

Review Article

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The Pathophysiology of COVID-19

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ABSTRACT

Background: On Dec 19, 2019, the public health department of China reported that an outbreak of pneumonia was caused by a novel Coronavirus. On March 11, 2020, the World Health Department (WHO) declared a worldwide pandemic. Understanding the pathophysiology of the SARS-CoV-2 virus is necessary for understanding the transmission, clinical presentation, associated risk factors, predicted outcomes, and provides guidance for treatment protocols.

Methodology: A comprehensive PubMed search was performed utilizing the terms: COVID-19 in combination with the terms virulence (507), and/or pathophysiology (490) leading to 997 results. These results were then screened for relevance. Categorized, and evaluated under the auspices of making good pathophysiological sense.

Results: The SARS-CoV-2 virus is much more virulent than either the SARs or MERs virus with its ability to cause serious disease inversely dependent on a person's ability to produce T-cells. The ability to produce T-cells declines linearly until the age of 65. The ACE-2 receptor binding site does not vary among different ethnic groups, but initial evidence suggests there may be differences ACE-2 expression levels. This variance in expression level may explain different infectivity rates but not clinical outcome. The clinical outcome seems more related to the cytokine storm. Obesity, asthma, and COPD may decrease one's likelihood of being infected but increases the morbidity rates once infected along with poor diet, hypertension, diabetes, and immunodeficiency.

Conclusions: The underlying pathophysiology of COVID-19 explains not only the virulence, and clinical presentation, and suggest adverse clinical responses are related to dysregulation of the immune response.

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Introduction

A novel pneumonia like illness was seen by local physicians in Wuhan, China, in November 2019 and later reported by the Public Health Department in China on December 19, 2019. This illness was found to be caused by new strain of coronavirus that is genetically similar to the viruses causing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronavirus (CoV). This newly emerged Corona Virus now named SARS-CoV-2 has since spread around the World infecting 8,900,000 individuals and has caused 466,000 deaths as of June 21, 2020. The name Coronaviruses (CoVs) comes from the crown-like spikes found on the surface (envelop) of these viruses that belong to the family Coronaviridae of the order Nidovirales. Majority of the members of this large family of viruses have the ability to infect respiratory, digestive, and nervous system infections or diseases. Their host range is quite wide including humans and animals for example camels, cattle, cats, bats, birds, snakes, mice and other wild animals. Since the mid-1960s till to date, seven species of this family of viruses have been identified as human coronaviruses (HCoVs) [1].

Fundamentally, coronaviruses are outsized, positive-sense enveloped ribonucleic acid (RNA) viruses in the Nidovirales order. These viruses are divided into four genera i.e. α , β , γ and δ . Out of these four genera three species of β -coronaviruses have been involved in deadly pneumonia outbreaks of in humans since the start of the 21st century. Five known human coronaviruses i.e.

HCoV-229E, OC43, NL63, and HKU1, can cause mild respiratory disorders, they have a broad distribution among vertebrates. Albeit, most of the human coronavirus infections are considered mild, still the epidemics caused by two members of betacoronaviruses; severe acute respiratory syndrome coronavirus (SARS-CoV-1), and the Middle East respiratory syndrome coronavirus (MERS-CoV), resulted in more than 10,000 cumulative cases during the last couple of years, with mortality rates of approximately 10% for SARS-CoV and 37% for MERS-CoV. As per world health organization's statement causative agent of current pandemic is a novel betacoronavirus, "the 2019 novel coronavirus (SARS-CoV-2)" which appears to be much more virulent and dangerous than either the SARs or MERS virus presenting a world-wide threat. (WHO 1, 2020) [2].

Interestingly, patients coming to medical facilities with SARS-CoV-2 are presenting with bilateral infiltrates representing an inflammatory pneumonia with evidence of damage to other organ systems especially the cardiovascular and gastrointestinal systems. Indeed, the virus appears more virulent than either the SARs or MERS virus and appears especially deadly in the elderly and those with specific comorbidities. Global trends indicate that SARS-CoV-2 may reach 30-40% of the population, in the absence of the practice of social distancing, improved diagnostics, treatment and vaccination. Exacerbating the spread and risk, is that this virus readily spreads from asymptomatic carriers [3-7].

