



A DESCRIPTIVE REVIEW OF NOVEL CORONAVIRUS DISEASE (NCOVID-19), ITS PRESENT STATUS AND FUTURE PROSPECT

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ABSTRACT

An outbreak of novel Coronavirus Disease, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing severe acute respiratory syndrome occurred in late 2019, which expanded globally from Wuhan city of Hubei Province, P.R. China. By March 11th, 2020 when the number of countries involved was 114, with more than 118,000 cases and over 4000 deaths, the WHO declared the pandemic status. This descriptive review aims to presents accredited and the most current studies pertaining to the basic sciences of SARS-CoV-2, epidemiology, pathophysiology, clinical presentation and disease course, diagnosis, management, public health interventions and future prospect of COVID-19.

This review aims to clarify the jargon in virology, describe the virion structure of SARS-CoV-2, evaluate the frequency of presentation of various symptoms, evaluate the limitations and statistical strength of the diagnostic tools currently in clinical practice, elucidate the clinical and epidemiological differences between COVID-19 and other infections causing outbreaks (SARS, MERS, H1N1), clarify the criteria on rapid screening, discharge from hospital and discontinuation of self quarantine, explain the involvement of micronutrients such as vitamin C and vitamin D and other novel therapies in COVID19 treatment and prophylaxis along with different prevention strategies.

This review will enable clarification and focus on the current status and direction in the planning of the management of this global pandemic.

Keywords: Coronavirus, COVID-19, pandemic, pathogenesis, screening, preparedness, public health emergency.

INTRODUCTION AND BACKGROUND

History of the Outbreak:

A cluster of 27 cases of pneumonia of unknown etiology, presenting with a constellation of symptoms such as fever, dyspnea, dry cough and bilateral lung opacities in radiological examinations was notified to the National Health Commission, China CDC and WHO by the Wuhan Health Commission in the Hubei province of the P.R. China on 31st December, 2019 [1]. Multiple intrinsic factors like Wuhan's large population density, proximity of the wet animal market and lack of early containment due to inability to accurately trace the history of exposure in the early patient cases contributed to rapid rate of spread in Wuhan, which eventually precipitate into the WHO declaring this viral pneumonia, the Coronavirus Disease 2019 (COVID-19) as an outbreak on 30th January, 2020 and a pandemic on 11th March, 2020, due to the global logarithmic expansion of the cases [2].

Virology and Pathogenesis:

The China CDC identified the virus called novel coronavirus 2019 (2019-nCoV) as the causative agent for the observed pneumonia cluster, after deep sequencing analysis from the lower respiratory tract samples, on 7th January, 2020 [3]. The World health Organization (WHO) renamed it to SARS-CoV-2 and on 11th February, 2020, named the disease caused by the "SARS-CoV-2" as "COVID-19" [4].

Corona Virus Disease 2019 (COVID-19) is a positive sense, single-stranded RNA virus, with a typical crown like appearance under an electron microscope due to the presence of glycoprotein spikes on its envelope [5]. It is not the first time that a coronavirus causing an epidemic has been a significant global health threat: in November, 2002, an outbreak of coronaviruses (CoVs) with severe acute respiratory syndrome (SARS)-CoV-1 started in the Guangdong province of China and again in September, 2012, the Middle East Respiratory Syndrome (MERS)-CoV appeared in the Middle East [6]. There are a myriad of coronaviruses that can cause the common cold like illness, mainly α -coronavirus (alpha CoV) & β -coronavirus (beta CoV) - probably present in bats and rodents, and δ -coronavirus (delta CoV) & γ -coronavirus (gamma CoV)-probably present in avian species [5-7]. These coronaviruses are zoonotic pathogens, when attains an animal reservoir can become infective and under adequate cellular environment, these viruses multiplies and undergoes genetic mutations, thus enabling them to cross species and infect and multiply within human hosts effectively.

