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Review Article

COVID-19 and preventive strategy

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Abstract: In December 2019, an unprecedented outbreak of the novel coronavirus disease 2019 (COVID-19), an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) began to spread internationally, now impacting more than 293,750,692 patients with 5,454,131 deaths globally as of January 5, 2022. COVID-19 is highly pathogenic and contagious which has caused a large-scale epidemic impacting more deaths than the severe acute respiratory syndrome (SARS) epidemic in 2002-2003 or the Middle East respiratory syndrome (MERS) epidemic in 2012-2013. Although COVID-19 symptoms are mild in most people, in those with pre-existing comorbidities there is an increased risk of progression to severe disease and death. In an attempt to mitigate this pandemic, urgent public health measures including quarantining exposed individuals and social distancing have been implemented in most states, while some states have even started the process of re-opening after considering both the economic and public health consequences of social distancing measures. While prevention is crucial, both novel agents and medications already in use with other indications are being investigated in clinical trials for patients with COVID-19. The collaboration between healthcare providers, health systems, patients, private sectors, and local and national governments is needed to protect both healthcare providers and patients to ultimately overcome this pandemic. The purpose of this review is to summarize the peer-reviewed and preprint literature on the epidemiology, transmission, clinical presentation, and available therapies as well as to propose a preventive strategy to overcome the present global pandemic.

Keywords: COVID-19, preventive strategy

Introduction

The novel coronavirus disease of 2019 (COVID-19) is caused by a single-stranded enveloped RNA β-coronavirus (SARS-CoV-2, previously known as 2019-nCoV). In December 2019, a cluster of pneumonia cases characterized by fever, cough, fatigue, and shortness of breath that led to acute respiratory distress syndrome (ARDS), were described in Wuhan, China and the causative viral structure was isolated from patients in Wuhan at that time. The virus likely had zoonotic origination with subsequent development of rapid human-to-human transmission via droplet, airborne, or fecal-oral routes, culminating in international spread of a viral syndrome causing mild to severe upper and lower respiratory infection with associated extrapulmonary manifestations. Compared with the severe acute respiratory distress syndrome (SARS) outbreak in 2002-2003 and the Middle East respiratory syndrome (MERS) outbreak in 2012-2013, SARS-CoV-2 has a lower case fatality rate (1.9% vs. 10% for SARS and 34.4% for MERS-CoV) [1, 2]; however, COVID-19 is more contagious and has a higher transmission capacity including human-to-human spread through aerosolized droplets and fecal-oral transmission [3]. It is crucial that healthcare workers, healthcare systems, researchers, patients, private sectors and local and national governments make efforts to collaborate in any

way needed to stop this global pandemic. We summarize the peer-reviewed and preprint literature of the epidemiology, transmission, clinical presentation, and specific available therapies for COVID-19 as well as propose prevention and global collaboration strategies to overcome the present global pandemic (**Table 1**).

Epidemiology

As a clinical entity, COVID-19 was first described in late December of 2019. It is thought to be from an animal market (i.e., the Huanan Seafood Market) that also traded live animals, similar to the SARS-CoV outbreak of 2002–2003. However, cases of now-described COVID-19 without links to the seafood market have been identified as early as December 1, 2019, with uncertainty estimates suggesting additional cases potentially circulated in the Hubei province of China as early as October to November 2019 [4]. Although initial reports identified two species of snakes that could be a possible reservoir of the COVID-19, there has been inconsistent evidence that snakes are SARS-CoV-2 reservoirs [5]. Several studies show that there is a short RNA-dependent RNA polymerase (RdRp) region from a bat coronavirus called the RaTG13 which is very similar to the SARS-CoV-2 genome sequence identity [6-8]. Most importantly, though, genomic sequence analysis of SARS-CoV-2 shows an 88% identity to the viruses bat-SLCoVZC45 and bat-SLCoVZXC21 in bats [6, 9]. Although bats are a known reservoir of SARS-CoV, how transmission from animals to humans occurred is not completely understood. Hypotheses regarding the origin of the epidemic include 1) SARS-CoV-2 was transmitted via other species as an intermediate host, and 2) the Huanan Seafood Market may not be the only source of SARS-CoV-2 spreading globally. For example, bats are the natural reservoirs of SARS-CoV and MERS-CoV, and prior analysis has shown that the viruses utilized intermediate hosts to spread to humans via the palm civets and dromedary camels, respectively [10].

