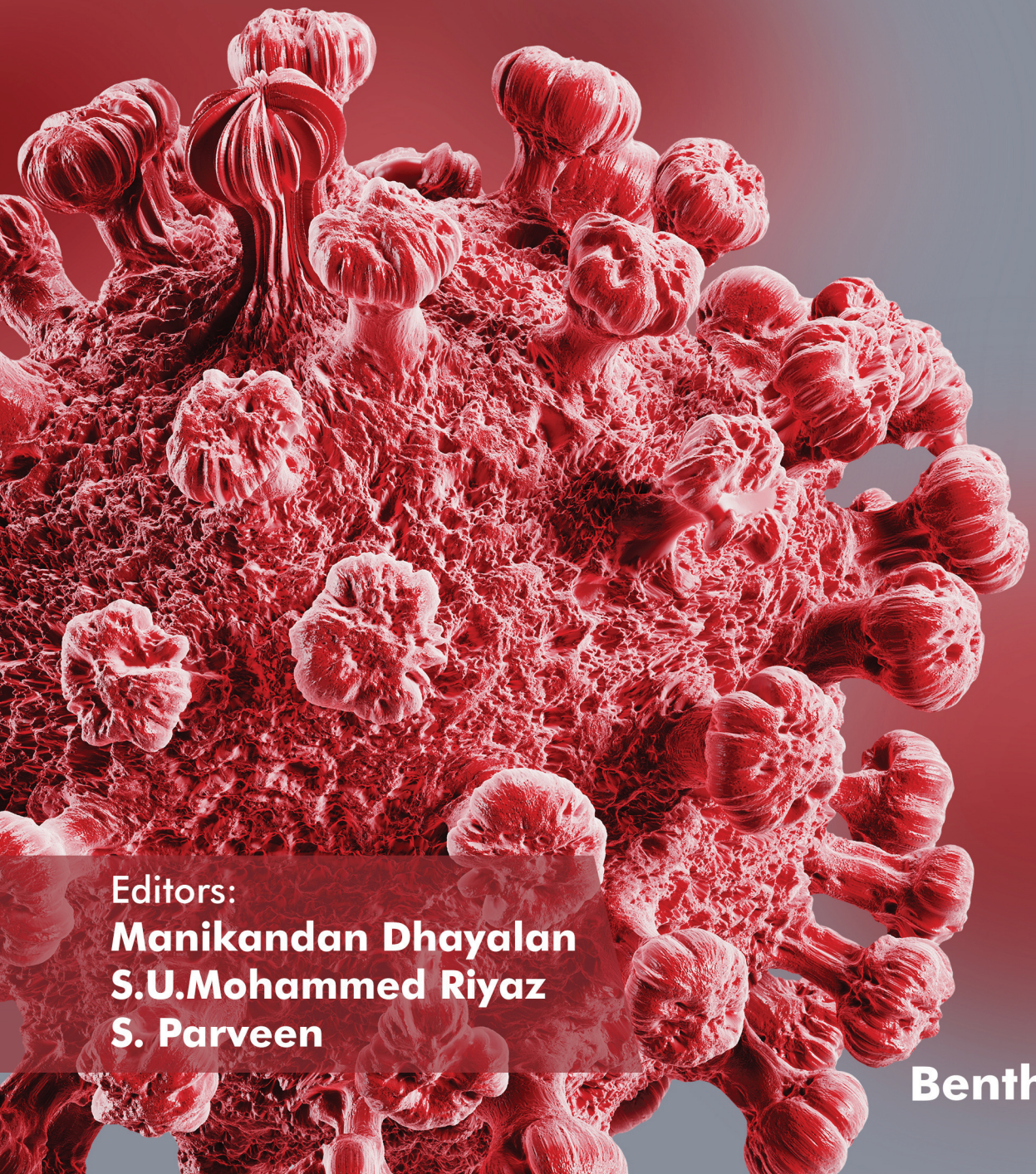
AN EPIDEMIOLOGICAL UPDATE ON COVID -19



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An Epidemiological Update on COVID -19

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An Epidemiological Update on COVID -19

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FOREWORD

I hope my letter finds you in the best of health and spirits. I am delighted to tell you that this book fulfilled all my expectations. Please, feel free to contact the editor in case you need more information. The pandemic has activated an extraordinary order for digital health technology and has revealed successful solutions. In this scenario, the thrust area of research towards this "**AN EPIDEMIOLOGICAL UPDATE ON COVID-19**" is welcomed. I am confident that this book was written in a well-defined manner. All the chapters are easily communicable to the research and student communities. With pleasure, I congratulate the editors and authors for their efforts to bring out this book.

These book chapters provide the vast knowledge of the COVID journey in this world and successfully serve as the basis of study for the renowned researchers in this field and the students specializing in this field. In addition, this edited book completely delivers the history and main aspects of COVID-19. This book describes the various topic related to COVID like Acute Respiratory Distress Syndrome (ARDS), Best and Worst Epidemiological Scenarios of Covid-19, Neuropathological Features of Covid-19, Human to Human Transmission of SARS – COV-2 *etc.,*and the authors gave a complete view on the "**An Epidemiological Update on COVID-19**".

I hope it can be very helpful and timely.

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PREFACE

Epidemics and pandemics have been frightening the human chase again and again. SARS, H1N1, Ebola, and more have exposed their real face in the past, but with every such outbreak. The coronavirus outbreak came to light on December 31, 2019 and this COVID-19 pandemic is the defining global health crisis of our time and the greatest challenge. As the global Covid-19 pandemic evolved, several countries faced a surge of acute and critically ill patients but had limited resources of space, staff, and stuff. In a relatively short period of time, the new coronavirus was recognized; the travel on COVID-19 has grown exponentially, from a single scientific report to over a few thousand publications, across numerous disciplines. The universality and clinical implications of our observations require further research to define. This pandemic has provoked an extraordinary requirement for digital health technology solutions and has exposed victorious solutions such as population screening, the pathway of the infection, projecting the use and allocation of resources, and designing targeted responses. In this scenario, the thrust area of research towards this "**AN EPIDEMIOLOGICAL UPDATE ON COVID -19**" is welcomed.

This edited book chapter has been fully revised and updated to suit the requirement of the readers and highlights the comprehensive overview of recent novel coronavirus infections, their biology and associated challenges for their treatment and prevention of novel Coronavirus Disease 2019 (COVID-19). A thoughtful of the topics covered in the book is very important in the context of designing strategies to protect the human race from further sufferers and harm due to SARS-CoV-2 infection-causing COVID-19.

The target audience will include advanced science, medical, pharmacy and nursing students and all the researchers. On behalf of all the chapter authors, we hope to spread the word that this book emphasizes all the thrust areas of COVID-19.

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Dedication

I dedicate this book to those individuals who have been very supportive of me in my career and social life, I would like to take this opportunity to thank Professors Dr. Jesus Simal Gandara (University of Vigo-Spain), Dr. Mika Sillanpaa (Aalto University - Finland) and Dr. Moonish Alikhan (King Saud University-Saudi Arabia), our CEO, Dr. Dun Yang (Anticancer Bioscience, Chengdu, China), our VP, Dr. Jing Zhang,(Anticancer Bioscience, Chengdu, China), my Ph.D. Supervisors, Dr. N. Nagendra Gandhi(Anna University, Chennai, India), Dr. K. Kathirvan (University of Madras, Chennai, India), well-wishers, my parents, and finally my lovable wife and daughter.

Dr. Manikandan Dhayalan

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CHAPTER 1

Acute Respiratory Distress Syndrome (ARDS)

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Abstract: The lungs' air sacs are filled with fluid, leading to a life-threatening lung injury known as acute respiratory distress syndrome (ARDS). The tiny blood vessels of the lungs are damaged in this condition. The amount of oxygen in the bloodstream decreases, giving rise to carbon dioxide in blood circulation. This makes breathing extremely difficult, ultimately leading to organ failure. Usually, the organs damaged due to this condition are the kidneys or brain. The variations in the severity of ARDS are dependent on different signs and symptoms. Most of the time, ARDS is represented by shortness of breath, dry hacking cough, fever, headaches, and fast pulse rate. Labored and unusually rapid breathing, Low blood pressure, mental confusion, and extreme tiredness could also be other signs. ARDS can also be associated with old age, chronic lung disease, a history of alcohol misuse, or smoking.

Keywords: ARDS, Carbon dioxide, Lungs, Oxygen, Shortness of breath.

INTRODUCTION

Ashbaugh and colleagues were the first to define acute respiratory distress syndrome (ARDS) in 1967. They believed that ARDS is associated with signs including acute non-cardiogenic, pulmonary oedema, and increased lung stiffness. In this condition, the process of breathing becomes difficult. It may give rise to pneumonia, trauma, sepsis, and aspiration, resulting in lung failure. It was defined as a condition associated with diffuse pulmonary oedema and respiratory failure by the American European Consensus Conference (AECC) in 1994. Its coexistence with left-sided heart failure was also pointed out at that time [8].

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The European Society of Intensive Care Medicine (ESICM) ARDS Definition Task Force proposed some minor changes in the definition of ARDS after reevaluation. Keeping in mind the 'mild', 'moderate', and 'severe' oxygenation levels, these alterations were done. The first case of ARDS was also reported from Denver in 1967 [7].

- Mild: 200 mm Hg < PaO_2/FiO_2 ratio ≤ 300 mm Hg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure ≥ 5 cm H_2O.
- Moderate: 100 mm Hg < PaO_2/FiO_2 ratio ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O.
- Severe: PaO_2/FiO_2 ratio ≤ 100 mm Hg with PEEP ≥ 5cm H_2O.

