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Review Article

A review analyzing what is COVID-19, its causes, pathogenesis, pathophysiology, and treatment

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is believed to be the causative agent for the 2019 novel coronavirus (COVID-19). The COVID-19 disease which also started from bats had mutated and it is believed to have infected pangolins as its intermediate host. Mutations of the viral pathogen thereafter led to it infecting humans. COVID-19 is considered a zoonotic disease i.e. diseases that spread from animals to humans. Community transmission from human to human has largely contributed to increasing infection rates across the globe. When the novel coronavirus was first detected, it took just 69 days to infect 100000 patients, then increased to 200000 in 12 days, then 300000 in 4 days, and 400000 days in less than a day. As of 1 September 2021, there are well over two hundred and seventeen million cases worldwide. Of concern, at least four and a half million confirmed COVID-19 deaths have been recorded as of 1 September 2021. The World Health Organization (WHO) has advised that the COVID-19 pandemic is far from over.

Keywords COVID-19, Pathogenesis, Pathophysiology, Treatment

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1. Introduction

Viral pathogens are a common cause of lower respiratory tract infections and one such virus is the novel coronavirus (COVID-19). Clinical data as per the International Journal of Infectious Diseases show that the significant contributors to the mortality rate in patients with the novel coronavirus stem from old aged patients (age greater than 60 years) and those with comorbidities such as cardiovascular conditions (10.6%), underlying pulmonary disease (7.3%) and immunosuppression due to cancer (5.6%). Patients who are greater than 60 years of age have a mortality rate of 5% and those who are above 80 years have a 14% mortality rate [1]. The severe acute respiratory syndrome coronavirus (SARS-CoV), first recognized in China in 2002, had spread from bats who were the primary host reservoir to palm civet cats, after acquiring mutations. From the palm civet cats, it had spread to humans [2]. However, its effects were not as damaging, just causing mild viral pharyngitis and viral laryngitis The middle east respiratory syndrome coronavirus (MERS-CoV), first reported in Saudi Arabia in 2012 which was another mutated form of the Corona family of viruses also resided in bats as its primary reservoir. The MERS-CoV had then spread to camels and further mutated to spread to humans [3, 4]. The SARS-CoV-2 is believed to be the causative agent for the COVID-19. The COVID-19 disease which also started from bats had mutated and it is believed to have infected pangolins as its intermediate host. Mutations of the viral pathogen thereafter led to it infecting humans. The COVID-19 is considered a zoonotic disease i.e. diseases that spread from animals to humans [5]. When the novel coronavirus was first detected, it took just 69 days to infect 100000 patients, then increased to 200000 in 12 days, then 300000 in 4 days, and 400000 days in less than a day. As of 1 September 2021, there are well over two hundred and seventeen million cases worldwide. Of concern, at least four and a half million confirmed COVID-19 deaths have been recorded as of 1 September 2021. The World Health Organization (WHO) has advised that the COVID-19 pandemic is far from over. (https://www.google.com/covid19-map/).

The reproductive ratio (R0) of COVID-19 is estimated to fall in the range of 2–3. This refers to the degree of spreadability in that one person could infect two to three people. This shows that the novel coronavirus is more contagious than the influenza virus, which has a reproductive ratio of 1 [6]. The respiratory droplets from an infectious person with COVID-19 could spread approximately three to six feet from their source and remains on surfaces such as cardboard/wood and copper for up to 24 hours. On surfaces such as plastic and stainless steel, the viable virus can be detected for up to 72 hours [7]. A recent study conducted and published in The New England Journal of Medicine on March 17, revealed that airborne droplets of COVID-19 could be detected for up to 3 hours [7]. Incubation Period refers to the time between exposure to a virus and the appearance of the first symptoms. The incubation period for COVID-19 is 4–14 days but can go up to 24 days.

Immunocompromised patients are likely to experience a more severe form of the disease, whereby symptoms are not easily warded off. Therefore, it is of paramount importance that we as a society strictly adhere to the rules and regulations of the national shutdown and carefully follow the guidelines of infection and prevention control (IPC) as set out by the WHO and the South African National Department of Health. Basic protective measures include regularly washing your hands with soap and water or an alcohol-based rub. Maintain social distancing i.e. being at least one to three meters from someone who coughs or sneezes. Avoid touching your eyes, nose, and mouth. If you, however, experience symptoms such as fever, cough, shortness of breath, then immediately go to a doctor [8]. Pathogens that enter your air sinuses (frontal, maxillary, ethmoidal, and sphenoidal air sinuses) cause infection which then leads to inflammation (sinusitis). The air-filled cavities become inflamed. If not treated, the pathogen enters the oral cavity, producing a dry cough. Thereafter the pathogen spreads to the pharynx, causing pharyngitis, then to the larynx, causing laryngitis, then penetrating the lung tissue spreading to the distal portions of the lungs, particularly the alveoli, causing the alveoli to lose their elasticity [9]. Consequently, the lung tissue becomes hard and its blood supply diminishes, resulting in hypoxemia and subsequent organ failure which then leads to death. Taking precautions and boosting your immunity is well advised by health care professionals. The intake of citrus fruits (vitamin C), oranges, nartjies, lemon, salted onions is beneficial, but if diabetic or hypertensive then be careful of your salt intake.

