuromuscular disorders (medical conditions that affect the nerves and muscles). An electromyography (EMG) records the electrical signals that travel from nerves to the muscles in the arms and legs. It may be

performed for people experiencing certain symptoms, such as tingling, numbness, muscle weakness, muscle pain or cramping. There are two parts to the testing. The first part, called nerve conduction studies (NCS), involve small patches (surface electrodes) that are placed on the skin over nerves at various locations. A stimulator is used to apply an electrical impulse to the nerve being tested and the nerve's resulting electrical activity is recorded by the surface electrodes. The distance and time it takes for impulses to travel between electrodes are used to determine the speed of the nerve signals. The second part of the testing is the actual electromyography (EMG) portion. This involves a physician inserting a very thin wire electrode into the muscle. The electrode works like an antennae and picks up the electrical activity given off by your muscles. This activity appears on a nearby monitor, and may be heard through a speaker. There are no electrical stimulations during this part of the study. After placement of the electrodes, patient may be asked to contract the muscle, for example bending patient arm. The electrical activity seen on the monitor provides information about how your muscle is working. This test is used to diagnose nerve and/or muscle damage or destruction.

-Electroneuronography or electroneurography (ENoG) is a neurological non-invasive test used to study the facial nerve in cases of muscle weakness in one side of the face (Bell's palsy). The technique of electroneuronography was first used by Esslen and Fisch in 1979 to describe a technique that examines the integrity and conductivity of peripheral nerves. In modern use, electroneurography (ENoG) is used to describe study of the facial nerve, while the term nerve conduction study is employed for other nerves. It consists of a brief electrical stimulation of the nerve in one point underneath the skin, and at the same time recording the electrical activity (compound action potentials) at another point of the nerve's trajectory in the body. The response is displayed in a cathode ray tube (CRT) or through the video monitor of a computer. The stimulation as well as the recording are carried out by disc electrodes taped to the skin, and the technician may use electrically conducting gel or paste to bolster the signals being input and output. Alternatively, the recording electrodes may also be used to pick up the electrical activity of a muscle innervated by that nerve. In such instances electroneuronography is closely related to electromyography. It is performed by an audiologist, who carries out tests to compare the two sides of the face. The stimulation electrode is located at the stylomastoid foramen and the recording electrode is located near the nasolabial fold. The electroneurography (ENoG) test is the only objective measure of facial nerve integrity.

-Embryo implantation: a process in which a developing embryo, moves as a blastocyst through a uterus, makes contact with the uterine wall and remains attached to it until birth.

-Empyema: it is the collection of pus in a cavity in the body, especially in the pleural cavity.

-Enkephalin: also called an enkephalin, it is a pentapeptide involved in regulating nociception in the body; the enkephalins are termed endogenous ligands, as they are internally derived and bind to the body's opioid receptors.

-Encephalitis: it refers to an acute, usually diffuse, inflammatory process affecting the brain. While meningitis is primarily an infection of the meninges, a combined meningoencephalitis may also occur. An infection by a virus is the most common and important cause of encephalitis, although other organisms may sometimes cause an encephalitis. An encephalitic illness caused by alteration of normal immune function in the context of a previous viral infection or following vaccination is also well recognized (acute disseminated encephalomyelitis, ADEM). An infectious encephalitis may also be difficult to distinguish from an encephalopathy that may be associated with numerous metabolic causes.

-Encephalitis lethargica (EL): this is also known as Economo's disease and sleeping disease. The clinical manifestations are characterized by atypical encephalitis that predominantly affected the basal ganglia resulting in movement, psychiatric, and sleep disorders.

-Encephalopathy: this is a disease in which the functioning of the brain is affected by some agent or condition (such as viral infection or toxins in the blood).

-Endosome: it is membrane-bound vesicle, formed via a complex family of processes collectively known as endocytosis, and found in the cytoplasm of virtually every animal cell. The basic mechanism of endocytosis is the reverse of what occurs during exocytosis or cellular secretion. It involves the invagination (folding inward) of a cell's plasma membrane to surround macromolecules or other matter diffusing through the extracellular fluid. The encircled foreign materials are then brought into the cell, and following a pinching-off of the membrane (termed budding), are released to the cytoplasm in a sac-like vesicle. The size of vesicles varies, and those larger than 100 nanometers in diameter are typically referred to as vacuoles.

-Endothelial injury or dysfunction: this is a common and early event in cardiovascular disease (CVD) happening when damage occurring to the vascular endothelium, the thin layer of cells that lines blood vessels, this damage impairing the function of the endothelium.

-Endotheliitis: this is an immune response within the endothelium in blood vessels, in which they become inflamed.

-End stage heart failure: Patients with end stage heart failure fall into stage D of the ABCD classification of the American College of Cardiology (ACC)/American Heart Association (AHA), and class III–IV of the New York Heart Association (NYHA) functional classification; they are characterized by advanced structural heart disease and pronounced symptoms of heart failure (HF) at rest or upon minimal physical exertion, despite maximal medical treatment according to current guidelines. This patient population has a 1-year mortality rate of approximately 50% and requires special therapeutic interventions. Every attempt should be made to identify and correct reversible causes for a worsening of heart failure, such as poor patient compliance, myocardial ischaemia, tachy- or bradyarrhythmias, valvular regurgitation, pulmonary embolism, infection, or renal dysfunction.

-End stage renal disease (ESRD): it is the last stage of chronic kidney disease (CKD); when ones kidneys fail, means they have stopped working well enough for human-being to survive without dialysis or a kidney transplant.

-Endothelial dysfunction: this is a type of non-obstructive coronary artery disease (CAD) in which there are no heart artery blockages, but the large blood vessels on the heart's surface constrict (narrow) instead of dilating (opening). This condition tends to affect more women than men and causes chronic chest pain.

-Endothelin: endothelin-1 (ET-1) is the most potent vasoconstrictor agent currently identified, and it was originally isolated and characterized from the culture media of aortic endothelial cells. Two other isoforms, termed endothelin-2 and endothelin-3, were subsequently identified, along with structural homologues isolated from the venom of *Actractapis eng-addensis* known as the sarafotoxins. Pulmonary arterial hypertension (PAH) is a progressive and fatal condition characterized by a sustained increase in pulmonary vascular resistance, leading to right ventricular failure and premature death. Endothelin-1 (ET-1) has been implicated as a mediator

of increased vascular tone and vascular remodeling in pulmonary hypertension. There is increasing evidence that pulmonary vascular smooth muscle cells, as well as endothelial cells, synthesize and release endothelin-1 (ET-1), particularly when stimulated by cytokines. Endothelin-1 (ET-1) is also produced in the lung in response to increased pressure. Expression of endothelin-1 messenger ribonucleic acid (ET-1 mRNA) increases in pulmonary vascular endothelial cells of patients with pulmonary hypertension. In patients with pulmonary hypertension, a significant correlation between serum levels of endothelin (ET) and pulmonary vascular resistance, right atrial pressure, and oxygen saturation has been reported. In thromboembolic pulmonary hypertension, it was shown that there is upregulation of the ET_B receptor in the pulmonary artery.

-Endotracheal intubation: this is a medical procedure in which a tube is placed into the windpipe (trachea) through the mouth or nose. In most emergency conditions, it is placed through the mouth.

-Enterovirus (EV): enteroviruses are a group of over 250 naked icosahedral virus serotypes that have been associated with clinical conditions that range from intrauterine enterovirus transmission with fatal outcome through encephalitis and meningitis, to paralysis.

-Enzyme-linked immunosorbent assay (ELISA): this assay (ELISA) is a rapid immunochemical test that involves an enzyme used for measuring a wide variety of tests of body fluids. Enzyme-linked immunosorbent assay (ELISA) tests detect substances that have antigenic properties, primarily proteins rather than small molecules and ions, such as glucose (Glc) and potassium. Some of these substances include hormones, bacterial antigens, and antibodies. Enzyme-linked immunosorbent assay (ELISA) tests are generally highly sensitive and specific.

-Eosinophilic myocarditis: this is a rare and potentially lethal disease characterized by eosinophil infiltration of the myocardium. The association between eosinophilia and myocardial injury is well established and may present several etiologies, from hypersensitivity and autoimmune diseases to neoplasias and infections. In some cases the etiology remains unknown, and it is denominated idiopathic hypereosinophilic syndrome. Clinical manifestations present a wide spectrum, ranging from mild symptomatology to severe symptoms such as retrosternal pain, rhythm disturbances, and sudden death. The definitive diagnosis is made through

endomyocardial biopsy. Cardiac magnetic resonance imaging is a valid alternative, identifying the main structural changes caused by myocarditis.

-Epilepsy: it is a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain.

-Epstein–Barr Virus (EBV), it is also called human herpesvirus 4, a lymphotropic herpesvirus and the causative agent of infectious mononucleosis (IM). It was first discovered in cells isolated from African Burkitt's lymphoma, later, it was recognized that it is highly prevalent worldwide. Similar to other herpesviruses, following a primary infection, the Epstein Barr virus (EBV) has a latency phase where it infects epithelial cells, enters the circulating B lymphocyte, and persists for the life in a latent state. According to epidemiological studies, the Epstein Barr virus (EBV) is estimated to be positive in more than 90% of the world's populations. Typically, the primary infection is asymptomatic and occurs during childhood. However, the infection could lead to infectious mononucleosis (IM) if it occurs in adults. In addition, this virus has been linked to a wide range of malignancies, such posttransplant lymphoproliferative diseases (PTLDs), nasopharyngeal carcinoma (NPC), Hodgkin's lymphoma, and gastric carcinoma (MS). The oral route is the primary route of the Epstein Barr virus (EBV) transmission. However, it has been reported that organ transplantation and blood transfusion can lead to Epstein Barr virus (EBV) spread. Infected epithelial cells can also be found in the uterine cervix or in the semen, suggesting the possibility of Epstein Barr virus (EBV) spread through sexual contact.

-Erythema: superficial reddening of the skin, usually in patches, as a result of injury or irritation causing dilatation of the blood capillaries.

-Erythrocyte sedimentation rate (ESR): An erythrocyte sedimentation rate (ESR) is a type of blood test that measures how quickly erythrocytes [red blood cells (RBCs)] settle at the bottom of a test tube that contains a blood sample. Normally, red blood cells (RBCs) settle relatively slowly. A faster-than-normal rate may indicate inflammation in the body. Inflammation is part of body immune response system. It can be a reaction to an infection or injury. Inflammation may also be a sign of a chronic disease, an immune disorder, or other medical condition. Erythrocyte

sedimentation rate (ESR) is a test detecting the presence of inflammation caused by one or more conditions such as infections, tumors or autoimmune diseases.

-Erythropoietic distress: i.e., stress erythropoiesis is resulting in the rapid production of new red blood cells (RBCs) and characterized by the rapid expansion of the erythroblast progenitor pool and marked transient elevation of reticulocyte numbers in the circulation.

-Extensor plantar responses: or Babinski reflex, this is stroking the sole produces extension (dorsiflexion) of the big toe, often with extension and abduction (fanning) of the other toes. This is an abnormal response.

-Familiar periodic paralysis: a rare autosomal dominant condition characterized by episodes of flaccid paralysis with loss of deep tendon reflexes and failure of muscle to respond to electrical stimulation.

-Ferritin: it is a protein produced in mammalian metabolism which serves to store iron in the tissues, i.e. iron stores in the body exist primarily in the form of ferritin. The ferritin molecule is an intracellular hollow protein shell composed of 24 subunits surrounding an iron core that may contain as many as 4000-4500 iron atoms. In the body, small amounts of ferritin are secreted into the plasma. The concentration of this plasma (or serum) ferritin is positively correlated with the size of the total body iron stores in the absence of inflammation. A low serum ferritin value reflects depleted iron stores, but not necessarily the severity of the depletion as it progresses. Normal ferritin concentrations vary by age and sex. However, ferritin is a positive acute phase response protein whereby concentrations increase during inflammation and thereby no longer reflect the size of the iron store.

-Fetal distress: compromise of a fetus during the antepartum period (before labor) or intrapartum period (during the birth process). The term fetal distress is commonly used to describe fetal hypoxia (low oxygen levels in the fetus), which can result in fetal damage or death if it is not reversed or if the fetus is not promptly delivered. Fetal distress can be detected via abnormal slowing of labor, changes in fetal heart rate, the presence of meconium (dark green fecal material from the fetus) or other abnormal substances in the amniotic fluid, or fetal monitoring with an electronic device that shows a fetal scalp pH of less than 7.2.

-Fever: although a fever technically is any body temperature above the normal of 98.6 F (37 C), in practice a person is usually not considered to have a significant fever until the temperature is above 100.4 F (38 C).

-Fibrinogen: it is a plasma protein that is produced in the liver and is converted into fibrin during blood clot formation.

-Fibrosing mediastinitis (FM): it is also known as mediastinal fibrosis or sclerosing mediastinitis, is an uncommon, benign and progressive condition characterized by an invasive proliferation of fibrous tissue within the mediastinum.

-Firm induration: this is localized hardening of soft tissue of the body. The area of the hands or feet, or both becomes firm, but not as hard as bone.

-Flaccid areflexic paralysis: this is a specific type of paralysis where muscles do not contract at all.

-Focal neuropathy: it is a condition in which one typically has damage to single nerves, most often in hand, head, torso, or leg.

-Foreign body aspiration: this occurs when a foreign body enters the airways and causes choking.

-Fraction of inspired oxygen (FiO₂): it is the molar or volumetric fraction of oxygen in the inhaled gas.

-Fragment crystallizable region (Fc region): this is the tail region of an antibody (Ab) that interacts with cell surface receptors called Fc receptors and some proteins of the complement system. This property allows antibodies (Abs) to activate the immune system.

- -1Frameshift: Programmed ribosomal frameshifting is involved in the expression of certain genes in a wide range of organisms such as viruses, bacteria and eukaryotes including humans. In this process, the ribosome switches to an alternative frame at a specific site in response to special signals in the messenger ribonucleic acid (mRNA). Programmed frameshifting plays a significant role in morphogenesis, autogenous control and in producing alternative enzymatic activities. The most common frameshift is a -1 frameshift, in which the ribosome slips a single

nucleotide in the upstream direction. The major elements of -1 frameshifting consist of a slippery site, where the ribosome changes reading frames, and a stimulatory ribonucleic acid (RNA) structure such as a pseudoknot or a stem-loop located a few nucleotides downstream. It is generally accepted that ribosomes pause at -1 frameshifts, but it was reported that pausing is not sufficient to mediate frameshifting. Most slippery sites consist of a heptameric sequence of the form X XXY YYZ in the incoming 0-frame, but there are other slippery sequences that do not conform to this motif. The slippery heptamer is separated from the stimulatory structure by a sequence of 5–9 nt (i.e., nucleotides), the so-called spacer. The length of the spacer is known to influence the efficiency of frameshifting. Frameshifts typically produce fusion proteins in which the N- and C-terminal domains are encoded by overlapping open reading frames (ORFs).

-Frostbite: it is injury to body tissues caused by exposure to extreme cold, typically affecting the nose, fingers, or toes and often resulting in gangrene.

-Fulminant myocarditis (FM): it is an uncommon syndrome characterized by sudden and severe diffuse cardiac inflammation often leading to death resulting from cardiogenic shock, ventricular arrhythmias, or multiorgan system failure.

-Functional asplenia: asplenia means the absence of a spleen. Asplenia can occur in a variety of clinical settings, and it can refer to an anatomic absence of the spleen or functional asplenia secondary to a variety of disease states. Functionally, the spleen's primary physiologic role is the filtration and processing of senescent blood cells (predominantly red blood cells or RBCs) and immunologically helps protect against encapsulated microorganisms and response to infectious pathogens. It contains both hematopoietic and lymphopoietic elements, providing a basis for extramedullary hematopoiesis when necessary. The spleen has two functionally and histologically distinct tissues where these processes take place: the white pulp and the red pulp. The white pulp has a large mass of lymphoid tissue that produces antibodies against recognized antigens, whereas the red pulp has a tight network of sinusoids called the cord of Billroth which helps in blood filtration. As the body's largest filter of blood, it helps to remove old red blood cells (RBCs) from the circulation aiding in the removal of bloodborne microorganisms. Asplenia can be caused by damage to the white pulp, the red pulp or both. The spleen is a direct and

indirect site of potential toxicity that can secondarily arise from underlying disease processes or infection.

-Functional residual capacity (FRC): it is the volume of air present in the lungs at the end of passive expiration. At functional residual capacity (FRC) the opposing elastic recoil forces of the lungs and chest wall are in equilibrium and there is no exertion by the diaphragm or other respiratory muscles.

-Gallstone disease: this refers to the condition where gallstones are either in the gallbladder or common bile duct. The presence of stones in the gallbladder is referred to as cholelithiasis.

-Gap 1 phase: this is the first of four phases of the cell cycle that takes place in eukaryotic cell division.

-Gastrin releasing peptide (GRP): it is a regulatory human peptide that elicits gastrin secretion and regulates gastric acid secretion and enteric motor function. The post-ganglionic fibers of the vagus nerve that innervate the G cells of the stomach release gastrin releasing peptide (GRP), which induces the G cells to secrete gastrin.

-Gaucher disease: this is a rare hereditary disorder of lipid metabolism caused by an enzyme deficiency and characterized by enlargement of the spleen and liver, bone lesions, and sometimes neurological impairment.

-Giant cell myocarditis: this is a rare cardiovascular disorder that occurs for unknown reasons (idiopathic). It is characterized by inflammation of the heart muscle (myocardium), a condition referred to as myocarditis. Inflammation is caused by widespread infiltration of giant cells associated with other inflammatory cells and heart muscle cell destruction. Giant cells are abnormal masses produced by the fusion of inflammatory cells called macrophages. Individuals with giant cell myocarditis may develop abnormal heartbeats, chest pain and, eventually, heart failure. Many individuals eventually require a heart transplant. The disorder most often occurs in young adults.

-Glutaric academia (GA): this is an inadequate levels of an enzyme that helping breaking down the amino acids lysine (Lys), hydroxylysine, and tryptophan (Trp), the resulting excessive levels

of these amino acids (AAs) and their intermediate breakdown products accumulate in the blood (acidemia) and in the urine (aciduria) leading to glutaric academia.

-Glycogen storage disease (GSD, also glycogenosis and dextrinosis): this is a metabolic disorder caused by enzyme deficiencies affecting either glycogen synthesis, glycogen breakdown or glycolysis (glucose breakdown), occurs typically in muscles and/or liver cells.

-Gonorrhea: colloquially known as the clap, is a sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*. Infection may involve the genitals, mouth, and/or rectum. Infected men may experience pain or burning with urination, discharge from the penis, or testicular pain. Infected women may experience burning with urination, vaginal discharge, vaginal bleeding between periods, or pelvic pain. Complications in women include pelvic inflammatory disease and in men include inflammation of the epididymis. Many of those infected, however, have no symptoms. If untreated, gonorrhea can spread to joints or heart valves.

-Graft vs host disease (GVHD): this occurs when immune cells transplanted from a donor (the graft) recognize the recipient (the host) as foreign, thereby initiating an immune reaction that causes disease.

-Granulocyte-colony stimulating factor (G-CSF or GCSF): it is known as colony-stimulating factor 3 (CSF 3). It is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Granulocyte colony-stimulating factor is a colony-stimulating factor that stimulates the production of neutrophils (a type of white blood cell). Functionally, it is a cytokine and hormone, a type of colony-stimulating factor, and is produced by a number of different tissues. Granulocyte colony stimulating factor (G-CSF) is produced by endothelium, macrophages, and a number of other immune cells. Granulocyte colony-stimulating factor (G-CSF) is a cytokine that belongs to the family of drugs called hematopoietic (blood-forming) agents. Also known as filgrastim.