Since no method can measure lung injury, various clinical manifestations lead us to the diagnosis of ARDS. These clinical manifestations include pathological samples of lung tissue, distal airspace, or blood samples. In the beginning, ARDS may look like pneumonia (bacterial and viral most frequently: fungal sometimes) or major trauma (such as blunt or penetrating injuries or burns). The other possible clinical condition could be non-pulmonary sepsis or aspiration of gastric and/or oral and esophageal contents worsened due to some infection. Some other probable causes of ARDS may include acute pancreatitis, transfusion of fresh frozen plasma, RBCs and platelets, and smoke inhalation. Sometimes a drug overdose and inhalation of fresh or saltwater may lead to the development of ARDS. The hemorrhagic shock or cardiopulmonary bypass and lung resection etc. may also lead to ARDS. Acute respiratory distress syndrome (ARDS) may also be caused by primary graft dysfunction following lung transplantation, high-altitude pulmonary oedema, and neurogenic oedema. The clinical disorders associated with ARDS vary depending on geography so it may have different clinical manifestations in different parts of the world. Another factor is the healthcare system across the globe that makes ARDS show different manifestations clinically. The understating of epidemiology, pathogenesis, and pathophysiology of ARDS is not an easy job as it has different clinical manifestations in different parts of the world. Thus it is considered a heterogeneous syndrome. Its patients are segregated into sub-phenotypes based on clinical and biological features. Specific therapies of ARDS may have different effects on different patients.

PATHOPHYSIOLOGY

Acute inflammation affects the process of gaseous exchange by affecting the lungs' gas exchange surface as well as the alveolar-capillary membrane [1]. A direct pulmonary or indirect extra-pulmonary insult could be the other physiological processes associated with the disease, as these may cause the proliferation of inflammatory mediators. Some elements of the blood may pass into the tissues as a result of perspiration. As a result, some mediators are secreted

by the Alveolar macrophages that accumulate inflammatory cells in the lung. This results in the inactivation of surfactants leading to the collapse of the alveolar epithelial barrier. Sometimes, there may be gaps in the alveolar epithelial barrier, leading to necrosis of types I and II alveolar cells. There is intravascular coagulation in the alveolar capillaries resulting in microthrombi. These physiological processes give rise to a condition known as pulmonary edema. There is a loss of surfactant, and dead cells or debris are deposited along the alveoli (hyaline membranes), resulting in compromising pulmonary compliance. There is a difficulty in the process of gaseous exchange. Chest radiography may reveal air space opacification or coarse reticular opacification, as shown in Fig. (**1**).

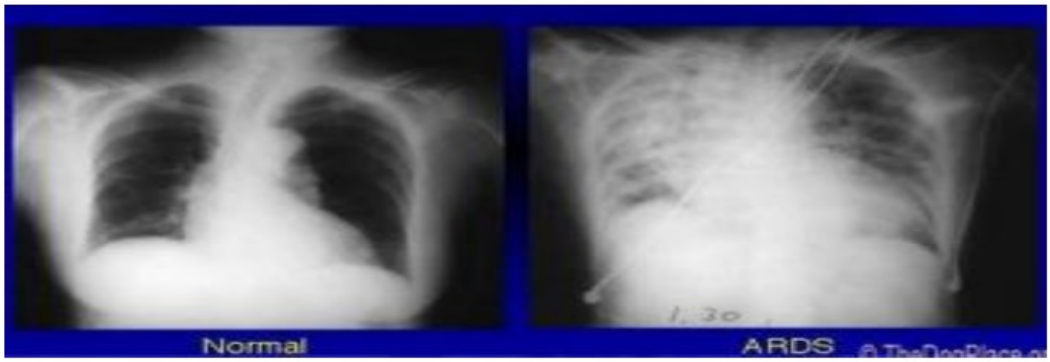

Fig. (1). Chest X ray of ARDS patient.

In The Lancet Respiratory Medicine, Giacomo Grasselli and colleagues [2] reported stark similarities between the pulmonary injuries caused by COVID-19 and ARDS. They noticed decreased pulmonary compliance and increased lung weight in the patients of both conditions. There is an increase in the high D-dimer concentrations and mortality due to the lung damage caused by both diseases.

These results indicate that the death in COVID-19 may be caused by pulmonary vascular thrombosis. Further investigations of pulmonary arterial pressure and right-sided heart anatomy and function could also test this hypothesis. The pathophysiological role of the heart–lung interactions is reported to be changed due to the damage caused to the pulmonary circulation, leading to ventricular dysfunction.

CAUSES OF ARDS

The causes of ARDS are not completely known and are being investigated. It has been reported that Direct or Indirect Injuries could possibly cause ARDS. Direct injuries are those which cause bruising of the lungs. The possible causes may be

CHAPTER 2

COVID – 19 Pandemic

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Abstract: Coronaviruses are known to infect both animals and humans. A strain of Coronaviruses known as SAR-CoV also belongs to the Coronaviruses family and is known to have caused Severe Acute Respiratory Syndromes (SARS) in 2002-03. This infection has also affected humans at a faster pace. Coronaviruses are found in various animal species like cattle and camels. Recently, Coronavirus disease, abbreviated as Covid-19, emerged as a highly transmittable and pathogenic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is believed to have been originated in Wuhan, China, around November 2019. Currently, almost all the countries of the world have been affected by this infection, and millions of people across the globe have died with the virus so far, and the overall toll is likely to go much higher. In March 2020, this infection was labelled as a pandemic by World Health Organization. Genome analysis was conducted, which revealed similarities of Covid-19 viruses with that of SARS. This led to a hypothesis that, like SARS, Bats can also be the possible primary reservoir for Covid-19 as well. There are many theories going around regarding the origin of SARS-CoV-2; one study pointed out that Covid-19 originated from Bats while the other indicated its origin from pangolin. Both the studies failed miserably to establish the spread of Covid-19 to humans as both the animals have no frequent contact with the humans. There are a lot of pieces of evidence suggesting SARS-CoV-2 as a possible zoonotic source for COVID-19. Some theories also pointed out the laboratory origin of COVID-19, but no evidence has been provided to this claim. Contrary to this claim, its genomic sequences do not contain a mix of known elements. Studies are being conducted to know the intermediate source of origin of COVID-19 and its possible transfer to humans. A lot of vaccines have been approved against it that are supposed to prevent its spread during clinical trials conducted across the globe. These are broad-spectrum antiviral drugs that could help recover the infected patients.

Keywords: Coronavirus, COVID-19, SARS-CoV-2.

INTRODUCTION TO CORONAVIRUS

Pathogens of the family Coronaviridae and subfamily Coronavirinae are known to infect birds and mammals across the globe. These are known as Coronaviruses.

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These are positive-sense RNA viruses containing four genera. These genera include Alphacoronavirus, Beta coronavirus, Gamma coronavirus, and Delta coronavirus 1 [1]. Alpha coronaviruses and beta coronaviruses are known to cause infections in mammals, while gamma coronaviruses and delta coronaviruses are associated with infections in Birds. These are viruses of small size, having a diameter of 65 to 125 nm. These viruses contain a single strand of RNA as their nucleic material. The size of the nucleic materials ranges from 26 to 32 kbs in length. Intensive research on the coronaviruses was initiated when (SARS) coronavirus became associated with severe acute respiratory syndrome in 2003 [2]. The widespread research across the globe gave rise to the discovery of many new members of the coronaviruses family in humans, pets, and wildlife [3 - 6]. This increased surveillance led to the discovery of coronavirus in bats and birds. Soon they were known to be the natural reservoirs of viruses [7 - 9]. Research on the Phylogeny of the coronaviruses associated with birds and bats revealed an ancient link with evidence of the same paths of divergence and coevolution with different hosts. Divergence was also noticed near the tips of the coronavirus phylogeny. Many pieces of evidence suggested that this divergence resulted from various inter-species transmission events [8, 10].

In order to avoid the infection caused by the coronavirus, it is important to know the answer to the following questions.

What is the possible source of origin of coronavirus?

What are the sources of possible transmission of the infection?

To investigate the spread of SARS-CoV, the researchers paid great attention to raccoon dogs and palm civets as possible reservoirs of infection. However, further investigations on the samples extracted from civets in the food market gave hints about the viral RNA. It was also revealed that the civet palm could be the possible secondary host, not the primary one [11]. Samples were taken from healthy Hong Kong people and molecular evaluation of these samples was taken. This showed an antibody frequency rate of 2.5% against the SARS coronavirus. This study also suggested that there was a possibility of the presence of SARS coronavirus in humans before causing the SARS infection in 2003 [12]. Later on, anti-SAR--CoV antibodies were discovered in Rhinolophus bats and thus hinting towards the viral replication roles of Bats [13]. Middle East respiratory syndrome coronavirus (MERS) emerged in 2012 in the Kingdom of Saudi Arabia [14]. MERS also belong to the beta coronavirus. Camels are known to be the zoonotic source or the primary host of this virus [15]. Recently the presence of MERS was also pointed out in Pipistrellus and Perimyotis bats [14]. This suggested that the bats are also the possible host associated with the transmission of the virus [16]

[17]. There were some theories pointing out snakes as a possible host, however,the genomic analysis revealed a similarity of coronaviruses with SARS-like bat viruses, not the snakes. Thus, bats and not snakes were the possible key reservoirs [18, 19]. A study of the homologous recombination suggested that a SARS-CoV (CoVZXC21 or CoVZC45) could give rise to novel coronavirus receptor-binding peak glycoprotein [19]. However, to eradicate the virus, a lot of research investigating the possible intermediate zoonotic source is required. This can only help in understanding the transmission of the virus from bats to humans.