The severity of viral infectious diseases in an individual are usually associated with the virus load, virulence power, mode of entry, age and overall immunity of the target all of which seem to be true with COVID-19. Yet, the overall mortality due to the SARS-CoV-19 virus seems to be most related to the individual's specific response to infection via a highly inflammatory process characterized by the cytokine storm [8,9]. Here we will attempt to explain the pathophysiology of virulence and hope to provide not only an overview of this disease but plausible pathways to approaching the treatment of COVID-19.

Survey Methodology

A comprehensive PubMed search was performed during December 20, 2019 and June 03, 2020 utilizing the term COVID-19 in combination with the term virulence (507), and/or pathophysiology (490) leading to 997 results. Initially, these 997 research papers were screened with duplications being removed and the remaining papers being chosen based on scientific merit by three content experts representing Medicine, Infectious disease and Pathophysiology who considered diversity of opinion, quality, reproducibility, and most importantly if the evidence made good pathophysiological sense. Mutual agreement on inclusion of information in this review by all three content experts provided the threshold of inclusion into this review.

Findings

Clinical Presentation

Most patients who are infected with COVID-19 will have either no symptoms only mild symptoms. This is especially true of those infected disease under the age of 15. Thus, this age group represents a pool of carriers who are infected unknown to themselves but may present a danger to others as this disease can pass from those that show no clinical symptoms. Severe disease seems to be correlated linearly with age up to about the age of 65 where the correlation begins to become exponential. The incubation period of this disease is about 4-5 days with about 5% of the population not showing clinical symptoms for as long as 14 day after initial exposure. Studies indicate that the virus sheds at high levels from the nose in both symptomatic and non-symptomatic patients in a way more like the influenza virus than the SARS virus. The virus also seems to be able to survive on fomites for 72 hours and in the air as an aerosol for 3-4 hours making transmission possible even if an infected person has not been around for hours from the air or days from inanimate objects [10-14].

The most important symptoms in adults are a fever 88%, cough 67.8%, fatigue 38%, difficulty breathing 18.7%, and myalgia. It has been shown however that children may show diarrhea as a sign of infection. For those with clinical symptoms the cough is often followed a day or two later by a slight fever with pneumonia appearing perhaps as early as 2-4 days after the initial cough. The blood labs indicate that about 83.7 percent of those infected have lymphocytopenia and 60.7 percent will have C-reactive protein above 10 mg/liter. Elevated liver enzymes are also relatively common indicating that the COVID – 19 virus has propensity for the liver which may also limit later therapeutic choices. Lymphocytopenia occurs in 87% of the cases in contrast to SARs where it is at 18%. This may indicate that COVID-19 may be overwhelming the immune system and/or targeting the immune system itself. Chest X-rays are often benign initially or may show signs of interstitial pneumonia with a ground glass appearance. The pneumonia however may progress rapidly into lobar or bronchopneumonia with CT scans similar to what was found with SARS. In terminal cases the chest X-rays may appear completed whited out. There is also evidence that the neuro-

invasion by the COVID-19 virus may play a role in respiratory failure [15-18].

The severity of pneumonia is often scored with the CURB65 score which uses as criteria 1 point for any of the following conditions: Confusion, Urea > 7 mmoles, Respiratory rate > 30, diastolic BP < 60, and Age > 65. In the absence of other risk factors, any score equals to 2 or more the patient is generally admitted, and a score equals to 3 or more the patient may be considered for intensive care. In addition to age, the following risk factors seem to elevate morbidity the most: hypertension, diabetes, hepatitis B infection, COPD, immunodeficiency and cancer [19,20].

Testing

As far as diagnosis is concerned, the preferred specimen for the COVID-19 according to Center for Disease Control (CDC) guidelines is a nasopharyngeal swab. In case nasopharyngeal swabs cannot be collected the other substitutes that can be collected are oropharyngeal, nasal mid-turbinate, or nasal swabs. Induction of sputum is not recommended; however, expectorated sputum could be collected from patients with productive cough. In patients who are intubated, it is recommended to collect a lower respiratory tract aspirate or bronchoalveolar lavage. Molecular techniques are considered a useful tool for successful identification of infectious agents. Besides, unbiased, high-throughput sequencing is a definitely a great tool for the detection of pathogens [21-23].