-Gut dysbiosis: it is an imbalance in the composition and metabolic capacity of gut microbiota. Dysbiosis can be defined through the loss or gain of bacteria that either promote health or disease, respectively.

-H1N1 virus: the H1N1 virus (swine flu) is an infection of the nose, throat, and lungs. It is caused by the H1N1 influenza virus.

-Haematoma: this is a solid swelling of clotted blood within the tissues.

-Haemin or hemin: it is haematin chloride; insoluble reddish-brown crystals formed by the action of hydrochloric acid on haematin in a test for the presence of blood. It is a red-brown to blue-black crystalline salt $C_{34}H_{32}N_4O_4FeCl$ derived from oxidized heme but usually obtained in a characteristic crystalline form from hemoglobin.

-Haemodynamic instability: it is defined as perfusion failure, represented by clinical features of circulatory shock and advanced heart failure (HF). It may also be defined as 1 or more out-of-range vital sign measurements, such as low blood pressure.

-Hallervorden-Spatz syndrome: this is a genetic disorder characterized by progressive neurologic degeneration with the accumulation of iron in the brain.

-Haptoglobin: it is a protein present in blood serum which binds to and removes free haemoglobin from the bloodstream.

-Heat stroke: this is a condition marked by fever and often by unconsciousness, caused by failure of the body's temperature-regulating mechanism when exposed to excessively high temperatures.

-HELLP syndrome: this is a serious complication in pregnancy characterized by hemolysis, elevated liver enzymes and low platelet count occurring in 0.5 to 0.9% of all pregnancies and in 10-20% of cases with severe preeclampsia. Preeclampsia is defined as gestational hypertension associated with new-onset maternal or uteroplacental dysfunction at or after 20 weeks' gestation. Gestational hypertension. systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 . Blood pressure should be repeated to confirm true hypertension.

-Hematopoiesis: it is the formation of blood cellular components that occurs during embryonic development and throughout adulthood to produce and replenish the blood system.

-Hemiparesis/hemiplegia: hemiparesis, or unilateral paresis, is weakness of one entire side of the body. Hemiplegia is, in its most severe form, complete paralysis of half of the

body. Hemiparesis and hemiplegia can be caused by different medical conditions, including congenital causes, trauma, tumors, or stroke.

-Hemoconcentration: this indicates a decrease in plasma volume, which causes a simultaneous increase in the level of red blood cells (RBCs) and other commonly tested constituents of the blood.

-Hemoglobin: this is the oxygen-binding protein within red blood cells (RBCs). It is a red protein responsible for transporting oxygen in the blood of vertebrates. Its molecule comprises four subunits, each containing an iron atom bound to a hem group.

-Hemolytic anemia: a disorder in which red blood cells are destroyed faster than they can be made.

-Hemolytic uremic syndrome (HUS): it is defined by the simultaneous occurrence of nonimmune hemolytic anemia, thrombocytopenia and acute renal failure. This leads to the pathological lesion termed thrombotic microangiopathy, which mainly affects the kidney, as well as other organs. Hemolytic uremic syndrome (HUS) is associated with endothelial cell injury and platelet activation, although the underlying cause may differ. Hemolytic uremic syndrome (HUS) is a group of blood disorders characterized by low red blood cells (RBCs), acute kidney failure, and low platelets.

-Hemophagocytic lymphohistiocytosis (HLH): it is also known as hemophagocytic syndrome (HPS), is a rare, life-threatening, hematologic disorder manifested by clinical findings of extreme inflammation and unregulated immune activation. In both its congenital (primary) and adult (secondary) forms, it is most often characterized by fevers, hepatomegaly or splenomegaly, and bi- or trilineage cytopenias. In addition, elevated liver enzymes, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia are commonly seen in hemophagocytic lymphohistiocytosis (HLH) patients.

-Hemoptysis: this is spitting up blood or blood-tinged sputum from the respiratory tract.

-Hemorrhagic shock: this is a condition of reduced tissue perfusion, resulting in the inadequate delivery of oxygen and nutrients necessary for cellular function.

-Heparin-induced thrombocytopenia: it is caused by antibodies (Abs) binding to complexes of heparin and platelet factor 4 (PF4), activating the platelets and promoting a prothrombotic state.

-Hepatic insufficiency: it refers to conditions in which the liver functions fall below the normal ranges.

-Hepatitis: the disease refers to an inflammatory condition of the liver. It's commonly caused by a viral infection, but there are other possible causes of hepatitis. These include autoimmune hepatitis and hepatitis that occurs as a secondary result of medications, drugs, toxins, and alcohol. Viral infections of the liver that are classified as hepatitis include hepatitis A, B, C, D, and E. A different virus is responsible for each type of virally transmitted hepatitis. Hepatitis A is always an acute, short-term disease, while hepatitis B, C, and D are most likely to become ongoing and chronic. Hepatitis E is usually acute but can be particularly dangerous in pregnant women.

-Hepatocyte growth factor (HGF): it is produced by stromal cells, and stimulates epithelial cell proliferation, motility, morphogenesis and angiogenesis in various organs via tyrosine phosphorylation of its receptor, c-Met. In fetal stages, hepatocyte growth factor (HGF)-neutralization, or *c-Met* gene destruction, leads to hypoplasia of many organs, indicating that hepatocyte growth factor (HGF) signals are crucial for organ development. Endogenous hepatocyte growth factor (HGF) is imperative for self-repair of injured livers, kidneys, lungs and so on. In addition, hepatocyte growth factor (HGF) exerts protective effects on epithelial and non-epithelial organs (including the heart and brain) via anti-apoptotic and anti-inflammatory signals. During organ diseases, plasma hepatocyte growth factor (HGF) concentrations noticeably elevated, while anti-hepatocyte growth factor (HGF) antibody infusion accelerated tissue destruction in rodents. Thus, endogenous hepatocyte growth factor (HGF) is necessary for minimization of diseases, while insufficient production of hepatocyte growth factor (HGF) results in organ failure.

-Herpes simplex virus (HSV): herpes an infection occurs by a herpes simplex virus (HSV). Oral herpes causing cold sores around the mouth or face. Genital herpes affects the genitals, buttocks or anal area.

-Herpes zoster (HZ): this is a herpesvirus that causes shingles and chickenpox.

-High-flow nasal cannula (HFNC): this therapy is an oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60 liters per minute.

-Human herpes virus (HHV): Herpesviridae is a large family of deoxyribonucleic acid (DNA) viruses that cause infections and certain diseases in animals, including humans. The members of this family are also known as herpesviruses. Herpesviruses are known to share six hallmark characteristics: ubiquity, latency, incurability, reactivation, unapparent infection, and opportunistic infection. Herpesviruses are very common within populations. Herpesviruses also cause latent infections. This is typical of this group of viruses, though the family name does not refer to latency. The ability of herpesviruses to exist within hosts in a state of concealment allows the viruses to reactivate at a later point in time. This characteristic of latency is what leads herpesviruses to ultimately be incurable. Although herpesviruses remain in latent states within most infected hosts, opportunistic herpesvirus infections often affect individuals with immunocompromised systems. Such individuals will experience more severe symptoms than would usually be seen. For example immunocompromised individuals who are infected with HSV-1 would experience severe orolabial sores that could evolve from papule to vesicle, ulcer, and crust stages on the lip. At least five species of the Herpesviridae – HSV-1 and HSV-2 (both of which can cause orolabial herpes and genital herpes), varicella zoster virus (the cause of chickenpox and shingles), Epstein–Barr virus (implicated in several diseases, including mononucleosis and some cancers), and cytomegalovirus – are extremely widespread among humans. More than 90% of adults have been infected with at least one of these, and a latent form of the virus remains in almost all humans who have been infected.

-Human immunodeficiency virus (HIV): this is a virus that attacks the body's immune system. If HIV is not treated, it can lead to AIDS (acquired immunodeficiency syndrome).

-Human T-cell lymphotropic virus 1 and 2: the human T-lymphotropic virus, human T-cell lymphotropic virus, or human T-cell leukemia-lymphoma virus (HTLV) family of viruses are a group of human retroviruses that are known to cause a type of cancer called adult T-cell leukemia/lymphoma and a demyelinating disease called HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP).

-Hyperammonemia (HA): this is a metabolic disturbance characterized by an excess of ammonia in the blood.

-Hyperbilirubinemia: it is a condition defined as elevated serum or plasma bilirubin levels above the reference range of the laboratory, due to disorders of bilirubin metabolism.

-Hypercapnia: it is also called hypercarbia and CO₂ retention, a condition of abnormally elevated carbon dioxide (CO₂) levels in the blood.

-Hypercapnic apnea: it is also known as hypercarbia and CO₂ retention, a condition of abnormally elevated carbon dioxide (CO₂) levels in the blood.

-Hypercoagulability: also called thrombophilia, it refers to the increased tendency of blood to thrombose.

-Hyperferremia: it is the medical condition of having too much iron in the body.

-Hyperglycemia: it is a high blood sugar. An elevated level specifically of the sugar glucose (Glc) in the blood. Hyperglycemia is often found in diabetes mellitus (DM). It occurs when the body does not have enough insulin or cannot use the insulin it has to turn glucose (Glc) into energy. Hyperglycemia may also occur in Cushing's syndrome and other conditions.

-Hyperhidrosis: this is a condition characterized by extreme and excessive sweating.

-Hyperinflated lungs: they are larger-than-normal lungs as a result of trapped air. It happens when one can't exhale, or push out all of the air that's in the lungs. The air gets trapped and takes up space, which can make it harder to get fresh air into the body.

-Hyperkalemia: Hyperkalemia is defined as a serum or plasma potassium level above the upper limits of normal, usually greater than 5.0 mEq/L to 5.5 mEq/L. While mild hyperkalemia is usually asymptomatic, high levels of potassium may cause life-threatening cardiac arrhythmias, muscle weakness or paralysis. Symptoms usually develop at levels higher levels, 6.5 mEq/L to 7 mEq/L, but the rate of change is more important than the numerical value. Having a blood potassium level higher than 6.0 mmol/L can be dangerous and usually requires immediate treatment.

-Hyperoxia: it refers to an excess of oxygen in tissues and organs. It is a higher than normal oxygen tension, such as that produced by breathing air or oxygen at greater than atmospheric pressures.

-Hyperplasia: it is the enlargement of an organ or tissue caused by an increase in the reproduction rate of its cells, often as an initial stage in the development of cancer.

-hyperreninemia: : it is a condition of elevated levels of renin in the blood, which may lead to aldosteronism and hypertension (HTN).

-Hypertension (HTN): it is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. However, increasing evidence indicates that the cardiovascular (CV) risk associated with elevation of blood pressure (BP) above approximately 115/75 mm Hg increases in a log-linear fashion.

-Hyperthyroidism: it indicates overactive thyroid occurs when the thyroid gland produces too much of the hormone thyroxine. Hyperthyroidism can accelerate the body's metabolism, leading to unintentional weight loss and a rapid or irregular heartbeat.

-Hypertriglyceridemia (HTG): it is a common clinical diagnosis, sometimes defined when plasma triglyceride (TG) concentration rises above a threshold value, such as the 90th or 95th percentile for age and sex. Hypertriglyceridemia (HTG) frequently co-exists with secondary conditions, including poor diet, alcohol use, obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM). Hypertriglyceridemia (HTG) is sometimes classified as primary, when a familial or inherited basis is suspected, or secondary, when one or more secondary factors contribute to the clinical presentation. Genetic factors can influence the severity of the plasma triglyceride (TG) elevation in the presence of a secondary factor. Hypertriglyceridemia (HTG) is usually a biochemical diagnosis, based on fasting plasma triglyceride (TG) concentration above a certain cut point. For instance, the 95th percentile for plasma triglyceride (TG) is ~250–300 mg/dL (~3.0–3.4 mmol/L) for North American adults. Severe Hypertriglyceridemia (HTG) is sometimes diagnosed for fasting plasma triglyceride (TG) concentration >1000 mg/dL (>11.2 mmol/L). Proposed hypertriglyceridemia (HTG) definitions vary. For instance the Adult Treatment Panel III guidelines of the National Cholesterol Education Program has suggested four discrete categories: normal fasting triglyceride (TG) is <150 mg/dL (<1.7 mmol/L), borderline

high triglyceride (TG) is 150–199 mg/dL (1.7–2.3 mmol/L), high triglyceride (TG) is 200–499 mg/dL (2.3–5.6 mmol/L) and very high triglyceride (TG) is >500 mg/dL (>5.6 mmol/L). The Endocrine Society has proposed another system with five clinical strata: normal triglyceride (TG) is <1.7 mmol/L (<150 mg/dL), mild hypertriglyceridemia (HTG) is 1.7–2.3 mmol/L (150–199 mg/dL), moderate hypertriglyceridemia (HTG) is 2.3–11.2 mmol/L (200–999 mg/dL), severe hypertriglyceridemia (HTG) is 11.2–22.4 mmol/L (1000–1999 mg/dL) and very severe hypertriglyceridemia (HTG) is >22.4 mmol/L (>2000 mg/dL). Very high triglyceride (TG) levels (>1000 mg/dL) are associated with chylomicronemia, since these particles have the highest capacity for carrying triglyceride (TG) in their core. Triglyceride (TG) levels >1000 mg/dL (>11.2 mmol/L) are almost always due to elevated chylomicrons. Familial chylomicronemia often presents during infancy or childhood, and generally becomes manifest by adolescence. Clinical features of hypertriglyceridemia (HTG) include failure to thrive, eruptive xanthomas over extensor surfaces and buttocks, lipemia retinalis, hepatosplenomegaly, recurrent abdominal pain, nausea and vomiting, and risk of acute pancreatitis. Less common clinical features include intestinal bleeding, pallor, anemia, irritability, diarrhea, seizures and encephalopathy.

-Hypoglycemia: this is a condition in which one's blood sugar (glucose, Glc) level is lower than normal. Glucose (Glc) is the body's main energy source. Hypoglycemia is often related to diabetes mellitus (DM) treatment. But other drugs and a variety of conditions- many rare-can cause low blood sugar in people who don't have diabetes mellitus (DM).

-Hypogonadism: it is a medical term for decreased functional activity of the gonads. The gonads (ovaries or testes) produce hormones (testosterone, estradiol, antimullerian hormone, progesterone, inhibin B, activin) and gametes (eggs or sperm). Male hypogonadism is characterized by a deficiency in testosterone - a critical hormone for sexual, cognitive, and body function and development. Clinically low testosterone levels can lead to the absence of secondary sex characteristics, infertility, muscle wasting, and other abnormalities. Low testosterone levels may be due to testicular, hypothalamic, or pituitary abnormalities. Hypogonadism in male patients with testicular failure due to genetic disorders (eg, Klinefelter's syndrome), orchitis, trauma, radiation, chemotherapy, or undescended testes, is known as hypergonadotropic hypogonadism or primary hypogonadism. Hypogonadism in male patients with gonadotropin deficiency or dysfunction as a result of disease or damage to the

hypothalamic-pituitary axis is known as hypogonadotropic hypogonadism, central hypogonadism, or secondary hypogonadism. This might be due to Kallmann's syndrome, tumor, trauma, radiation, sarcoidosis, or tuberculosis. In addition, men older than 50 years might have low testosterone levels with functional abnormalities at multiple levels of the hypothalamic-pituitary-testicular axis. Secondary and tertiary hypogonadism are the result of pituitary and hypothalamic failure, respectively. Since hypothalamic causes of hypogonadism are relatively rare, our focus will primarily be on secondary causes.

-Hypomania: this is a mild form of mania, marked by elation and hyperactivity.

-Hypomimia: it is a reduction in the expressiveness of the face, marked by diminished animation and movement of the facial muscles.

-Hyponatremia: it is defined as a serum sodium <135 meq/l. Hyponatremia results from the inability of the kidney to excrete a water load or excess water intake.

-Hypoperfusion (shock): this is the inadequate delivery of vital oxygen and nutrients to body tissues, which if left unchecked will result in organ system failure and death.

-Hypothermia: the definition of hypothermia is an involuntary drop in body temperature below 35C. Hypothermia takes place when the body dissipates more heat than it absorbs or creates, leaving the body unable to generate sufficient heat to maintain homeostasis and proper bodily function. While the underlying cause of accidental hypothermia is excessive cold stress and inadequate heat generation from the body (thermogenesis), other factors increase the risk of developing hypothermia. Functional central and peripheral nervous systems, along with proper behavioral adaptation, are important components.

-Hypoxemic respiratory failure: this is characterized by not having enough oxygen in blood, but carbon dioxide levels are close to normal.

-Hypoxia: this indicates deficiency in the amount of oxygen reaching the tissues.

-Idiopathic inflammatory myelitis: this is a rare immune mediated inflammatory demyelinating disorder of the spinal cord with motor, sensory and autonomic involvement.

-Idiopathic Pulmonary Fibrosis (IPF): it is a chronic interstitial pneumonia characterized by the invariably progressive deposition of fibrotic tissue in the lungs and overall poor prognosis. Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive disease characterized by the aberrant accumulation of fibrotic tissue in the lungs parenchyma, associated with significant morbidity and poor prognosis.

-Idiopathic transverse myelitis: this is a rare immune-mediated inflammatory demyelinating disorder of the spinal cord with motor, sensory and autonomic involvement.

-Immunoglobulin A (Ig A): it is also referred to as sIgA in its secretory form. It is an antibody (Ab) that plays a crucial role in the immune function of mucous membranes. The amount of immunoglobulin A (IgA) produced in association with mucosal membranes is greater than all other types of antibody (Ab) combined. In absolute terms, between three and five grams are secreted into the intestinal lumen each day. This represents up to 15% of total immunoglobulins (Igs) produced throughout the body. Immunoglobulin A (IgA) has two subclasses (IgA1 and IgA2) and can be produced as a monomeric as well as a dimeric form. The immunoglobulin A (IgA) dimeric form is the most prevalent and is also called secretory immunoglobulin A (sIgA). Secretory immunoglobulin A (sIgA) is the main immunoglobulin (Ig) found in mucous secretions, including tears, saliva, sweat, colostrum and secretions from the genitourinary tract, gastrointestinal tract (GIT), prostate and respiratory epithelium. It is also found in small amounts in blood. The secretory component of secretory immunoglobulin A (sIgA) protects the immunoglobulin (Ig) from being degraded by proteolytic enzymes; thus, secretory immunoglobulin A (sIgA) can survive in the harsh gastrointestinal tract (GIT) environment and provide protection against microbes that multiply in body secretions. Secretory immunoglobulin A (sIgA) can also inhibit inflammatory effects of other immunoglobulins. Immunoglobulin A (IgA) is a poor activator of the complement system, and opsonizes only weakly.

-Immunoglobulin G (IgG): it is a type of antibody (Ab) representing approximately 75% of serum antibodies (Abs) in humans. Immunoglobulin G (IgG) is the most common type of antibody (Ab) found in blood circulation. Immunoglobulin G (IgG) molecules are created and released by plasma B cells. Each immunoglobulin G (IgG) has two antigen binding sites. Antibodies (Abs) are major components of humoral immunity. Immunoglobulin G (IgG) is the main type of antibody (Ab) found in blood and extracellular fluid, allowing it to control infection

of body tissues. By binding many kinds of pathogens such as viruses, bacteria, and fungi, immunoglobulin G (IgG) protects the body from infection. Immunoglobulin G (IgG) antibodies are generated following class switching and maturation of the antibody (Ab) response, thus they participate predominantly in the secondary immune response. There are four immunoglobulin G (IgG) subclasses (IgG1, 2, 3, and 4) in humans, named in order of their abundance in serum (IgG1 being the most abundant).