Furthermore, prior to SARS-CoV and MERS-CoV, other coronaviruses were known to infect humans and relied on intermediate hosts such as cattle and alpaca for transmission from natural reservoirs [11]. It is thus possible that there is an intermediate host that transmitted SARS-CoV-2 from bats to humans, however the animals responsible for such intermediate transmission have not been clearly identified. The Malayan pangolin has emerged as an important animal for study regarding intermediate host transmission as multiple recent studies have identified similar viruses to SARS-CoV-2 in this mammal [12-16]. However, no study has conclusively shown a direct transmission from the pangolin and other animals may be implicated in intermediate host transmission.

To summarize, it is now suggested that the index case of COVID-19 caused by the originally sequenced SARS-CoV-2 variant occurred as early as November 2019 via zoonotic transmission from a bat reservoir through an unclear intermediary host, potentially the pangolin, in the Hubei province. It likely circulated in low volume until mid to late December 2019, when it spread rapidly and was subsequently identified in Wuhan. International human-to-human spread followed, initially travel-related and then community-based. Interestingly, there are also reports of SARS-CoV-2 genetic material detection in France [17], Italy [18], and US [19] dating from December 2019 to January 2020, though the spread patterns suggest against these ca ses being causative of the pandemic proper [4].

Delta variant

The B.1.617.2 variant emerged as early as in December 2020 in India, subsequently spreading to the UK and other countries and was eventually identified in the US in March 2021 [20]. It was designated as the Delta variant, initially a variant of interest in April 2021 and later reclassified as a variant of concern in May 2021. The Delta variant was highly transmissible, particularly among unvaccinated cohorts [21], compared to prior variants - though now at time of this review it represents only 4.6% of cases in the US [22], supplanted by the Omicron variant. Various global studies [23-25] suggested increased severity of disease with the Delta variant that was mitigated with full-series vaccination.

Omicron variant

The B.1.1.529 variant emerged and was first isolated in Botswana and South Africa as early as November 2021 and reported to the WHO from South Africa on 24 November 2021 following a distinct surge of infections in the Gauteng region of South Africa [26]. The variant was promptly designated as the Omicron variant and classified as a variant of concern by the

Table 1. Considerations for All sector collaboration in COVID-19 crisis

Providers/health systems	Private sectors	Individuals	Government
Telehealth for clinic visit, post-PCI follow-up and patient management, when feasible	Biotech company should spend R&D on SARS-CoV-2 and medical equipment. Non-medical company should joint effort with Biotech company or do indirect way to help.	Strict personal hygiene measures (e.g., wash hands with soap frequently, don't touch the face or eyes, wear face mask)	Pay for medical expenses of uninsured patients with confirmed COVID-19
Train in donning and doffing and adherence to guidelines for optimal use of PPE	Textile industries should directly or indirectly help with facemask or N95 production	Individuals with preexisting CVD should avoid public exposure and public gatherings	Offer free drive-through COVID-19 testing for everyone
Self-reporting symptoms and, if present, self-isolation and frequent testing	Pharmaceutical industry should develop candidate vaccines	Avoid unprotected contact with farm or wild animals	Support research related to COVID-19
Minimize unnecessary elective procedures if not urgent/emergent	Developing home screening Test	Individuals with symptoms of acute airway infection should cover coughs or sneezes with disposable tissues or clothes and wash their hands	Regulate travel restrictions, park and transport system utilization
Advocate for PPE and healthcare situations (e.g., lobby administrators for lockdown or save trainees)	Grocery stores should offer drive-through or walk in screening	Stay home if don't feel well or ill	Regulate and improve long-term care facilities
Well-being for healthcare professionals, trainees and colleagues	Restaurants should offer take out and home delivery	Practice social distancing	Provide PPE and medical equipment's for overwhelmed hospital
Cancelation of unnecessary meeting and conduct virtual meeting instead of physical meeting	Medical content sources (e.g., UpToDate®) should offer open access for COVID contents for physicians globally	Avoid airplane travel	Plan to bail out essential industries and small-medium businesses
Drive-through testing	Global collaboration in basic science research and clinical trials (e.g., The Manhattan project)	Optimize nutrition, sleep hygiene and exercise with precautions	Regulate traffic and lockdown of villages/cities
Remote/online cardiology consultation	Magazine/news (e.g., wall street journal) should make COVID related contents freely accessible	Carry hand sanitizer	Air disinfection of cities and communities
Public health education using social media to reduce anxiety and misinformation (e.g., ACEI, hydroxychloroquine, face mask, come to hospital if severe chest pain)	Improving public health and public education regarding indications for self-quarantine (e.g., social media post or mention in website pages)	Disinfect frequently touched household objects	Plan for support unemployment