Considering ss-RNA nature of viral nucleic acid, and due to the fact that this virus was previously not known, the reliable and suggested method other than culture for SARS-CoV-2 RNA is use of reverse-transcription polymerase chain reaction (RT-PCR). First sequence of the genome of current SARS-COV-2 was reported by Dr. Wang Jianwei and the team who are working at the Chinese Academy of Medical Sciences, Institute of Pathogen Biology, and China. They used next generation sequencing (NGS) to explore the genome [24,25]. Samples they used were the bronchoalveolar lavage (BAL) fluid samples from the COVID-19 patients. They reported the correlation of genome sequence with the coronaviruses family that includes the SARS-CoV and the Middle East respiratory syndrome-related (MERS).

The first PCR tests for COVID-19 were developed very rapidly i.e. only within two weeks of the disease being identified and those tests are now part of the World Health Organization (WHO)'s recommended protocol for dealing with the disease. A positive test for SARS-CoV-2 or presence of SARS-COV-2 "RNA" in patient's sample confirms the diagnosis of COVID-19, but we cannot overlook the chances of false-positive and false negative tests. Even if initial testing is negative but the doubt for COVID-19 rests, the WHO recommends resampling and testing from multiple respiratory tract sites (WHO 2, 2020) and look for other sample types too as this virus have been found in other body samples too including feces and blood samples [2].

There are reports of negative RT-PCR test results in oropharyngeal samples although CT scans were suggestive of viral pneumonia, and same patients found positive for SARS-CoV-2 in later stages of the disease. As compared to RT-PCR, serologic tests (mostly Enzyme Linked Immuno Sorbent Assay or ELISA based) are considered more rapid yet less reliable. These these serological tests will help the clinicians to identify patients having current or previous infection, asymptomatic patients and patients with negative PCR results. In one study Guo et al, reported the effectiveness of combining IgM Elisa assay with RT-PCR giving a 98.6 % sensitivity. Wenling Wang et. al. (2020) reported presence

of Virus in specimens collected from multiple sites [26-28]. According to them majority of respiratory tract samples came positive for the SARS-CoV-2, but they also detected the live virus in feces, suggesting that SARS-CoV-2 can also be transmitted by oral- fecal route. They also found a small percentage of blood samples positive for COVID-19 PCR test, suggesting systemic infection.

SARS-COV-2 Virus

Coronaviruses are a group of viruses that cause about 20% of all common colds in humans, among them the four strains 229E, OC43, NL63, and HKU1 classically cause upper respiratory symptoms in immunologically competent individuals. SARS-CoV-2 the virus behind current pandemic is classified as a novel betacoronavirus that belongs to the subgenus sarbecovirus of Coronaviridae family. Apparently, the genome sequence of this SARS-CoV-2 has about 89% similarity with bat SARS-like-CoVZXC21 and approximately 82% homology to human SARS-CoV [29]. Like the SARs-CoV, the SARs-CoV-2 virus has the ability to invade both the upper and lower respiratory tracts. Coronaviruses have unique error prone RNA-dependent RNA polymerases (RdRP), mutations and recombination events frequently occur among these viruses, resulting in quasi-species diversity. This diversity is closely associated with their adaptive evolution property and their capability to cause the disease that can be as severe as this current COVID-19. There are reports indicating the evidence of mutated strains of SARS-COV-1 during 2002-2004 epidemic, and most of those mutations were in viral spikes to enhance binding to its cellular receptor and replication in human cells, resulted in accelerated infectivity [1]. There are currently over 300 sub-strains of SARs CoV-2. The genetic sequence of this new SARS-CoV-2, as we have previously mentioned has approximately 89% homology with the bat SARS-like-CoVZXC21 and approximately 82% homology with that of human SARS-CoV-1. Because of these homologies, the new virus was given the name SARS-CoV-2. The genome itself is a single-stranded RNA that contains 29891 nucleotide bases and can code for 9860 amino acids. Even though its origins are not entirely understood, available sequence studies advocate that the SARS-CoV-2 most likely evolved from a coronavirus strain mostly found in bats. The possibility amplifying mammalian host that could be an intermediate link between bats and humans, is not yet confirmed though it has been reported that pangolins could have served as the intermediate host. Coronaviruses use the homotrimers of the spike (S) glycoprotein found on their envelope to promote the attachment to the host cell receptors and fusion of the viral particle and cellular membrane of host cell for the entry. This S glycoprotein is the main antigen present at the viral surface, and this is the one that is the target of neutralizing antibodies produced by the host body during the course of infection. That is why this S antigen is the focus of vaccine design and treatment efforts. In short, S is a class I viral fusion glycoprotein synthesized as a single polypeptide chain precursor of approximately 1,300 amino acids [29-32].