COVID-19 is from the beta coronavirus family. It is a spherical or pleomorphic enveloped particles containing single- stranded, positive sense RNA associated with a nucleoprotein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein projections. Some coronaviruses also contain a hemagglutinin esterase protein (HE) (Fig. 1) [8]. Coronaviruses possess the largest genomes among all known RNA viruses. The genomic RNA is 30Kb, one vital encoded structural protein is the spike glycoprotein (S), that consists of three S1-S2 heterodimers which binds to the angiotensin- converting enzyme 2 (ACE 2) receptors on type-II pneumocyte [9,10]. The entry of SARS-CoV-2 into the type-II pneumocyte is via endocytosis and then multiplies in the cytoplasm. The high protein manufacturing stress induced upon the type-II pneumocytes lead to apoptosis. Additionally, the RNA from the SARS-CoV-2 acts as a pathogen-associated molecular pattern

(PAMP) and is recognized by the pattern recognition receptor or toll like receptors, which leads to chemokine surge causing neutrophil migration and activation, and damages the alveolar capillary walls. This leads to a loss in the interface between the intra-alveolar space and the surrounding stroma and therefore the fluids leaks through and fills into the alveolar sacs [2].

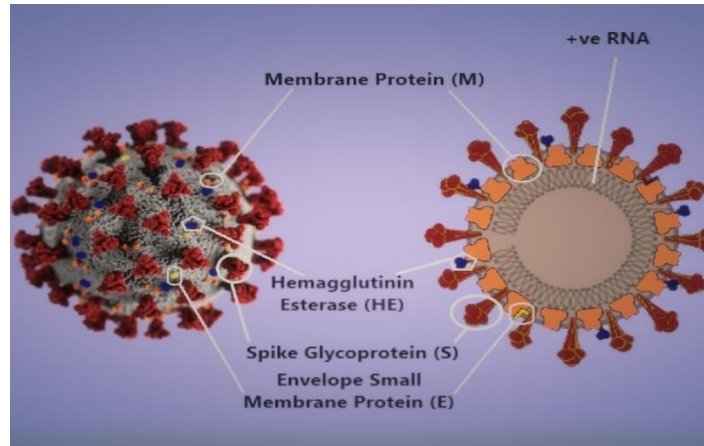


Figure 1: 3-D model of the SARS-CoV-2 virion and a schematic diagram of its structural proteins and genome. *Image component retrieved from CDC Public Health Image Library (ID 23312: Alissa Eckert and Dan Higgins)*

The pathogenic mechanism that produces pneumonia is complex. The viral infection is capable of producing an excessive immune reaction in the host- “cytokine storm”, which have extensive damage to the tissues. The protagonist of this storm is interleukin 6 (IL-6), which is produced by activated leukocytes [11]. IL-6 stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and central nervous system functions [12]. IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and in some malignancies [13]. It is also implicated that the pathogenesis of the cytokine release syndrome (CRS) is characterized by fever and multiple organ dysfunction [14].

Origin and Evolution of SARS-CoV-2:

It was reported that 27 of the first 41 infected patients had been exposed to the Huanan Seafood Market in Wuhan [15]. Thus, it was believed that the new coronavirus originated from this seafood market and spread from animal hosts to human in the process of wildlife trade. Bats have the most variety of coronaviruses in their bodies and are the hosts of many kinds of coronaviruses, such as the SARS-CoV and the MERS-CoV [16]. At the whole genome level, the SARS-CoV-2 shares an 87.99% sequence identity with the bat SL-CoVZC45 and 87.23% sequence identity with the bat SL-CoVZXC2, less genetically similar to the SARS-CoV 9 (about 79%) and MERS-CoV (about 50%) [17]. The SARS-CoV and the MERS-CoV are considered highly pathogenic, and it is very likely that the SARS-CoV was transmitted from bats to palm civets and the MERS-CoV from bats to dromedary camels and finally to humans [18,19]. Given the high sequence similarity between the SARS-CoV-2 and the SARS-like bat CoVs from *Hipposideros* bats in China, the natural host of the SARS-CoV-2 may be the *Hipposideros* bats.