WHO on 26 November 2021 [27], and has since spread internationally. Omicron demonstrates multiple genomic differences, particularly at least 30 amino acid substitutions, 3 deletions, and an insertion in the spike glycoprotein genome [28]. These genomic alterations raise concern for increased transmissibility, infectivity, and immune escape, particularly against vaccines designed to target the spike protein of prior variants. Indeed, early epidemiological models suggest higher transmissibility and immune erosion with Omicron [29]. Furthermore, existing vaccines demonstrate reduced neutralization of Omicron compared to prior variants, though booster doses improved neutralization [30], and T-cell based immunity appears to be maintained from prior vaccination [31]. Population-level data at time of this review is limited, though pre-print and early peer-reviewed data comparing the prior beta- and delta-predominant waves with the omicron wave in South Africa show lower rates of hospitalization and severe disease [32, 33], as well as in UK-based studies [34]. It is unclear whether the reduced severity is a function of the genomic mutations or improved immunity in the form of prior infection and/or increasing vaccination rates. Nonetheless, Omicron continues to spread globally and data regarding its infectivity, severity, and response to treatments are emerging.

Transmission

Similar to MERS-CoV, SARS-CoV, and Influenza virus, SARS-CoV-2 can spread via either direct contact (person-to-person) or indirect contact (respiratory droplets or fecal-oral). A preliminary study showed SARS-CoV-2 positive RT-PCR from the conjunctival swab of COVID-19 patients, which suggests the possibility of eye transmission [35]. Similar to MERS-CoV, for example, SARS-CoV-2 demonstrates a robust capability to remain infectious outside of the body (up to 60 minutes after aerosolization) [36]. Some studies suggest that SARS-CoV-2 airborne transmission may also be possible since the virus can remain viable and infectious in aerosols for hours as well as on surfaces for days [37]. Specifically, SARS-CoV-2 remains stable for up to three hours in the aerosolized form, up to 24 hours on cardboard, and as many as three days on plastic or stainless steel [37]. Given the various potential sources of SARS-CoV-2 that could be used for testing, false-negative test results could become a significant problem. One study suggested that testing of specimens should be performed from multiple sites because they found moderate viral loads in nose-throat swabs and high viral loads in fecal samples [38].

Asymptomatic transmission of COVID-19 has been confirmed by several studies, suggesting possible transmission during the incubation period or a mild influenza-like illness prodrome [39, 40]. The median incubation time is 3-5 days and could be up to 2 weeks, while most patients will experience symptoms within 11.5-12.5 days of exposure [39, 40].

Clinical presentation

The most common presenting symptoms of acute COVID-19 include fever, fatigue, dry cough, shortness of breath, diarrhea, anosmia, and ageusia [41]. Mild symptoms include but are not limited to fever, rhinorrhea, nasal congestion, fatigue, dry cough, mild fever, sore throat, headache, myalgia, nausea, vomiting, and diarrhea. Patients with severe disease can present with severe pneumonia, refractory hypoxemia, acute respiratory distress syndrome (ARDS), septic shock, cardiac injury or myocarditis, myocardial infarction, the elevation of BNP or NT-proBNP in the absence of elevated filling pressures or clinical heart failure, decompensated heart failure, stress-induced cardiomyopathy, cardiogenic shock or multiple organ dysfunction [42]. Importantly, troponin levels are often significantly increased in COVID-19 patients with severe disease compared to those without severe disease [42]. Chronic symptoms of COVID-19, deemed Long COVID, are described below.