COVID-19 cellular pathogenesis

Among coronaviruses, S is the viral surface glycoprotein molecule targeted by host proteases to generate two subunits, designated S1 and S2. The N-terminal of S1 subunit comprises of four β -rich domains that are designated as A, B, C and D. The domain A or B can act as receptor-binding domains in different strains of coronaviruses. The similar domains can also add to the stabilization of the pre-fusion state of the membrane-anchored C-terminal- S2 subunit. This C-terminal S2 subunit contains the

metastable spring-loaded fusion machinery of the virus that makes the attachment strong. Further proteolytic cleavage takes place at the S2' site, immediately up stream of the fusion peptide. This second cleavage step is a common occurrence in all coronaviruses and is said to prepare the protein for membrane fusion, causing conformational changes [33-35].

The main role of ACE-2 is the degradation of Ang II resulting in the formation of angiotensin 1-7 (A (1-7)) which opposes the actions of Ang II. Another well-recognized role of a (1-7) is in stimulation of hematopoiesis and recovery of circulating white blood cells. Other consequences of the virus-receptor interaction may be comorbidity with patients with high blood pressure or diabetes being treated with ACE-1 inhibitors or angiotensin-receptor antagonists since both drug classes increase the expression of ACE-2. Lei, 2020) [36,38]. It is also reported that the recombinant receptor binding domain (RBD) protein has the ability to bound firmly to the human ACE-2 (hACE-2) receptor molecules and bat ACE-2 (bACE-2) receptors. RBD can block the entry of SARS-CoV-2 and SARS-CoV into their corresponding hACE-2-expressing cells that suggests the possibility of RBD as a viral attachment inhibitor against both SARS-CoV-2 and SARS-CoV viruses [39].

ACE-2 is a type I transmembrane metallo-carboxy-peptidase that has homology to the ACE, which is an enzyme long-known to have a prominent role in the Renin-Angiotensin system (RAS) and is also considered as a target for the treatment of hypertension issues. ACE-2 protein receptors are largely expressed in vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes. It has been suggested that the SARS CoV-2 may effect male fertility. Reports suggest that in these patients serum luteinizing hormone (LH) is significantly elevated with a decreased testosterone (T) to LH ratio implying hypogonadism [40, 41].

Angiotensin II is degraded by ACE-2 resulting in generation of Angiotensin 1-7, which negatively regulates the RAS protein a protein important in cellular mitosis [36]. This down regulation of cellular mitosis may impair the ability of type II pneumocytes to replicate and repair damaged lung tissue. To show the interaction between ACE-2 and viral entry Hoffmann et al (2020) reported that when Vero-E6 cells (a monkey kidney cell line known to permit SARS-CoV replication) were treated with an Anti-ACE-2 antibody, it blocked the entry of Vesicular stomatitis virus (VSV) pseudotypes that express the SARS-CoV-2 S like protein [42]. Another important step to consider is priming of S protein by the Transmembrane protease, serine 2 (TMPRSS2), this step is crucial for SARS-CoV fusion with the target cells and spread of the virus throughout the host's body. Hoffmann et al., (2020) also studied the dependency of SARS-CoV-2 entry on S protein priming by TMPRSS2, they treated the Calu-3 human lung cell line with the serine protease inhibitor camostat mesylate that partially blocked the entry of VSV pseudotypes.