-Immunoglobulin M (IgM): it is the largest antibody (Ab), and it is the first antibody (Ab) to appear in the response to initial exposure to an antigen. In the case of humans and other mammals that have been studied, the spleen, where plasmablasts responsible for antibody (Ab) production reside, is the major site of specific immunoglobulin M (IgM) production. Immunoglobulin M (IgM) is the first immunoglobulin (Ig) expressed in the human fetus (around 20 weeks) and phylogenetically the earliest antibody to develop. Immunoglobulin M (IgM) antibodies appear early in the course of an infection and usually reappear, to a lesser extent, after further exposure. Immunoglobulin M (IgM) antibodies do not pass across the human placenta [only isotype immunoglobulin G (IgG)]. These two biological properties of immunoglobulin M (IgM) make it useful in the diagnosis of infectious diseases. Demonstrating immunoglobulin M (IgM) antibodies in a patient's serum indicates recent infection, or in a neonate's serum indicates intrauterine infection (e.g. congenital rubella syndrome).

-In situ hybridization (ISH): this is a type of hybridization that uses a labeled complementary deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or modified nucleic acids strand (i.e., probe) to localize a specific deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequence in a portion or section of tissue (in situ) or if the tissue is small enough (e.g., plant seeds, drosophila embryos), in the entire tissue (whole mount in situ hybridization (ISH)), in cells, and in circulating tumor cells (CTCs). This is distinct from immunohistochemistry, which usually localizes proteins in tissue sections.

-Incontinence: this indicates lack of voluntary control over urination or defecation.

-Ineffective erythropoiesis: it is defined as a suboptimal production of mature erythrocytes originating from a proliferating pool of immature erythroblasts.

-Infantile bilateral strial necrosis (IBSN): this is a neurological disorder characterized by symmetrical degeneration of the caudate nucleus, putamen, and occasionally the globus pallidus, with little involvement of the rest of the brain.

-Inferior vena cava (IVC): it is a large vein carrying deoxygenated blood into the heart.

-Influenza: it is a highly contagious viral infection of the respiratory passages causing fever, severe aching, and catarrh, and often occurring in epidemics. Influenza or flu is a common viral disease of the upper respiratory tract. There are three types of influenza virus: A, B and C. Major outbreaks of influenza are associated with influenza virus types A or B. Infection with type B influenza is usually milder than with type A. Influenza C is common but rarely causes disease.

-Innate immunity: it refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include physical barriers such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body. The innate immune response is activated by chemical properties of the antigen.

-Insomnia: it refers to habitual sleeplessness or inability to sleep.

-Intrauterine growth restriction (IUGR): this refers to poor growth of a fetus while in the mother's womb during pregnancy.

-Interferon (IFN): interferons (IFN) are soluble glycoproteins with strong antiviral effects. Three types of interferons (IFNs), types I, II and III, have been classified depended on their genetic, structural, and functional characteristics and their cell-surface receptors. Interferon (IFN) biological activities involve antiviral, antiproliferative and immunomodulatory effects in the host response to viral or bacterial infection. As a result, interferon (IFN) induction is a potent tool in the host response to cancer or viral infection. In general, interferon-alpha (IFN- α) is produced by leukocytes while interferon-beta (IFN- β) is a fibroblast product. A limited number of interferons (IFNs) are produced under healthy conditions. Interferon-alpha/beta (IFN- α/β) would be significantly upregulated by viral infections or exposure to double-stranded and single-stranded nucleic acids via Toll-like receptor3 (TLR3) or retinoic acid-inducible gene I (RIG I). Retinoic acid-inducible gene I, RIG-I, is a cytosolic pattern recognition receptor (PRR) responsible for the type-1 interferon (IFN1) response. Retinoic acid-inducible gene I (RIG I) is

an essential molecule in the innate immune system for recognizing cells that have been infected with a virus such as infection with coronavirus (CoV).

-Interferon-gamma (IFN- γ): it is described as an agent with antiviral activity, it has since been characterized as a homodimeric glycoprotein with pleiotropic immunologic functions. Interferon-gamma (IFN- γ) is primarily secreted by activated T cells and natural killer (NK) cells, and can induce macrophage activation, mediate antiviral and antibacterial immunity, enhance antigen presentation, orchestrate activation of the innate immune system, coordinate lymphocyte–endothelium interaction, regulate Th1/Th2 balance, and control cellular proliferation and apoptosis. Interferon-gamma (IFN- γ) is a cytokine that plays a strong role in inducing and modulating an array of immune responses. Cellular responses to interferon-gamma (IFN- γ) are mediated by its heterodimeric cell-surface receptor (IFN- γ R), which activates downstream signal transduction cascades, ultimately leading to the regulation of gene expression.

-Interferon gamma (IFN- γ)-inducible protein 10 (also called CXCL10/IP-10): it is a member of the CXC chemokine family with pro-inflammatory and anti-angiogenic properties. It is the tenth member of the CXC family of small chemotactic cytokines and plays an essential role in the recruitment of T-helper-1 (Th1) cells, natural killer (NK) cells, macrophages (M Φ), and dendritic cells (DCs) into sites of tissue inflammation. This chemokine has been proposed to be a key link between inflammation and angiogenesis.

-Interferon regulatory factor 3 (IRF3): it is a transcription factor that controls multiple IFN-inducing pathways, including the Toll-like receptor3 (TLR3) pathway, which can be triggered by double stranded ribonucleic acid (dsRNA), and the pathways triggered by other ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) sensors. Interferon regulatory factor 3 (IRF3) is normally activated by TBK1 and/or IKK ϵ kinases. Interferon regulatory factor 3 (IRF3) has a crucial role in the Toll-like receptor3 (TLR3)-mediated interferon-beta (IFN- β) gene transcription.

-International normalised ratio (INR): it is a laboratory measurement of how long it takes blood to form a clot.

-Interstitial lung disease (ILD): this is an umbrella term used for a large group of diseases that cause scarring (fibrosis) of the lungs.

-Interstitial pancreatitis: also known as interstitial edematous acute pancreatitis, which is characterized by acute inflammation of the pancreatic parenchyma and peripancreatic tissues, but without recognizable tissue necrosis.

-Intestinal ischemia: this is occurring when blood flow to the bowels is reduced. The condition can be acute or chronic and may affect the large and/or the small intestine.

-Invasive mechanical ventilation: invasive mechanical ventilation is a lifesaving tool commonly used in the care of hospitalized patients. It includes an endotracheal tube (ETT) and a mechanical ventilator (as opposed to noninvasive ventilation in which the interface is a face mask). In addition to serving as the conduit for delivery of mechanical breaths, the endotracheal tube (ETT) protects the airway, allows for suctioning of secretions, and facilitates select procedures, including bronchoscopy. Invasive mechanical ventilation helps stabilize patients with hypoxemic and hypercapnic respiratory failure, decreases inspiratory work of breathing, redistributes blood flow from exercising respiratory muscles to other tissues in patients with shock, and allows for the implementation of lung-protective (low tidal volume) ventilation in patients with acute respiratory distress syndrome (ARDS).

-Intrapulmonary shunting: it is a pathological condition resulting when the alveoli of the lungs perfused with blood as normal, but ventilation (the supply of air) failing to supply the perfused region; In other words, the ventilation/perfusion ratio (the ratio of air reaching the alveoli to blood perfusing them) is zero.

-Intravenous bolus: this is indicating a large volume of fluid or dose of a drug given intravenously and rapidly at one time.

-IP-10: it is also called CXCL10, form a structurally and functionally related subgroup of non-ELR CXC chemokines that regulate the migration of T helper1 (Th1)-polarized effector T cells to inflamed sites during the adaptive immune response. CXCL10 has been associated with a wide spectrum of lung inflammatory diseases through both pro- and antifibrotic effects and its ability to recruit cells that secrete or respond to interferon-gamma (IFN- γ). It is considered to refer to ELR which indicates a conserved glutamic acid-leucine-arginine (Glu-Leu-Arg) motif N-terminal to cysteine-1 (Cys-1), which is required for CXCR2 activation. Among the non-ELR-

CXC chemokines, only CXCL12 (SDF-1 (stromal cell-derived factor-1)), which binds CXCR4, not CXCR2, attracts neutrophils; it is also angiogenic.

-Ischaemia: this is an inadequate blood supply to an organ or part of the body, especially the heart muscles.

-Ischemia-reperfusion injury (IRI): reperfusion injury, sometimes called or reoxygenation injury, is the tissue damage caused when blood supply returns to tissue (re- + perfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia). The absence of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress rather than (or along with) restoration of normal function. In other words, ischaemia-reperfusion injury (IRI) is defined as the paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to previously ischaemic tissues.

-Ischemia/reperfusion injury (IRI): sometimes called reperfusion injury or reoxygenation injury, is the tissue damage caused when blood supply returns to tissue (reperfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia).

-Ischemic heart disease (IHD): this is the result of a limited blood supply to the heart muscle. In more than 95% of cases, the cause of ischemic heart disease (IHD) is coronary blood flow reduction caused by coronary artery atherosclerosis, therefore the term “coronary heart disease” is often used to describe this syndrome.

-Ischemic stroke: it is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Ischemic stroke is caused by thrombosis or embolisms. An acute stroke refers to the first 24-hour-period of a stroke event. Stroke is classified as either ischaemic (caused by thrombosis or embolisms) or haemorrhagic (caused mainly by rupture of blood vessel or aneurysm). The occlusion of the cerebral artery causes decreased blood flow and ischaemia.

-Jactitation: this refers to restless picking at things characteristic of severe infection.

-Juvenile Huntington disease (JHD): the name given to Huntington’s disease (HD) incident before the patient is 20 years of age, it is characterized by uncontrolled movements, loss of intellectual abilities, emotional disturbances, and a rapid decline in school performance.

-Kaliuresis: this is the condition of excreting potassium in the urine.

-Kartagener syndrome: this is a rare, autosomal recessive genetic ciliary disorder comprising the triad of situs inversus, chronic sinusitis, and bronchiectasis. The basic problem lies in the defective movement of cilia, leading to recurrent chest infections, ear/nose/throat symptoms, and infertility.

-Kawasaki disease (KD): this is a systemic vasculitis mostly affecting medium-sized arteries. Main symptoms include fever, conjunctivitis, skin and mucous membrane affection, and cervical lymphadenopathy. Generally, inflammatory changes to arterial vessels of all body regions can be present, however, coronary arteries are most commonly affected. In cases of delayed treatment, missed diagnosis, or in treatment refractory cases, aneurysms can result and cause severe sequelae, including cardiac infarctions.

-Kinesia paradoxical: this is a phenomenon most often seen in people with Parkinson's disease where individuals who typically experiencing severe difficulties with the simple movements performing complex movements easily.

-Kupffer cells (KCs): these are phagocytic cells forming the lining of the sinusoids of the liver and are involved in the breakdown of red blood cells(RBCs).

-Labored breathing: or labored respiration, it is an abnormal respiration characterized by evidence of elevated effort to breathe, involving the use of accessory muscles of respiration, stridor, grunting, or nasal flaring.

-Lactate dehydrogenase (LDH or LD): it is an enzyme involved in energy production that is found in almost all of the body's cells, with the highest levels found in the cells of the heart, liver, muscles, kidneys, lungs, and in blood cells. Lactate dehydrogenase (LDH) catalyzes the conversion of lactate to pyruvate and back, as it converts nicotinamide adenine dinucleotide (NAD⁺) to reduced form nicotinamide adenine dinucleotide (NADH) and back. A dehydrogenase is an enzyme that transfers a hydride from one molecule to another. Lactate dehydrogenase (LDH) is expressed extensively in body tissues, such as blood cells and heart muscle. Because it is released during tissue damage, it is a marker of common injuries and disease such as heart failure.

-Lactic acidosis: this is a medical condition characterized by the buildup of lactate (especially L-lactate) in the body, with formation of an excessively low pH in the bloodstream.

-Laxative abuse: it indicates the ingestion of cathartic drugs to relieve perceived constipation when none is present or to prevent the absorption of nutrients, e.g., in bulimia. Individuals consuming excessive quantities of laxatives are complaining of chronic diarrhea or experiencing illness resulted from electrolyte deficiencies.

-Left ventricular failure (LVF), or left ventricular dysfunction or systolic dysfunction: this causes classic heart failure with edema of the lower extremities and lungs, poor perfusion of the brain and kidneys, tachycardia, and peripheral venous distension. Left ventricular dysfunction is the result of many cardiac disorders causing a mechanical alteration of cardiac performance. More importantly it can be the main cause of congestive heart failure. Given the clinical and prognostic impact of congestive heart failure, it is clear why much attention is paid to both the prevention and treatment of left ventricular dysfunction. Left ventricular dysfunction can involve the entire left ventricle (overall left ventricular dysfunction) or only part of it (regional left ventricular dysfunction). The latter is particularly common in coronary artery disease, because of the regional nature of the disease and can, moreover, evolve into more severe overall left ventricular dysfunction and dilatation (left ventricular remodeling phenomenon). Lastly, left ventricular dysfunction can be either systolic or diastolic, the latter being less uncommon than previously thought.

-*Legionella spp.*: Legionellosis is the generic term used to describe infections caused by different varieties of *Legionella spp.*, including Legionnaires' disease (LD), a severe and potentially fatal form of pneumonia, and Pontiac fever, a self-limited flu-like illness. Legionellosis is usually acquired through inhalation or aspiration of aerosols containing *Legionella spp.* These bacteria can cause acute consolidating pneumonia in susceptible patients who are at an advanced age, have underlying debilitating diseases, or are immunodeficient. The main natural reservoir for *Legionella* is water and this pathogen colonizes many different natural and man-made freshwater environments such as water networks, cooling towers, and water systems in buildings and hospitals.

-Leigh encephalopathy: also called Leigh syndrome and subacute necrotizing encephalomyelopathy (SNE), it is a rare inherited neurometabolic disorder affecting the central nervous system (CNS).

-Leprosy: this is a chronic, progressive bacterial infection caused by the bacterium *Mycobacterium leprae*. It primarily affects the nerves of the extremities, the skin, the lining of the nose, and the upper respiratory tract. Leprosy is also known as Hansen's disease. Leprosy produces skin ulcers, nerve damage, and muscle weakness. If it isn't treated, it can cause severe disfigurement and significant disability.

-Lethargy: it is a lack of energy and enthusiasm.

-Leucopenia: this is a reduction in the number of white cells in the blood. This is typical of various diseases.

-Leukemia: this is a malignant progressive disease in which the bone marrow and other blood-forming organs produce increased numbers of immature or abnormal leucocytes; these suppress the production of normal blood cells, leading to anemia and other symptoms.

-Leukocytosis: it refers to an increase in the number of white cells in the blood, especially during an infection.

-Livedo reticularis: this is a cutaneous physical sign characterized by transient or persistent, blotchy, reddish-blue to purple, net-like cyanotic pattern. It is a mottled purplish discoloration of the skin.

-Loop diuretic: this is a powerful diuretic which inhibits resorption of water and sodium from the loop of Henle.

-Low tidal volume ventilation (LTVV): it is one of the interventions specifically designed to prevent ventilator-associated conditions (VAC).

-Lung abscess: it is a type of liquefactive necrosis of the lung tissue and formation of cavities (more than 2 cm) containing necrotic debris or fluid caused by microbial infection. It can be

caused by aspiration, which may occur during altered consciousness and it usually causes a pus-filled cavity.

-Lung compliance: pulmonary compliance (PAC) is an attribute in the pulmonary system that, in simple terms, can be defined as a change in lumen area for a given change in pressure. Lung compliance, or pulmonary compliance, is a measure of the lung's ability to stretch and expand (distensibility of elastic tissue).

-Lung consolidation: it occurs when the air that usually fills the small airways in the lungs is replaced with something else. Depending on the cause, the air may be replaced with: a fluid, such as pus, blood, or water. a solid, such as stomach contents or cells. A chest X-ray finding indicating the presence of a radio-opaque area in the lung. The opacification is caused by fluid or solid material within the airways or lung parenchyma.

-Lung parenchyma: The lung parenchyma comprises a large number of thin-walled alveoli, forming an enormous surface area, which serves to maintain proper gas exchange. The alveoli are held open by the transpulmonary pressure, or prestress, which is balanced by tissues forces and alveolar surface film forces. Gas exchange efficiency is thus inextricably linked to three fundamental features of the lung: parenchymal architecture, prestress, and the mechanical properties of the parenchyma. The prestress is a key determinant of lung deformability that influences many phenomena including local ventilation, regional blood flow, tissue stiffness, smooth muscle contractility, and alveolar stability. The main pathway for stress transmission is through the extracellular matrix. Thus, the mechanical properties of the matrix play a key role both in lung function and biology. These mechanical properties in turn are determined by the constituents of the tissue, including elastin, collagen, and proteoglycans. In addition, the macroscopic mechanical properties are also influenced by the surface tension and, to some extent, the contractile state of the adherent cells.

-Lung vascular hydrostatic pressure: blood hydrostatic pressure is the force exerted by the blood confined within blood vessels or heart chambers. The primary force driving fluid transport between the capillaries and tissues is hydrostatic pressure, which can be defined as the pressure of any fluid enclosed in a space.

- **Lupus anticoagulant:** an immunoglobulin that binds to phospholipids and proteins associated with the cell membrane.

-**Lupus erythematosus:** this is a systemic autoimmune disease occurring when body's immune system attacking own tissues and organs.

-**Luteal phase of the menstrual cycle:** it is the time between ovulation and before the start of menstruation, when the body prepares for a possible pregnancy; progesterone is produced, peaks, and then drops.

-**Lyme disease:** also known as Lyme borreliosis, is an infectious disease caused by the *Borrelia* bacterium which is spread by ticks. The most common sign of infection is an expanding red rash, known as erythema migrans, that appears at the site of the tick bite about a week after it occurred. The rash is typically neither itchy nor painful. Approximately 70–80% of infected people develop a rash. Other early symptoms may include fever, headache and tiredness. If untreated, symptoms may include loss of the ability to move one or both sides of the face, joint pains, severe headaches with neck stiffness, or heart palpitations, among others.

-**Lymphadenectasis:** this refers to an increase in size and/or volume of a lymph node.

-**Lymphangiomyomatosis (LAM):** this is a rare lung disease that affects mostly women of childbearing age. In people who have lymphangiomyomatosis (LAM), abnormal muscle-like cells begin to grow out of control in certain organs or tissues, especially the lungs, lymph nodes, and kidneys.

-**Lymphopenia:** it is a condition in which there is a lower-than-normal number of lymphocytes.

-**Lymphoproliferative disorders (LPDs):** these are several conditions in which lymphocytes are produced in excessive quantities. They are typically occurring in people having a compromised immune system.

-**Macrophage (MΦ):** it is a large phagocytic cell found in stationary form in the tissues or as a mobile white blood cell (WBC), especially at sites of infection.

-Macrophage activated syndrome: this is referring to a condition caused by excessive activation and expansion of T lymphocytes and macrophagic histiocytes that exhibit hemophagocytic activity.

-Macrophage colony-stimulating factor (M-CSF): it is produced by osteoblasts and osteoblast precursors, but large amounts of macrophage colony-stimulating factor (M-CSF) are also produced by osteocytes. Macrophage colony-stimulating factor (M-CSF) is a hematopoietic growth factor that regulates the proliferation, differentiation, and functional activation of monocytes. Normally detected in human serum. Macrophage colony-stimulating factor (M-CSF) plays an important role in enhancing the effector functions of mature monocytes and macrophages.