2. Structure of the COVID-19

The COVID-19 is an enveloped, non-segmented, single-stranded RNA virus that is enclosed in a nucleocapsid. The virus contains a positive-sense single-stranded RNA genome that is made up of 29,891 nucleotides, encoding for 9,860 amino acids [10]. This is the largest known viral genome with a size ranging from 26 to 32 kilobases. Surrounding the virion nucleocapsid are two different types of spike proteins: the spike glycoprotein trimmer (S) that can be found in all CoVs, and the hemagglutinin-esterase (HE) that exists in some CoVs [11]. The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the S proteins in the virus envelope. These S-spike proteins serve to attach the viral particle to the Angiotensin-Converting Enzyme type 2 (ACE-2) receptor of the human host cell to gain entry and subsequently synthesize many more viral particles [12].

3. Pathogenesis of COVID-19

The SARS CoV-2 which causes the COVID-19 infection is essentially an infection of the lower respiratory system i.e. bronchi and alveoli. The novel coronavirus attacks type 2 alveolar pneumocytes of the lower respiratory tract. This then causes a cascade of events such as the inflammatory response, interstitial oedema, hyaline membrane formation, and diffuse alveolar damage which eventually leads to severe acute respiratory distress syndrome [13]. The virus which has an S-spike protein on its outer surface attaches to the Angiotensin-Converting Enzyme type-2 receptor on the human host cell. After attachment, the viral pathogen enters the endosome to release its positive-sense single-stranded RNA (+ssRNA) into the cytoplasm [13]. The enzyme RNA-dependent RNA polymerase initiates transcription of the viral RNA through replication. Once the viral RNA has replicated, it then migrates to the ribosome of the host cell [14]. The host cell ribosome translates the viral RNA to make proteins, thereafter forming a long chain of proteins – a polypeptide. Thereafter, this polypeptide chain is cleaved by the enzyme proteases to make small proteins that together with the newly formed positive-sense single-stranded RNA form complete viral particles [15]. The viral particle is now ready to be released from the cell and infects many more host cells.

4. Pathophysiology of COVID-19

Type 2 alveolar pneumocytes are destroyed during the COVID-19 infection. When the cell is destroyed by the virion, specific inflammatory mediators are released which stimulates alveolar macrophages to release interleukin-6 (IL-6) alongside interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) [16]. These inflammatory mediators stimulate the capillary endothelium to become more permeable thus allowing fluid to leak into interstitial spaces causing interstitial oedema, alveolar oedema with diffuse alveolar damage, and promoting vasodilation causing extravasation of fluid into tissue spaces [17]. Consequently, a gaseous exchange is reduced leading to hypoxemia and subsequent necrosis of lung tissue. Interleukin – 1 and interleukin – 6 migrate into the blood and travel to the hypothalamus to stimulate the release of prostaglandins and endotoxic pyrogens which elevate the average setpoint body temperature, thereby causing fever. Therefore, inhibiting the inflammatory response by inhibiting the release of the inflammatory mediators (interleukin-6, interleukin-1, tumor necrosis factor-alpha) with the use of Tocilizumab may prove to be beneficial in the therapeutic management of COVID-19 [18].

Type 2 alveolar pneumocytes which ordinarily produce surfactant to lower the surface tension and improve compliance of the lungs become damaged. Due to the increase in alveolar oedema, the surfactant is drowned out and as a result, the surface tension of the lung increases, causing the alveoli to collapse [16]. The decreased partial pressure of oxygen (pO2) stimulates peripheral chemoreceptors to stimulate the sympathetic nervous system (SNS) to increase the heart rate. Additionally, stimulation of the sympathetic nervous system increases the respiratory rate, to compensate for the reduced gaseous exchange. Patients soon develop acute respiratory distress syndrome [19]. White blood cells (WBCs) such as neutrophils are attracted to the site of inflammation. Neutrophils release reactive oxygen species (ROS) and protease enzymes that not only destroy the virus but also destroy type 1 and 2 pneumocytes. This negatively affects gaseous exchange by damaging the respiratory membrane and further reducing surfactant production [16]. Accumulation of fluid, proteins, and cellular debris from damaged type 1 and 2 alveolar cells in the central alveoli space leads to consolidation. If inflammation spreads throughout the pulmonary circulation, this could lead to septic shock. Patients become hypotensive due to vasodilation, reduced total pulmonary resistance (TPR), and decreased blood volume. This leads to multiorgan failure [20].