Furthermore genomic similarity of 85.5% to 92.4% between SARS-CoV-2 and pangolin coronavirus, suggests pangolins should be considered as possible hosts in the emergence of SARS-CoV-2 [20].

Two major lineages- designated as L (leucine)-type and S (serine)-type co-exists with SARS-CoV-2 [21]. About 30% and 70% frequencies of S-type and L-type correspond to patients in Wuhan. Moreover, although the S-type is ancestral lineage, surprisingly the majority of the early cases in Wuhan were of L-type lineage and globally the S-type is more prominent [2]. A patient in the USA tested positive for co-infection with S-type and L-type SARS-CoV-2, but it is unclear if it will cause any significant clinical severity due to co-infection [2]. There is no any current evidence that immunity against one of the lineages will provide cross-reactivity against the other lineage. Thus, future vaccines must be designed to cover both the lineages.

Mode of Transmission:

COVID-19 appears to be transmitted by droplets from coughs and sneezes and exposure to droplet-contaminated surfaces. Based on current evidence, COVID-19 is transmitted when the virus enters the body via the mucosae (mouth and nose) or conjunctiva (eyes) which can occur through- direct person-to-person contact, respiratory droplets > 5-10 μ m in diameter (e.g. from coughing and sneezing), and indirect contact from touching infected environmental surfaces/fomites and transferring viral particles to the mucosa or conjunctiva [22].

As SARS-CoV-2 virions are shed throughout the clinical course, patients with COVID-19 can spread the infection prior to symptom presentation, during the symptomatic course and during recovery period. While respiratory symptoms increase the risk of transmitting the virus via saliva and mucus expressed by coughing and sneezing, asymptomatic patients not displaying any symptoms may also be infectious [23]. COVID-19 when aerosolized can remain in the air for up to 3 hours and can also remain on surfaces while gradually degrading for up to 72 hours on plastic, 48 hours on stainless steel, 24 hours on cardboard, and 4 hours on copper [24]. COVID-19 does not appear to be airborne under normal everyday conditions. It is observed that COVID-19 is not readily transmitted as 'airborne' molecules (i.e. transmissible via droplet nuclei <5 μ m in diameter that can remain in the air for up to 3 hours and travel >1m) in typical settings, rather it is transmitted in similar fashion as of influenza and rhinovirus [25].

Similarities and Differences between Common Cold, COVID-19 and Influenza:

Common cold is caused by a myriad of viruses- majority are rhinoviruses and also from some forms of coronaviruses. Common cold and COVID-19 both have a gradual course to symptom presentation in comparison to the flu, which is caused by the various strains of Influenza (orthomyxovirus family).

Fever is rare in common cold, but most notable symptom in both COVID-19 and influenza. Presentation of cough and fatigue is rare in common cold. Coryzal symptoms such as rhinorrhea and nasal congestion are predominant in the common cold and are rare in influenza and COVID-19 [2]. A COVID-19 and influenza virus both causes respiratory disease, presenting wide range of illness from asymptomatic to mild to severe disease and death. Both viruses are transmitted by contact, droplets and fomites.

Influenza has a shorter median incubation period (the time from infection to appearance of symptoms), and a shorter serial interval (the time between successive cases) than COVID-19 virus. As per WHO, the serial interval for COVID-19 virus is estimated to be 5-6 days, while for influenza virus is 3 days, which suggests that influenza can spread faster than COVID-19. The WHO estimates, the reproductive number (the number of secondary infections generated from one infected individual) for COVID-19 virus between 2 and 2.5, which is higher than for influenza virus.

For COVID-19, studies from WHO, suggest that 80% of infections are mild or asymptomatic, 15% are severe infection, requiring oxygen and 5 % are critical infections, requiring ventilation, which is much higher than what is observed in influenza infection and mortality of COVID-19 is between 3-4%, which is much higher than that for influenza (0.1%).