THE EMERGENCE OF THE CORONAVIRUS

Now it has been established that Severe acute respiratory syndrome coronavirus (SARS-CoV), Influenza A H5N1, Coronavirus H1N1 2009, and Middle East respiratory syndrome (MERS-CoV) can cause acute lung injury (ALI), ultimately leading to lung failure and death. Before the spread of severe acute respiratory syndrome (SARS) by SARS-CoV, in 2002 in Guangdong, China [20], these viruses were known to cause infections in animals only. Only a decade later, another virus from the same family known as MERS-CoV caused Middle East respiratory syndrome in Middle Eastern countries, especially the Kingdome of Saudi Arabia [21]. Recently, in late 2019, Wuhan, an emerging commercial hub in China, witnessed the outbreak of Covid-19, a pandemic that has killed 1,800 and infected more than 70,000 people in 50 days of its occurrence. This virus appeared to be a member of a b coronaviruses. This virus was initially named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov). Later on, The International Committee on Taxonomy of Viruses (ICTV) named the virus SARS-CoV-2 and the disease COVID-19 [3, 4].

STRUCTURE OF THE CORONAVIRUS

These viruses are enveloped and non-segmented viruses. They contain positive-sense, single-stranded RNA as their nucleic acid. Their size ranges from 26 to 32 kilobases, which are the largest known viral RNA genomes. A nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid protein (N) represents their virion. Their virion is present inside phospholipid bilayers. This is also covered by two different types of spike proteins. One is the spike (S) glycoprotein cutter that is believed to be associated with all CoVs, while the hemagglutinin esterase (HE) is only present in some of the coronaviruses. The membrane protein (M) is a type III transmembrane glycoprotein, and the envelope protein (E) is among the S proteins found in the virus envelope.

The downstream regions of ORF1 of all the viruses contain some genes that are associated with encoding proteins during the process of viral replication,

CHAPTER 3

Best and Worst Epidemiological Scenarios of COVID-19

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Abstract: This chapter aims to assess the social, healthcare, and economic impacts of SARS-Corona Virus 2019 globally since the World Health Organization declared it a global pandemic in March 2020. The primary focus of this study is to assess the management of this disaster, our emergency response to it, and our preparedness. Currently, the pandemic has spread across the globe, leaving its impression in 196 countries, so a complete analysis of it can only be made once the pandemic ends. The epidemiological techniques and statistical modelling data of this highly infectious virus across the globe are important for conducting such studies. Currently, this data is inconsistent depending upon the climate and case-to-case scenarios. There is an urgent need for government and non-governmental organizations to work together in a coherent way to fight this disease. This deadly virus can only be neutralized by public awareness, social distancing, and vaccination.

Keywords: Epidemiological, Manifestation, Pandemic, SARS- Corona Virus.

INTRODUCTION

The covid-19 has not only affected the economy of the world, but it has played havoc with almost every aspect of humankind, including history, development, and religion. Infectious diseases have been a great threat to human civilization since ancient times. Such diseases have the potential to affect the entire population on this planet. Millions of lives have already been lost due to these pandemics in the past. That is why epidemiology is a broad field discussing the aspects of the spread of a pandemic, source of transmission, and measures to contain these infections based on the analytical studies.

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20th Century witnessed the spread of many epidemics. In 1918, there was an outbreak of the H1N1 influenza virus, affecting one-third of the globe's entire population. There occurred 50 million death worldwide during this infection, and it rightly claimed to be the deadliest epidemic in the history of human civilization. This epidemic remerged in 1957-1958 and claimed 1.1 million lives this time. The primary concern of the researchers during epidemics is studying the measures that could possibly be taken to control the disease. This requires close monitoring of the infectious organism, as well as its mutation and genetic translation. A summary of the various epidemics that humankind has so far dealt with can be reached here (according to available sources; WHO, CDC, Salik.com, and MPfoneline.com) (Fig. **1**).

Fig. (1). WHO coronavirus Dashboard.

COVID-19 has changed the way we would interact with each other in the future. Our homes, workplaces, and ways of communication have been changed altogether. Traveling across the glove has not been the same. It has affected every spare of our lives. Some people have lost their jobs, while others have been devastated by the loss of their loved ones. The inequalities between various sections of society have been deepened. Various parts of the world are witnessing third and fourth waves of the covid-19. The governments contemplate choosing between complete lockdown, smart lockdown, or reopening schools, offices, and businesses. The decisions being made by the governments are widening the gap between the developed and developing countries. Since these key decisions negatively affect our lives, reliable data is the key requirement to decide during and post-pandemic [1].

THE SPREAD OF THE VIRUS

This deadly virus can be transmitted when an infected person coughs, sneezes, or breathes. These droplets hang in the air. They are very heavy and fall to the floor or surfaces quickly. The virus in the droplets may be transferred by air or direct contact. You can become infected by inhaling the virus near any of the covid-19 patients or by touching a contaminated surface and then by your eyes, nose, or mouth.

Overview

The past weeks have witnessed a great surge in the confirmed cases of covid-19 and deaths caused by the viruses. 4 million new cases and 60 000 new deaths have been recorded in the past few weeks, and the numbers are worsening. In total, 53.7 million confirmed WHO has reported cases and 1.3 million deaths across the globe till the 15th of November, 2020 (Fig. **2**). Turkmenistan was reported to be the only country till October 2020 not to have a single case of covid-19. WHO experts decided to visit Turkmenistan, but it took considerable in resolving the problems associated with logistics. WHO experts visited Turkmenistan and found that their claim was right. Still, they advised the Turkmenistan government to pretend as if they were affected by the COVID-19 [2].

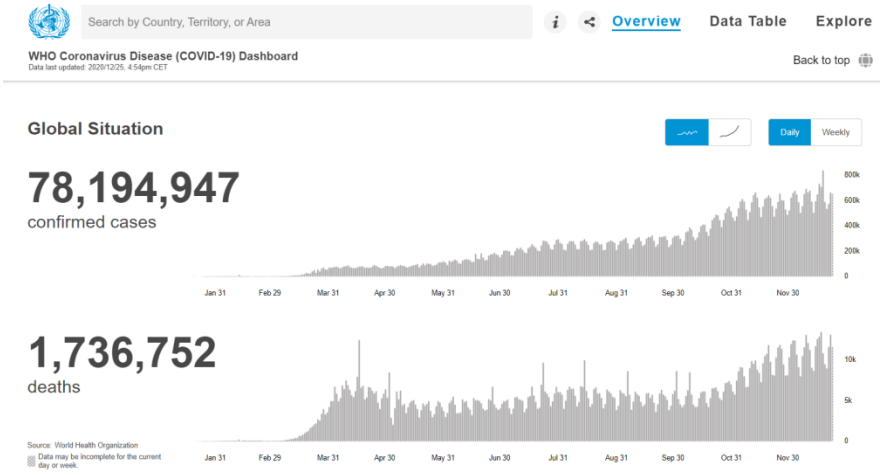

Fig. (2). Comparison of increase in Covid-19 confirmed cases and deaths across the globe.

1. $12 billion were approved by the World Bank for financing the COVID-19 vaccination plan in underdeveloped countries. In total, $160 billion were allocated by the World Bank till June 2021 for combating Covid-19 [3].

2. Safe burials were held This covid-19, the funeral was well attended by many

CHAPTER 4

Neuropathological Features of Covid-19

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Abstract: In December 2019, the world witnessed the spread of a new pandemic from the Wuhan city, China, which was later known as Coronavirus disease (COVID-19) caused by SARS-CoV-2. The main effects of Coronavirus disease (COVID-19) have been reported on human respiratory and cardiovascular systems, but neurological impacts have also been witnessed in most of the patients. Some common symptoms of COVID-19, such as stroke, anosmia, and dysregulation of breathing, are somehow related to the neuropathological processes. The detailed studies dealing with the neurological impacts of COVID-19 have revealed that the central nervous system is affected by SARS-CoV-2. Still, this disease also impacts the peripheral nervous system (PNS) and the muscles as well. T Guillain-Barré syndrome, Miller Fisher syndrome, polyneuritis cranialis, and viral myopathy with rhabdomyolysis are some of the diseasesthat affect muscles and the peripheral nervous system (PNS), but these diseases are usually less frequent. Usually, the symptoms of Coronavirus disease (COVID-19) impacting the neurological system are reported in cases of severe illness. Thus care must be taken during the treatment of Coronavirus (COVID-19) patients. A careful diagnosis is key before starting the treatment. This chapter aims to discuss the neuropathological impacts of the infection caused by SARS-CoV-2.

Keywords: Central nervous system (CNS), COVID-19, Neurological manifestations, Neuropathology, Peripheral nervous system (PNS), SARS-CoV-2.