A meta-analysis of six studies inclusive of 1,527 patients with COVID-19 suggests that patients with pre-existing cardiovascular disease (CVD) are at increased risk for severe symptoms in comparison to those without risk factors [43]. These findings are similar to a previous meta-analysis, which showed that severe symptoms due to MERS-CoV infection were more likely to occur in patients with underlying CVD [44].

Long COVID

As more people are diagnosed with COVID-19 and continued to be followed by healthcare professionals, the long term effects of this virus

are becoming better understood. Long COVID refers to an array of persistent symptoms after infection. The term has been discussed on several occasions with a specific timeline and array of symptoms becoming difficult to delineate. However, the WHO developed a clinical case definition [45]: Individuals with a history of probable or confirmed SARS CoV-2 infection with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis, typically 3 months from the onset of COVID-19.

The reported most frequent residual symptoms are nonspecific and include fatigue, dyspnea, chest pain, cognitive changes, and decreased quality of life [46]. It is estimated that approximately one third of patients diagnosed with COVID-19 will develop Long COVID [47].

Long COVID may impact the respiratory, cardiovascular, and neurologic systems. While pulmonary effects are the main target of the acute infection, Long COVID patients present with persistent cough and dyspnea [48]. It is thought that the pathophysiology of these effects is similar to the acute phase, with persistent endotheliopathy and inflammation of the lungs. However, there has been no relation of symptoms to radiographic or functional studies [48]. Optimal treatment of the respiratory symptoms of Long COVID is not clear, though clinicians have employed corticosteroids with some improvement [49]. As for the circulatory system, both cardiac effects and others such as POTS (postural orthostatic tachycardia syndrome) have been reported [50]. The most common symptoms have been chest pain and palpitations with other complications such as heart failure and myocardial infarction being less common [46]. The inflammation and fibrosis may cause arrhythmia and other complications such as heart failure [48]. Lastly, the brain involvement of COVID-19 includes both neurological and psychiatric sequelae [51]. The pathogenesis is thought to be inflammatory migration of leukocytes across the blood brain barrier and/or direct damage of cerebral cells by virus [48]. The effects are heterogenous, but include anosmia, amnesia, ataxia, fatigue [50]. As for mood, clinical depression, PTSD, anxiety and insomnia are described, which may be related to direct viral effects and/or indirect viral effects (i.e. social isolation related to quarantine) [46]. Neuroinflammation may cause reduction in neurotransmitters such as serotonin that later cause neurotoxicity or reduction in neurogenesis and synaptic plasticity [48]. Integration of the viral genome into host DNA is described, with subsequent production of viral antigen that may lead to a persistent immune response [48]. We suspect persistence of chronic inflammation accounts for continued symptoms in Long COVID, with a possible role of altered immune response an/or autoantibody generation. Further study of the pathologic mechanisms behind Long COVID will guide application of current and novel treatment modalities.

Prevention

First and foremost, basic precautions including washing hands with soap for at least 20 seconds, reducing aerosols when sneezing and coughing, wearing a face mask and minimizing hand-to-face contact, and utilizing hand sanitizer should be performed routinely. For healthcare facilities, elective procedures should be deferred, and clinic visits should be performed virtually. In academic institutions, minimizing the number of people who scrub into procedures may be helpful. Integral subspecialty care teams may be required with the separation of individuals with overlapping skillsets (e.g., infectious disease specialists for rapid consultation in the ED). Learning from the experiences of healthcare workers in China, Spain, or Italy is also crucial.

Second, vaccination has been a worldwide effort that has proven to be crucial in preventing disease. There has been a worldwide effort to develop vaccines during the pandemic. Several different platforms have been used with the most popular being mRNA, inactivated virus, and subunit. The efficacy rates of these vaccines have been impressive, particularly in preventing severe disease. However, waning immunity has been a concern, with booster dosages developed to further prevent disease. As new strains arise, existing vaccine efficacy comes into question as well as the need for newer vaccines.