Clinical Presentation and Disease Course of COVID-19:

The clinical spectrum of COVID-19 varies from asymptomatic to more severe disease characterized by severe respiratory failure necessitating mechanical ventilation and intensive care unit (ICU) support, to multi-organ and systemic manifestations in terms of sepsis, septic shock and multiple organ dysfunction syndromes (MODS) [26]. Although, there are no specific clinical features that can reliably distinguish COVID-19 from other viral respiratory infections, pneumonia appears to be the most frequent serious manifestation of infection, primarily characterized by fever, cough, dyspnea and bilateral infiltrations on chest imaging [27]. Headaches, sore throat and rhinorrhea are some less common symptoms, in addition to some gastrointestinal symptoms like nausea and diarrhea in few cases.

Patients with COVID-19 present with pyrexia in 85% of cases during their illness course, but only 45% are febrile on early presentation [28]. Moreover, cough is seen in 67.7% of patients and sputum is produced in 33.4%. Respiratory symptoms such as dyspnea, sore throat and nasal congestion present in 18.6%, 13.9% and 4.8% of cases, respectively [28]. Constitutional symptoms like muscle and bone aches, chills and headaches are seen in 14.8%, 11.4% and 13.6% of the cases, respectively [28]. Gastrointestinal (GI) symptoms such as nausea or vomiting and diarrhea are seen in 5% and 3.7% of the cases respectively. These findings are consistent with other studies as well [29-32]. According to the WHO-China joint report, the median age of the patients with COVID-19 is 47 years [28]. One study of single cell transcription, suggests that Asian cell donors have higher ACE-2 receptors density than Caucasian and African American donors, suggesting that Asian population are more susceptible to COVID-19 virus [2].

More severe insult on the lung tissues can result in acute respiratory distress syndrome (ARDS) which can further precipitate septic shock, contributing more to the Intensive Care Unit (ICU) support and to mortality in COVID-19 patients older than 60 years, with smoking history and comorbid medical conditions. This is due to higher density of ACE-2 receptors in smokers and older age group patients. The leading comorbid condition likely to develop complications with COVID-19 includes hypertension, cardiovascular and cerebrovascular disease, and diabetes [33].

The WHO has reported an incubation period for COVID-19 between 2 and 10 days. However, some literature suggests that the incubation period can last longer than two weeks and it is possible that a very long incubation period could reflect double exposure [34]. Many studies suggest a 14 days as a cut-off for self quarantine. Guan et al. estimates that the mean incubation period is three days and 95% of patients with COVID-19 developed illness within 10 days of onset [28]. Incubation period has been found to be 19, 24 and 27 days in some outlier cases. Wang et al. showed that the median time from the preliminary symptoms to dyspnea, hospital admission and ARDS was 5, 7 and 8 days, respectively and the median hospital stay was 10 days in patients that were discharged [29]. Zhou et al. showed that the survivors group developed ARDS and sepsis on days 9 and 10, respectively and in non-survivors group on days 10 and 12 respectively. The non-survivor group developed more complications such as acute kidney injury and secondary infections by days 15 and 17, respectively. Survivor groups were discharged from the hospitals by day 22 and non-survivors group died by day 19 [2].

Epidemiology:

As of June 7, 2020, the WHO estimates that globally there have been 7,038,957 confirmed cases of COVID-19, including 403,400 deaths and 3,442,479 recovered cases. Out of 3,193,078 active cases, currently 3,139,350 (98%) are in mild condition whereas 53,728 (2%) of cases are in critical or serious condition. Based on the data we have so far, the estimated case fatality ratio among medically attended patients is approximately 2 % [35]. The current estimate of COVID-19 basic reproduction number (R_0) is 2-2.5 [36, 37]. This can be interpreted as every case of COVID-19 can spread the disease to two to three new people. As of June 7, 2020, the WHO estimates, the countries with most number of deaths are USA (109,038), UK (40,465), Brazil (35,026), Italy (33,846), France (29,084) and Spain (27,135). Mortality rate increases in the 60 years and above cohort to 8.8% in comparison to 0.46% for patients less than 60 years of age [38]. The mortality rate has a predilection for male gender (M: F=1.7:1). Furthermore, the mortality rate also increases in patients with additional comorbidities with cardiovascular diseases, diabetes and hypertension leading the cohort of mortality rates.