Cao et al (2020) cited that a previous study showed that residues near lysine 31, and tyrosine 41, 82-84, and 353-357 in human ACE-2 were significant for the attachment of S-protein in coronavirus but at the same time they were not able to find any mutation among different ethnic groups of these residues. They also showed that there was a deficiency of natural resistant mutations for coronavirus S-protein binding in populations. Similarly, a study by Zhao et al (2020) reported that ACE-2 has been found to be elevated in Asian men, with Caucasian's and Africans having lower levels, respectively. Collectively, the differences in allele frequencies of ACE-2 coding variants among promoters in

different groups provides evidence that the diverse genetic might affect ACE-2 levels among different populations. It is assumed that the higher levels in Asians should also translate into higher levels of ACE-2 in Native American populations, as there are evidences that Native American tribes began their migration to the New World about 15,000-25,000 years ago from Siberia and are genetically Asian overall and related to tribes in the Altaic region. Higher risks of morbidity and mortality in BAME group (Black, Asian and Minority Ethnic) individuals may in part be related to higher degrees of obesity (Blacks, Hispanics) and/or percentage of body fat (South Asians). Both are related to a higher risk of type 2 diabetes and cardiovascular disease and hence COVID-19 morbidity and mortality. It is postulated that Obesity may slightly reduce the chances of COVID-19 infection through lower tidal volumes of gas exchange in the lungs [43-47].

Differentiating COVID-19 Pulmonary Infection/ Pneumonia

The initial cases of SARS-CoV-2 associated infections were identified as “pneumonia of unknown etiology”, and also defined as a disease of unknown etiology with fever, with or without a recorded temperature, X-rays showed the evidence of pneumonia, with low or normal leukocyte count or sometimes low lymphocyte count during the early stage of disease. There was no improvement, with symptoms getting worst even after 3–5 days of antimicrobial treatment as per standard medical guidelines [48].

If we look for similar clinical features between COVID-19 and previously known betacoronavirus infections we will see that majority of the patients were presented with fever, dry cough, dyspnea, and bilateral ground-glass opacities seen on chest CT scans. These features of SARS-CoV-2 infection are similar to SARS-CoV and MERS-CoV infections. Yet, few patients with this novel coronavirus infection showed noticeable upper respiratory tract signs and symptoms for example rhinorrhea, sneezing, or sore throat. This indicates that the target cells could be located in the lower respiratory tract. Additionally, SARS-COV-2 patients unless a child hardly shows the intestinal signs and symptoms (e.g., diarrhea), as compare to MERS-CoV or SARS infection, where about 20–25% of patients had diarrhea too. Additionally, CoVID-19 also needs to be distinguished from other non-viral causative agents that might cause pneumonia-like symptoms and signs for example Mycoplasma, chlamydia, Streptococcus, Haemophilus, and variety of invasive fungi etc. It is also important to consider that patients with the signs and symptoms of viral pneumonia could also be test positive for many other viruses, and that is the reason why the possibility and severity of a combined viral infection with this SARS-CoV-2 should not be overlooked. If we compare the pathology of all three i.e. SARS-CoV-1, MERS and SARS-CoV-2, we will see that the major visceral macroscopic changes in fatal SARS-CoV-1 cases have been reported as edematous lungs with increased gross weights, multiple areas of congestion, lymph nodes enlargement in the thoracic and the abdominal cavity, along with the reduction in size and weight of spleen. Presence of large numbers of SARS-CoV particles and RNA were not only detected within the circulating lymphocytes and monocytes; lymphoid tissues and epithelial cells of the respiratory tract, the intestinal mucosa, and renal distal tubules, but they were also detected in, neurons in the brain, and tissue-resident macrophages from different organs [49-53]. Pathophysiology and virulence mechanisms of coronaviruses, and for that reason also of SARS-CoV-2 have links to the function of the non-structural proteins (nsps), and structural proteins. These nsps are able to block the host innate immune response [38]. With reference to functions of structural proteins, the envelope of the

virus is the main eccentric part as it promotes viral assembly and release. Though, many of these features need more detailed studies.