Third, the utilization of innovative technologies to mitigate travel restrictions, self-isolation, school closings, and mass social distancing are crucial to reduce viral exposure and

spreading. One example has been the utilization of virtual platforms to continue meetings and conferences (e.g., gotowebinars, Cisco, Google G, Zoom). Notably, the American College of Cardiology (ACC) conducted its ACC.20 and 21/WCC Scientific Sessions virtually. Patients with non-urgent conditions should be monitored from home using HIPAA-compliant video communication. Additionally, artificial intelligence may be used to analyze symptoms or chest imaging to determine which patients may warrant further COVID-19 testing and/or isolation. For example, some small studies using convolutional neural networks demonstrated reasonable sensitivity and specificity in identifying COVID-19 from CT imaging [52, 53].

Fourth, studies have shown that short sleep duration may be linked to viral infection susceptibility via the dysregulation of immune function (e.g., decreased T-cell function) [54, 55]. Additionally, sleep deprivation is directly associated with an increase in IL-6 and decreases in circulating natural killer cells [56]. Sleep deprivation has also been found to attenuate antibody response to influenza immunizations [57]. Most importantly, several studies, including the national survey, showed that short sleep duration is associated with increased susceptibility to the common cold and increased risk of pneumonia [58, 59]. Finally, the study has shown that poor sleep quality is associated with lower CD4 count in individuals with HIV [60]. Therefore, optimal sleep hygiene may be useful in mitigating or decreasing the severity of COVID-19 infections.

Fifth, optimal nutrition has been shown to improve T-cell function and suppress inflammation. Several studies showed that certain diets might help improve immune function, leading to a reduction in viral infection. Multiple studies, including clinical trials, have shown that consumption of fruits and vegetables can reduce the risk of acute respiratory infections [61], moderate or severe common cold symptoms [62], and influenza-like symptoms [63]. Furthermore, consumption of fruits and vegetables has been shown to improve the vaccination antibody response [64]. Numerous studies and randomized clinical trials have shown that the Mediterranean diet is associated with significantly lower concentrations of IL-6 [65]. While these studies are heterogeneous and relatively low level of evidence, supporting a healthy eating pattern prioritizing natural fruits and vegetables should be universally advised, given the multiple health benefits of such a diet.

Sixth, substantial evidence demonstrates that physical activity and exercise improve immune function (e.g., upregulation of the ACE2, T-cell function) and decrease IL-6 levels [66, 67]. One meta-analysis of four randomized controlled trials found that moderate-intensity exercise may have a positive effect on the prevention of the common cold [68]. Study showed that moderate exercise was also associated with lower mortality from influenza virus [69]. Moderate exercise has also been shown to be associated with improvement of URI symptoms [70], vaccination antibody response [71] and HIV [72]. Exercise may also increase numbers of natural killer cells [73]. Interestingly, one study showed that aerobic exercise might regulate the ACE2 receptor activation [74]. While self-isolation and regular exercise can be challenging, especially with many recreation centers and gyms closed during national social distancing measures, exercise in public spaces is still generally possible as long as individuals take precautions to avoid close contact with other people. Alternatively, routine exercises in a home environment (e.g., home treadmill, dumbbells, pushups, squats, yoga, tai chi, or qigong) should also be considered.

Seventh, while the potential association between tobacco use and COVID-19 disease remains unknown, smoking is an important risk factor for developing chronic obstructive pulmonary disease (COPD) and CV disease. In animal studies, smoking selectively augments the airway and alveolar inflammatory and remodeling responses induced in the murine lung by viral PAMPs and viruses. In addition, there is evidence from both animal and human studies which suggests that smoking may upregulate the ACE2 receptor, thereby increasing smokers' susceptibility to COVID-19 [75]. Smoking has been shown to increase the risk of viral infections such as URI [76], common cold [77], and influenza hospitalization [78]. Smoking cessation should universally be encouraged.