DIAGNOSIS

Screening Tools:

Two prominent screening tools have been developed by the WHO and CDC, which have evolved over the progression of the outbreak. Table 1 is the most updated COVID-19 screening tool developed by the CDC [39].

Clinical Features	Epidemiologic Risk (within 14 days of symptom onset)
Pyrexia OR Respiratory symptoms (cough, dyspnea, sore throat, and nasal congestion)	AND Close contact with RT-PCR confirmed COVID-19 patient
Pyrexia AND Respiratory symptoms (cough, dyspnea, sore throat, and nasal congestion) requiring hospitalization	AND History of travel to CDC flagged areas
Pyrexia AND Severe Respiratory illness (pneumonia, ARDS) requiring hospitalization AND without any alternative diagnosis	AND No discernment of exposure history

Table 1: Updated summary of CDC COVID-19 screening criteria

Diagnostic Tools:

For patients suspected with COVID-19 infection, reverse transcriptase polymerase chain reaction (RT-PCR) assays are used as gold standard to detect the positive nucleic acid of SARS-CoV-2 in sputum, throat swabs, and secretion of the lower respiratory tract samples [40], although it is only 66-80% sensitive. Variance in the sensitivity can be attributed to the patients being tested early in the disease course wherein the viral load is beneath detection level or due to lack of automation in sample preparation for RT-PCR. Single negative RT-PCR does not rule out COVID-19, thus a repeat RT-PCR must be performed, with ideal window period between 24-72 hours of the negative test.

CT- chest has shown 95% sensitivity in making an early diagnosis of COVID-19, which most commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia [41]. One study has suggested that CT-chest abnormalities are more likely to be bilateral, with peripheral distribution involving the lower lobes. Pleural thickening, pleural effusion and lymphadenopathy are lesser known findings [31, 42].

Contrastingly, chest x-rays have poor sensitivity, but patients are imperative for isolation, if ground-glass opacities are demonstrated.

Laboratory Examinations:

Standard blood investigations in patients with COVID-19, may show variance in the white blood cell count- from leucopenia to leukocytosis to most commonly lymphopenia [43, 44]. Furthermore, there is a systemic elevation of pyrogenic cytokines such as IL-6, IL-10 and TNF- α [28, 32]. Elevated lactate dehydrogenase and ferritin levels are common and elevated aminotransferase levels have also been observed in some COVID-19 patients. ICU care patients were found with elevated serum prolactin levels [28]. High D-dimer levels and more severe lymphopenia have been associated with mortality [28]. In critical COVID-19

patients, neutrophilia, increased plasma blood urea nitrogen (BUN) and creatinine are also documented [28-32, 41].

MANAGEMENT

Currently no specific antiviral treatment and vaccines are available for COVID-19 infection. The treatment for COVID-19 is predominantly supportive and symptomatic. Oxygen therapy represents the major treatment intervention for patients with severe infection. Supplementary oxygen at 5 L/min must be administered for patients that require management of severe respiratory distress and the oxygen saturation (SaO₂) target must be ≥92-95% in pregnant patients and ≥90% in all other patients [45].

Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock [46]. Some patients may develop superimposed bacterial or fungal infection in the middle to later course of COVID-19, as such appropriate empiric antimicrobial coverage must be provided. Home management is appropriate for asymptomatic or paucisintomatic patients. They need a daily assessment of body temperature, blood pressure, oxygen saturation and respiratory symptoms for about 14 days. Management of such patients should focus on prevention of transmission to others and monitoring for clinical status with prompt hospitalization if needed. Outpatients with COVID-19 should stay at home and try to separate themselves from other people in the household. They should wear a face mask when in the same room (or vehicle) as other people and when presenting to health care settings. Disinfection of frequently touched surfaces is also important. The optimal duration of home isolation is uncertain, but in consideration of incubation time around 14 days without symptoms (fever, dyspnoea, others) are considered sufficient to end home isolation. The latest version (6th edition) of the Guidelines for the Prevention, Diagnosis, and Treatment of COVID-19 by the National Health Commission (NHC) of China has recommended a combination regimen of protease inhibitors (lopinavir and ritonavir) with INF- α . The rationale for this combination treatment is based on experience with this regimen in reducing the mortality rates in SARS. The WHO recommends usage of extracorporeal membrane oxygenation (ECMO) in patients that sustain hypoxia refractory to supplementary oxygen [44]. Alternatively, convalescent plasma and IgG are used as rescue therapy in critical cases but there is no robust evidence for this practice.