-Macrophage inflammatory protein-1alpha (MIP-1 α /CCL3): it is a chemotactic chemokine secreted by macrophages. It performs various biological functions, such as recruiting inflammatory cells, wound healing, inhibition of stem cells, and maintaining effector immune response. Macrophage inflammatory protein-1alpha (MIP-1 α) is distinct but highly homologous CC chemokine produced by a variety of host cells in response to various external stimuli and share affinity for CCR5. To better elucidate the role of these CC chemokines in adaptive immunity, it has been characterized the effects of macrophage inflammatory protein-1alpha (MIP-1 α) on cellular and humoral immune responses. Macrophage inflammatory protein-1alpha (MIP-1 α) stimulated strong antigen (Ag)-specific serum immunoglobulin G (IgG) and immunoglobulin M (IgM) responses. Macrophage inflammatory protein-1alpha (MIP-1 α) elevated Ag-specific immunoglobulin G1 (IgG1) and immunoglobulin G2b (IgG2b) followed by immunoglobulin G2a (IgG2a) and immunoglobulin G3 (IgG3) subclass responses. However, macrophage inflammatory protein-1alpha (MIP-1 α) effectively enhanced antigen (Ag)-specific cell-mediated immune responses. In correlation with macrophage inflammatory protein-1alpha (MIP-1 α) selective effects on humoral and cellular immune responses, this chemokine also differentially attract CD4⁺ versus CD8⁺ T cells and modulate CD40, CD80, and CD86 expressed by B220⁺ cells as well as CD28, 4-1BB, and gp39 expression by CD4⁺ and CD8⁺ T cells in a dose-dependent fashion. Studies propose that these CC chemokines differentially enhance mucosal and serum humoral as well as cellular immune responses. Macrophage inflammatory protein-1alpha (MIP-1 α) activates bone resorption cells and directly induces bone destruction. Cells

that secrete macrophage inflammatory protein-1 alpha (MIP-1 α /CCL3) are increased at sites of inflammation and bone resorption.

-Macrophage inflammatory protein-1beta (MIP-1 β): it is also known as CCL4. It is a CC chemokine with specificity for CCR5 receptors. It is a chemoattractant for natural killer (NK) cells, monocytes and a variety of other immune cells. CCL4 is produced by: neutrophils, monocytes, B cells, T cells, fibroblasts, endothelial cells, and epithelial cells. Concentration of this chemokine has been shown to be inversely related with microRNA-125b. Concentration of CCL4 within the body increases with age, which may cause chronic inflammation and liver damage.

-Macular disease: macular degeneration, also known as age-related macular degeneration (AMD or ARMD), is a medical condition which may result in blurred or no vision in the center of the visual field. Early on there are often no symptoms.

-Magnetic Resonance Imaging (MRI) this is a modern diagnostic technique for acquiring information from the interior of a body. Usually this is a human body or an animal, but magnetic resonance imaging (MRI) is also used in the industry for more technical purposes. The greatest advantage of magnetic resonance imaging (MRI) is that it can create three-dimensional images of the object under study without hurting the object in any way and without using any ionizing radiation. The body to be imaged is placed in a strong magnetic field; more than ten thousand times as strong as the magnetic field of the Earth. A radio signal in the form of one or more short pulses is sent into the body, where it is absorbed by nuclei of hydrogen atoms. These are also called protons. The radio signal is of the same kind as radio waves used by TV and FM radio stations. The hydrogen nuclei of the body respond by creating a slowly decaying radio signal in a receiver coil. The strength of this signal mirrors the amount of protons; i.e. the concentration of hydrogen in various parts of the imaged body. When creating an image of an organ within a body, the signal must be acquired from every part of the organ point by point by a scanning procedure. To accomplish this, the magnetic field is varied with successive gradients in three dimensions. The monitored signal is the sum of signals from every unique volume element within the body. In this way the instrument receives thousands or even millions of data creating a set of equations from which the signal magnitude of every single volume element can be calculated. Most parts of the body have a roughly equal concentration of hydrogen. Thus, the radio signals from different tissues have similar strengths resulting in an image with low

contrast. However, signals from protons decay with unequal speeds depending on their various environments. Hydrogen atoms exist in 2 different compounds and in different tissues. This fact can considerably influence the so-called relaxation time. Therefore the magnitude of the induced radio signal is monitored sometime after the end of the primary radio frequency pulses which had started the whole process. Now various tissues show different signal strengths, from which it is possible to build an image with desired contrast. This is often excellent, even for soft tissues. Of special interest is that hydrogen in lesions and tumors may have other relaxation times than surrounding tissues and therefore can be detected in the image.

-Malignant hypertension: it is extremely high blood pressure that develops rapidly and causes some type of organ damage. Normal blood pressure is below 120/80. A person with malignant hypertension has a blood pressure that's typically above 180/120. Malignant hypertension should be treated as a medical emergency.

-Mania: this is mental illness marked by periods of great excitement or euphoria, delusions, and overactivity.

-Marked first-degree atrioventricular (AV) block: this is when the PR interval ≥ 0.30 s, PR interval measured from the onset of atrial depolarization (P wave) to the onset of ventricular depolarization (QRS complex).

-Masquerade syndromes: these are disorders that occur with intraocular inflammation and are often misdiagnosed as a chronic idiopathic uveitis.

-Mast cell: it is a cell filled with basophil granules, found in numbers in connective tissue and releasing histamine and other substances during inflammatory and allergic reactions.

-Mastitis: it is inflammation of the mammary gland in the breast or udder, typically due to bacterial infection via a damaged nipple or teat.

-Matrix metalloproteinase-9 (MMP-9): this is a class of enzymes belonging to the zinc-metalloproteinases family involved in the degradation of the extracellular matrix.

-MCP-3: this chemokine (C-C motif) ligand 7 (CCL7) is a small cytokine known as a chemokine that was previously called monocyte-chemotactic protein 3 (MCP3). Due to CCL7

possessing two adjacent N-terminal cysteine (Cys) residues in its mature protein, it is classified among the subfamily of chemokines known as CC chemokines. CCL7 specifically attracts monocytes, and regulates macrophage (MΦ) function. It is produced by certain tumor cell lines and by macrophages (MΦ).

-Measles: an infectious viral disease causing fever and a red rash, typically occurring in childhood.

-Megacaryocyte: it a large bone-marrow cell having a lobulate nucleus, regarded as the source of blood platelets.

-Meibomian gland dysfunction (MGD): this is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.

-Meningismus: this is a group of symptoms similar to meningitis (stiff neck, reaction to light and headache) without inflammation of the membranes lining the brain.

-Meningitis: it is defined as inflammation of the meninges. The meninges are the three membranes (the dura mater, arachnoid mater, and pia mater) that line the vertebral canal and skull enclosing the brain and spinal cord. Encephalitis, on the other hand, is inflammation of the brain itself.

-Messenger ribonucleic acid (mRNA): it is ribonucleic acid (RNA) that carries information from deoxyribonucleic acid (DNA) to the ribosome, the site of protein synthesis (translation) within a cell. The messenger ribonucleic acid (mRNA) is initially transcribed from the corresponding deoxyribonucleic acid (DNA) sequence and then translated into protein. However, several regions of the messenger ribonucleic acid (mRNA) are usually not translated into protein, including the 5' and 3' UTRs.

-Metabolic acidosis: a serious electrolyte disorder characterized by an imbalance in the body's acid-base balance.

-Metabolic alkalosis: this is a metabolic condition where the pH of tissue elevated beyond the normal range (7.35–7.45).

-Metalloproteinase or metalloprotease: it is any protease enzyme whose catalytic mechanism involves a metal.

-Metastatic infection: it is defined as deep-seated infection including endocarditis, osteomyelitis, spondylodiscitis, and muscle or visceral abscesses.

-Methylmalonic acidemia: this is an inherited disorder where the body is not capable of processing certain proteins and fats properly.

-Methyl malonic aciduria: also called methylmalonic acidemia, it is an autosomal recessive metabolic disorder disrupting normal amino acid (AA) metabolism.

-Microaneurysms: these are saccular outpouchings of the capillary walls that can leak fluid and result in intraretinal edema and hemorrhages.

-Microangiopathic hemolytic anemia (MAHA): this is a Coomb's-negative hemolytic anemia characterized by red blood cell (RBC) fragmentation (schistocytes). Thrombotic microangiopathy anemia, including thrombotic thrombocytopenia and hemolytic-uremic syndrome, malignant hypertension, preeclampsia are among the most common causes.

-Microangiopathy: it is a disease of blood capillaries where the capillary walls becoming so thick and weak thus bleed, leak protein, and slow the flow of blood.

-Microglia: these are a specialised population of macrophages found in the central nervous system (CNS). These cells are the immune cells of the central nervous system (CNS) and consequently play important roles in brain infections and inflammation. Recent in vivo imaging studies have revealed that in the resting healthy brain, microglia are highly dynamic, moving constantly to actively survey the brain parenchyma. These active microglia can rapidly respond to pathological insults, becoming activated to induce a range of effects that may contribute to both pathogenesis, or to confer neuronal protection. However, interactions between microglia and neurons are being recognized as important in shaping neural circuit activity under more normal, physiological conditions. During development and neurogenesis, microglia interactions with neurons help to shape the final patterns of neural circuits important for behavior and with implications for diseases. In the mature brain, microglia can respond to changes in sensory activity and can influence neuronal activity acutely and over the long term. Microglia seem to be particularly involved in monitoring the integrity of synaptic function.

-Microinfarcts: these are microscopic lesions, of cellular death or tissue necrosis, which are a result of pathologies involving small vessels.

-Microlithiasis: biliary microlithiasis refers to the creation of small gallstones less than 3mm in diameter in the biliary duct or gallbladder.

-Microvascular thrombosis: thrombosis is often present in the microcirculation in a variety of significant human diseases, such as disseminated intravascular coagulation (DIC), thrombotic microangiopathy, sickle cell disease, and others. Further, microvascular thrombosis has recently been demonstrated in patients with coronavirus disease 2019 (COVID-19), and has been proposed to mediate the pathogenesis of organ injury in this disease. In many of these conditions, microvascular thrombosis is accompanied by inflammation, an association referred to as thromboinflammation.

-Miscarriage: this is the spontaneous or unplanned expulsion of a fetus from the womb before it its ability to survive independently.

-Mitochondrial antiviral-signaling protein (MAVS): it is a protein that is crucial for antiviral innate immunity. Mitochondrial antiviral-signaling protein (MAVS) is located in the outer membrane of the mitochondria, peroxisomes, and endoplasmic reticulum (ER). Upon viral infection, a group of cytosolic proteins will detect the presence of the virus and bind to mitochondrial antiviral-signaling protein (MAVS), thereby activating mitochondrial antiviral-signaling protein (MAVS). The activation of mitochondrial antiviral-signaling protein (MAVS) causes the virally infected cell to secrete cytokines. This induces an immune response which kills the host's virally infected cells, leading to clearance of the virus. Mitochondrial antiviral-signaling protein (MAVS) is also known as IFN- β promoter stimulator I (IPS-1), caspase activation recruitment domain adaptor inducing I FN- β (CARDIF), or virus induced signaling adaptor (VISA).

-Mitosis: this is a type of cell division that results in two daughter cells each having the same number and kind of chromosomes as the parent nucleus, typical of ordinary tissue growth.

-Mitral valve prolapse: this is also called MVP, is a condition in which the two valve flaps of the mitral valve don't close smoothly or evenly, but bulge (prolapse) upward into the left

atrium. Mitral valve prolapse is also known as click-murmur syndrome, Barlow's syndrome or floppy valve syndrome.

-Mitral valve regurgitation: it refers to leakage of blood backward through the mitral valve each time the left ventricle contracts.

-Monocyte: it is a large phagocytic white blood cell (WBC) with a simple oval nucleus and clear, greyish cytoplasm.

-Monocyte chemoattractant peptide (MCP)-1: these chemokines play a principal role in selectively recruiting monocytes, neutrophils, and lymphocytes, as well as in stimulating chemotaxis through the activation of G-protein-coupled receptors. Monocyte chemoattractant protein-1 (MCP-1/CCL2) is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Both CCL2 and its receptor CCR2 have been demonstrated to be induced and involved in various diseases. Migration of monocytes from the blood stream across the vascular endothelium is required for routine immunological surveillance of tissues, as well as in response to inflammation.

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-Mononuclear phagocytic system (MPS): it is also known as the reticuloendothelial system or macrophage system. It is a part of the immune system consisting of the phagocytic cells located in reticular connective tissue.

-Multiciliate differentiation and DNA synthesis associated cell cycle protein: The gene encoding this protein which is a member of the geminin family of proteins. The encoded nuclear protein is required for the generation of multiciliated cells in respiratory epithelium. Mutations in this gene cause a rare mucociliary clearance disorder associated with recurring respiratory infections in human patients, known as reduced generation of multiple motile cilia (RGMC).

-Multiple infarcts: these are multiple areas of the brain have been injured due to a lack of blood from a series of small strokes.

-Multiple sclerosis (MS): it is a potentially disabling disease of the brain and spinal cord (central nervous system, CNS). In multiple sclerosis, the immune system attacks the protective sheath (myelin) that covers nerve fibers and causes communication problems between the brain and the rest of the body. It is a chronic, typically progressive disease involving damage to the sheaths of nerve cells in the brain and spinal cord, whose symptoms may include numbness, impairment of speech and of muscular coordination, blurred vision, and severe fatigue.

-Myalgia: this describes muscle aches and pain, which can involve ligaments, tendons and fascia, the soft tissues that connect muscles, bones and organs. Injuries, trauma, overuse, tension, certain drugs and illnesses can all bring about myalgia.

-*Mycobacterium tuberculosis*: it is a species of pathogenic bacteria in the family Mycobacteriaceae and the causative agent of tuberculosis.

-Myeloid differentiation primary response 88 (MYD88): it is a protein. In humans, myeloid differentiation primary response 88 (MYD88) is encoded by the *MYD88* gene. The MYD88 gene provides instructions for making a protein included in signaling within immune cells. The myeloid differentiation primary response 88 (MYD88) protein functions as an adapter, connecting proteins that receive signals from outside the cell to the proteins that relay signals inside the cell.

-Myeloproliferative disorders: these are malignant diseases of certain bone marrow cells including those that give rise to the red blood cells, the granulocytes (types of white blood cells), and the platelets (crucial to blood clotting).

-Myocardial bridges: these are fragments of myocardium crossing on top of the coronary artery leading to obstruction with physiological contraction.

-Myocardial infarction (MI): myocardial infarction (MI) (ie, heart attack) is the irreversible death (necrosis) of heart muscle secondary to prolonged lack of oxygen supply (ischemia). Myocardial infarction is a life-threatening condition occurring when blood flow to the heart muscle being abruptly cut off, causing tissue damage, usually the result of a blockage in one or more of the coronary arteries. The diagnosis of myocardial infarction requires evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia. These criteria require detection of a rise and/or fall in cardiac biomarker levels (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit, with at least one of the following: (1) symptoms of myocardial ischaemia, (2) new or presumed new significant ST-segment T-wave changes or new left bundle branch block, (3) development of pathological Q-waves on the electrocardiogram, (4) imaging evidence of loss of viable myocardium or new regional wall motion abnormality or (5) identification of intracoronary thrombus by angiography or autopsy.

-Myocardial injury: acute myocardial injury is classified where troponin (Tn) concentrations are elevated with evidence of dynamic change in the absence of overt myocardial ischemia, whereas in chronic myocardial injury troponin (Tn) concentrations remain unchanged on serial testing. This is an important distinction, as the underlying pathological mechanisms in acute and chronic myocardial injury are likely to differ. The majority of cardiac troponin (cTn) is intracellular, with >90% of troponin (Tn) isoforms located within the sarcomere, and the remainder unbound within the cytoplasmic pool. The mechanisms of cardiac troponin (cTn) release into the circulation are thought to include myocyte necrosis, apoptosis, formation and release of membranous blebs, increased membrane permeability and release of proteolytic troponin (Tn) degradation products.

-Myocardial ischemia: it occurs when blood flow to heart is reduced, thus preventing the heart muscle from receiving enough oxygen.

-Myocarditis: it is an inflammation of the heart muscle (myocardium).

-Myoclonus: this indicates involuntary twitching of a muscle or group of muscles. This is spasmodic jerky contraction of groups of muscles.

-Myofibroblast: it is a cell that is in between a fibroblast and a smooth muscle cell in phenotype. Myofibroblasts are found subepithelially in many mucosal surfaces, for example, throughout almost the whole of the gastrointestinal and genitourinary tracts. Here they not only act as a regulator of the shape of the crypts and villi, but also act as stem-niche cells in the intestinal crypts and as parts of atypical antigen-presenting cells. They have both support as well as paracrine function in most places.

-Natriuresis: it refers to the excretion of sodium in the urine.

-Natural killer (NK) cells: these are lymphocytes in the same family as T and B cells, coming from a common progenitor. However, as cells of the innate immune system, natural killer (NK) cells are classified as group I Innate Lymphocytes (ILCs) and respond quickly to a wide variety of pathological challenges. Natural killer (NK) cells are best known for killing virally infected cells, and detecting and controlling early signs of cancer. As well as protecting against disease, specialized natural killer (NK) cells are also found in the placenta and may play an important role in pregnancy. Inhibitory receptors act as a check on natural killer (NK) cell killing. Most normal healthy cells express major histocompatibility complex class I (MHC I) receptors which mark these cells as self. Inhibitory receptors on the surface of the natural killer (NK) cell recognize cognate major histocompatibility complex class I (MHC I), and this switches off the natural killer (NK) cell, preventing it from killing. Cancer cells and infected cells often lose their major histocompatibility complex class I (MHC I), leaving them vulnerable to natural killer (NK) cell killing. Once the decision is made to kill, the natural killer (NK) cell releases cytotoxic granules containing perforin and granzymes, which leads to lysis of the target cell.

-Narcotic: this is a drug which induces drowsiness, stupor, or insensibility, and relieves pain.

-Necrotising fasciitis: this is an acute disease in which inflammation of the fasciae of muscles or other organs leads to quick destruction of overlying tissues.

-Necrotizing pancreatitis: acute pancreatic necrosis is a term usually applied to a serious, often fatal, disease of the pancreas which is due to autodigestion of the gland, presumably by

activation within the ducts of trypsinogen to trypsin, the latter being a powerful proteolytic ferment. Necrotizing acute pancreatitis, is characterized by inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis.

-Neonatal asphyxia: also known as perinatal asphyxia or birth asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain.

-Neovascularization: this is the natural formation of new blood vessels, usually in the form of functional microvascular networks, capable of perfusion by red blood cells, that form to serve as collateral circulation in response to local poor perfusion or ischemia.

-Nephrotoxicity: this is defined as rapid deterioration in the kidney function due to toxic effect of medications and chemicals.

-Nested polymerase chain reaction: a modification of polymerase chain reaction intended to reduce non-specific binding in products due to the amplification of unexpected primer binding sites. Nested polymerase chain reaction involves two sets of primers, used in two successive runs of polymerase chain reaction, the second set intended to amplify a secondary target within the first run product. This allows amplification for a low number of runs in the first round, limiting non-specific products. The second nested primer set should only amplify the intended product from the first round of amplification and not non-specific product. This allows running more total cycles while minimizing non-specific products. This is useful for rare templates or PCR with high background.

-Neuromyelitis optica: this is a heterogeneous condition consisting of the inflammation and demyelination of the optic nerve (optic neuritis) and the spinal cord (myelitis). It can be monophasic or recurrent.

-Neurosarcoidosis: this is a form of sarcoidosis; a long-term (chronic) disease of the central nervous system (CNS), encompassing the brain, spinal cord and optic nerve, and characterized by inflammation within one or more of these areas.

-Neutralizing antibodies (Nabs): they are an important specific defense against viral invaders. Neutralizing antibodies (Nab) not only to bind to a virus, they bind in a manner that blocks

infection. A neutralizing antibody (Nab) might block interactions with the receptor, or might bind to a viral capsid in a manner that inhibits uncoating of the genome. Only a small subset of the many antibodies (Abs) that bind a virus are capable of neutralization. After an infection, it can take some time for the host to produce highly effective neutralizing antibodies (Nab) but these persist to protect against future encounters with the agent.