Lastly, in our current digital era, there has been misinformation disseminated throughout various social media platforms regarding face mask utilization, SARS-CoV-2 transmission,

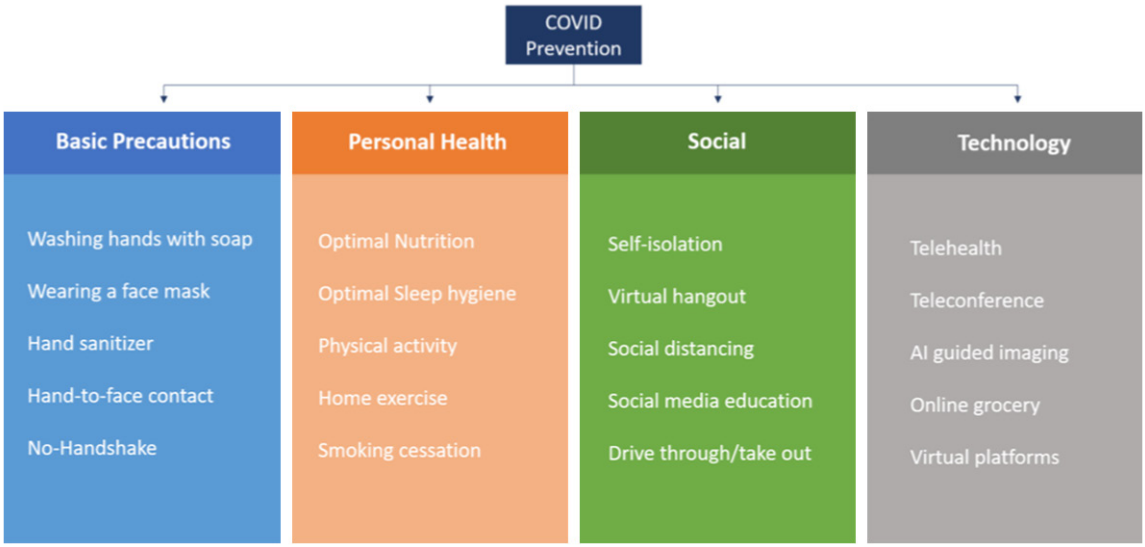

Figure 1. Prevention strategies for COVID-19. Prevention strategies should focus on basic precautions, personal health, social aspects of individual. Emerging technology should be considered to keep social engaging, education and optimal essentials for life in this global pandemic.

chloroquine prophylaxis, and PPE shortages. Given the current global pandemic, medical social media platforms have been increasingly utilized. Several cardiovascular societies have been actively engaged with audiences on these platforms in an attempt to clarify essential issues related to COVID-19. **Figure 1** demonstrated COVID-19 and preventive strategy.

COVID-19 vaccine

At the time of this review approximately 580 million vaccine doses have been administered in the United States, accounting for 64% of the eligible population [79]. Those eligible include everyone 5 years and older as well as a booster for those 12 years and up. At the time of this review, there are a total of 33 approved vaccines, 137 vaccines in clinical development and 194 in pre-clinical development, with 10 vaccines in phase 4 of the clinical phase of development [80]. The approved vaccines use a variety of different platforms, including inactivated virus, non-replicating viral vector, RNA-based, and protein subunit. Vaccine effectiveness, referring to the reduced risk of infection or disease after vaccination, has been studied with different clinical endpoints with very promising results.

mRNA-based

While mRNA vaccine technology has been in development for a number of years, the Pfizer/BioNTech and Moderna COVID-19 vaccines were the first large-scale application of this technology [81]. The technology for mRNA vaccines is not new, it has been created for a variety of other pathogens including influenza, ebola, cytomegalovirus, and zika [82]. The COVID-19 mRNA vaccine involved development of a genetic footprint for spike protein. The mRNA is encapsulated by a lipid nanoparticle that that protects it from degradation. The positively charged capsule is attached to the negative charges of cell membranes, facilitating endocytosis and subsequent transcription of the spike proteins. These spike proteins are later recognized by the immune system and generate antibodies against COVID-19 [83].