INTRODUCTION

SARS-CoV-2 is the causative organism that spreads a life-threatening infection known as COVID-19,which is commonly known to have respiratory symptoms. Coronaviruses have also caused a few other diseases of the respiratory system in

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recent pasts known as (SARS-CoV) in 2002 and Middle East respiratory syndrome CoV (MERS-CoV) in 2012. A new virus, SARS-CoV-2, emerged at the end of 2019 and caused a pandemic across the globe [1, 2]. COVID-19 has been the focus of many studies since the start of the pandemic. A lot of information has been provided by various researchers about its origin [3], its genome [4], structural characterizations [5, 6], epidemiology [7 - 10], and pathology [11]. Although respiratory and cardiovascular problems preferentially arise from COVID-19, several patients are reported to have neurological symptoms. Although it has been established that coronavirus disease has various neurological impacts on humans, these impacts range from mild to complex ones. The headache, nausea, vomiting, languidness, myalgia, and unstable walking are some of the common mild symptoms, while cerebral hemorrhage, meningitis, encephalitis could be the possible complex signs associated with this pandemic [12, 13]. Various researchers have revealed that neurological impacts in COVID-19 include the central nervous system (CNS), peripheral nervous system (PNS), and muscle.The impact of olfaction and taste could be the other possible problems associated with this [14 - 17]. The possible entry points of SARS-CoV-2 into the CNS may include the hematogenic route, retrograde or anterograde neuronal transport [18, 19]. Much investigation has been done on each pathway to understanding the pathological impacts of entry via each route and the consequences. These investigations have led to various improvements in the diagnosis and management of the disease. This chapter aims at discussing the neuropathological features of COVID-19.

Animal Models of Neurotropic Coronavirus Infections

Research has revealed that the impacts of coronaviruses go beyond the respiratory system. These viruses have the capacity to enter the nervous system and cause infection into the brain with or without neurological illness [20]. There is a lot of experimental evidence regarding the coronavirus entry into the animals' brains. The possible entry routes may be from the lungs to the circulatory system. The axonal transport and transneuronal spread from olfactory and trigeminal nerve endings in the nasal epithelium could be the other possible route. The airway mechanoreceptors and chemoreceptors to the medullary cardio-respiratory centersare one of the entry routes [21]. The circumventricular organs, which usually don’t have a blood-brain barrier (BBB), also facilitate the entry of the virus into the central nervous system. These organs that lack the blood-brain barrier (BBB) include dorsal root ganglia and autonomic (including cardiac) ganglia [22, 23].

SARS-CoV-2 is known to infect the vascular endothelium of peripheral organs, including the kidney, lung, heart, kidney, and liver. Thus endothelium of neural

vasculature is very likely to be affected by the direct infection. It was reported by Varga and colleagues [24] that endothelial cells are infected by SARS-CoV-2 as a result of endotheliitis. Vasoconstriction and edemaare promoted by this systemic vascular endotheliitis leading to a procoagulant state with implications like cerebrovascular stroke [25]. Flammer *et al.* [26] reported that vascular endothelium is an active paracrine, endocrine, and autocrine organ that plays an important role in maintaining vascular tone as well as vascular homeostasis. Endothelial microvascular dysfunction may result in vasoconstriction, leading to subsequent organ ischemia, inflammation with associated tissue edema, and a pro-thrombotic state. Endothelial dysfunction is associated with atherosclerosis [25, 26].

Mechanism of CNS Invasion

Coronaviruses are not neurotropic in nature. Their first and foremost target is the respiratory epithelium. The angiotensin-converting enzyme-2 receptor (ACE 2) facilitates the binding of the virus as well as its entry into the host. Once the entry has been secured, the RNA of the virus is released into the cytoplasm, which undergoes translation and replication immediately. As soon as the envelope protein is formed and the RNA is incorporated into it, the virus is ready to make entry into the human circulation.

Glial cells in the brain and spinal neurons also contain ACE 2 receptors. There are chances that the virus may attach to it and replicate, ultimately causing damage to the tissues of the central nervous system. A retrograde transfer via the olfactory epithelium facilitated the entry of the virus into the brain during an experiment that was carried out in mice. The other way of entry of the virus into the brain is through cribriform bone. The virus takes 7 days to reach the target site i-e, the brain. Now there is a viremia phase of the disease that disrupts the blood-brain barrier. As a result, the virus enters the brain. Another mechanism for viral entry into the brain is through invading peripheral nerve terminals. The synapse-connected route gives way to the virus and allows its entry into the brain. Similarities have been observed between Covid-19 and Severe Acute Respiratory Syndrome, it is assumed by various reserachers that SARS-CoV-2 follows the same way for invading CNS like SARS CoV [27].

POTENTIAL ROUTES AND MECHANISMS OF CNS INVOLVEMENT IN COVID-19

Principle Mechanisms of SARS-CoV-2 CNS Infection

The spike (S) glycoprotein and the host ACE2 receptors facilitate the attachment of virus in CNS as these are found in both neurons and endothelial cells.

CHAPTER 5

Intermediate Host of CoV and SARS-CoV-2

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Abstract: Wuhan, a Chinese city, caught the world's attention after the outbreak of a pandemic caused by the coronavirus 2019-nCoV. Coronaviruses are a group of single-stranded positive-sense RNA that are supposed to cause various diseases in animals, including humans. The four genera of CoVs are αCoV, βCoV, ϒCoV, δCoV.CoVs. Initially, it was thought that the infection caused by these groups of viruses is only limited to their animal host. But now, they are believed to have passed from their animal host to humans and caused disease in humans. The pieces of evidence of this cross between animal-human species barrier have been supported by CoVs like the SARS CoV and MERS CoV, which has caused diseases in humans. 96% homology of the coronavirus isolated from humans matches with beta coronaviruses. The beta coronaviruses are usually found in bats in the genus *Rhinolophus*. Similarly, 92% homology of the SARS-CoV matches with SARS-like viruses that are found in bats. The majority of the SARS-like viruses are found in the *Rhinolophus* genus of the bats. This match of homology between COVID-19 virus and beta coronavirus suggests that COVID-19 virus is somehow associated with the *Rhinolophus* genus in Bats. Bats of this genus are widespread across Asia, the Middle East, Africa, and Europe. These links point out that there must be an intermediate host that could have probably facilitated the transfer of this virus from an animal reservoir to humans (civets were implicated as an intermediate host for SARS-CoV). Thus the similarities between SARS-CoV and the COVID-19 virus are being further investigated, and efforts are being made to identify the intermediate host.

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Keywords: Bats, CoV, Intermediate host, SARS CoV.

ROLE OF INTERMEDIATE HOST- PLACE OF RE-ASSORTMENT

The host is the person/animal infected by the pathogen. In the transmission cycle, the host would act as both reservoir and source of the pathogen. Intermediate hosts usually allow the exchange of viruses to some new host. This re-assortment results in the initiation of new pandemics. The lives of the people were saved only when there was clear knowledge about the intermediate host, which is the mediator of the spread of the disease between the animals and humans. The effective intervention of the transmission pathway would definitely prevent the outbreak of a pandemic. The animal selection theory suggests that the novel coronavirus CoV-19 was present in one or more species of animals before making its entry into the human and causing infection. The virus acquired some features that help it bind to the human receptor; an animal host would likely provide or act as an intermediate host; usually, these intermediate hosts must be in high population density. This mechanism has allowed the efficient processing of natural selection.

CORONAVIRUS

Coronaviruses are genetically classified into four major genera: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus.* In which *Alpha and Betacoronavirus* infect mammals whereas *Gamma* and *Deltacoronavirus* infects birds.

The composition of coronavirus is based on sRNA, non-structural proteins, and structural proteins. These structural proteins are (Spike (S), Envelope (E), Membrane (M), and Nucleocapsid (N) protein). The receptor-binding domain (RBD) of S protein plays an important role in facilitating coronavirus entry. These proteins facilitate the binding of human angiotensin-converting enzyme 2(hACE-2), forming a complex. This RBD and ACE2 complex is the hot topic for researchers to investigate the viral mechanisms and to search the possible intermediate host. CD 26, CD147, and RBD have also been reported to facilitate virus entry. A further investigation is required aimed at exploring the other potential viral receptors.

NATURAL RESERVOIRS OF VIRUS - BATS

Bats are favorable animals that act as natural reservoirs for viruses. The viruses are the obligatory intracellular microbes; their evolutionary origins depend on their host's coevolution. More than 200 viruses have been associated with bats, and surprisingly, most of them are RNA viruses. The lack of viral RNA

polymerases contributes a major hand as they lack proofreading activity, enhancing higher mutation rate to RNA virus than the DNA virus. Further, RNA virus frequently modifies their genome through genetic reassortment, thus favoring high genetic variability. Bats with high species biodiversity thus act as the base source of the evolution of such new viruses. The ecological distribution and the biological characters of the bats show that they are potential animals to be brand as the intermediate host and disseminate the viruses.

Except, Polar Regions and a few oceanic islands, bats are widespread in all parts of the world. These are commonly found in caves, rock crevices, birds nest, tree cavities, mines, tombs, and unhabituated buildings, which bring them close to other living organisms. Bats are usually found in large colonies about 10 to 2, 00000 and the longevity of up to 35 years. Bats transmit the virus to humans and other livestock through various routes like to spread through the urine as aerosol generated during defecation, bites, and scratches. Ingestion of food is not possible by Frugivorous bats due to their aerodynamics off-light; chewing fruits helps in the extraction of nutrients by bats. The un-ingested residue spit is a possible source of causing infection as this is polluted by viral contents. Other animals take this partially digested food, and transmission of the virus is linked to this process. Another unique characteristic of bats that can be considered one of the most important ways of spreading the viruses is that bats can fly long distances through which the viruses can be disseminated. Direct infection from bats is also possible. The human can ingest the infected bat meat as bats are being used as a food source. Another direct way of being infected by the bats is through bat's bite, as in the case of rabies virus. B Bats remain asymptomatic during viral infection, [1]. The anal swabs of the infected bats showed a high viral load but remained asymptomatic; only the infected bats weighed lesser than the uninfected bats. The lack of B cell-mediated responses facilitates the bats carrying the virus without being infected. The other features like The low metabolic rate and suppressed immune response during the period when bats hibernate also result in delayed viral clearance.

