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COVID-19

An Update on the Epidemiological, Clinical, Preventive, and Therapeutic Management of 2019 Novel Coronavirus Disease

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The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) remains a serious issue for global health, given widespread infectivity and a high contagion rate. A tremendous amount of data has been generated since it was first identified in December 2019. It is vital to keep up with these data from across the world at a time of uncertainty and continuously evolving guidelines and clinical practice. This review provides an update on recent developments concerning epidemiology, clinical presentation, treatment options, and scientific advancements to combat the COVID-19 pandemic. **Key words:** *coronavirus*, *corticosteroid*, *COVID-19*, *remdesivir*, *vaccine*

SEVERE acute respiratory syndrome coronavirus (SARS-CoV-2) was first identified in December 2019 as the cause of illness in Wuhan, the capital of Hubei province, from where it rapidly spread across China. SARS-CoV-2 led to thousands of deaths in China, subsequently spreading to Italy and other European countries and the United States.[1-3] Since then, it has resulted in a worldwide pandemic with widespread infectivity and a high contagion rate. There have been more than 28 million cases of COVID-19 worldwide as of September 12, 2020.[4,5] Here, we review the recent updates since COVID-19 has been declared a pandemic.

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EPIDEMIOLOGY

There have been reported COVID-19 cases in more than 188 countries, including all 50 states of the United States. As of September 12, 2020, COVID-19 has caused 6 427 058 cases and 192 388 death in the United States.[6] In the first wave of the infection until May 2020, a rapidly increasing number of cases overwhelmed health system resources. Analysis of 1.3 million cases of SARS-CoV-2 reported in the United States till May 2020 indicates that 14% of patients required hospitalization, 2% admission to intensive care, and 5% death rate.[7] Patients with the underlying medical condition were 6 times more likely to be hospitalized and 12 times more likely to have died, compared with those without medical conditions.[7] The higher mortality rate was seen in those 70 years and older,

regardless of chronic medical conditions.[8-10] Studies have noted the prevalence of cardiovascular disease in 32%, diabetes in 30%, and chronic lung disease in 18% of those who have a higher mortality rate.[9-12] Other conditions that place a higher risk of severe COVID-19 infection include obesity, kidney disease, cancer, and immunocompromised conditions.[8-14]

In the second wave of July-August, case numbers have increased at a slower rate while the mortality rate has remained relatively low compared with the first wave. There is a higher infection rate in the younger age group in the second wave, a widespread use of masking in population, and a decreased burden on health care resources. Masking reduces viral inoculum to which the wearer is exposed.[15] Universal facial masking reduces the severity of disease and ensures that a more significant proportion of new infections are asymptomatic.[16]

A recent analysis of 22 studies involving human coronaviruses revealed that the virus can persist on surfaces such as plastic, metal, and glass for up to 9 days but can be effectively inactivated within 1 minute via surface disinfection using 0.1% sodium hypochlorite, 62% to 71% ethanol, and 0.5% hydrogen peroxide.[17] Also, the most available data support that social distancing of 1.5 m prevents airborne transmission. The current data suggest that the average incubation period is around 4.2 days. The average number of individuals an affected person can infect [ie, the reproduction number (R_0)] is around 5.7 with a broad 95% CI of 3.8 to 8.9.[18] R_0 is based on the assumption of an exponential growth rate seen in the pandemic setting, as well as factors including latent prior and an infectious period are known with COVID-19 disease. The structural analysis of the SARS-CoV-2 shows a higher affinity to the cell entry receptor than to the 2003 severe acute respiratory syndrome (SARS) virus; this provides scientific grounds for the higher infectious nature of SARS-CoV-2.[19]