Work on the mRNA vaccine started in January 2020 under BioNTech with the later help of Pfizer. The vaccine underwent clinical trials, including an independent analysis by the FDA. The results showed the vaccine had an efficacy rate of about 95% [84]. Israel also launched its own trials that further proved its efficacy, showing it to be about 92% effective after the second dose [85]. The side effects were minor, limited to self-resolving headaches, fever, fatigue [86]. As for Moderna, clinical trials started in March 2020 and in November announcements about its efficacy showed it be 93% [87]. In the USA, a study looked at vaccine effectiveness among healthcare personnel, and found a 82% reduction in PCR positive cases after a

single dose of Pfizer or Moderna and 90% effectiveness against infection [85]. Pfizer/BioNTech and Moderna, received EUA from the FDA on December 11, 2020 and December 18th, 2020, respectively. Both vaccines were later studied on children as young as 12 years with promising results and eventual authorization of the Pfizer vaccine by the FDA in January 2022.

Non-replicating viral vector

Non-replicating viral vector vaccines, developed by Janssen, Serum Institute of India, and AstraZeneca/Oxford, have been authorized for use in many countries. However only the Janssen vaccine has been approved for use in the United States, receiving EUA from the FDA on February 27th 2021. Non-replicating viral vector vaccines utilize another different virus as a vector to enter genes of the pathogen to replicate its antigen. For COVID-19 the vector is Adenovirus type 26 (Ad26) containing the genes of the spike protein, activating the body's immune response [88].

The work by Johnson and Johnson's with the Adenovirus vaccine had been in process for almost a decade; using Ad26 for vaccines against other pathogens such as Ebola. However in January 2020, work begun to develop a vaccine against COVID-19, receiving financial support from the US government. Trials begun that initially showed the vaccine to be effective as a single dose, with an efficacy of 66% [89]. However, the side effects became an issue as cases of blood clots emerged. Further studies showed that the vaccine could cause VITT (vaccine induced thrombotic thrombocytopenia) or TTS (thrombosis with thrombocytopenia syndrome), a syndrome with clotting and low platelet counts [90]. After a temporary pause in recommendation, the FDA Advisory Committee on Immunization Practices (ACIP) reaffirmed its recommendation for the use of the Janssen vaccine, albeit with patient-provider discussion regarding the increased risk of thrombosis.

Booster

Another challenge poised is the development of breakthrough infections in the setting of waning vaccine immunity and emerging SARS-COV-2 variants. In fact after one dose of the Pfizer vaccine, antibody levels wane within 12 weeks [85]. This led to the advent of booster vaccines. Based on a study in Israel showing that booster vaccines protected against infection, severe disease, hospitalization, and death, the U.S. adopted the recommendation for the booster [91]. The use of homologous and heterologous boost strategies have been studied with proven effectiveness in both arms [91].

Future

A new area of interest includes nanoparticle vaccine technology. This technology involves engineered nanoparticles with improved antigen structure and stability to improve immunogenicity and immune responses, and the technology is in development for potential use in influenza, EBV, malaria, and most recently SARS-CoV-2 [82]. In pre-clinical studies, a SARS-CoV-2 spike ferritin nanoparticle (SpFN) vaccine induced neutralizing antibodies against SARS-CoV-2 wild-type and 4 variants of concern including the Delta variant [92].

Effective vaccines remain a safe and effective tool for prevention and reduction of COVID-19 globally. With the advent and ongoing development of highly efficacious vaccines, the future is promising for mitigation of the COVID-19 pandemic.

COVID-19 specific therapy

To date, multiple clinical trials have assessed the use of various treatment modalities in COVID-19 with varied outcomes.

Chloroquine and hydroxychloroquine

The IDSA provides a strong recommendation with moderate certainty of evidence against the use of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19 [93]. China's National Health Commission initially published guidelines reporting that chloroquine was associated with reduced progression of COVID-19 disease and decreased duration of symptoms. Chloroquine and hydroxychloroquine were thought to inhibit SARS-CoV-2 through multiple mechanisms, including inhibition of pH-dependent steps related directly to viral replication (e.g., increased endosomal pH) [94], immunomodulatory effects, or inhibition of autophagy [95]. Important cardiotoxic effects of chloroquine must not be ignored, and include

complete atrioventricular block, QT prolongation, and cardiomyopathy.