The major reason for the spread of the coronavirus disease 2019 (COVID-19), which was first identified in Wuhan, China, was the consumption of undercooked bat meat. Bat meats are still consumed in China, Guam, and some parts of Asia. In the absence of detailed information, it was assumed that the spillover of the viruses was likely to take place in the Huanan Seafood Wholesale Market, where the wild species of the livestock were sold. The exact transmission path was still unclear, but it was evident that the bats acted as intermediated hosts to transfer the new novel coronavirus and other viruses.

CHAPTER 6

Lung Recruitability in COVID-19

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Abstract: In December 2019, a new infectious respiratory disease emerged in Wuhan, Hubei province, China. A novel coronavirus, SARS-coronavirus 2 (SARS-CoV-2), shows features that were similar to that SARS-CoV. Soon it was believed to have caused a new lung disease later on known as COVID-19. Originally, the susceptible index patient was asymptomatic and later was confirmed as COVID positive with fever, cough, and sore throat-like symptoms. Later the index patient symptoms rapidly severed along with a high respiratory rate. The severe acute respiratory syndrome coronavirus (SARS-CoV) is associated with lung injury, while acute respiratory distress syndrome may result in a pulmonary failure resulting in mortality. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) soon captured the world's attention due to its capacity to widespread fatality leading to the failure of the healthcare system across the globe. It was also revleaed by the researchers that both SARS-CoV-2 and SARS-CoV exhibited the same features while making their entry into the host cells. They made use of host angiotensin-converting enzyme II (ACE2) for their entry into the host. This enzyme is present on the host cell surface, especially in epithelial cells of respiratory organs like lungs and small intestine in humans. From the accumulated existing published data, it is obvious that the SARS-CoV-2 employs two ways for making its entry into the host cells: one path is initiated by transmembrane protease serine 2 (TMPRSS2) that lies on the surface of the cell while the other is mediated by angiotensin converting enzyme II (ACE2) endosomal pathway. On the other hand, Cholesterol and sphingolipid-rich lipid raft, and micro-domains in the plasma membrane that are used as several physiological signalling pathways, are also involved in virus entry.

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This chapter aims at briefly evaluating the pathogenesis of SARS-CoV and new anti-viral drugs against the disease.

Keywords: ACE2, Endocytic entry, SARS-CoV-2, TMPRSS2.

INTRODUCTION

Coronaviruses are RNA viruses that have been long associated with the spread of infection in birds and mammals. The nature of their infection in birds and humans ranges may range from moderate to lethal one. In humans, the mild symptoms of the disease may include cold, cough, and fever, while lethal diseases caused by the coronaviruses include SARS, MERS, and COVID-19. Coronaviruses constitute the subfamily Orthocoronavirinae, within the family Coronaviridae, order Nidovirales. One of the most important RNA viruses reported to date with its genome size ranging from 26 to 32 kb is coronaviruses. Their name is derived from the appearance they reveal in electron micrographs: they appear to have characteristic club-shaped spikes projections on their surfaces, giving them a solar appearance. The name corona came from the Latin word Corona which means “crown” or “wreath”. They were first named as coronaviruses by June Almeida and David Tyrrell, who were the first virologist who studied viral disease caused in humans. The Coronaviruses were accepted as a genus by the International Committee for the Nomenclature of Viruses in 1971. With the discovery of new species associated with coronaviruses, the genus was divided into four genera, amely Alphacoronavirus, Betacoronavirus, Deltacoronavirus, and Gammacoronavirus in 2009. Till now, 45 species of coronaviruses have been recognized.

The symptoms and diseases produced by coronaviruses in humans are severe. These include Middle East respiratory syndrome that emerged in the Middle East, as the name indicates. Severe acute respiratory syndrome coronavirus and the covid-19 are the other two renowned pandemics caused by these viruses. HCoV-OC43, HCoV-HKU1, HCoV-229E, and HCoV-NL63 are the most prevalent human coronaviruses. These viruses have been found to circulate in persons with mild symptoms of the common cold. These are viruses that infect people of all ages, including children, all around the world. It has been revealed that 15% of the common cold is caused by these viruses, while rhinoviruses are associated with causing 40 to 50% of cold.

These viruses are spherical bodies having projections on their outer surfaces known as spikes. They vary in size from 0 to 120 nm, and their molecular mass is around 40,000 kDa. These are enveloped by protein molecules completely. The protein molecules are surrounded by a lipid bilayer. The nucleocapsid is

responsible for the protection of the virus itself when it is present outside the body of the host cell. The lipid bilayer encloses the whole body of the virus, including membrane, envelope, and spike structural proteins. The E:S:M ratio of the lipid bilayer is around 1:20:300. The E and M are the proteins that combine in a way to facilitate the maintenance of the size of the virus. The diameter of the complete envelope is 85 nm. The E proteins are only associated with forming the structure of the virus and show variations in different species of the viruses. The studies have revealed that there could be around 20 copies of E proteins in a single coronavirus particle. Their size is almost 8.4 to 12 kDa, and 76 to 109 amino acids are involved in forming the structure of this protein. These viruses have spikes that are 20 nm long and consist of a trimer of the S protein. The S protein further has subunits S1 and S2 in its structure. The S protein is a class I fusion that helps in the binding of the virus on the host cell by making a fusion of both the virus and the host cell protein membranes. The head of the spikes is formed by the S1 subunits and helps in the receptor-binding domain, while the S2 subunits are associated with the formation of a stem that facilities the anchoring of the spike formation in the viral envelope. The activation of the protease facilitates the fusion process. The two subunits S1 and S2 are bonded together in a non-covalently manner until they ensure the attachment of the viral cells to the protein of the host cells.

There are some other features of S1 proteins as well. These are also associated with the causing of infection as well as host cell specificity. They are known to have two major domains named N-terminal (NTD) and C-terminal domain (CTD). These are involved in receptor-binding. The sugars lying on the surface of the host are recognized and bound by NTDs. MHV NTD is an exception to this as it binds to a protein receptor carcinoembryonic antigen-related cell adhesion molecule 1. CTDs of the S1 proteins help in making the recognition of different protein receptors such as angiotensin-converting enzyme 2, aminopeptidase N, and dipeptidyl peptidase 4. There is a nucleocapsid present inside the viral envelope that is made up of multiple copies of the nucleocapsid proteins. This, in turn, is connected the positive-sense single-stranded RNA genome. This continues just like the beads-on-a-string.

The tissue tropism, infectivity, and species range of the released virus are determined by the interaction of the coronavirus spike protein with its complementary cell receptor. The prime target of the coronaviruses is the epithelial cells of the host. The respiratory droplets discharged by the infected person are responsible for the spread of the viruses. These droplets are discharged as a result of coughing and sneezing. The healthy person gets infected by inhaling these droplets. The other possible way of getting infection could also be touching the surfaces with these droplets containing viruses. The virus makes its entry into

CHAPTER 7

A Randomized Trial of Hydroxychloroquine as Post-exposure Prophylaxis for COVID-19

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Abstract: Research revealed that *in vitro* activity ofchloroquine and the derivative molecule of hydroxychloroquine is against the infection caused by the SARS-CoV and SARS-CoV-2. The US FDA approved the use of both hydroxychloroquinesulfate and chloroquine phosphate for the critical patients of COVID-19. The clinical trials supported that the hydroxychloroquine did not substantially reduce the system severity in non-hospitalized persons. Moreover, it also produces severe side effects like drowsiness, hypokalaemia, nausea, convulsions, shock, and even death.

Keywords: Controlled randomized trial, COVID-19, Hydroxy chloroquine (HCQ), Post exposure prophylaxis, SARS-CoV-2, Therapy.

INTRODUCTION

COVID-19 emerged as a new pandemic across the globe after December 2019. Soon it was revealed that SARS-CoV-2 is the causative organism for this infection. Coronavirus is a group of enclosed viruses that have a huge RNA. Their RNA is positive-sense single-stranded RNA. These are dispersed in a wide array of organisms, especially animals and with thepotential to infect humans. Primarily, the pulmonary system and gastrointestinal tract seem infected due to infection caused by these viruses. There are four types of coronaviruses that are well-established and include alpha, beta, gamma, and delta coronavirus. Usually, the mammals like bats are considered as the hosts of alpha- and beta-coronaviruses, while delta-coronaviruses are known to have avian origin [1]. The 21st century is facing the third pandemic caused by the coronaviruses: the earlier

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two pandemics caused by these viruses were acute respiratory syndrome (SARS-CoV) and the middle east respiratory syndrome (MERS-CoV). The infection caused by the SARS-CoV-2 may be asymptomatic in the beginning and may result in lung failure leading to death subsequently [2]. The researchers have revealed that the incubation period of the COVID-19 virus can be 5.1 days, and the symptoms associated with the virus may end at the 12th day of infection [3]. The start of symptoms may occur from the 6th day [4]. Fever, dry cough, and fatigue are symptoms that are commonly associated with the COVID-19 infection [5, 6]. In some patients, the disruption of gastrointestinal system associated with diarrhea and nausea has also been reported before the start of fever. The symptoms like dyspnoea, sputum production, headache, haemptyosis [7] and lymphopenia [6] havealso been associated with COVID-19. Pneumonia, subsequently leading to the acute respiratory distress syndrome (ARDS), is the hallmark of this disease that is very common in all fatalities [6].