CLINICAL PRESENTATION

There is significant variability concerning the clinical presentation of COVID-19. A recent meta-analysis of 61 studies from 11 countries involving 59 254 patients report mild cases in 81.4%, severe in 13.9%, and critical in 4.7%.[20] All-cause mortality was 0.3%.[20] The most common disease-related symptoms include fever (82%; 95% CI, 56-99), cough (61%; 95% CI, 39-81), muscle aches (36%; 95% CI, 18-55), shortness of breath (26%; 95% CI, 12-41), headache (12%; 95% CI, 4-23), sore throat (10%; 95% CI, 5-17), and gastrointestinal symptoms (9%; 95% CI, 3-17).[20]

The uncommon symptoms include rash, which is seen in 8.8% of confirmed patients identified in the UK COVID Symptom study.[21] The most common type of rash seen is maculopapular eruptions in the Spain nationwide consensus study.[22] Confusion and dizziness were seen in 11% of patients in one cohort of confirmed cases of 24 410 adults.[23] More recently, anosmia has been described in COVID-19 patients.[24-27]

Patients with severe COVID-19 infections can develop severe and fatal complications, including acute respiratory distress syndrome (ARDS), acute kidney injury, neurologic complications, shock, and death. There has been a high incidence of thromboembolic events in patients with COVID-19; the pooled prevalence is placed at 26% in hospitalized patients.[28] Molecular pathogenesis includes system dysfunction involving increased platelet activity, endothelial dysfunction, hypercoagulable state, hypoxic injury, and cytokine storm.[29] A variety of presentations and complications involving the cardiovascular system have also been seen with severe COVID-19 disease, which include myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death. Time course is variable, which makes it challenging as it can present early or develop over the course of the illness.[30-32] Invasive pulmonary aspergillosis

has been seen in moderate to severe COVID-19 ARDS patients with an incidence of one-third of mechanically ventilated patients in one observational study.[33]

In addition, in the early phase of the COVID-19 pandemic, the focus has been on cytokine release syndrome, which is identified by elevated proinflammatory cytokines.[34] Patients were noted to have a higher level of interleukin (IL)-6, IL-10, and tumor necrosis factor-alpha.[35] Recently published comparative studies of critically ill patients with COVID-19 complicated by ARDS show circulating cytokine levels being lower than in patients with bacterial sepsis and other critically ill patients.[36,37]

CLINICAL MANAGEMENT

There are no approved drugs for curative treatment of COVID-19, and a vaccine is not yet available. The focus of management is on supportive care, treating symptoms, and preventing complications. As the pandemic has accelerated worldwide, there has been a noticeable increase in the fast-track efforts to develop an effective therapy to treat COVID-19 and develop a vaccine. Most of the pharmacological treatment drugs are based on in vitro antiviral activity, anti-inflammatory effects, immunomodulatory drugs, or limited observational studies. Now, we have a better understanding of emerging therapies than at the start of the pandemic. However, a robust efficacy and safety assessment continues to be needed, particularly concerning use in comorbid conditions, as reviewed later.

Chloroquine and hydroxychloroquine

Mechanisms of action of both chloroquine and hydroxychloroquine involve increasing the endosomal pH and inhibiting the infusion of SARS-CoV-2 and cell membranes. In addition, they block the transport of SARS-CoV-2 from endosomes to endolysosomes, which prevents the release of the viral genome.[38-40]

A series of early clinical trials from China and a nonrandomized study from France showed a clinical benefit from hydroxychloroquine. However, more extensive studies, including an observational study of 1376 patients, did not show efficacy for COVID-19.[41-43] Furthermore, a randomized controlled trial of 1542 hospitalized patients reported no significant difference in mortality when compared with standard of care.[44] The World Health Organization (WHO) and the National Institutes of Health (NIH) have discontinued their clinical trials of hydroxychloroquine, citing a lack of efficacy. NIH and the Infectious Diseases Society of America (IDSA) do not recommend hydroxychloroquine for the treatment of COVID-19 patients.[45] In addition, the emergency use authorization was revoked by the Food and Drug Administration (FDA), given the unclear benefit in the face of potential and known risks.[46]