5. Treatment for COVID-19

Remdesivir, previously used for the treatment of the Ebola virus, could also be used as a potential approach for the treatment of COVID-19. Remdesivir which is currently undergoing phase 3 clinical trials has been shown to inhibit the enzyme RNA-dependent RNA polymerase thereby inhibiting the replication of single-stranded viral RNA [21]. In effect, the viral pathogen cannot multiply thereby impeding its ability to infect other host cells. Another potential target for the treatment of COVID-19 is to inhibit the viral pathogen entry into the endosome. The drug chloroquine and its derivative hydroxychloroquine could be used in this regard. Essentially, these drugs block/inhibit the binding of the S-spike of the viral pathogen to the ACE-2 receptors on the surface of human cells [22]. A major disadvantage of this potential strategy for the treatment of COVID-19 is that chloroquine and hydroxychloroquine have to be used in high doses which increases the risk of toxicity, and in some cases, hydroxychloroquine may cause cardiomyopathy resulting in cardiac failure [23]. This is where President Donald Trump was ill-formed when he called chloroquine and hydroxychloroquine a "game-changer "I feel good about it."

Ritonavir/Lopinavir is two antiretroviral drugs that are used in combination for the management of HIV/AIDS. They have also been shown to have potential in the therapeutic management of COVID-19. Ritonavir inhibits the protease enzyme intracellularly thereby allowing for increased blood levels of Lopinavir which inhibits HIV protease thus inhibiting the translation of viral particles. Tocilizumab, a monoclonal antibody that inhibits the Interleukin-6 signaling pathway is also being researched as a potential therapeutic agent in treating COVID-19 [24].

"Drug Repurposing" or otherwise known as "Drug Repositioning" serves as a useful strategy to find new and effective uses for existing drugs whose safety in humans has already been adequately established in clinical practice [25]. Owing to the urgency for a cure, "Drug Repurposing" has been the concept adopted, by the WHO and many pharmaceutical companies worldwide, whereby existing drugs that have been safely passed for use through rigorous experimentation and scientific validation, are now being investigated for the treatment of COVID-19 [26].

Many small-scale trials for these drugs have been conducted but none have yielded any favorable outcomes. However, WHO believes that large-scale trials are needed to test the efficacy of these drugs in the treatment of COVID-19. The WHO has since launched a global mega trial called SOLIDARITY which aims at determining whether any of the four drugs could potentially be used in the therapeutic management of COVID-19 [27]. Through a website with an online database created by WHO, SOLIDARITY aims at utilizing randomized evidence whereby once a confirmed case of COVID-19 is deemed eligible, all the relevant patient's data is captured and the patient signs a consent form which is uploaded to the website. The website will then randomize the patient to any of the drugs that are under investigation and the physician will then record the patient's response to treatment during their hospital stay. Through this initiative, many thousands of patients with COVID-19, who are given treatment, in dozens of countries, will be tracked and traced. Subsequently, data that is made available will be analyzed [27].

The first trial was conducted in Wuhan City (China), which included 199 patients who were given two pills twice daily of the combination antiretroviral drugs Ritonavir/Lopinavir had shown no favorable clinical outcomes. Reports indicate that the patients may have been given the drugs too late in their condition as they had been severely ill before the trial commenced [28]. The first COVID-19 patient diagnosed in Washington D.C. (United States) was given Remdesivir once his condition worsened. His condition improved the next day. Another COVID-19 patient from California whom doctors believed had little chance of surviving from the virus was given Remdesivir. His condition had also improved [29]. In China, more than 20 COVID-19 studies used chloroquine or hydroxychloroquine, but none have reported positive clinical outcomes [30]. However, WHO recommends that more robust trials be conducted, and more collaboration is needed to avail data for rigorous clinical research.

5.1. What is herd immunity?

Herd immunity refers to an infection preventive strategy, particularly in vaccination programs whereby the majority of the population is infected with a disease and subsequently recover from that disease. Once recovered, patients develop an immunological memory of the disease that enables them to fight off the disease if exposed to the pathogen in the future [31]. Once a large proportion of the population develops an immune memory to the disease, the spread of that disease is significantly reduced and those who are most vulnerable to the disease are protected. Herd immunity could potentially be used as a public health strategy to slow down the spread of COVID-19 thus protecting an entire population from the deadly infectious disease [32]. Corticosteroids that decrease inflammation by inhibiting phospholipase A2 may also show beneficial therapeutic outcomes in treating COVID-19, however, this is yet to be tested.

5.2. Vaccines

Multiple candidate vaccines are currently being tested and tried for COVID-19 through clinical trials in the United States and China. However, the WHO estimates that a vaccine for COVID-19 may only be available towards the end of 2021. One vaccine called mRNA-1273 (which was developed by using messenger RNA) would stimulate the host cells to release a protein that will boost the immune system to fight the virus. It has worked well in animals and is ready to be tested in humans [33].

6. Conclusion

COVID-19 continues to have devasting consequences amongst the global population and resulting in instability through social, cultural, and political unrest. Feelings of uncertainty, insecurity, and instability for both the present and future are common when faced with public health enemy number one i.e. COVID-19. As asymptomatic cases constitute the majority of infected patients, to date, no one knows with any exactitude the real number of cases globally. The effects of this unprecedented global crisis will remain with us for many years to come. Undoubtedly, COVID-19 is modern history's gravest public health emergency. However, lessons learned from the pandemic will foster greater collaboration between nations concerning how countries strategically prepare, respond, and recover from pandemics.

Conflict of Interest

The author of this article declares no conflict of interest.

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