In the majority of the cases, public health measures are vital for the management of the spread of COVID-19. If public health measures for containment are not adequate, then there will be a patient burden that supersedes the capacity of available ICU beds and mechanical ventilation. Therefore, the entire objective of the COVID-19 management rests on the premise of social distancing to suppress the rapid emergence influx of new cases in a short time frame. This epidemiological concept is referred to as the “flattening of the curve”. The mainstay of public health must be to identify the infective cases, isolate these cases, attain contact tracing and isolate contacts that present with symptoms.

Discharge criteria:

Four major discharge criteria exist, and these are from Italy, China, USA and Singapore which differ only in their cutoffs.

The China CDC discharge criteria state that all four conditions must be met to satisfy a discharge from the hospital [47].

- ❖ A patient must remain afebrile for at least three consecutive days.
- ❖ All respiratory symptoms (cough, dyspnea, sore throat, and nasal congestion) must be resolved.
- ❖ Chest CT must demonstrate marked resolution of the exudative lesion.
- ❖ Two serial RT-PCRs must be negative for SARS-CoV-2 RNA from the nasopharyngeal collection; these assays must be spaced by 24 hours.

Quarantine discontinuation criteria:

Two separate quarantine discontinuation criteria for COVID patients in self-quarantined at home have been developed by Italy and USA. The CDC quarantine discontinuation criteria state that both conditions must be met to satisfy the criteria [47].

- ❖ At least two serial RT-PCRs must be negative for SARS-CoV-2 RNA. These swabs must be nasopharyngeal collections; these assays must be spaced by 24 hours.
- ❖ The patient must remain afebrile for at least 72 hrs without antipyretic medication use, and resolution of respiratory signs and symptoms. A minimum of seven days have passed since the preliminary symptom appeared.

A number of investigational agents are being explored for antiviral treatment of COVID-19. Certain investigational agents have been described in observational studies or are being used anecdotally based on in vitro or extrapolated evidence. It is important to emphasize that there are no controlled data supporting the use of any of these agents, and their efficacy for COVID-19 is unknown.

Remdesivir (GS-5734) is a nucleoside inhibitor that is the strongest candidate for COVID-19 treatment. Remdesivir is a monophosphoramidate prodrug that causes premature termination of viral RNA replication and was originally developed against Ebola, MERS-CoV, and SARS-CoV. The compassionate use of remdesivir through an investigational new drug application has been described in various studies [48, 49]. Any clinical impact of remdesivir on COVID-19 remains unknown.

Lopinavir and Ritonavir are protease inhibitors, is usually a part of the HAART regimen to treat HIV. The lopinavir and ritonavir combination has also been shown to be effective against SARS in vitro [50]. However, there was no difference in time to clinical improvement or mortality at 28 days in a randomized trial of 199 patients with severe COVID-19 given lopinavir-ritonavir (400/100 mg) twice daily for 14 days in addition to standard care versus those who received standard of care alone [51].

Umifenovir is a non-nucleoside broad-spectrum antiviral licensed for influenza treatment and prophylaxis in Russia and China. It has not received FDA approval yet. Umifenovir is a membrane fusion inhibitor. Current regimens of Umifenovir used in China include a PO dose of 200 mg TDS for a duration of 10 days [52].