-Neutrophil extracellular traps (NETs): neutrophils are the most abundant leukocytes in mammals and, as a first line of defense against microbes, they play crucial roles in innate immune responses. The mechanisms used by neutrophils to eliminate microbes include phagocytosis, reactive oxygen species' (ROS) generation and the release of microbicidal molecules from granules (degranulation). In 2004, another distinct antimicrobial activity was described: neutrophils extrude a meshwork of chromatin fibers that are decorated with granule-derived antimicrobial peptides and enzymes such as neutrophil elastase, cathepsin G, and myeloperoxidase (MPO). These structures, called neutrophil extracellular traps (NETs), represent an important strategy to immobilize and kill invading microorganisms. The NET scaffold consists of chromatin fibers with a diameter of 15–17 nm; DNA and histones represent the major NET constituents (2). Mass spectrometry has identified various additional proteins associated with NETs, including components from various types of granules.

-Non-alcoholic fatty liver disease (NAFLD): also known as metabolic (dysfunction) associated fatty liver disease (MAFLD), it is excessive fat build-up in the liver without another clear cause such as alcohol use. There are two types; non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), with the latter also including liver inflammation. Non-alcoholic fatty liver disease (NAFLD) is less dangerous than non-alcoholic steatohepatitis (NASH) and usually does not progress to non-alcoholic steatohepatitis (NASH) or liver cirrhosis. When non-alcoholic fatty liver disease (NAFLD) does progress to non-alcoholic steatohepatitis (NASH), it may eventually lead to complications such as cirrhosis, liver cancer, liver failure, or cardiovascular disease.

-Non-celiac gluten sensitivity (NCGS): or gluten sensitivity, it is a clinical entity induced by the ingestion of gluten leading to intestinal and/or extraintestinal symptoms.

-Nonconvulsive status epilepticus (NCSE): this is a state of ongoing seizure or intermittent seizure activity with minimal or no motor movements and alteration of consciousness.

-Nonvalvular atrial fibrillation: Atrial fibrillation, or A-fib, refers to an erratic heart rhythm. This can result from leaky or blocked valves in the heart. However, the valves are not always involved. In this case, the diagnosis is nonvalvular atrial fibrillation (nonvalvular A-fib). Nonvalvular causes of atrial fibrillation (AFib) may include: exposure to heart stimulants, such as alcohol or caffeine or tobacco, sleep apnea, high blood pressure, lung problems, hyperthyroidism, or an overactive thyroid gland, and stress due to a severe illness, such as pneumonia. Valvular causes of atrial fibrillation (AFib) include having a prosthetic heart valve or a condition known as mitral valve stenosis.

-Noradrenaline: also called norepinephrine (NE), it is a hormone which is released by the adrenal medulla and by the sympathetic nerves and functions as a neurotransmitter. It is also used as a drug to raise blood pressure.

-0.9Normal saline (NS): this is prepared by adding usually 20 mmol potassium chloride (KCl) to 100 ml of 0.9 sodium chloride (NaCl).

-Normokalemia: it is the state of having a normal concentration of potassium in one's blood.

-Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B): it is a protein complex that controls transcription of deoxyribonucleic acid (DNA), cytokine production and cell survival. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway has long been considered a prototypical pro-inflammatory signaling pathway, largely based on the role of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) in the expression of pro-inflammatory genes including cytokines, chemokines, and adhesion molecules.

-Nucleotide: it is the basic building block of nucleic acids. Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) are polymers made of long chains of nucleotides. A nucleotide consists of a sugar molecule [either ribose in ribonucleic acid (RNA) or deoxyribose in deoxyribonucleic acid (DNA)] attached to a phosphate group and a nitrogen-containing base.

The bases used in deoxyribonucleic acid (DNA) are adenine (A), cytosine (C), guanine (G), and thymine (T). In ribonucleic acid (RNA), the base uracil (U) takes the place of thymine.

-Nystagmus: this indicates rapid, involuntary eye movement.

-Obesity: it is a disorder in systems regulating body weight characterized by accumulation of excess body fat. Obesity is when body mass index (BMI) $\geq 30 \text{kg/m}^2$. Notably, body mass index (BMI) was calculated by dividing the body weight in kilograms (Kg) by the square of height in meters (m).

-Obsessive compulsive disorder (OCD): this is an anxiety disorder in which time people have recurring, unwanted thoughts, ideas or sensations (obsessions) that make them feel driven to do something repetitively (compulsions).

-Obstructive sleep apnea syndrome (OSA): it is a sleep-related breathing disorder that involves a decrease or complete halt in airflow despite an ongoing effort to breathe. It occurs when the muscles relax during sleep, causing soft tissue in the back of the throat to collapse and block the upper airway. This leads to partial reductions (hypopneas) and complete pauses (apneas) in breathing that last at least 10 seconds during sleep. Most pauses last between 10 and 30 seconds, but some may persist for one minute or longer. This can lead to abrupt reductions in blood oxygen saturation, with oxygen levels falling as much as 40 percent or more in severe cases.

-Ocular adnexal tumors: orbital and adnexal tumors develop from tissue, such as from muscle, nerve, or skin around the eyeball. The orbit – also known as the eye socket-consists of the tissues surrounding the eyeball. The adnexal structures of the eye include the eyelids and tear glands.

-Ocular amyloidosis: amyloidosis is a diverse, heterogeneous group of disorders characterized by the deposition of hyaline extracellular material into various tissues throughout the body including the eye and ocular adnexa. Ocular amyloidosis has been reported in almost every part of the eye as well as adnexal and orbital tissues.

-Ocular hypertension: this is characterized by high intraocular pressure but no clinical signs of glaucomatous damage to the optic nerve or visual field.

-Oculogyric crisis (OGC): this is the name of a dystonic reaction to certain drugs or medical conditions characterized by a prolonged involuntary upward deviation of the eyes.

-Oliguria: it is defined as a urine output that is less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children, and less than 400 mL daily in adults. It is one of the clinical hallmarks of renal failure and has been used as a criterion for diagnosing and staging acute kidney injury (AKI), previously referred to as acute renal failure. At onset, oliguria is frequently acute. It is often the earliest sign of impaired renal function and poses a diagnostic and management challenge to the clinician.

-Open reading frame (ORF): In molecular genetics, an open reading frame (ORF) is the part of a reading frame that has the ability to be translated. An open reading frame (ORF) is a continuous stretch of codons that begins with a start codon (usually AUG) and ends at a stop codon (usually UAA, UAG or UGA). An ATG codon (AUG in terms of RNA) within the open reading frame (ORF) (not necessarily the first) may indicate where translation starts. The transcription termination site is located after the open reading frame (ORF), beyond the translation stop codon. If transcription were to cease before the stop codon, an incomplete protein would be made during translation. In the context of gene finding, the start-stop definition of an open reading frame (ORF) therefore only applies to spliced messenger ribonucleic acids (mRNAs), not genomic deoxyribonucleic acid (DNA), since introns may contain stop codons and/or cause shifts between reading frames. An alternative definition says that an open reading frame (ORF) is a sequence that has a length divisible by three and is bounded by stop codons.

-Ophthalmoplegia: this refers to paralysis of the muscles within or surrounding the eye.

-Opiate: it is a drug derived from or related to opium. Opium is a reddish-brown heavy-scented addictive drug prepared from the juice of the opium poppy, used illicitly as a narcotic and occasionally in medicine as an analgesic.

-Opsonin: it is a substance binding to foreign microorganisms or cells making them more susceptible to phagocytosis. Phagocytosis is the ingestion of bacteria or other material by phagocytes and amoeboid protozoans.

-Optic neuritis: this is an inflammation of the eye's optic nerve.

-Osmotic myelinolysis: or CPM, central pontine myelinolysis, it is a complication of severe and prolonged hyponatremia, particularly when corrected too rapidly.

-Osteomyelitis: it is inflammation of bone or bone marrow, usually due to infection.

-Osteoporosis: it is a medical condition in which the bones become brittle and fragile from loss of tissue, typically as a result of hormonal changes, or deficiency of calcium or vitamin D.

-Over hydration: it is the state of an excess of water in the body.

-Over-expression of rhodopsin: this is attributed to mutations in genes involved in the termination of rhodopsin signaling activity have been shown to cause degeneration by persistent activation of the phototransduction cascade.

-Overload the right ventricle: volume overload of the right ventricle with no or minimal change in pressure, is basically associated with a preserved ejection fraction, while both end-diastolic volume and ejection fraction of the left ventricle are decreased.

-Oxidative stress: it is a phenomenon caused by an imbalance between production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. Reactive oxygen species (ROS) can play, and in fact they do it, several physiological roles (i.e., cell signaling), and they are normally generated as by-products of oxygen metabolism; despite this, environmental stressors (i.e., UV, ionizing radiations, pollutants, and heavy metals) and xenobiotics (i.e., antitubercular drugs) contribute to greatly increase reactive oxygen species (ROS) production, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress). Superoxide radicals ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\cdot OH$), and singlet oxygen (1O_2) are commonly defined reactive oxygen species (ROS); they are generated as metabolic by-products by biological systems. Processes, like protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation, are all dependent on a proper reactive oxygen species (ROS) production and presence inside cells that need to be kept at a low level. When reactive oxygen species (ROS) production increases, they start showing harmful effects on important cellular structures like proteins, lipids, and nucleic acids. A large body of evidences shows that oxidative

stress can be responsible, with different degrees of importance, in the onset and/or progression of several diseases (i.e., cancer, diabetes, metabolic disorders, atherosclerosis, and cardiovascular diseases).

-Oxygenation index: this is a calculation used in intensive care medicine to measure the fraction of inspired oxygen (FiO_2) and its usage within the body. A lower oxygenation index is better - this can be inferred by the equation itself. As the oxygenation of a person improves, they will be able to achieve a higher PaO_2 (Partial pressure of oxygen in arterial blood) at a lower FiO_2 (fraction of inspired oxygen).

-p120-catenin: this is an armadillo-repeat protein, regulates the stability of classical cadherins).

-Pain disorder: this is chronic pain experienced by a patient in one or more areas, and thought to be caused by psychological stress.

-Palpable dorsalis pedis: this is when artery pulse palpated readily lateral to the extensor hallucis longus tendon (or medially to the extensor digitorum longus tendon) on the dorsal surface of the foot, distal to the dorsal most prominence of the navicular bone which serves as a reliable landmark for palpation.

-Pancreatitis: the pancreas is a large gland behind the stomach and close to the first part of the small intestine. It secretes digestive juices into the small intestine through a tube called the pancreatic duct. The pancreas also releases the hormones insulin and glucagon into the bloodstream. Pancreatitis is inflammation of the pancreas. It happens when digestive enzymes start digesting the pancreas itself. Pancreatitis can be acute or chronic. Either form is serious and can lead to complications.

-Panic disorder: this is an anxiety disorder characterized by reoccurring unexpected panic attacks, as panick attacks characterized by sudden periods of intense fear accompanied by palpitations, sweating, shaking, shortness of breath, numbness, or a feeling that something terrible may be going to happen.

-Paradoxical hemolysis: A patient with classical cold agglutinin disease initially experienced haemolytic episodes during cold exposure. However, with advancing disease cold-induced haemolysis ceased and was substituted with a haemolytic disposition at elevated body temperatures. To investigate this paradoxical development of disease manifestations, we

performed a clinical and immunological study. Our results indicate that the patient's complement system became exhausted during the later phase of his disease, probably due to continual consumption of complement components. Initially, the patient had slightly decreased C4 concentrations and moderately reduced total haemolytic activity (CH50). Later C4 fell to undetectable levels and CH50 declined to zero. The increased haemolytic activity experienced during febrile episodes is probably due to a cold agglutinin with a high thermal amplitude, combined with enhanced synthesis of complement molecules during the acute phase response. Although C4 concentrations never increased to detectable levels during infections or inflammations an acute phase reaction was determined each time, as evidenced by increased concentrations of CRP. By reconstituting the patient's serum with active complement from donor serum or plasma, increased haemolytic activity was observed. These results indicate that some patients with cold agglutinin disease may experience deleterious haemolytic consequences if transfused with plasma-containing blood products.

-Paraesthesiae: paresthesia refers to a burning or prickling sensation (pins and needles) that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body. The sensation, which happens without warning, is usually painless and described as tingling or numbness, skin crawling, or itching. it is an abnormal sensation, typically tingling or pricking, resulted chiefly by pressure on or damage to peripheral nerves.

-Paralytic ileus: this refers to obstruction of the intestine due to paralysis of the intestinal muscles.

-Paraplegia: this indicates paralysis of the legs and lower body, typically caused by spinal injury or disease.

-Paresis: a condition of muscular weakness caused by nerve damage or disease; partial paralysis.

-Paresthesia: this is an abnormal sensation, typically tingling or pricking, caused chiefly by pressure on or damage to peripheral nerves.

-Pars planitis: this is a disease of the eye that is characterized by inflammation of the narrowed area (pars plana) between the colored part of the eye (iris) and the choroid. This may lead to blurred vision; dark, floating spots in the vision; and progressive vision loss.

-Partial pressure of oxygen (PaO₂): it is a measurement of oxygen pressure in arterial blood. It reflects how well oxygen is able to move from the lungs to the blood, and it is often altered by severe illnesses.

-Paroxysmal nocturnal hemoglobinuria (PNH): this is a rare disorder where red blood cells (RBCs) easily destroyed by certain immune system proteins.

-Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT or APTT): it is a blood test characterizing coagulation of the blood.

-Parvovirus B19 (B19V): human parvovirus B19 (B19V), now termed erythrovirus, has been associated with many clinical situations (neurological and myocardium infections, persistent B19V DNAemia) in addition to the prototype clinical manifestations, i.e., erythema infectiosum and erythroblastopenia crisis.

-Passive immunity: this is the short-term immunity which results from the introduction of antibodies (Abs) from another person or animal.

-Patchy pneumonia: this is atypical pneumonia refers to the radiological pattern associated with patchy inflammatory changes, often confined to the pulmonary interstitium.

-Patent foramen ovale (PFO): this is a hole between the left and right atria (upper chambers) of the heart.

-Pattern recognition receptors (PRRs): proteins capable of recognizing molecules frequently found in pathogens (the so-called Pathogen-Associated Molecular Patterns—PAMPs), or molecules released by damaged cells (the Damage-Associated Molecular Patterns—DAMPs).

-Pericardial effusion: it is the buildup of excess fluid in the sac-like structure around the heart (pericardium).

-Pericarditis: this refers to inflammation of the pericardium, two thin layers of a sac-like tissue that surround the heart, hold it in place and help it work. A small amount of fluid keeps the layers separate so that there's no friction between them. A common symptom of pericarditis is chest pain, caused by the sac's layers becoming inflamed and possibly rubbing against the heart. It may feel like pain from a heart attack. Pericarditis is often the result of an infection such

as: viral infections that cause a chest cold or pneumonia, infections with bacteria (less common), and some fungal infections (rare).

-Pericytes: they are cells present at intervals along the walls of capillaries (and post-capillary venules). In the central nervous system (CNS), they are important for blood vessel formation, maintenance of the blood–brain barrier (BBB) , regulation of immune cell entry to the central nervous system (CNS) and control of brain blood flow. However, it has become clear that much of the flow increase is generated by dilation of capillaries, rather than of arterioles (which dilate more slowly), and that this is achieved by a relaxation of contractile pericytes. Pericytes also play a key role in pathology: in ischaemia pericytes constrict capillaries, trapping blood cells, which prevents microcirculatory reperfusion after clot removal in stroke. This has made pericytes an important therapeutic target.

-Peripheral artery disease (PAD): it is now the preferred term for partial or complete obstruction of ≥ 1 peripheral arteries. Peripheral artery disease (PAD) refers to atherosclerotic occlusive disease of the lower extremities. Other terms used for this condition are peripheral vascular disease, peripheral arterial occlusive disease, and lower extremity arterial disease.

-Peripheral blood mononuclear cell (PBMC):this is any peripheral blood cell having a round nucleus. These cells consist of lymphocytes (T cells, B cells, NK cells) and monocytes, whereas erythrocytes and platelets have no nuclei, and granulocytes (neutrophils, basophils, and eosinophils) have multi-lobed nuclei.

-Peripheral edema: it refers to edema (accumulation of fluid causing swelling) in tissues perfused by the peripheral vascular system, usually in the lower limbs.

-P-glycoprotein (P-gp): it is a plasma membrane efflux pump that is commonly associated with therapy resistances in cancers and infectious diseases. P-glycoprotein (P-gp) can lower the intracellular concentrations of many drugs to subtherapeutic levels by translocating them out of the cell. Because of the broad range of substrates transported by P-glycoprotein (P-gp), overexpression of P-glycoprotein (P-gp) causes multidrug resistance.

-Phlebitis: this is the inflammation of the walls of a vein.

-Phylogenetic tree or evolutionary tree: it is a branching diagram or "tree" showing the evolutionary relationships among various biological species or other entities—their phylogeny—based upon similarities and differences in their physical or genetic characteristics.

-Pigment dispersion syndrome: this is a condition that happens when pigment rubs off of the back of the iris of the eye when the fibers supporting the lens rub against it. This pigment is deposited in the trabecular meshwork of the eye, where the fluid drains out.

-Plasmapheresis: this is a method of removing blood plasma from the body by withdrawing blood, separating it into plasma and cells, and transfusing the cells back into the bloodstream.

-*Plasmodium falciparum*: this is a unicellular protozoan parasite of humans, and the deadliest species of *Plasmodium* causing malaria in humans.

-Platelet: it is small disk-shaped body in the bloodstream that aids in the clotting process.

-Platelet-activating factor: it is a potent phospholipid activator and mediator of many leukocyte functions, platelet aggregation and degranulation, inflammation, and anaphylaxis. Anaphylaxis is an acute allergic reaction to an antigen to which the body has become hypersensitive.

-Platelet factor 4 (PF4): it is also called CXCL4 and it is a rather atypical chemokine because its leukocyte chemoattractant activity is not that prominent. However, CXCL4 influences a large range of processes via interaction with a diversity of cellular receptors. These receptors are expressed on leukocytes, endothelial, epithelial and mesangial cells and also tumor cells and involve classical chemokine receptors as well as glycosaminoglycans (GAG). Its most prominent activity is inhibition of angiogenesis and, consequently, of tumor growth and metastasis. The first extracellular molecules binding CXCL4 were identified to be chondroitin sulphate-containing proteoglycans. These glycosaminoglycans (GAG) mediate the effects of CXCL4 on monocytes and neutrophils and pass intracellular signals to tyrosine kinases of the Src family, members of the mitogen-activated protein kinase (MAPK or MAP kinase) family and monomeric GTPases. CXCL4 also has high affinity for heparin and heparan sulphate. Through its ability to bind and neutralize heparin, CXCL4 influences blood coagulation. More so, the

interaction of CXCL4 with heparan sulphate proteoglycans on endothelial cells is responsible for the rapid clearance of CXCL4 from the circulation and prevents degradation of the chemokine.

-Pleocytosis: this refers to the presence of an abnormally large number of lymphocytes in the cerebrospinal fluid.

-Plethora: it means a large or excessive amount of something.

-Pleural effusion: it is sometimes referred to as water on the lungs, it is the build-up of excess fluid between the layers of the pleura outside the lungs. The pleura are thin membranes that line the lungs and the inside of the chest cavity and act to lubricate and facilitate breathing.

-Pleurisy: it refers to inflammation of the pleurae, which impairs their lubricating function and causes pain when breathing. It is caused by pneumonia and other diseases of the chest or abdomen.