Lopinavir/ritonavir

Lopinavir is a protease inhibitor given with ritonavir and has been used previously for HIV/AIDS treatment. Lopinavir/ritonavir was used during the SARS-CoV epidemic in Hong Kong. Early in the pandemic, 2 studies conducted in South Korea reported a reduction in viral load and faster recovery of patients.[47,48] However, a randomized controlled trial of 199 severely ill COVID-19 patients demonstrated no significant difference in mortality, time to clinical improvement, or the amount of viral RNA detected.[49] A recent finding from the RECOVERY trial of 1596 patients demonstrated no statistical or clinical significance concerning 28-day mortality, length of stay, or clinical deterioration with lopinavir/ritonavir.[50] Moreover, lopinavir/ritonavir is associated with hepatotoxicity, hyperglycemia, hyperlipidemia, and insulin resistance.[50-53] NIH and IDSA recommend against their use for the treatment of COVID-19.[45,54]

Remdesivir

Remdesivir is a novel nucleoside analog with broad antiviral activity studied in COVID-19 infection. Remdesivir inhibits

viral RNA polymerases, causing a decrease in viral RNA production by premature termination of viral RNA transcription. In in vitro models, remdesivir inhibit SARS-CoV and MERS-CoV in human airway epithelial models.[55,56] A case series of compassionate use of remdesivir in patients with severe COVID-19 infection demonstrated clinical improvement in 68% of patients, with 13% mortality and acceptable safety profile.[57]

A randomized, multinational, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT-1]) in 1063 hospitalized patients showed that a 10-day course of remdesivir led to faster recovery time among patients who received oxygen.[58] Average recovery time in the treatment group of 11 days versus 15 days in the placebo group showed the difference was statistically significant. The study also showed reduced mortality, but the difference was not statistically significant. In subgroup analyses of ACTT-1, there was no observed benefit for remdesivir in people with COVID-19 who did not require supplemental oxygen. Similarly, those who were requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline (n = 272), there was no observed difference in the time to recovery and mortality rate by day 14 between the remdesivir and placebo groups.[58] A randomized, open-label trial of the hospitalized patient evaluated the duration of therapy of 5 days versus 10 days. The trial did not demonstrate a benefit between a 5-day course and a 10-day course of therapy.[59]

Remdesivir was also studied in patients with moderate COVID-19 infection in a randomized trial using a 1:1:1 ratio to receive a 5-day course of remdesivir (n = 199), a 10-day course of remdesivir (n = 197), and standard care (n = 200). There was a better clinical status with 5 days of remdesivir treatment, which was statistically significant compared with those who received standard of care at 11 days. There was no benefit with a 10-day course of treatment. The clinical significance is uncertain of such finding.[60]

Based on the results of ACTT-1, the FDA issued an emergency use authorization for remdesivir for the treatment of hospitalized COVID-19 patients.[61] Currently, NIH recommends using remdesivir only in those patients who require supplemental oxygen without requiring a high-flow oxygen system, noninvasive ventilation, invasive mechanical ventilation, or ECMO.[54] Despite proven efficacy, there were adverse events with remdesivir therapy in 60% of patients of which 12% were severe.[62] These included septic shock, acute kidney injury, and multiple-organ dysfunction syndromes. Therefore, use remdesivir with caution in comorbid patients who are susceptible to these adverse effects and represent an area that needs further study to identify the efficacy and safety profile in various comorbid conditions.