Chloroquine and hydroxychloroquine have antiviral activity in vitro, as well as anti-inflammatory activities. They act on interference with the cellular receptor ACE2, on impairment of acidification of

endosomes and on activity against many pro-inflammatory cytokines (e.g., IL-1 and IL-6) [53, 54]. Other experiments have shown that azithromycin in combination with hydroxychloroquine appeared to have additional benefit, but there are methodologic concerns about the control groups for the study, and the biologic basis for using azithromycin in this setting is unclear [55]. Despite the limited clinical data, given the relative safety of short-term use of hydroxychloroquine (with or without azithromycin), the lack of known effective interventions, and the *in vitro* antiviral activity, some clinicians think it is reasonable to use one or both of these agents in hospitalized patients with severe or risk for severe infection, particularly if they are not eligible for other clinical trials. The possibility of drug toxicity (including QT interval (QTc) prolongation and retinal toxicity) should be considered prior to using hydroxychloroquine, particularly in individuals who may be more susceptible to these effects including epilepsy, porphyria, myasthenia gravis, and retinal pathology—glucose-6-phosphate dehydrogenase (G6PD) deficiency [54, 56].

SARS-CoV-2 enters the type II pneumocytes via the ACE2 receptor, and this is also a functional receptor. The functional role of the ACE2 receptor has a reciprocal physiological action to ACE1, it converts the angiotensin II back into angiotensin I. Therefore, patients taking ARBs will have an increased plasma level of angiotensin II. Contrastingly, patients taking ACE-I will have low levels of angiotensin II. There is an upregulation of ACE2 receptors in the kidney and heart in response to ACE-I or ARB dosing in rats and humans [57-59]. There is no data available on its effect in the alveolar tissue. If there is a similar upregulation of ACE2 receptors then there will be heightened infectivity of SARS-CoV-2 along with subsequent clinical illness severity. Discontinuation of ACE-I or ARBs is not recommended yet as hypertension is an acute risk of discontinuation and can exacerbate the clinical course and increase mortality of COVID-19 if infected by SARS-CoV-2. This view of not discontinuing ACE-I and ARBs has been supported by the council on hypertension from the European Society of Cardiology.

Ibuprofen has shown to upregulate ACE2 receptors [60]. There is no current evidence indicating that ibuprofen worsens the clinical course of COVID-19. The current standpoint of the WHO is to continue the use of ibuprofen as antipyretic agent. The first-line antipyretic remains to be acetaminophen.

Glucocorticoids should not be used in patients with COVID-19 pneumonia unless there are other indications (e.g., exacerbation of chronic obstructive pulmonary disease) [61, 62]. Glucocorticoids have been associated with an increased risk for mortality in patients with influenza and delayed viral clearance in patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Although they were widely used in management of severe acute respiratory syndrome (SARS), there was no good evidence for benefit, and there was persuasive evidence of adverse short- and long-term harm [63, 64].

PREVENTION

Self-Protection:

Hand washing for at least 20 seconds after visiting public spaces. Soap or hand sanitizer with at least 60% of ethanol is recommended [65]. It is also recommended to avoid touching the denoted facial T-zone (eyes,

nose, and mouth) as this is the access point for virions into the upper respiratory tract [65]. Avoiding contact with people who are already presenting with symptoms, as well as avoiding gathering or crowded places. Travel to outbreak areas must be prohibited. A healthy individual must maintain at least six feet distance from individuals presenting with symptoms [65]. The sterilization of frequently handled surfaces is beneficial.

All healthcare workers managing COVID-19 patients require full personal protective equipment (PPE) containing surgical masks, double gloves, full-sleeved procedural gowns, and eye shield [65]. The N95 masks which prevent 95% of the droplets from entering the mask must be exclusively donned prior to performing procedures associated with a higher risk for aerosol exposure such as tracheostomy, tracheal intubation, bronchoscopy, cardiopulmonary resuscitation (CPR), and noninvasive ventilation (NIV) [65]. These procedures have the potential to aerosolize the virus.

Containment of community transmissions is achieved by the closure of educational institutions, businesses, airspace, and sports events. High-risk individuals such as those older than 65 or having chronic comorbidities without any symptoms are also required to self quarantine to decrease the likelihood of COVID-19 contraction [65].