Pulmonary Damage Cascade – Cytokine Storm

The virus enters the respiratory tract usually through air droplets. There are reports of SARS-COV-2 virus associated cases with slight upper respiratory tract symptoms, signifying the possibility for pre- or oligo symptomatic transmission [54]. Once in the respiratory tract the virus eventually enters the alveoli targeting the ACE-2 receptor which is predominant on type II pneumocytes. It is the type II pneumocytes that normally produce surfactant which functions to increase pulmonary compliance, prevent atelectasis at the end of expiration and to help recruit collapsed airways and open these up. The type II pneumocytes are destroyed once infected by COVID-19 during the budding out process from these cells thus, reducing surfactant levels. The destroyed type II pneumocytes then recruit macrophages to destroy the dead debris and tissue. In turn the macrophages secrete interleukin 1, interleukin 6 and tumor necrotic factor TNF α . Interleukin-1 forms an important part of the inflammatory system causing vasodilation, increased body temperature, increased sensitivity to pain and localized fluid build-up. Interleukin 1 also increases the number of adhesion molecules in endothelium cells enhancing the migration of neutrophils and lymphocytes to the area. Interleukin 6 mediates acute phase proteins to be produced. TNF induces cachexia, fever and cell death of other infected cells. The alveoli begin to become full of fluid and debris which decreases the diffusion of oxygen across the alveoli causing hypoxemia. Additional, bronchial epithelial denudation, loss of cilia, and squamous metaplasia and acute fibrinous with organizing pneumonia in later stages [55]. This in turn can permanently damage the lung. As the lung is further damaged the pneumonia can turn to acute respiratory disease, septic shock and multi organ failure. Interestingly, the use of ACE inhibitors and ARB's by those with hypertension causes an upregulation of the ACE-2 receptor which may partly explain the increase in risks for those with hypertension.

Comparatively we saw for MER-CoV infection the target receptor was dipeptidyl peptidase 4 (DPP4; also known as CD26). Targets in the lung included pneumocyte, multinucleated epithelial cells, and bronchial submucosal gland cells. Reported pathogenesis of MERS-CoV infection include exudative diffuse alveolar damage with hyaline membranes, type II pneumocyte hyperplasia, pulmonary edema, interstitial pneumonia, and multinucleate syncytial cells formation. Bronchial submucosal gland necrosis had also been observed. These bronchial lesions embrace the pathologic basis for the respiratory failure, and abnormalities that can be seen on radiologic exams of MERS-CoV infection and resulted in nearly 45% of death rate [56-59].

Treatment

As of now, to fight with current coronavirus pandemic or COVID-19, scientists have started working on three different strategies that might help in development of appropriate drug(s). First to test the already available broad-spectrum anti-virals. For example, interferons, ribavirin, and cyclophilin inhibitors that already been used to treat coronavirus pneumonia considered into this category. Second, to use present molecular databases to screen for molecules that may have therapeutic effect against coronavirus. Third, using current genomic information and pathological features develop completely new targeted drug(s) from scratch. Among some of the treatments that are currently on hand and have been used in China and other places are zinc, chloroquine/hydroxychloroquine, and Azithromycin. Though each

of these inexpensive medications have not yet been approved by the FDA for the treatment of COVID-19 infection, they have been approved for other disorders and have been used extensively overseas in the treatment of the COVID-19 virus [60,61].

Zinc

Zinc has been shown to limit the duration of colds (many of which are caused by coronaviruses) by 40% in duration. Zinc is the most common trace metal found in the human cell following iron. Zinc is a cofactor for many enzymes that help maintain a healthy immune system and is involved in nearly every aspect of immune response. Zinc is especially important for humoral immunity that is the release of antibodies that opsonize the COVID-19 virus for phagocytosis by immune cells, kill infected cells by the NK cells and block the entrance of the virus into the cells. Zinc also may also interfere with RNA dependent RNA polymerase which is essential for the replication of the COVID-19 virus. Zinc enters the cell through the Zrt1p and Zrt2p transporters and can also utilize the voltage-dependent calcium channels, NMDA receptors and AMPA-Rs receptors [62,65].