A lot of drugs have been reported to subside this viral infection: some of these include hydroxychloroquine (HCQ) and aminoquinolines [8]. The use of HCQ and chloroquine against COVID-19 infection has been highly recommended by the EU European Medicines Agency and US Food and Drug Administration (FDA) [9, 10]. The reason for this recommendation is *in vitro* trials. These two drugs are known to block viral replication in SARS-CoV-2 cell cultures [11, 12]. A high-level evaluation was conducted into it, keeping in mind the extracellular lung concentrations and its *in vitro* efficacy, and it was established that there is a limited potential of HCQ for *in vivo* activity at regular dosing intervals [13].

Endocytic Pathway for SARS-CoV2 Entry

It was reported by Wang *et al.* [14] in 2008 that theendocytic pathway is another pathway different from direct fusion with the plasma membrane. This was indicated in their remarks about SARS-CoV [14]. It was pointed out that thevirus secures its entry into the host cell *via* pH and receptor-mediated endocytosis. The internalization of SARS-CoV receptor ACE2 into the host cell and cytoplasmic compartments is induced by spike (S) protein itself or pseudovirus-containing S protein. Lysosomotropic drugs were also known to block ACE2 receptors in vesicles, thus not allowing their replication. The inhibition of pH acidification also affected the pseudoviruses. Thus it is obvious that the infection of cells by SARS-CoV is done by endocytic pathway also found in clathrin and caveolin-independent manner (Fig. **1**).

After the entry into the host cell is secured by the virus, its disassembling starts and the nucleocapsid and the viral genome are released. The open reading frame (ORF) 1a/b into two polyproteins (pp1a and pp1ab) is interpreted by Host

ribosomes. These, in turn, encode 16 non-structural proteins (nsps). The structural and accessory proteins are encoded by the remaining open reading frames. The main protease (3CLpro, nsp5) and the papain-like protease (PLpro, nsp3) are the two proteases that take part in the cleavage of polyproteins and producensp2-16,which in turn takes part in replication-transcription complex (RTC) [15]. There is a possibility that among them, some are RNA-dependent RNA polymerase (RdRp, nsp12) and helicase (nsp13). Afterward, the virion components are assembled into the endoplasmic reticulum, Golgi intermediate compartment complex. The infected cells release these by exocytosis [16].

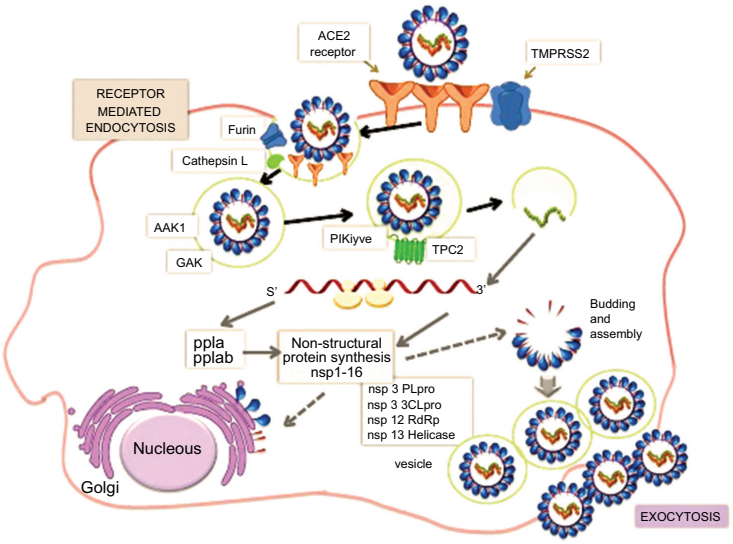

Fig. (1). SARS-CoV-2 infection cycle.

Coronavirus Structural Proteins

The coronavirus structural proteins that form the viral particle are described below:

1. **Spike glycoprotein (S-protein)**: It has a key role in virus pathogenesis and organ tropism. It secures the viral entry into the host cell through membrane fusion and receptor recognition.
2. **Envelope protein (E-protein)**: Smallest structural protein, but it has a big role in envelope formation, assembly, virulence, and budding (Fig. **2**).
3. **Main function protein (M-protein)**: To develop viral assemblies because of membrane-bending properties.
4. **Nucleocapsid protein (N-protein)**: Multifunctional protein that is bundled with the virus-related RNA genome into a ribonucleoprotein complex and is involved in defending the genome.

CHAPTER 8

Immunogenicity of SARS CoV-2 Vaccine

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Abstract: At present, we are in a crucial situation to find out and understand the immune response for severe acute respiratory syndrome coronavirus inside of human body systems. The novel coronavirus (SARS cov-2) has to cause 35 million infections and more than 1 million deaths worldwide as on October, 2020, according to the WHO dashboard. The explosive unfolds of SARS-CoV-2 indicate that a vaccine could be required to cease this global pandemic. Progress in SARS-CoV-2 vaccine improvement thus far has been faster than for some other pathogen in history. There were 42 vaccines in clinical research, and nearly 150 vaccines are in preclinical study. The immunogenicity alone data will help to attain a goal of design and development of good and safe vaccine averse to SARS CoV-2 infections in many countries and it also helps to predict the efficacy of the COVID-19 vaccine. Still now, we do not have a particular vaccine for COVID-19 infections, only we boost up our immune system to reduce the Covid-19 infections. So, we must know about our immune systems as well as the immunogenicity of the bio-active compounds for the prediction of the valuable and most powerful vaccine. A vaccine against SARS CoV-2 must control the infection and be capable of controlling the disease or transmission. For these reasons, we can detail explaining about fundamentals and application of Immunogenicity and also discuss its application to find out the potent SARS CoV-2-vaccine in this present study.

Keywords: Covid-19, Immune system, SARS CoV-2, Vaccine.

INTRODUCTION

The coronavirus disorder 2019 (COVID-19) caused by extreme acute respiration syndrome coronavirus 2 (SARS-CoV-2) has posed a critical hazard to public health [1 - 3]. SARS-CoV-2 belongs to the β-coronavirus of the own family Coronaviridae, and typically induces breathing signs, which include fever, unproductive cough, myalgia, and fatigue [4, 5].

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Several studies have been carried out to higher understand the virus, techniques have been mounted with the goal to prevent in addition spread of COVID-19 and also to expand green and safe capsules and vaccines [6]. For instance, the structures of viral proteins, which include in the spike protein (S protein), foremost protease (Mpro), and RNA-established RNA polymerase (RdRp), have been exposed [7 - 9] providing information for the design of medication against SARS-CoV-2. In addition, elucidating the immune responses against SARS-CoV-2 is accelerating the development of therapeutic processes. In essence, numerous small molecule pills and vaccines are being developed to deal with COVID-19. According to the arena health business enterprise (WHO), 36 vaccines out of 146 vaccines were analyzed in the preclinical evaluation to deal with COVID-19. The inactivated vaccine is also used to prevent and control challenging infection diseases which are occurred due to the influenza virus and poliovirus [10]. The novel COVID-19 virus was initially caused to humans because of the seafood wholesale seafood market at Wuhan, China [11, 12]. The present COVID-19 infections were similar and different from its prior severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) outbreaks. Bats and Camels are zoonotic transmitters of SARS (2002-2003) and MERS (2012-ongoing) in China and Saudi Arabia, respectively [13, 17]. The symptoms of these 3 infections were the same, that are fever, cough with poor respiration. The present corona virus named as Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses and the influenced disease refered as COVID-19 on February, 2020 [14]. The SARS-CoV-2 fusion and sustained along spike glycoprotein showed acceptable protection and immunogenic for the patients who all had their age from 18-55 years [15]. The above-mentioned vaccines can be applied for prophylaxis for SARS-CoV-2 infection. Most of the tests and studies carried out from the affected patients outlined that the infections belong to the type of viral infections. The patients were treated with anti-viral drugs, but the drugs were only effective on virus-infected patients and the vaccines were used as protecting shield for unaffected humans from specific virus attack. So, the immune-based vaccines were the permissible solution for the current pandemic situations. In this assessment discussed the recent progress of various therapeutic vaccines candidates against SARS-CoV-2. Furthermore, it summarizes the protection issues that researchers may be confronted in the improvement of immune vaccines and describe some effective techniques to improve the vaccine safety and efficacy that were hired inside the improvement of vaccines against other pathogenic sellers, with the hope that this review will aid inside the improvement of therapeutic strategies in opposition to COVID-19.

Root of COVID-19

Coronovirus belongs to the single-standed RNA virus, which are affected many animal species and humans. There was only twelve animal or human coronavirus identified until the year 2003. In 2003, SARS-CoV made 18096 cases in that 774 cases died and in the year 2012, the virus first identified in Saudi Arabia known as MERS-CoV, it infected 2,442 persons in that 842 died. Finally, SARS-CoV-2 were identified in Wuhan, China 2019 exploded the current global pandemic [18].

Immunogenicity

Immunogenicity is one of the challenging key factors in biotherapy to predict the immunogenic potential of novel therapeutics. It is the ability to induce the immune response system in living things. There are several challenges in biotherapy to predict the immunogenic potential of novel protein therapeutics. (i) immunogenicity data of developed countries are not transferable to developing and undeveloped countries. (ii) Another one, we can't consider how immunogenicity of the vaccine changes according to age. Hence, WHO said that the immunogenicity investigation by using animal models and *in-vitro* models could not perfectly predict the immune response in humans.