-Pleuritic chest pain: it is characterized by sudden and intense sharp, stabbing, or burning pain in the chest when inhaling and exhaling. It is exacerbated by deep breathing, coughing, sneezing, or laughing.

-Pleuritis: it refers inflammation of the pleura which may be caused by infection, injury or tumor. When the pleura becomes inflamed, it can produce more than the normal amount of fluid, causing a pleural effusion.

-Pneumocystis pneumonia: *Pneumocystis* is an opportunistic fungal pathogen that causes an often-lethal pneumonia in immunocompromised hosts. This unusual lung infection was known as plasma cellular interstitial pneumonitis of the newborn, and was characterized by severe respiratory distress and cyanosis with little or no fever and no pathognomic physical signs. At that time, only anecdotal cases were reported in adults. Usually these patients had an underlying malignancy that led to a malnourished state.

-Pneumocytes: they are the surface epithelial cells of the alveoli. They are of two types: the type I pneumocytes form part of the barrier across which gas exchange occurs and they can be identified as thin, squamous cells whose most obvious feature is their nuclei; type II pneumocytes are larger, cuboidal cells and occur more diffusely than type I cells and they appear

foamier than type I cells because of they contain phospholipid multilamellar bodies, the precursor to pulmonary surfactant. Capillaries form a plexus around each alveolus.

-Polycythemia: this is an abnormally increased concentration of haemoglobin in the blood, either through reduction of plasma volume or increase in red cell numbers. It may be a primary disease of unknown cause, or a secondary condition linked to respiratory or circulatory disorder or cancer.

-Polyarteritis nodosa (PAN): it is a rare disease that results from blood vessel inflammation (vasculitis) causing injury to organ systems. The areas most commonly affected by polyarteritis nodosa (PAN) include the nerves, intestinal tract, heart, and joints.

-Polyps: these are small growth, usually benign and with a stalk, protruding from a mucous membrane.

-Porphobilinogen: it is a dicarboxylic acid derived from pyrrole, found in the urine in acute porphyria, and that on condensation of four molecules yields uroporphyrin and other porphyrins.

-Porphyria cutanea tarda (PCT): it is a form of porphyria primarily affecting the skin. People affected by this condition generally experiencing photosensitivity, which causes painful, blistering lesions to develop on sun-exposed areas of the skin (i.e. the hands and face).

-Porphyrin: any of a class of pigments (including haem and chlorophyll) whose molecules contain a flat ring of four linked heterocyclic groups, sometimes with a central metal atom.

-Positive end-expiratory pressure (PEEP): it is the pressure in the lungs (alveolar pressure) above atmospheric pressure (the pressure outside of the body) that is present at the end of expiration.

-Positive-sense single-stranded RNA virus (or (+)ssRNA virus): it is a virus that uses positive sense single stranded ribonucleic acid (RNA) as its genetic material. Single stranded ribonucleic acid (RNA) viruses are classified as positive or negative depending on the sense or polarity of the ribonucleic acid (RNA). The positive-sense viral ribonucleic acid (RNA) genome can serve as messenger ribonucleic acid (mRNA) and can be translated into protein in the host cell. Positive-sense single stranded ribonucleic acid (ssRNA) viruses belong to Group IV in the

Baltimore classification. Positive-sense ribonucleic acid (RNA) viruses account for a large fraction of known viruses, including many pathogens such as the hepatitis C virus, West Nile virus, dengue virus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) coronaviruses, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as well as less clinically serious pathogens such as the rhinoviruses that cause the common cold. Positive-sense single stranded ribonucleic acid (ssRNA) viruses have genetic material that can function both as a genome and as messenger ribonucleic acid (mRNA); it can be directly translated into protein in the host cell by host ribosomes. The first proteins to be expressed after infection serve genome replication functions; they recruit the positive-strand viral genome to viral replication complexes formed in association with intracellular membranes. These complexes contain proteins of both viral and host cell origin, and may be associated with the membranes of a variety of organelles-often the rough endoplasmic reticulum, but also including membranes derived from mitochondria, vacuoles, the Golgi apparatus, chloroplasts, peroxisomes, plasma membranes, autophagosomal membranes, and novel cytoplasmic compartments. The replication of the positive-sense single stranded ribonucleic acid (ssRNA) genome proceeds through double-stranded ribonucleic acid (RNA) intermediates, and the purpose of replication in these membranous invaginations may be the avoidance of cellular response to the presence of double stranded ribonucleic acid (dsRNA). In many cases subgenomic ribonucleic acids (RNAs) are also created during replication. After infection, the entirety of the host cell's translation machinery may be diverted to the production of viral proteins as a result of the very high affinity for ribosomes of the viral genome's internal ribosome entry site (IRES) elements; in some viruses, such as poliovirus and rhinoviruses, normal protein synthesis is further disrupted by viral proteases degrading components required to initiate translation of cellular messenger ribonucleic acid (mRNA). All positive-sense single stranded ribonucleic acid (ssRNA) virus genomes encode RNA-dependent RNA polymerase (RdRP), a viral protein that synthesizes ribonucleic acid (RNA) from a ribonucleic acid (RNA) template. Host cell proteins recruited by positive-sense single stranded ribonucleic acid (ssRNA) viruses during replication include RNA-binding proteins, chaperone proteins, and membrane remodeling and lipid synthesis proteins, which collectively participate in exploiting the cell's secretory pathway for viral replication.

-Posterior reversible encephalopathy syndrome (PRES): it is a clinico-radiological syndrome characterized by a headache, seizures, altered mental status and visual loss and characterized by white matter vasogenic edema affecting the posterior occipital and parietal lobes of the brain predominantly.

-Posterior tibial pulses: these are pulses felt over the posterior tibial artery just posterior to the ankle bone on the inner aspect of the ankle.

-Postphlebotic syndrome: it is also called postthrombotic syndrome. It refers to symptomatic chronic venous insufficiency after deep venous thrombosis (DVT).

-Posttraumatic stress disorder: this is a mental health condition triggered by a terrifying event - either experiencing it or witnessing it, symptoms including flashbacks, nightmares, severe anxiety, and uncontrollable thoughts about the event.

-PR interval: this refers to the time from the onset of the P wave to the start of the QRS complex. It reflects conduction through the atrioventricular (AV) node.

-Preeclampsia: also called premature birth, this refers to the birth of a baby at fewer than 37 weeks' gestational age.

-Preterm delivery: it refers to any birth before 37 weeks completed weeks of gestation.

-Preventive therapies: or preventive medicine, these are medical practices that are designed to avert and avoid disease.

-Primary hyperaldosteronism: also called primary aldosteronism, PA, or Conn's syndrome, an illness where adrenal gland(s) produce too much aldosterone leading to hypertension (HTN) and low blood potassium levels.

-Procalcitonin (PCT): it is a protein that consists of 116 amino acids (AAs) and it is the peptide precursor of calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Procalcitonin arises from endopeptidase-cleaved proprocalcitonin. The reference value of procalcitonin (PCT) in adults and children older than 72 hours is 0.15 ng/mL or less.

-Progressive multifocal leucoencephalopathy (PML): this is a disease of the white matter of the brain, caused by a virus infection that targets cells that make myelin--the material that insulates nerve cells (neurons).

-Prone positioning: this is a body position in which the person lies flat with the chest down and the back up; in anatomical terms of location, the dorsal side is up, and the ventral side is down.

-Prothrombin: it is a protein present in blood plasma which is converted into active thrombin during coagulation.

-Prothrombin time (PT): it is a blood test that measures the time it takes for the liquid portion (plasma) of blood to clot.

-Pseudo-exfoliation syndrome: this is an eye condition that often leads to glaucoma. Called the pseudoexfoliation syndrome because deposits on the surface of the lens look like flakes of dandruff, as if the lens capsule has exfoliated (shed the flakes).

-Psychosis: this is characterized by an impaired relationship with reality, a symptom of serious mental disorders, having either hallucinations or delusions.

-Pulmonary angiography: this is a test to see how blood flows through the lung. Angiography is an imaging test that uses x-rays and a special dye to see inside the arteries. Arteries are blood vessels that carry blood away from the heart.

-Pulmonary dead space: this is the volume of a breath that does not participate in gas exchange.

-Pulmonary edema: it occurs when fluid accumulates in the air sacs of the lungs--the alveoli--making it difficult to breathe. This interferes with gas exchange and can cause respiratory failure. Pulmonary edema can be acute (sudden onset) or chronic (occurring more slowly over time). If it is acute, it is classed as a medical emergency needing immediate attention. The most common cause of pulmonary edema is congestive heart failure, where the heart cannot keep up with the demands of the body.

-Pulmonary embolism (PE): it is the blockage of a branch of the pulmonary artery by a substance that has traveled from elsewhere in the body through the bloodstream. The majority of pulmonary embolisms are caused by venous thromboembolism (VTE) but in some cases it may also come from other sources (fat, injuries, orthopedic surgeries or amniotic fluid during childbirth). Pulmonary embolism (PE) is a blood clot occurring in the lungs causing damage part of the lung and other organs and decreasing oxygen levels in the blood.

-Pulmonary consolidation: it is a region of normally compressible lung tissue that has filled with liquid instead of air.

-Pulmonary function tests (PFTs): these are noninvasive tests that show how well the lungs are working. The tests measure lung volume, capacity, rates of flow, and gas exchange. This information can help the healthcare provider diagnose and decide the treatment of certain lung disorders.

-Pulmonary langerhans cell histiocytosis (PLCH): this is a rare sporadic cystic lung disease of unknown aetiology that is characterised by the infiltration and destruction of the wall of distal bronchioles by CD1a⁺ Langerhans-like cells.

-Pulmonary wedge pressure (PWP): or cross-sectional pressure (also called the pulmonary arterial wedge pressure or PAWP, pulmonary capillary wedge pressure or PCWP, or pulmonary artery occlusion pressure or PAOP), is the pressure measured by wedging a pulmonary catheter with an inflated balloon into a small pulmonary arterial branch. It estimates the left atrial pressure.

-Purpura fulminans: this is an acute, often fatal, thrombotic disorder manifesting as blood spots, bruising and discolouration of the skin resulting from coagulation in small blood vessels within the skin and rapidly leading to skin necrosis and disseminated intravascular coagulation (DIC).

-qSOFA score (also known as quick SOFA): it is a bedside prompt that may identify patients with suspected infection who are at greater risk for a poor outcome outside the intensive care unit (ICU). The score ranges from 0 to 3 points.

-QT interval: this is the time from the start of the Q wave to the end of the T wave, representing the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

-Quadriplegia: this indicates paralysis of all four limbs, tetraplegia.

-RANTES: it is also called chemokine (C-C motif) ligand 5 (also CCL5), a selective attractant for memory T lymphocytes and monocytes.

-Raynaud's disease: this is a disease characterized by spasm of the arteries in the extremities, especially the fingers (Raynaud's phenomenon). It is occurring because an abnormal spasm of the blood vessels causing a diminished blood supply to the local tissues. It is typically brought on by constant cold or vibration, and leads to pallor, pain, numbness, and in severe cases, gangrene. It is a condition resulting in discoloration of fingers and/or toes when a person is exposed to changes in temperature (cold or hot) or emotional events and it is associated with connective tissue disease.

-Reactive hyperemia: it is a well-established technique for noninvasive assessment of peripheral microvascular function and a predictor of all-cause and cardiovascular morbidity and mortality. In its simplest form, reactive hyperemia represents the magnitude of limb reperfusion following a brief period of ischemia induced by arterial occlusion.

-Recurrent pregnancy loss: it is classically defined as occurrence of three or more consecutive pregnancy loss; however, American Society of Reproductive Medicine (ASRM) has recently redefined recurrent pregnancy loss as two or more pregnancy losses.

-Reiter syndrome: this is a form of arthritis that produces pain swelling redness and heat in the joints.

-Remittent fever: it is a type or pattern of fever in which temperature does not touch the baseline and remains above normal throughout the day.

-Renin-angiotensin-aldosterone system (RAAS) inhibitors: these are a group of drugs that act by inhibiting the renin-angiotensin-aldosterone system (RAAS) and include angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and direct renin

inhibitors. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are commonly used in the treatment of patients with hypertension, heart failure with reduced ejection fraction, certain types of chronic kidney disease, and patients who have suffered a myocardial infarction. They are particularly important in the treatment of hypertensive diabetic patients, as they prevent the development of diabetic nephropathy.

-Resistant hypertension: this is a condition where blood pressure remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.

-Respiratory acidosis: this is a condition that occurs when the lungs cannot remove all of the carbon dioxide the body produces. This causes body fluids, especially the blood, to become too acidic.

-Respiratory failure (RF): this is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. It is defined as the acute or chronic impairment of respiratory system function to maintain normal oxygen and carbon dioxide values when breathing room air.

-Respiratory support: this includes oxygen supplementation and positive-pressure ventilation. positive-pressure ventilation means that airway pressure is applied at the patient's airway through an endotracheal or tracheostomy tube; the positive nature of the pressure causes the gas to flow into the lungs until the ventilator breath is terminated.

-Respiratory syncytial virus (RSV): Respiratory Syncytial Virus (RSV) is a common virus that infects children and adults; however, children younger than two years of age tend to develop more serious respiratory symptoms. It is responsible for 45%–90% of episodes of bronchiolitis, 15%–35% of pneumonia, 6%–8% of croup, and is also a cause of apnea and otitis media.

-Resting potential: The resting potential is mostly determined by the concentrations of the ions in the fluids on both sides of the cell membrane and the ion transport proteins that are in the cell membrane. The resting potential of a cell can be most thoroughly understood by thinking of it in terms of equilibrium potentials. In the example, model cell given only one ion (potassium) and so in this case, the resting potential of this cell would be the same as the

equilibrium potential for potassium. If the inside of a cell becomes more electronegative (i.e., if the potential is made greater than the resting potential), the membrane or the cell is said to be hyperpolarized. If the inside of the cell becomes less negative (i.e., the potential decreases below the resting potential), the process is called depolarization.

-Retinitis pigmentosa (RP): this is a group of rare, genetic disorders that involve a breakdown and loss of cells in the retina - which is the light sensitive tissue that lines the back of the eye. Common symptoms include difficulty seeing at night and a loss of side (peripheral) vision.

-Reverse transcriptase (RT) enzyme: it is an enzyme used to generate complementary deoxyribonucleic acid (cDNA) from a ribonucleic acid (RNA) template, a process termed reverse transcription. Reverse transcriptases are used by certain viruses such as human immunodeficiency virus (HIV) and the hepatitis B virus to replicate their genomes, by retrotransposon mobile genetic elements to proliferate within the host genome, and by eukaryotic cells to extend the telomeres at the ends of their linear chromosomes.

-Reye syndrome: this is a rare but serious condition causing swelling in the liver and brain.

-Rhabdomyolysis: it is a condition in which damaged skeletal muscle breaks down rapidly. Symptoms may include muscle pains, weakness, vomiting, and confusion. There may be tea-colored urine or an irregular heartbeat. Some of the muscle breakdown products, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure. The muscle damage is most often the result of a crush injury, strenuous exercise, medications, or drug abuse. Other causes include infections, electrical injury, heat stroke, prolonged immobilization, lack of blood flow to a limb, or snake bites. Rhabdomyolysis is also the destruction of striated muscle cells, especially in severe hypokalemia. Some people have inherited muscle conditions that increase the risk of rhabdomyolysis.

-Rheumatoid arthritis (RA): it is an autoimmune and inflammatory disease, which means that the immune system attacks healthy cells in the body by mistake, causing inflammation (painful swelling) in the affected parts of the body. Rheumatoid arthritis mainly attacks the joints, usually many joints at once)

-Rhinovirus (RH): Rhinovirus (RV) was first isolated in 1956 by Dr. Winston Price at Johns Hopkins University and was quickly determined to be the most common cause of cold symptoms

in adults. In non-asthmatic individuals, symptoms of rhinovirus (RV) infection are generally limited to the upper respiratory tract. Rhinorrhea and nasal obstruction, the most prominent symptoms, are associated with a neutrophilic inflammatory response that is associated with increased vascular permeability and stimulation of mucus hypersecretion. Cough is a less common but bothersome manifestation of rhinovirus upper respiratory infection (URI). The pathogenesis of cough may involve irritation from posterior pharyngeal drainage or direct infection of the large airways. It was demonstrated sinus involvement in many individuals with typical common cold symptoms. The sinus disease resolved without intervention suggesting that these upper respiratory illnesses should be more accurately characterized as a viral rhinosinusitis. However, the inflammation associated with obstruction of sinus openings and secondary Eustachian tube dysfunction can predispose to acute bacterial sinusitis and otitis media, respectively. In contrast, lower respiratory symptoms associated with rhinovirus (RV) infection are most prominent in patients who have underlying asthma or other chronic lung disease.

-Right heart catheterization (RHC): in a right heart catheter procedure, a catheter is passed into a vein in the neck or groin to measure the pressure in the heart and lungs. The procedure helps the doctor to work out how well the heart is working. A right heart catheter helps to diagnose or manage conditions like: heart failure, shock, congenital heart disease, heart valve disease, and pulmonary hypertension

-Right ventricular failure (RVF): The normal right ventricle (RV) function is an interplay between preload, contractility, afterload, ventricular interdependence and heart rhythm. Most cases of right ventricle (RV) failure follow existing or new-onset cardiac or pulmonary diseases or a combination of both, which may increase right ventricle (RV) afterload, reduce right ventricle (RV) contractility, alter right ventricle (RV) preload or ventricular interdependence or cause-related arrhythmias.

-Sarcoidosis: it is a multisystemic disorder of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar adenopathy, pulmonary infiltration, ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones and other organs may also be involved. The diagnosis is established when clinico-radiographic findings are supported by histological evidence of noncaseating epithelioid cell granulomas. Granulomas of unknown causes and local sarcoid

reactions must be excluded. Frequently observed immunological features are depression of cutaneous delayed type-hypersensitivity and a heightened Th-1 [T-helper cell type-1] immune response at sites of disease. Circulating immune-complexes along with signs of B-cell hyperactivity may also be found. The course and prognosis may correlate with the mode of the onset, and the extent of the disease. An acute onset with erythema nodosum or asymptomatic bilateral hilar adenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrapulmonary lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs.

-Sarcopenia: it is a geriatric disease characterized by a progressive loss of skeletal muscle mass and loss of muscle function, constitutes a rising, often undiagnosed health problem. Its prevalence in the elderly population is largely considered variable, as it ranges from 5% to 50% depending on gender, age, pathological conditions as well as diagnostic criteria.

-Schistosomiasis (bilharzia): it is a neglected tropical disease caused by parasitic flatworms (blood flukes) of the genus *Schistosoma*, with considerable morbidity in parts of the Middle East, South America, Southeast Asia and, particularly, in sub-Saharan Africa. Infective larvae grow in an intermediate host (fresh-water snails) before penetrating the skin of the definitive human host. Mature adult worms reside in the mesenteric (*Schistosoma mansoni* and *Schistosoma japonicum*) or pelvic (*Schistosoma haematobium*) veins, where female worms lay eggs, which are secreted in stool or urine. Eggs trapped in the surrounding tissues and organs, such as the liver and bladder, cause inflammatory immune responses (including granulomas) that result in intestinal, hepato-splenic or urogenital disease. Diagnosis requires the detection of eggs in excreta or worm antigens in the serum, and sensitive, rapid, point-of-care tests for populations living in endemic areas are needed.

-Scleroderma-associated renal crisis (SRC): this is an infrequent but serious complication of systemic sclerosis (SSc), associated with increased vascular permeability, activation of coagulation cascade, and renin secretion. It may lead to the acute renal failure typically associated with accelerated hypertension (HTN).