Convalescent plasma

Another therapeutic approach includes the use of convalescent plasma. Convalescent plasma has previously been used during H1N1 pandemic and SARS and Middle East respiratory syndrome (MERS) epidemic, during which it demonstrated reasonable efficacy and safety.[63-65]

Early in the pandemic, a small pilot study involving 10 severe COVID-19 patients who received transfusion reported no serious adverse events, and all patients experienced reduced symptoms within 1 to 3 days posttransfusion.[66]

An open-label, multicenter, expanded access program study of more than 35 000 patients who were given convalescent plasma shows 7-day mortality of 8.7% in hospitalized patients when given within 3 days of diagnosis and of 11.9% when given 4 or more days after diagnosis.[67]

A meta-analysis and systematic review of 5444 patients found reduced mortality, increased viral clearance, and resulted in clinical improvement with the use of convalescent plasma in patients with COVID-19; however, the quality of evidence was low, and this requires further robust clinical

trials.[68] According to the NIH panel, there is insufficient evidence to recommend either for or against the use of convalescent plasma for COVID-19 infection.[54] Similarly, IDSA only recommend it in the setting of clinical trial.[45]

Corticosteroids

Corticosteroids have potent anti-inflammatory properties that are useful in the setting of systemic inflammatory response, lung injury, and multi-organ dysfunction. The role of corticosteroids in critically ill patients with ARDS has been studied previously with variable results.[69-71] A meta-analysis that included 7 randomized trials of 851 patients with ARDS demonstrated a reduction in all-cause mortality and duration of mechanical ventilation.[72] Limited data available from MERS and SARS outbreak showed delayed viral clearance with the use of corticosteroids.[73,74] With this background, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was designed: a multicenter, randomized, open-label trial in hospitalized patients with COVID-19 involving 6425 participants, with dexamethasone arm including 2104 participants and the standard of care arm including 4321 participants. The trial demonstrated a lower mortality rate among patients who received dexamethasone than those who received standard of care.[75] The benefit was most apparent in those receiving mechanical ventilation, followed by patients requiring oxygen therapy at enrollment. Patients who were not requiring supplemental oxygen did not benefit from dexamethasone. Based on the preliminary results from the RECOVERY trial, the NIH panel recommends using dexamethasone to treat COVID-19 among patients requiring either supplemental oxygen or invasive mechanical ventilation.[54]

Currently, only preliminary analysis of the RECOVERY trial is available, and results for several secondary endpoints (eg, cause-specific mortality, need for renal replacement, significant cardiac arrhythmia) have not yet been reported.

IL-6 inhibitors

IL-6 is a pleiotropic, proinflammatory cytokine produced by various cells that are considered the critical cytokine responsible for the induction of cytokine release syndrome during SARS-CoV, MERS-CoV, and SARS-Cov-2 infections.[76-78] In the phase 3 COVACTA trial (ClinicalTrials.gov identifier NCT04320615), 450 severe COVID-19 patients were randomized to receive tocilizumab or placebo. The trial failed to show improvement in clinical condition, 4-week mortality, and ventilator-free days.[79]

An open-label, prospective trial of 63 patients hospitalized with COVID-19 and treated with tocilizumab showed resolution of fever and improvement in oxygenation suggested a reduction in mortality.[80] The study had limitations of no comparison group, nor any specified a priori comparisons.[80] Similarly, a retrospective cohort study failed to demonstrate clinical and 28-day mortality benefits between tocilizumab and standard of care.[81] Currently, NIH recommends against the use of anti-IL-6 inhibitors to treat COVID-19, except in a clinical trial.[54] Furthermore, the safety of the use of anti-IL-6 when used in combination with antiviral agents and other comorbid therapies has not been established.

Vaccines

The most obvious way to spare the devastating effects of COVID-19 is by promoting measures to reduce both transmission and severity of illness. SARS-CoV-2 is highly transmissible and as such efforts to eradicate it have proven difficult, even with strict community control measures; therefore, all-out efforts in developing a vaccine are essential. Multiple vaccine candidates are in various phases of development; types include adenovirus vector vaccines, mRNA and DNA platform vaccines, inactivated virus vaccines, and spike glycoprotein nanoparticle vaccines.[82]

Russia became the first country to approve a vaccine in early August 2020. The type of vaccine is a recombinant adenovirus type 26 (rAd26) vector and a recombinant

adenovirus type 5 (rAd5) vector. However, only phase 1/2 data are published, which included 76 participants.[83] Here, we briefly discuss vaccine candidates in the advanced development phase. The detailed discussion of all candidates is beyond the scope of this topic.