Corona Viral Genome Structure

The coronavirane came from the coronaviridae family is known as the subfamily of Corona virus (positive-strand RNA virus) and this subfamily consists of 4 genera: α, β, γ and δ-coronavirus. The 5'cap and 3'-poly-A tail contained single stranded positive-sense RNA was the genomic structure of Coronavirus (Fig. **1**). The translate poly proteins 1a/1ab (pp1a/pp1ab) known as non-structural one form replicated and transcript the complex into a double-membrane vesicle using genomic RNA. After that, the sub-genomic RNAs (sgRNAs) which one has nested set were also produced through the same RTC *via* discontinuous transcription manner and formed these subgenomic messenger RNAs have 3'-terminal and 5'-leader sequences. The termination of transcription and acquisition of subsequent of the leader RNA obtained in the transcription regulatory sequences present at open reading frames. These type of '-'strand sgRNAs is essence to synthesis of subgenomic messenger RNAs. The 6 open reading frames were present in the typical coronavirus genomic and sub-genomic structure and its sequence was 58% identical to non-structural proteins and 43% similar to the structural protein-coding regions [16, 27].

SARS-CoV-2 Virus

SARS-CoV-2 is an emerging, enveloped, non-segmented about 30-kilobase

CHAPTER 9

SARS-CoV-2 Recombinant of Drug

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Abstract: At the end of 2019, there was a global pandemic jeopardizing the lives of millions of people, with reports on the spread of novel coronavirus (nCoV-2019). COVID-19 or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated from bats and was transmitted to humans through an unknown source in Wuhan city located in China and spread across the globe in early 2020. The nCoV-19 uses its spike glycoprotein receptor to bind to the host cell angiotensin-converting enzyme 2 (ACE2) sites to launch a combination of events leading to server acute respiratory syndrome. In the past 100 years, the COVID-19 pandemic is the most destructive and life-threatening disease affecting the lives of millions of people after the Spanish flu. Hence, it requires a speedy measure to curtail the spread and combat the death rates. As it is said, vaccines are found to be a commendable strategy to alleviate the viral strains. The data required for the vaccine development, including the whole genome and protein sequence of SARS-CoV-2, were made available, which enabled numerous researchers and scientists across the countries to develop multiple vaccines for prophylactic and treatment of COVID-19. All these vaccines are in various stages of clinical trials. To date, globally, only 115 vaccine candidates have been developed, out of which 78 were found to be active and 37 yet to be confirmed. Vaccine development to prevent SARS-CoV-2 has potential hurdles where regulatory and medical decisions are taken based on the ratio between benefit and risk factors. Data on the specific SARS-CoV-2 antigen(s) used in vaccine development are highly limited in public resources. The vaccine developed mainly aimed to induce neutralizing antibodies against the viral spike (S) protein, preventing uptake *via* the human ACE2 receptor. However, it is unclear how different forms and/or variants of the S protein used in different vaccine candidates relate to each other or the genomic epidemiology

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of the disease. The most advanced candidates have recently moved into clinical development, including mRNA-1273 from Moderna, Ad5-nCoV from CanSino Biologicals, and INO-4800 from Inovio. Numerous other vaccine developers have indicated plans to initiate human testing in 2020. In this review, we focus mainly on the development of the SARS-CoV-2 vaccine using recombinant technology.

Keywords: SARS-CoV-2, Spanish flu, Spike.

INTRODUCTION

In December 2019, a new infectious respiratory disease emerged in Wuhan, Hubei province, China. Soon it became a global pandemic that affected the whole world. Millions of people were infected by this disease, and many of them died. This pandemic destabilised the healthcare systems across the globe as well as the economy. Now, the causative organism of this disease is known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and the disease is called COVID-19 by World Health Organization (WHO) on March 11, 2020. It took only 6 months to spread the pandemic up to more than 212 countries of the world. By May 2021, the average number of people affected by the disease were 33,000, and 1300 deaths daily. An aggressive campaign to develop an effective campaign against the COVID-19 pandemic is undergoing. A new pandemic vaccine development paradigm has been suggested that can help in reducing the vaccine development time from 10–15 years to 1–2 years [1]. However, the process of vaccine development is still facing a lot of bottlenecks. The constituents of a safe and immunologically effective COVID-19 vaccine are not yet known. There is a lack of clarity in defining the successful endpoints in vaccine efficacy testing. The chapter aims to discuss the guiding immunological principles that could be helpful in vaccine development, as well as the current COVID-19 vaccine landscape and the challenges associated with this.

Vaccine Development Stages

The process of vaccine development consists of exploratory, pre-clinical and clinical stages. The exploratory is limited to the research undertaken in the laboratory-based on the idea of an antigen against the disease, and this step may take 2-4 years to complete [2].

Pre-clinical Stage

In this stage the safety of the candidate vaccine and its immunogenicity is tested. The platform of tissue culture or cell-culture systems and animal testing is done during this stage. Animals like mice, rabbits, guinea pigs, monkeys, *etc*. are used keeping in mind the antigen. These animals help in assessing the immune

response and also side-effects of a candidate vaccine. From these tests, researchers evaluate the possible response of the candidate vaccine on human bodies. Soon after this, the safest dose and safest method for administration of the vaccine is given by the researchers. The animals are used to know how a vaccine candidate can be possibly used against a viral attack to stop the infection and its severity. The testing is a lengthy process that will take 1-2 years. Only 6 possible vaccine candidates out of 100 may pass this testing phase. The data of the successful vaccine is shared with the regulatory authorities. After sharing this date, the sponsor companies may show interest in manufacturing the vaccine, and the clinical stage is initiated. The clinical stages consist of 4 stages. A post-marketing safety evaluation is also conducted at the end of the clinical stage.

Clinical Trial Phase I

In this phase, healthy volunteers are recruited and their number may vary. The doses of candidate vaccines are administered to these volunteers. If a vaccine is being prepared for children, the tests are conducted on adults with a gradual shift to individuals with low age. This trial is most of the time an open-label trial, which means the subjects are also provided the details about the vaccine. In this phase, the safety and immune response of the candidate vaccine is assessed. Sometimes the subjects may undergo a challenge posed by a pathogen in a well-monitored environment to find the effect of the vaccine candidate. The data of the clinical trial is analyzed. If the findings are supportive, the next phase is initiated.

In **Phase II,** the number of participants in trials may increase to hundreds. Some of the subjects may belong to that group, which can be affected by the disease. The trials include a placebo group as these are well-monitored and randomized. In this stage, not only the vaccine's safety and immunogenicity is studied, but the proposed doses are also estimated, including the schedule and route of vaccine administration.

In **Phase III,** the group of the subject is further expanded. If there is a possibility of 1 side-effect among 1000 subjects, the group of subjects is expanded to 6000 people. The immunogenicity of the vaccine is further investigated and the critical level of antibodies/ cell-mediated immunity is also known. It is also estimated if the vaccine has the potential to fight the infection and capacity to protect from the disease. Once phase III of the clinical trials are completed, the sponsors apply for the biological license to the licensing authority. In India, the licensing authority is the Drug Controller General of India. The authority also tests the efficacy of the vaccine before giving permission for its use. After a post-licensure process, the vaccine is carefully monitored, and its adverse reactions are listed. Many pharmaceutical companies conduct phase 1V to further assess the vaccine's safety

CHAPTER 10

Human To Human Transmission of SARS – CoV-2

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Abstract: Coronavirus is a vast family of RNA viruses causing diseases from fever to severe illness and even death. Initially, it was called 2019 novel coronavirus (2019-nCoV) and labelled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The disease caused by coronavirus has been named coronavirus disease 2019 (COVID-19). Coronaviruses are widespread amongst birds, reptiles, cats, dogs, pigs, monkeys, rabbits, bats, and as well as in humans. SARS-CoV-2 is highly contagious and transmissible from human to human with an incubation period of up to 24 days, although the mortality rate seems to be significantly lower than SARS-CoV and MERS. Statistical data showed that on an average, an individual infected person can infect 5.7 cases.

Keywords: Asymptomatic, MERS, SARS-CoV-2, Transmission.

SPREAD OF CORONAVIRUSES

The first case of COVID-19 was reported in China on November 17, 2019, and the virus spread subsequently all over 150 provinces of China on December 1, 2019. In late December 2019, Chinese physicians noticed and identified a series of pneumonia cases in Wuhan, China. It has been found that the infections were epidemiologically associated with a wet seafood market where live and dead animals are sold, raised a suspicion that the infection had dropped into the human population related to the SARS epidemic which took place in the year 2002. SARS-CoV primarily infected leaf-nosed bats; subsequently spread to horseshoe bats, then to Asian palm civets and humans lastly. SARS-CoV-2 is the virus that

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causes COVID-19, a respiratory sickness. SARS-CoV-2 belongs to the family Coronaviridae under the genus Betacoronavirus. SARS-CoV-2 has many variants like 501.V2 variant, B.1.1.248, Cluster 5, and Variant of concern 2020/12/01. Viruses usually attain mutations over time and give rise to new variants. A new variant that appears in any population is commonly called as emerging variant. Few consequences of emerging variants are increased transmissibility, morbidity, mortality, ability to evade natural immunity, *etc.* SARS-CoV-2 is zoonotic in origin and genetically similar to bat coronaviruses. Hence, SARS-CoV-2 has emerged from a bat-borne virus; thus, SARS-CoV-2 ought to be introduced to humans in late 2019 [3]. There were about 60,412 confirmed cases with 1370 fatalities as of February 13, 2020 in 25 different countries.