-Scotomata: it is an area of partial alteration in the field of vision consisting of a partially diminished or entirely degenerated visual acuity that is surrounded by a field of normal-or relatively well-preserved – vision.

-Second-degree or higher atrioventricular (AV) block: this is diagnosed when one or more (but not all) of the atrial impulses fail to conduct to the ventricles due to impaired conduction.

-Secondary Ciliary Dyskinesia (SCD): The system of mucociliary clearance has the important task to remove from the airways inhaled substances and locally formed secretions. Inborn disorders of the mucociliary transport are due to ciliary dysfunction (Primary Ciliary Dyskinesia) (PCD) or of increased viscosity of the bronchial secretions (Cystic Fibrosis). To differentiate Primary Ciliary Dyskinesia (PCD) from the ultrastructural abnormalities found during or after injuries such as respiratory infections, the name of Secondary--or acquired--Ciliary Dyskinesia (SCD) was created. In controls, less than 4% of the cilia may show ultrastructural abnormalities. The most frequent of these are the compound cilia and the peripheral microtubular abnormalities. Compound cilia often appear after infection and therefore are thought to arise secondarily. Secondary ultrastructural abnormalities of cilia include also blebs of the axoneme membrane, ciliary disorientation, and absence of axoneme membrane. No increase in ultrastructural ciliary abnormalities has been found in a variety of respiratory disorders: smoking, asthma and allergic rhinitis, chronic rhinitis and sinusitis, chronic bronchitis, cystic fibrosis, and lung carcinoma. But severe modifications of the respiratory epithelium can be seen. Important for the secondary ciliary disorders is their local and reversible character. To distinct from ultrastructural images between primary and secondary ciliary dyskinesia is often uneasy because some of the findings in secondary ciliary dyskinesia obviously mimic those dedicated to primary ciliary dyskinesia

-Secondary hemophagocytic lymphohistiocytosis (sHLH): this is an uncommon hematologic disorder, secondary hemophagocytic lymphohistiocytosis (sHLH) associated with, and thought to be promoted, by malignant and non-malignant diseases that likewise weaken the ability of the immune system ability to attack Epstein-Barr virus (EBV)-infected cells.

-Secretin: this is a hormone released into the bloodstream by the duodenum (especially in response to acidity) to stimulate secretion by the liver and pancreas. Secretin is a hormone that regulates water homeostasis throughout the body and influences the environment of the duodenum by regulating secretions in the stomach, pancreas, and liver. It is a peptide hormone produced in the S cells of the duodenum, which are located in the intestinal glands. In humans, the secretin peptide is encoded by the SCT gene. Secretin helps regulate the pH of the

duodenum by (1) inhibiting the secretion of gastric acid from the parietal cells of the stomach and (2) stimulating the production of bicarbonate from the ductal cells of the pancreas. It also stimulates bile production by the liver; the bile emulsifies dietary fats in the duodenum so that pancreatic lipase can act upon them.

-Segmental pulmonary hypertension: it encompasses any condition with abnormal underlying cardiac or vascular anatomy, usually including varied sources of pulmonary blood supply, which results in distal pulmonary vascular disease that affects various lung segments to differing degrees.

-Sensorium: it is the sensory apparatus or faculties considered as a whole.

-Sepsis: it is a serious condition resulting from the presence of harmful microorganisms in the blood or other tissues and the body's response to their presence, potentially leading to the malfunctioning of various organs, shock, and death. Sepsis is now increasingly being considered a dysregulated systemic inflammatory and immune response to microbial invasion that produces organ injury for which mortality rates are declining to 15–25%. sepsis has become less of an immediate life-threatening disorder and more of a long-term chronic critical illness, often associated with prolonged inflammation, immune suppression, organ injury and lean tissue wasting. Furthermore, patients who survive sepsis have continuing risk of mortality after discharge, as well as long-term cognitive and functional deficits. Earlier recognition and improved implementation of best practices have reduced in-hospital mortality, but results from the use of immunomodulatory agents to date have been disappointing. Similarly, no biomarker can definitely diagnose sepsis or predict its clinical outcome. Because of its complexity, improvements in sepsis outcomes are likely to continue to be slow and incremental.

-Septic shock: this is a severe and potentially fatal condition that occurs when sepsis leads to life-threatening low blood pressure. Sepsis develops when the body has an overwhelming response to infection. It remains defined as sepsis with hyperlactataemia and concurrent hypotension requiring vasopressor therapy, with in-hospital mortality rates approaching 30–50%. With earlier recognition and more compliance to best practices.

-Septum deviation: this is a condition in which the nasal septum- the bone and cartilage dividing the nasal cavity of the nose in half - is significantly off center, or crooked, making breathing difficult.

-Sequential Organ Failure Assessment (SOFA): is a mortality prediction score that is based on the degree of dysfunction of 6 organ systems. The score is calculated at admission and every 24 hours until discharge, using the worst parameters measured during the prior 24 hours. The scores can be used in several ways, including: first, as individual scores for each organ to determine the progression of organ dysfunction; second, as a sum of scores on a single intensive care unit (ICU) day; third, as a sum of the worst scores during the intensive care unit (ICU) stay. The sequential organ failure assessment (SOFA) score stratifies mortality risk in intensive care unit (ICU) patients without restricting the data used to admission values.

-Serial hematocrit: hematocrit is the volume occupied by packed red cells. Serial hematocrit is based on the extent hemodilution processes occur following blood loss.

-Serositis: this refers to small pleural, pericardial, and ascitic effusions.

-Serum amyloid A (SAA): this is a superfamily of acute-phase proteins. The level of serum amyloid A (SAA) in the blood increases dramatically in response to tissue injury and inflammation. Serum amyloid A (SAA) also acts as a cytokine, influencing cell adhesion, migration, proliferation and aggregation. Serum amyloid A is so-named because it is related to the A proteins of secondary amyloidosis.

-Severe hypoxia: this indicates damage to cells resulting only from decreased oxygen tension.

-Severe preeclampsia: this refers to new onset hypertension (HTN) in pregnancy after 20 weeks gestation with proteinuria.

-Shear stress: it is defined as the frictional force generated by blood flow in the endothelium, the force that the blood flow exerts on the vessel wall, expressed in force-area unit (typically dynes/cm²).

-Sickle cell anemia (SCA): it is a disease that is caused by the formation of an abnormal hemoglobin type, which can bind with other abnormal hemoglobin molecules within the red blood cells (RBCs) to cause rigid distortion of the cell. This distortion prevents the cell from passing through small blood vessels; leading to occlusion of vascular beds, followed by tissue ischemia and infarction. Infarction is frequent all over the body in patients with sickle cell

anemia (SCA), leading to the acute pain crisis. Over time, such insults result in medullary bone infarcts and epiphyseal osteonecrosis. In the brain, cognitive impairment and functional neurologic deficits may occur due to white matter and gray matter infarcts. Infarction may also affect the lungs increasing susceptibility to pneumonia. The liver, spleen, and kidney may show infarction as well. Sequestration crisis is an unusual life-threatening complication of sickle cell anemia (SCA), in which a significant amount of blood is sequestered in an organ (usually the spleen), leading to collapse. Lastly, since the red blood cells (RBCs) are abnormal, they are destroyed, resulting in a hemolytic anemia. However, the ischemic complications in patients with sickle cell anemia (SCA) disease far exceed the anemia in clinical significance.

-Single stranded RNA (positive and negative sense RNA): single stranded ribonucleic acid (RNA) viruses are classified as positive or negative depending on the sense or polarity of the ribonucleic acid (RNA). A negative-sense single-stranded ribonucleic acid (RNA) virus [or (-) ssRNA virus] is a virus that uses negative sense, single-stranded RNA as its genetic material. The negative viral ribonucleic acid (vRNA) is complementary to the messenger ribonucleic acid (mRNA) and must be converted to a positive ribonucleic acid (RNA) by RNA polymerase before translation. Negative sense single stranded ribonucleic acid (ssRNA) viruses need RNA polymerase to form a positive sense ribonucleic acid (RNA). The positive-sense ribonucleic acid (RNA) acts as a viral messenger ribonucleic acid (mRNA), which is translated into proteins for the production of new virion materials. With the newly formed virions, more negative sense ribonucleic acid (RNA) molecules are produced. Positive-sense single stranded ribonucleic acid (ssRNA) viruses have their genome directly utilized as messenger ribonucleic acid (mRNA), with host ribosomes translating it into a single protein that is modified by host and viral proteins to form the various proteins needed for replication. One of these includes RNA-dependent RNA polymerase (RNA replicase), which copies the viral ribonucleic acid (vRNA) to form a double-stranded replicative form. In turn, this double stranded ribonucleic acid (dsRNA) directs the formation of new viral ribonucleic acid (vRNA).

-Sinoatrial (SA) node: it represents a cluster of myocytes with pacemaker activity. Under normal circumstances, it generates electrical impulses that set the rhythm and rate of the heart. Any dysfunction of the SA (sinus) node can affect the heart's rate and rhythm.

-Sjögren's syndrome: this also known as Mikulicz disease or Sicca syndrome is a systemic autoimmune disease in which immune cells attack and destroy the exocrine glands that produce tears and saliva. It can exist by itself (primary Sjogren syndrome) or develop in association with another disorder such as rheumatoid arthritis, systemic sclerosis, primary biliary cirrhosis or Hashimoto thyroiditis (associated Sjogren syndrome). Hallmarks are the dry mouth and dry eyes known as the Sicca syndrome.

-Skin bullae: a bulla is a fluid-filled sac or lesion appearing when fluid trapped under a thin layer of skin; a type of blister; bullae the plural of bulla.

-Sleep apnea syndrome: it is defined as 30 or more apneic episodes (the cessation of airflow at the mouth and nose for more than 10 s). Typical subjective complaints of SAS are excessive daytime sleepiness, loud and irregular snoring, disturbed nighttime sleep, mental deterioration and depression. Collapse between the base of the tongue and adjacent posterior and lateral pharyngeal wall is the most prevalent site of airway closure. The obstruction may occur also at the level of the soft palate if it is particularly long. These anatomical factors, combined with a functional loss of muscle tone in the upper airway during sleep, result in obstruction of the airway due to the negative pressure exerted by continued diaphragmatic effort. Periods of apnea frequently last 10 to 30 s, and some continue for more than 100 s. Without adequate ventilation, the blood carbon dioxide pressure eventually increases to a level that arouses the patient. The patient awakens briefly, inhales, and then returns to sleep, without consciously remembering the episode. This sleep pattern disturbance repeats itself throughout the night. As a result of the disturbed sleep, excessive daytime somnolence, cognitive dysfunction and memory loss occur. This has significant sequelae in the professional and social world. In addition, the patients with this condition are at increased risk of death from automobile accidents.

-Sleep arousals: these are interruptions of sleep lasting 3 to 15 seconds, occurring spontaneously or as a result of sleep-disordered breathing or other sleep disorders.

-Sleep disordered breathing (SDB): it describes a group of disorders characterized by: abnormal respiratory patterns (e.g. the presence of apneas or hypopneas); or insufficient ventilation during sleep. An apnea is when a patient stops breathing for 10 seconds or more, and wakes up just enough to take a breath. A hypopnea is when a patient doesn't stop breathing, but

the patient's breathing becomes shallow (i.e., at least a 30% decrease in airflow) for 10 seconds or more, with an associated oxygen desaturation or arousal. Either way, sleep disordered breathing disrupts the patient's sleep pattern, night after night, which not only makes the patient tired and exhausted the next day, but may also put excessive strain on the patient's nervous system and major organs.

-Somnolence: this is sleepiness, the state of feeling drowsy, ready to fall asleep.

-Spherocytes: these are erythrocytes sphere-shaped rather than bi-concave disk shaped as normal. Spherocytes found in all hemolytic anemias to some degree.

-Sphincterotomy: this is surgical incision of a sphincter.

-Splenectomy: this is a surgical operation involving removal of the spleen.

-Splenomegaly: it is abnormal enlargement of the spleen.

-Stasis: it is a slowing or stoppage of the normal flow of a bodily fluid or semifluid: such as a slowing of the current of circulating blood.

-Sterile pyuria: this is the persistent finding of white cells in the urine in the absence of bacteria, as determined by means of aerobic laboratory techniques.

-Stillbirth: it is the birth of an infant died in the womb (strictly, after having survived through at least the first 28 weeks of pregnancy, earlier instances being regarded as abortion or miscarriage).

-Stimulator of interferon genes protein (STING): Stimulator of interferon genes (STING; also known as MITA and MPYS, and encoded by *TMEM173*) is a signaling molecule associated with the endoplasmic reticulum (ER) and is crucial for controlling the transcription of numerous host defense genes, involving type I interferons (IFNs) and pro-inflammatory cytokines, following the recognition of aberrant deoxyribonucleic acid (DNA) species or cyclic dinucleotides (CDNs) in the cytosol of the cell. The sources of deoxyribonucleic acid (DNA) that induce cyclic dinucleotides (CDNs) involve the genome of invading pathogenic agents, whereas certain bacteria can secrete cyclic dinucleotides (CDNs) following infection of the host. Reports have shown that strong activators of the stimulator of interferon genes protein (STING) pathway may

also include self-deoxyribonucleic acid (DNA) that has leaked from the nucleus of the host cell, perhaps following cell division or as a consequence of deoxyribonucleic acid (DNA) damage. Such deoxyribonucleic acid (DNA) species may be responsible for causing various autoinflammatory diseases, such as systemic lupus erythematosus (SLE) or Aicardi–Goutières syndrome (AGS), and may influence inflammation-associated cancer.

-Stocking-and-glove hypesthesia: this refers to nerves in the arms and legs incur damage, a diminished capacity for physical sensation.

- *Streptococcus pneumoniae*: this bacterium is one of the most important human pathogens, and pneumococcal disease is endemic all over the world. For more than a century *S. pneumoniae* has been known as the most common cause of acute otitis media, sinusitis, and pneumonia and one of the most important causes of bacterial meningitis.

-Stress-cardiomyopathy: it is also referred to as broken heart syndrome, takotsubo cardiomyopathy, and apical ballooning syndrome, a condition in which intense emotional or physical stress causing rapid and severe heart muscle weakness (cardiomyopathy).

-Striatonigral degeneration: this is a neurological disorder caused by a disruption in the connection between two areas of the brain-the striatum and the substantia nigra. These two areas are working together and enabling balance and movement.

-Stroke: this is the sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain. It is a disease affecting the arteries leading to and within the brain, occurring when a blood vessel carrying oxygen and nutrients to the brain either blocked by a clot or burst (or rupture).

-Stupor: a state of near-unconsciousness or insensibility.

-Subcutaneous emphysema: it occurs when air gets into tissues under the skin. This most often occurs in the skin covering the chest wall or neck, but can also occur in other parts of the body.

-Subdural effusions: these are collection of cerebrospinal fluid (CSF) trapped between the surface of the brain and the outer lining of the brain (the dura matter).If this fluid infected, the condition is called a subdural empyema.

-Subgenomic ribonucleic acid (sgRNA): synthesis of subgenomic (SG) messenger RNAs (mRNAs) by (+)-strand ribonucleic acid (RNA) viruses allows the differential expression of specific viral genes, both quantitatively and temporally. Subgenomic ribonucleic acids (SG RNAs) have the following properties: first, they are made in infected cells but do not interfere with the normal course of viral replication; second, the subgenomic ribonucleic acid (SG RNA) sequences are shorter than their cognate genomic ribonucleic acids (RNAs); third, their sequences are usually co-terminal with the 3' genomic sequence but sometimes are co-terminal with the 5' sequences. Yet other viruses make subgenomic ribonucleic acids (SG RNAs) which contain a 5' co-terminal leader joined to a 3' co-terminal sequence; fourth, typically, whether a messenger subgenomic ribonucleic acid (SG RNA) contains only one open reading frame (ORF), or multiple open reading frames (ORFs), with some rare exceptions, only the 5' ORF is translated. Although most subgenomic ribonucleic acids (SG RNAs) function as messengers and are translated, other subgenomic ribonucleic acid (SG RNAs), generally those with 5' co-terminal sequences, have other functions. Following the synthesis of the viral RNA-dependent RNA polymerase (RDRP), the (+) strand ribonucleic acid (RNA) is copied into a genome-length (-) strand which then serves as a template for the genomic (G) and the SG (+) strand RNAs. Thus, the (-) strand ribonucleic acid (RNA) contains at least two different promoters, one for the synthesis of genomic ribonucleic acid (G RNA) at or near the 3' end, and one or more internal or subgenomic promoters (SGPs). To synthesize a subgenomic ribonucleic acid (SG RNA), the viral RNA-dependent RNA polymerase (RDRP) recognizes and binds to the subgenomic promoter (SGP) and initiates transcription.

-Surfactant dysfunction: Surfactant dysfunction is a lung disorder that causes breathing problems. This condition results from abnormalities in the composition or function of surfactant, a mixture of certain fats (called phospholipids) and proteins that lines the lung tissue and makes breathing easy. Without normal surfactant, the tissue surrounding the air sacs in the lungs (the alveoli) sticks together (because of a force called surface tension) after exhalation, causing the alveoli to collapse. As a result, filling the lungs with air on each breath becomes very difficult, and the delivery of oxygen to the body is impaired. The signs and symptoms of surfactant dysfunction can vary in severity. The most severe form of this condition causes respiratory distress syndrome in newborns. Affected babies have extreme difficulty breathing and are unable to get enough oxygen. The lack of oxygen can damage the baby's brain and other organs. This

syndrome leads to respiratory failure, and most babies with this form of the condition do not survive more than a few months. Less severe forms of surfactant dysfunction cause gradual onset of breathing problems in children or adults. Signs and symptoms of these milder forms are abnormally rapid breathing (tachypnea); low concentrations of oxygen in the blood (hypoxemia); and an inability to grow or gain weight at the expected rate (failure to thrive). Mutations in genes encoding proteins needed for normal surfactant function and metabolism cause acute lung disease in newborns and chronic lung disease in older children and adults. While rare these disorders are associated with considerable pulmonary morbidity and mortality. The identification of genes responsible for surfactant dysfunction provides clues for candidate genes contributing to more common respiratory conditions, including neonatal respiratory distress syndrome and lung diseases associated with aging or environmental insults.

-Sympathetic nervous system (SNS): this is part of the autonomic nervous system (ANS), an extensive network of neurons regulating the body's involuntary processes.

-Syncope: it refers to temporary loss of consciousness caused by a fall in blood pressure.

-Syndrome of inadequate antidiuretic hormone (SIADH): this is condition in which the body makes too much antidiuretic hormone (ADH); this hormone aids the kidneys control the amount of water the body loses through the urine.

-Syphilis: it is a chronic infectious disease, caused by a spirochete, *Treponema pallidum*, usually venereal in origin but often congenital, and affecting almost any organ or tissue in the body, especially the genitals, skin, mucous membranes, aorta, brain, liver, bones, and nerves.

-Systemic juvenile idiopathic arthritis (sJIA): It was originally called systemic-onset juvenile rheumatoid arthritis or Still's disease. Systemic juvenile idiopathic arthritis (sJIA) is an autoinflammatory disease that causes swelling in the joints. The immune system normally helps to fight off harmful, foreign substances such as bacteria or viruses by becoming more active. The immune system activity returns to normal when the body has successfully dealt with the harmful substance or infection. In an autoinflammatory disease, such as Systemic juvenile idiopathic arthritis (sJIA), the immune system becomes active for reasons that are not clear. It then remains active and begins to attack healthy cells and tissues. This results in inflammation of the joints

causing them to become red, swollen, painful or hot to the touch and more widespread inflammation of the body resulting in features such as fever and rash.

-Systemic lupus erythematosus (SLE): this is a chronic inflammatory condition caused by an autoimmune disease (AID), occurring when the body's tissues attacked by its own immune system. It can be affecting skin, joints, kidneys, brain, and other organs.