Chloroquine/Hydroxychloroquine

Chloroquine is a very inexpensive drug and has been around since 1934 having been used as an antimalarial and immunosuppressant. Chloroquine has been shown to form an ionophore in the cellular membrane allowing doubling the amount of zinc that can enter the cell at clinically relevant levels. Chloroquine is a very alkaline medication that can readily distribute throughout one's cells and settle in those areas that are especially acidic such as the endosomes which are small vacuoles that the COVID -19 virus uses to enter the cell after attachment at the cellular membrane. Chloroquine can increase the pH of the endosome inhibiting the ability of the COVID-19 virus to enter the cell [66,67]. In a clinical trial of 100 patients in China using chloroquine it was found that the course of the disease was shortened, and the pneumonia exasperation inhibited [61]. No serious adverse effects were seen. Hydroxychloroquine may have greater inhibitory potential than chloroquine and may be safer as it does not have the same risk to cause retinal damage.

Azithromycin

Azithromycin may serve a dual purpose in the treatment of COVID-19 by reducing the risk of secondary bacterial infections and by taking advantage of recently uncovered anti-viral properties. As an anti-viral has been shown in patients with compromised lung function to induce interferon- β and interferon- γ [68,69]. Interferons are critical for innate and adaptive immunity against viral infections. Additionally, Azithromycin inhibits the bronchial excretion of mucin which when excreted narrows the bronchial passageways inhibiting breathing. Azithromycin may also limit inflammation [70].

Lopinavir-Ritonavir

There are several COVID-19 clinical trials looking at different combinations of Interferons with and without antivirals. A systematic review of the evidence related to lopinavir-ritonavir and SARS and MERS suggests it could be a potential treatment for COVID-19 infections. Lopinavir/Ritonavir with or without interferons are being used regularly in the treatment of COVID-19 [71].

Summary/Conclusion

The COVID-19 pandemic is the third coronavirus-caused disease to arise in the 21st century. Cultural and lifestyle changes of the last fifty years have created a world in which these newly seen viral infections can spread worldwide in day and weeks. The need

to prepare for future pandemics is apparent. Rapid identification, basic public health interventions such as social distancing, followed as quickly as possible by development of diagnostic tests to monitor in real time the spread of the disease should become standard reactions to new viral disease. Preparatory measure such as availability of enough personal protective equipment, specific medications, as well as costly instrumentation such as ventilators, extracorporeal membrane oxygenation (ECMO) are essential in fighting this disease. SARS-CoV-2 mutates rapidly, infects with high efficiency, and causes severe illness in a high proportion of infections [72]. These qualities should be expected in future outbreaks. Yet, according to a fundamental principle of microbiology that the more common an infectious agent becomes the less virulent it becomes we should also see an end to the COVID pandemic through evolutionary adaptation.

Entry of the virus via interaction with ACE-2 suggest a variety of potential therapeutic directions to develop and some effort should be made to develop pan-coronavirus interventions. Role of poor diet or malnutrition, age, diabetes, hypertension, and obesity are some of the important factors that cannot be neglected while ACE-2 shows possible patterns of ethnic and anatomic expression consistent with the spread of the disease among different ethnic groups and the pulmonary and immune suppression that are major features of the severe acute respiratory syndrome –Coronavirus 2 (SARS-COV-2 syndrome). Public health CANDOR regarding future infections; will prepare the public for realistic scenarios and greater compliance with traumatic interventions ranging from social distancing, stay-at-home orders, job loss, economic costs and end-of-life care that will enhance our ability to conquer future pandemics faster and at less cost than it will require to overcome COVID-19 [73].

Conclusion

The pathophysiology of COVID -19 clearly explains the susceptibility to disease, clinical presentation, progress of disease, morbidity and points to treatment approaches. The underlying pathophysiology of COVID-19 explains not only the virulence, and clinical presentation, and suggest adverse clinical responses are related to dysregulation of the immune response.

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