On January 20, 2020, during the COVID-19 pandemic, it was confirmed that SARS-CoV-2 spreads from human to human [1, 4], 49% of them were found to have visited the Huanan seafood wholesale market [2]. Both direct and indirect transmission occurred during the pandemic. Reports revealed that transmission of viruses took place initially through respiratory droplets from coughs and sneezes within a range of 6ft. Other studies revealed that the virus gets transmitted along with the aerosols; hence the viruses could be airborne; also, indirect transmission took place in contact with contaminated surfaces. Full length genome sequences of SARS-CoV-2 are 96.2% identical with a bat coronavirus of SARS-CoV species. Respiratory droplets, either directly or indirectly, are the leading transmission mechanisms during the outbreak of novel coronavirus SARS-CoV-2. Indirect contact infection spreads when an infected person coughs, sneezes and contaminates the atmospheric air around them; if a healthy person inhales that virus-loaded air or the contaminated droplets land directly in their eyes, mouth, or nose, the risk of becoming infected is high. The virus-carrying droplets could travel between 6ft and land on objects, including doorknobs, tables, telephones, or dry surfaces. Indirect transmission of the virus occurred through public contact with contaminated objects that were not directly curtailed. Partial and complete lockdown was introduced by every country's government to curtail the spread of COVID-19 through the transmission of SARS-CoV-2. Residents were allowed to leave their homes only for essential reasons like food and health.

Asymptomatic and Human To Human Transmission of SARS-CoV-2

Symptoms of COVID-19 include breathing difficulties accompanied by cough, high fever, and fatigue. A cluster of 7 COVID-19 patients case between inter and intrafamilial transmission confirmed asymptomatic and human to human transmission of SARS-CoV-2 diagnosed in families and hospitals. A 56-year-old man departed from Guangzhou, China, on January 14, 2020 known as the index patient, and reached Xuzhou, China, after 6 hours, showed no symptoms and

transmitted the virus to his 2 daughters and son-in-law. Further, the spread was to a 62-year-old man who shared the same ward with the index patient's son-in-law at the hospital and to the old man's son, who took care of him. On January 25, the index patient's symptoms were confirmed with COVID-19 positive symptoms that include cold, cough, sneezing, sore throat, and high fever led to respiratory trouble.

Consequently, after January 26, 6 other individuals belonging to 2 different families were tested positive for SARS-CoV-2. Overall, 372 contacts of travelers from Wuhan, China, and familial cases in Illinois, USA, were identified. Human-to-human transmission of SARS-CoV-2 occurred primarily when two persons had unexpected, prolonged, unprotected exposure. Studies demonstrated asymptomatic and human-to-human transmission of SARS-CoV-2 infection through close contact in both familial and hospital environments.

A piece of remarkable official news was noticed in China on March 6; no doctors and nurses who worked for more than 2 months were infected with COVID-19 symptoms from the fact that the hospitals in Wuhan, China, formulated strict rules to prevent nosocomial infections. The core rule is to avoid direct physical contact with the patients excretory products, including feces, urine, and nasal mucus. The medical staff must wear protective disposable medical clothing and latex gloves. The hospitals' wards and the administration offices were frequently cleansed and disinfected. The surfaces of medical instruments, door handles, computers and elevators were also cleaned and disinfected to avoid viral transmission [5]. This helped the infection rate a lot lesser in controlling the contagion. The viruses with pandemic potential like SARS-CoV-2 can remain alive for a longer duration on any surfaces that could result in a broad contamination rate in the surrounding environment. Improving human behaviors can overcome the pandemic, resulting in less human-to-human transmission and global management of the outbreak.

Strengths and Limitations

Total infection cases issued by the authorities during the epidemic are unpredictable and unstable and vary with time. This instability and unpredictability might be due to a lack of proper diagnosis tools, uncontrollable mortality rates, and overcrowded hospitals. A lot has happened over the past year. One of the major concerns is the adherence or presence of infection-causing virus particles responsible for transmission to humans during and after the pandemic. What could be the extent of the role of surface contact in the transmission of the virus? According to research, the likelihood of catching COVID-19 via surface evidence is minimal. The foremost means of transmission are spread by the air, either by large droplets via close contact or by small droplet aerosol forms.

CHAPTER 11

Immune Response for SARS CoV-2

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Abstract: COVID 19 is the third one among zoonotic coronavirus, first and second being SARS-CoV and MERS-CoV, respectively. WHO has declared the coronavirus disease 2019 a pandemic on March 11th, 2020. The last pandemic was reported in the year 2009, which was H1N1 flu. The early eradication of COVID 19 seems impossible as it has never been identified in humans previously. There is a need to understand the basic immunology of this disease, to develop vaccines and medicines to save the global population from this novel coronavirus. The immune system protects against pathogens by producing antibodies to kill the pathogens that enter our bodies. Lymphocytes play a major role because they recognize the virus and produce antibodies against them, but people infected with COVID 19 showed a decline in the number of lymphocytes. Lymphocytes include T-cells, B-cells, Natural killer cells. About 15% of COVID 19 patients develop pneumonia, and about 5% end up in multiple organ failure where the immune response is critically impaired. The clinical conditions associated with Covid-19 include cytokine storm and acute respiratory distress syndrome (ARDS). In addition, changes in Acute Phase Reactants proteins (APR) have also been reported. This chapter aims to improve the understanding of the immune response and immunopathological changes that have been witnessed in patients suffering from this disease.

Keywords: Antibodies, COVID 19, Immune response, Immunopathology.

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INTRODUCTION

Coronavirus is a large group of viruses belonging to the coronaviride family. These are pleomorphic RNA viruses having peplomers that are crown-shaped and give the virus a sun-like appearance. The virus is highly infectious and is known to infect and cause diseases in different hosts like animals and humans. These viruses are known to causerespiratory tract diseases,including the common cold and severe conditions like SARS. The immunity of an organism is its ability to prevent itself from diseases. It helps in identifying between the foreign material and the self-antigen. Its function is to neutralise, eliminate, or to metabolise foreign matter. When a foreign material gains entry into the body, a series of chemical and mechanical actions are initiated that defend the body cells and tissues from external damage. The foreign substances are made up of protein and are known as an antigen. This antigen will be recognised by the immune cells, and the body fights against this antigen to preventinfection.

MECHANISM OF IMMUNE SYSTEM IN THE BODY

There are two levels in the body's defence mechanism, which are innate immunity and adaptive immunity. Innate immunity is a non-specific defence mechanism, which is the first defence barrier that prevents infection (Fig. **1**). The features of innate immunity include:

- Skin, mucosal epithelia, antimicrobial molecules which are part of Physical and Chemical Barriers.
- PHAGOCYTIC CELLS- dendritic cells, NK cells (natural killer) and other innate lymphoid cells.
- BLOOD PROTEINS which are part of the complement system and other mediators of inflammation.

The specialized sets of cell receptors known as PRR identify several microorganisms that have gained entry into the host. These receptors may also be known as pattern recognition receptors that activate the process of innate immunity. These microorganisms bind to the receptor, and microbial disposal mechanisms are activated. Macrophages or neutrophils are responsible for engulfing or phagocytizing bacteria. As a result, antiviral interferons are released. Most of the innate immunity mechanism is responsible for tissue damage, with the production of inflammation.

Adaptive immunity could be specific or acquired one. This is responsible for the recognition and response to microbial and nonmicrobial substances. Adaptive immunity is specific, and it has the ability to recognise different invading

substances. The memory is defined as the process of vigorous response to an attack by a similar microbe. The lymphocytes are the main components of adaptive immunity and these produce antibodies. As soon as a foreign microbe invades the cell, a specific immune response is induced. The lymphocytes recognise the invading organism and antibodies known as antigens are released.

In addition to this, some lymphocytes, either B or T CELLS (includes both CD8+ cytotoxic T-cells) are known to invade and kill the tumour cells. CD4+ helper T-cells regulate CD8+ T-cell and B-cell function. B cells play a major role in the adaptive immune system, which includes antigen-presenting cells, cytokine secretion, antibody-producing cells. B cells can produce specific antibodies in response to a variety of antigens.

Humoral and cellular are the two main mechanisms of adaptive immunity. Humoral immunity is may also be known as antibody- mediated immunity. Helper T Cell mediates B cells to differentiate into plasma B cells. As a result, antibodies are produced against specific antigens. Consequently, the free circulating antigens of the microbe are dealt. This also deals with the antigens that are present around the infected cells. The B plasma cells produce antibodies that bind to the antigen, neutralize them, or cause lysis of antigen by producing lysine.

The process of cellular immunity happens inside the cells which are infected by the invasion of microbes and T-lymphocytes mediate the cellular immunity. These antigens are expressed on the surface of the cells or an antigen-presenting cell. Cytokines are released by the Helper T cells that facilitate the binding of activated T cells with the infected cells. MHC or major histocompatibility complex, which is an antigen complex, is created. This helps in the differentiation of T Cells into a cytotoxic T CELL, as a result, the infected cells undergo lysis.

IMPACT OF COVID-19 ON THE HUMAN BODY

COVID-19 may result in the production of cytokines by WBC. There is increased production of catecholamines which contributes to cytokine storm. As a result, a systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), multi-organ injury, shock, or death may occur.

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