Ad5-nCoV is developed by CanSino Biologics. It is a recombinant adenovirus type 5 (Ad5) vectored vaccine expressing the SARS-CoV-2 spike glycoprotein. Ad5-nCoV has undergone phase 1 and phase 2 trial.[84,85] The vaccine was immunogenic, inducing humoral responses (peaking 28 days after vaccination) and T-cell responses (peaking 14 days after vaccination) in most participants. At least one adverse effect was reported in 83% of low/medium-dose group and 75% of high-dose group of participants.[84,85] Phase 3, a multicenter clinical trial for Ad5-nCoV, is ongoing.

AZD1222 (formerly known as ChAdOx1 nCoV-19) was developed by AstraZeneca and Oxford University, including an adenovirus vector vaccine that carries the SARS-CoV-2 spike protein. The dose is 5×10^{10} viral particles, with 2 doses given 28 days apart; the vaccine requires 2°C to 8°C for storage. A phase 1/2, randomized controlled, single-blind trial found the vaccine to be immunogenic.[86] Local and systemic reactions were seen more commonly in the AZD1222 group, which resolved with acetaminophen. There were no serious adverse events reported in the 28 days following vaccination.[86] The UK-based phase 3 trial is currently halted after a vaccine participant experienced an unexplained illness. Enrollment is on hold, and an independent panel will assess the vaccine's safety.[87]

mRNA-1273, which is developed by Moderna and the National Institute of Allergy and Infectious Diseases, uses a novel mRNA technology not previously utilized in humans. The mRNA encodes for the full-length spike protein of SARS-CoV-2. The dose is 100 μg, with 2 doses given 28 days apart. The vaccine requires −70°C cold chain for storage. A phase 1 dose-escalation, open-label trial found the vaccine to be immunogenic.[88] Local and systemic side effects were seen in more than half of the participants. Systemic adverse events were reported after the second vaccination, particularly with the highest dose. There were no trial-limiting safety concerns identified.[88] The FDA has granted the vaccine fast-track designation, and phase 3 trials are ongoing.

BNT162b1, which is developed by Pfizer and BioNTech, also uses the novel mRNA technology. The mRNA encodes for the full-length spike protein of SARS-CoV-2. The dose is 30 μg, with 2 doses given 21 days apart. The vaccine requires −70°C cold chain for storage. A phase 1/2 study found the vaccine to be immunogenic with Receptor Binding Domain-binding immunoglobulin G antibodies and SARS-CoV-2 neutralizing antibodies detected in all subjects 28 days after 2 doses.[89] Adverse reactions, including local and system events, were dose-dependent and reported in 50% of mild to moderate subjects in nature and noted to be transient.[89] The FDA has granted the vaccine fast-track designation, and phase 3 trials are ongoing.

CONCLUSION

The COVID-19 pandemic is the most significant health care crisis of the 21st century. The pandemic has resulted in a global disruption with an astronomical infection rate, significant loss of life, and widespread social and economic disruption. With time and an all-out effort, we have learned a lot about COVID-19, but a lot remains unknown. From knowing who is at a higher risk for severe illness to more robust treatment options, the unknown is daunting and eclipses that which we know. There are a large number of ongoing studies to develop safe and effective therapeutic and preventive options as well as efforts to use innovative and sophisticated technologies to achieve better disease surveillance, contact tracing, testing, containment, and ultimately decrease illness severity. There is a vast investment in vaccine development with hopes being pinned not just on infection

prevention but also on decreasing the severity of illness by increasing the proportion of cases whereby the disease is mild or asymptomatic. Ultimately, the COVID-19 pandemic is a test of scientific advancement and it will be interesting to see how we apply the research principles honed over the last few decades to best solve one of the biggest challenges our world has faced yet.

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