Herd Protection:

On the development of any symptoms, the potential patient should remain quarantined in self isolation away in a separate room with a separate bathroom for at least 14 days. This self isolation must be extended to pets as well, as there is a recorded case of a human-to-dog transmission [44]. If there are any further concerns about COVID-19, then immediate contact with the public health hotline or general practice clinic via telemedicine must be established to attain a potential diagnosis. Face masks (N95) are needed for COVID-19 patients to prevent droplet spread [44].

Role of Vitamins:

Vitamin C (L-ascorbic acid) has a pleiotropic physiological role, but there is evidence supporting the protective effect of high dose intravenous vitamin C (HDIVC) during sepsis-induced ARDS. Vitamin C reinforces the maintenance of the alveolar epithelial barrier and transcriptionally upregulates the protein channels regulating the alveolar fluid clearance [66]. HDIVC has been implicated in reducing plasma cell-free DNA formed from the neutrophil extracellular trap (NET) which is the facilitator of systemic inflammation in sepsis-induced multi-organ failure [67, 68]. Interestingly, elevated levels of syndecan-1 in the plasma correlate with increased mortality in severe sepsis and ARDS, and this endothelial glycocalyx can be reduced significantly by HDIVC [68].

Vitamin D is known to mitigate the scope of acquired immunity and regenerate endothelial lining. This may be beneficial in minimizing the alveolar damage caused in ARDS. One evidence shows that, there is a 12% overall protective effect of vitamin D supplementation against bacterial and viral acute respiratory tract infection [69]. These protective effects increased to 19% in those individuals on the daily or weekly regimen of vitamin D compared to those dosing on a monthly bolus of vitamin D.

Vaccines:

Unfortunately, there is no approved vaccine against COVID-19 as of June 2020. Some vaccine manufacturers are currently running on Phase-I for developing a vaccine against COVID-19. Hopefully, we will develop a competent vaccine in near future for COVID-19.

FUTURE PROSPECT

The COVID-19 outbreak is proving to be an unprecedented disaster, especially affecting health, social and economic status. If high income countries, especially those already affected by the outbreak, seem to face a catastrophic perspective, in low-income countries there seem to be much bigger problem. Extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. A guideline was published for the medical staff, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV. The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection. The public services and facilities should provide decontaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as faecal and urine samples that can potentially serve as an alternative route of transmission. China and other countries including the US have implemented major prevention and control measures including travel screenings to control further spread of the virus. Epidemiological changes in COVID-19 infection should be monitored taking into account potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs. There remain a considerable number of questions that need to be addressed. These include, but are not limited to, details about who and how many have been tested, what proportion of these turned positive and whether this rate remains constant or variable. Very few paediatric cases have so far been reported; is this due to lack of testing or a true lack of infection/susceptibility? Of the ones that have so far been tested, how many have developed severe disease and how many were tested positive but showed no clinical sign of disease? These are some basic questions that would provide a framework for which more specific and detailed public health measures can be implemented.

CONCLUSION

This COVID-19 pandemic is a reminder of the volatility in the ongoing planning to manage the primary and secondary infection of SARS-CoV-2. This planning can be improved by accurate modeling of current data and by eliminating the misinformation in our era of data surplus.

This review comprehensively summarizes the most relevant into the COVID-19 current situation and its relation to the individual parameters that influence the clinical course, public health impact,

pathophysiology, diagnosis, case management, emergency response and preparedness. Due to the lack of available and validated therapeutics, most of the counter measures rely on the usage of public health containment and quarantine approaches. Primary learning points from this COVID-19 pandemic are to uphold transparency to prevent delays in threat identification. Secondly, delays in travel restriction and self-quarantine measures led to a logarithmic expansion of cases. Lastly, there is a need to increase investments towards research and development in COVID-19.

Only once this pandemic ends, one will be able to assess the health, social and economic impact of this global disaster and we should be able to learn lessons especially in terms of public and global health for any future similar pandemics.

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