-Tachycardia: this is an abnormal rapid heart rate. It is the medical term for a heart rate over 100 beats per minute. There are many heart rhythm disorders (arrhythmias) that can cause tachycardia. Sometimes, it's normal for one to have a fast heartbeat.

-Tachypnea: it is a condition that refers to rapid breathing. The normal breathing rate for an average adult is 12 to 20 breaths per minute. In children, the number of breaths per minute can be a higher resting rate than seen in adults.

-Tactile fremitus: chest inspection, palpation, and auscultation are key components of the physical examination of patients with respiratory disease. Palpation ascertains the signs suggested by inspecting and assessing the state of the pleura and lung parenchyma by studying the vocal fremitus. Vocal (tactile) fremitus is palpation of the chest wall to detect changes in the intensity of vibrations created with certain spoken words in a constant tone and voice indicating underlying lung pathology.

-Tailored treatment: this aims to cure a patient who suffers from a specific disease with an effective and safe drug, based on the complex interactions among patient's characteristics, disease physiopathology and drug metabolism.

-Telangiectasis: this is a condition characterized by dilatation of the capillaries causing them to appear as small red or purple clusters, often spidery in appearance, on the skin or the surface of an organ.

-Terminal ileitis: Terminal ileitis (TI) is an inflammatory condition of the terminal portion of the ileum that may occur acutely with right lower quadrant pain followed or not by diarrhea, or exhibit chronic obstructive symptoms and bleeding and normally it is associated to Crohn's disease (CD) although it may be associated to other different conditions. This review intended to contribute to a better understanding of terminal ileitis (TI) in order to help in the diagnosis, medical approach and patient care. This work was performed on a survey of articles collected in

different databases and a retrospective search was carried out to identify relevant studies in the field. Pathological conditions such as ulcerative colitis, the intake of non-steroidal anti-inflammatory drugs, infectious diseases, eosinophilic enteritis, malignant diseases, spondyloarthropathies, vasculitides, ischemia, sarcoidosis, amyloidosis and others may be related to ileitis but it is commonly referred to Crohn's disease (CD). To a correct therapeutic approach, it is necessary to understand the causes of this inflammation process. The performance of a clinical, laboratory, endo-sopic, and histopathological evaluation of the individuals is crucial to the correct diagnosis and treatment once the inflammation of the ileum may occur due to different pathological conditions besides Crohn's disease (CD), leading to difficulties in the diagnosis. Thus, an individual approach is necessary once the correct diagnosis is crucial for the immediate therapeutic approach and recovering of the patient.

It is important to refer that Crohn's disease is characterized by the involvement of the gastrointestinal tract (GIT) from mouth to anus, with a transmural pattern of inflammation of gastrointestinal (GI) wall layers.

-Testosterone (T): it is a steroid hormone that stimulates development of male secondary sexual characteristics, produced mainly in the testes, but also in the ovaries and adrenal cortex.

- The Food and Drug Administration (FDA or USFDA): it is a federal agency of the United States Department of Health and Human Services, one of the United States federal executive departments. The Food and Drug Administration (FDA) is responsible for protecting and promoting public health through the control and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed and veterinary products.

-Thrombocytopenia: it refers to deficiency of platelets in the blood, thus causing bleeding into the tissues, bruising, and slow blood clotting after injury. It indicates a platelet count below the lower limit of normal (ie, $<150,000/\text{microL}$ ($150 \times 10^9/\text{L}$) for adults). Moderate thrombocytopenia is where platelet count ranges from $(50,000 \text{ to } 99,000)/\text{microL}$.

-Thrombophilia: it is a medical term used to describe the condition where the blood has an increased tendency to clot. Hereditary thrombophilia is a common cause of thrombosis and is

diagnosed by genetic testing. It can be caused by one of a number of genetic mutations which can change the proteins involved in the blood coagulation cascade. This leads to an increased risk of inappropriate blood clotting and thrombophilia.

-Thrombotic thrombocytopenic purpura (TTP): it is a clearly defined entity of the thrombotic microangiopathies (TMA), a heterogeneous group of disorders characterized by microangiopathic hemolytic anemia with red cell fragmentation, thrombocytopenia and organ dysfunction due to disturbed microcirculation. Thrombotic thrombocytopenic purpura (TTP) is characterized by a severe deficiency of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), an enzyme responsible for physiological cleavage of von Willebrand factor (VWF). Organ dysfunction can be severe and life-threatening, and immediate start of appropriate therapy is necessary to avoid permanent damage or death.

-Thrombotic microangiopathy (TMA): this is a pathology that results in thrombosis in capillaries and arterioles, due to an endothelial injury. It may be seen in association with thrombocytopenia, anemia, purpura and kidney failure. Thrombotic microangiopathy (TMA) is clinical syndrome defined by the presence of hemolytic anemia [destruction of red blood cells (RBCs)], low platelets, and organ damage due to the formation of microscopic blood clots in capillaries and small arteries.

-Thyroid diseases: all forms of thyroid diseases are much more frequently observed in women than men, although the reasons are still not completely elucidated. Hyperthyroidism is defined by elevated circulating free thyroid hormones. The prevalence is about 2 % in women and 0.2 % in men. The most frequent causes are various forms of thyroid autonomy in elderly women and Graves' disease, which occurs mostly in younger women. Hypothyroidism is defined by a lack of thyroid hormones. It is a common endocrine disorder caused by autoimmune thyroiditis (Hashimoto thyroiditis), iodine deficiency or following surgery or radioiodine therapy. Thyroxine requirements depend on fat-free mass and are, therefore, somewhat higher in males who are more often undersubstituted. In pregnancy lower TSH-reference ranges have to be considered and thyroid function should be monitored throughout pregnancy to avoid harm to the foetus caused by maternal thyroid dysfunctions. If overtreated women more often feature fractures, whereas males more often develop atrial fibrillation.

-Thyrotoxicosis: also called hyperthyroidism, overactivity of the thyroid gland, resulting in a rapid heartbeat and an increased rate of metabolism.

-Tidal overdistension: or pulmonary overdistention, defined as a decrease in dynamic compliance of $>$ or $=20\%$ when compared with a compliance measured at a baseline tidal volume of 10 mL/kg.

-Tidal ventilation: tidal volume is the amount of air that moves in or out of the lungs with each respiratory cycle. It measures around 500 mL in an average healthy adult male and approximately 400 mL in a healthy female. It is a vital clinical parameter that allows for proper ventilation to take place.

-Tingling: this is experiencing or causing to experience a slight prickling or stinging sensation.

-TIR-domain-containing adapter-inducing interferon- β (TRIF): it is an adapter in responding to activation of toll-like receptors (TLRs). It mediates the rather delayed cascade of two Toll-like receptor (TLR)-associated signaling cascades, where the other one is dependent upon a MyD88 adapter. Toll-like receptors (TLRs) recognize specific components of microbial invaders and activate an immune response to these pathogenic agents. After these receptors recognize highly conserved pathogenic patterns, a downstream signaling cascade is activated in order to stimulate the release of inflammatory cytokines and chemokines as well as to upregulate the expression of immune cells. All Toll-like receptors (TLRs) have a TIR domain that initiates the signaling cascade through TIR adapters. Adapters are platforms that organize downstream signaling cascades leading to a particular cellular response after exposure to a given pathogen.

-Toll-like receptors (TLRs): they are membrane molecules that function in cellular activation by a wide range of microbial pathogens. Toll-like receptors (TLRs) are classified as Pattern recognition receptors (PRRs) because they recognize pathogen- or microbe-associated molecular patterns (PAMPs or MAMPs) and signal to the host the presence of an infection.

-Toxic shock syndrome (TSS): this is a condition caused by certain strains of bacteria producing toxins, and might be be life-threatening.

-Traction retinal detachment: this happens when scar tissue or other tissue grows on the retina and pulls it away from the layer underneath. It can lead to serious vision loss. This type is often found in

people with diabetes mellitus (DM) who have severe diabetic retinopathy, or damage to blood vessels in the retina.

-Traditional Chinese medicine (TCM): it is including herbal medicine and acupuncture, as one of the most important parts in complementary and alternative medicine (CAM), plays the key role in the formation of integrative medicine.

-Transient ischemic attacks (TIAs): these are brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.

-Transient syncope: it is defined as a transient, self-limited loss of consciousness with an inability to maintain postural tone followed by spontaneous recovery.

-Tremor: it refers to an involuntary quivering movement.

-*Trypanosoma cruzi* : Chagas disease is an inflammatory, infectious disease caused by the parasite *Trypanosoma cruzi*, which is found in the feces of the triatomine (reduviid) bug. Chagas disease is common in South America, Central America and Mexico, the primary home of the triatomine bug. Rare cases of Chagas disease have been found in the southern United States, as well. Also called American trypanosomiasis, Chagas disease can infect anyone. Left untreated, Chagas disease later can cause serious heart and digestive problems.

-Tuberculosis (TB): this is an infectious disease usually caused by *Mycobacterium tuberculosis* (MTB) bacteria. Tuberculosis generally affects the lungs, but can also affect other parts of the body.

-Tumor necrosis factor alpha (TNF α): it is also known as endotoxin-induced factor in serum, cachectin, and differentiation inducing factor, tumor necrosis factor (TNF) causes tumor cell necrosis (a process that involves cell swelling, organelle destruction, and finally cell lysis) and apoptosis (a process that involves cell shrinking, the formation of condensed bodies, and deoxyribonucleic acid (DNA) fragmentation). Tumor Necrosis Factor alpha (TNF- α), is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation and is responsible for a diverse range of signaling events within cells, leading to necrosis or apoptosis. Moreover, studies in tumor necrosis factor-alpha (TNF α) have revealed that tumor necrosis factor (TNF) plays an important role in the regulation of embryo development and the sleep-

wake cycle, and that tumor necrosis factor (TNF) is important for lymph node follicle and germinal center formation as well as host defense against bacterial and viral infection. Tumor necrosis factor (TNF) has been shown to be an endogenous pyrogen that causes fever.

-Tunica intima: this is the innermost tunica (layer) of an artery or vein, made up of one layer of endothelial cells and supported by an internal elastic lamina.

-Unfractionated heparin (UFH): it is a fast-acting blood thinner working together with antithrombin, a natural protein in the body, to block clot formation.

-Uremic toxins: these are compounds that are usually filtered and excreted by the kidneys. In the setting of chronic kidney disease (CKD), these compounds may accumulate and exert their uremic effects on various systems, including the immune system.

-Urinary retention: this refers to the inability to completely or partially empty the bladder.

-Urine output: this refers to the amount of urine secreted by the kidneys.

-Urticaria or hives: these indicate vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated papules or plaques (wheals), erythematous and often attended by severe pruritus; Individual lesions resolving without scarring in several hours.

-UTR: in molecular genetics, an untranslated region (or UTR): it refers to either of two sections, one on each side of a coding sequence on a strand of messenger ribonucleic acid (mRNA). If it is found on the 5' side, it is called the 5' UTR (or leader sequence), or if it is found on the 3' side, it is called the 3' UTR (or trailer sequence). The 5' UTR is upstream from the coding sequence. Within the 5' UTR is a sequence that is recognized by the ribosome which allows the ribosome to bind and initiate translation. The mechanism of translation initiation differs in prokaryotes and eukaryotes. The 3' UTR is found immediately following the translation stop codon. The 3' UTR plays a critical role in translation termination as well as post-transcriptional modification. Although they are called untranslated regions, and do not form the protein-coding region of the gene, uORFs located within the 5' UTR can be translated into peptides.

-3' UTR pseudoknot in coronavirus (CoV): it is a ribonucleic acid (RNA) structure found in the coronavirus (CoV) genome. Coronaviruses (CoVs) contain 30 kb single-stranded positive-sense ribonucleic acid (RNA) genomes. The 3' UTR region of these coronavirus (CoV) genomes contains a conserved ~55 nucleotide pseudoknot structure which is necessary for viral genome replication. The mechanism of cis-regulation is unclear, but this element is postulated to function in the plus-strand.

-Vagal nerves: the vagus nerve is a nerve that supplies nerve fibers to the pharynx (throat), larynx (voice box), trachea (windpipe), lungs, heart, esophagus, and intestinal tract, as far as the transverse portion of the colon. The vagus nerve also brings sensory information back to the brain from the ear, tongue, pharynx, and larynx.

-Vagus nerve (VN): this is the principal component of the parasympathetic nervous system, a mixed nerve composed of 80% afferent and 20% efferent fibers.

-Valve vegetations: it refers to any variably sized excrescence that may be present on heart valves.

-Valvitis: it indicates inflammation of the valves of the heart.

-Vascular endothelial cadherin: this is a divergent member of the type II classical cadherin family of cell adhesion proteins, mediates homophilic adhesion in the vascular endothelium.

-Vascular endothelial growth factor (VEGF): it is a potent angiogenic factor and was first described as an essential growth factor for vascular endothelial cells; also known as vascular permeability factor (VPF), originally described as an endothelial cell-specific mitogen. It is a signal protein produced by cells that stimulates the formation of blood vessels.

-Vascular filling pressures: this is the mean circulatory filling pressure (Pmcf) and it is defined as the mean vascular pressure that exists after a stop in cardiac output and redistribution of blood, so that all pressures are the same throughout the system.

-Vasculitis: it is characterized by histologic evidence of blood vessel inflammation. When vasculitis occurs, it can lead to blood vessel stenosis/occlusion, causing organ ischemia or thinning of the blood vessel and resulting in aneurysm formation or hemorrhage. Vasculitis can be thought of in 2 broad categories: secondary vasculitides, in which blood vessel inflammation

occurs in association with an underlying disease or exposure, or primary vasculitides, which are entities of unknown cause in which vasculitis is the pathologic basis of tissue injury.

-Vasoactive intestinal peptide: also known as vasoactive intestinal polypeptide or VIP, is a peptide hormone that is vasoactive in the intestine; vasoactive intestinal peptide (VIP) is a peptide of 28 amino acid (AA) residues that belongs to a glucagon/secretin superfamily, the ligand of class II G protein-coupled receptors. Vasoactive intestinal polypeptide (VIP) is produced in many tissues of vertebrates including the gut, pancreas, and suprachiasmatic nuclei of the hypothalamus in the brain. Vasoactive intestinal polypeptide (VIP) stimulates contractility in the heart, causes vasodilation, increases glycogenolysis, lowers arterial blood pressure and relaxes the smooth muscle of trachea, stomach and gall bladder.

-Vasodilatory/distributive shock: distributive shock, also known as vasodilatory shock, is one of the four broad classifications of disorders that cause inadequate tissue perfusion. Systemic vasodilation leads to decreased blood flow to the brain, heart, and kidneys causing damage to vital organs. Distributive shock also leads to leakage of fluid from capillaries into the surrounding tissues, further complicating the clinical picture. Due to the complexities of this disease, the causes and treatments for distributive shock are multimodal. The most common causes of distributive shock in the emergency department are sepsis and anaphylaxis. In cases of trauma, the neurogenic shock should also be on the differential. Other less common causes of distributive shock include adrenal insufficiency and capillary leak syndrome. Drug overdose or toxicity should always be considered, particularly potent vasodilators such as calcium channel blockers and hydralazine. Distributive shock as a result of sepsis occurs due to a dysregulated immune response to infection that leads to systemic cytokine release and resultant vasodilation and fluid leak from capillaries. These inflammatory cytokines can also cause some cardiac dysfunction, called septic cardiomyopathy, which can contribute to the shock state.

-Vasovagal syncope: this happens when one faints because the body overreacts to certain triggers, such as the sight of blood or extreme emotional distress. It may also be called neurocardiogenic syncope. The vasovagal syncope trigger causes one's heart rate and blood pressure to drop suddenly.

-Venous sinus thrombosis: the cerebral venous sinus thrombosis (CVST) is a thrombosis (blood clot) in the brain.

-Venous stasis: it is a condition of slow blood flow in the veins, usually of the legs.

-Venous thromboembolism (VTE): it is a condition in which a blood clot forms most often in the deep veins of the leg, groin or arm (known as deep vein thrombosis, DVT) and travels in the circulation, lodging in the lungs (known as pulmonary embolism, PE). Together, deep vein thrombosis (DVT) and pulmonary embolism (PE) are known as venous thromboembolism (VTE) - a dangerous, potentially deadly medical condition.

-Ventilator-associated lung injury (VALI): it is an acute lung injury (ALI) that progresses during mechanical ventilation and is termed ventilator-induced lung injury (VILI) if it can be proven that the mechanical ventilation caused the acute lung injury (ALI).

-Ventilation: it is the process by which oxygen and carbon dioxide are transported to and from the lungs. Normally, alveolar ventilation is unconsciously regulated to maintain constant arterial blood gas tensions (particularly carbon dioxide), despite variable levels of oxygen consumption and carbon dioxide production. Ventilation of the lungs is the process that mixes fresh inspired gas with alveolar gas.

-Ventricular arrhythmias: these are abnormal heartbeats that originate in your lower heart chambers, called ventricles. These types of arrhythmias cause heart to beat too fast, which prevents oxygen-rich blood from circulating to the brain and body and may result in cardiac arrest.

-Ventilation-perfusion (VQ) scanning: a ventilation/perfusion lung scan, also called a V/Q lung scan, is a type of medical imaging using scintigraphy and medical isotopes to evaluate the circulation of air and blood within a patient's lungs, in order to determine the ventilation/perfusion ratio. The ventilation part of the test looks at the ability of air to reach all parts of the lungs, while the perfusion part evaluates how well blood circulates within the lungs. As Q in physiology is the letter used to describe bloodflow the term V/Q scan emerged.

-Viremia: this indicates the presence of viruses in the blood.

-Vital signs: this refers to the clinical measurements, specifically pulse rate, temperature, respiration rate, and blood pressure, that indicate the state of a patient's essential body functions.

-Wernicke encephalopathy (WE): this is an acute neurological condition characterized by a clinical triad of ophthalmoparesis with nystagmus, ataxia, and confusion.

-Wet age-related macular degeneration: wet macular degeneration is a chronic eye disorder that causes blurred vision or a blind spot in the visual field. It's generally caused by abnormal blood vessels that leak fluid or blood into the macula.

-White blood cell count (leukocyte count): it is the number of white blood cells (WBCs) in the blood. The white blood cells (WBCs) are usually measured as part of the complete blood count (CBC). White blood cells (WBCs) are the infection-fighting cells in the blood and are distinct from the red (oxygen-carrying) blood cells known as erythrocytes. There are different types of white blood cells, including neutrophils (polymorphonuclear leukocytes; PMNs), band cells (slightly immature neutrophils), T-type lymphocytes (T cells), B-type lymphocytes (B cells), monocytes, eosinophils, and basophils. All the types of white blood cells (WBCs) are reflected in the white blood cell count. The normal range for the white blood cell count varies between laboratories but is usually between 4,300 and 10,800 cells per cubic millimeter of blood. This can also be referred to as the leukocyte count and can be expressed in international units as $4.3 - 10.8 \times 10^9$ cells per liter. A low white blood cell count is called leukopenia. A high white blood cell count is termed leukocytosis.

-Wilson disease: this is a genetic disorder characterized by building up of excess copper in the body.

-X-linked agammaglobulinemia (XLA): also known as Bruton's agammaglobulinemia, it is the name for a condition that affects the body's ability to make antibodies and fight infections. It belongs to a group of conditions known as antibody deficiencies. XLA affects only boys and its features include repeated episodes of bacterial infections affecting the ears, sinuses, nose, eyes, skin and the gastrointestinal tract.

-Xerophthalmia: abnormal dryness of the conjunctiva and cornea of the eye, with inflammation and ridge formation, typically associated with vitamin A deficiency.

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