Combined protease inhibitors

Lopinavir-ritonavir is a combined protease inhibitor that was approved for treatment of HIV. At present, the IDSA recommends against treatment with lopinavir/ritonavir in hospitalized patients with COVID-19 [93], and it has no mortality benefit in patients with COVID-19 compared to standard care [96]. Patients with pre-existing CVD who are started on lopinavir–ritonavir for COVID-19 should be monitored closely as ritonavir is an inhibitor of the cytochrome P450 3A4 which can result in increased levels of statins, apixaban, rivaroxaban, ticagrelor, dabigatran, amiodarone, coumadin or colchicine. Specifically, lovastatin and simvastatin should be avoided due to the risk of myopathy and rhabdomyolysis, while atorvastatin and rosuvastatin should be administered at the lowest possible dose. Importantly, rhabdomyolysis has been reported as a potential late complication of COVID-19, so clinical monitoring for early signs of rhabdomyolysis is prudent in any patient with COVID-19 on statin therapy [97]. Additionally, some data suggests that lopinavir-ritonavir may have cardiotoxic effects, including dilated cardiomyopathy and heart block [98], as well as QT prolongation.

Convalescent plasma

Convalescent plasma therapy from recovered patients has been used to improve the survival rate of patients with SARS [99] and Ebola virus disease [100]. It is thought that the neutralizing antibodies from convalescent plasma could suppress viremia and lead to an expedited recovery. However, clinical trials regarding the efficacy of such treatment have been variable. Currently, the IDSA recommends against use of convalescent plasma among ambulatory and hospitalized patients with COVID-19 [93].

Ivermectin

At present, the IDSA recommends against ivermectin in hospitalized and ambulatory patients with COVID-19 [93]. Ivermectin, an FDA-approved anti-parasitic drug, has been shown in vitro to inhibit viral replication, possibly through inhibition of the IMPα/β1-mediated nuclear import of viral proteins [101], however it has no proven therapeutic utility and requires considerably higher concentrations than is achieved in human plasma to exert its in vitro effects [93]. At this time, there is no firm evidence of ivermectin associated cardiotoxicity or drug interactions with CV medications.

Vitamin C

Vitamin C has been proposed as a potential COVID-19 treatment option though evidence of its use with viral infections is conflicting. Given the potential benefits of vitamin C, clinical trials of vitamin C and COVID-19 treatment are also ongoing (e.g., NCT04264533). Currently, however, there is no clear evidence to suggest that vitamin C supplementation can reduce the risk of having SARS-CoV-2 infection or provide treatment efficacy in COVID-19 patients.

Systemic corticosteroid

Glucocorticoids, particularly dexamethasone, are now a mainstay of treatment for hospitalized COVID-19 patients with severe and/or critical disease, though their use is not recommended in non-severe illness [93]. Dexamethasone use reduced 28-day mortality in hospitalized, critically ill patients and severely ill patients by 34% and 17% respectively [102].

IL-6 inhibition

At present, the IL-6 inhibitors tocilizumab and sarilumab have been investigated fpr use in COVID-19 and tocilizumab (and if unavailable, sarilumab) are recommended for use by the IDSA in patients with progressive severe or critical COVID-19 with elevated markers of systemic inflammation [93]. Regarding patients with CVD, drug interactions between standard CV medicines and IL-6 inhibitors are mostly unknown. The up-regulation of IL-6 reduces the activity of cytochrome P450 (CYP) enzymes [103]. Thus, blockade of this cytokine may enhance the CYP function. Theoretically, IL-6 receptor inhibitors may restore or normalize CYP450 enzyme levels resulting in increased metabolism of other medications.

Remdesevir

At present, remdesivir is recommended in a variety of circumstances for COVID-19. It is recommended for use in hospitalized patients

with severe COVID-19 and in those on supplemental oxygen without mechanical ventilation or ECMO, as well as for use in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease [93]. Remdesivir, an antiviral medication initially developed for ebola, interrupts viral RNA replication by acting as a 1'-cyano-substituted adenosine nucleotide analog. In preliminary results, remdesivir was demonstrated to have in vitro activity against SARS-CoV-2 by targeting the viral RNA-dependent RNA polymerase [104]. Although drug interactions between current CV medications and remdesivir have not yet been reported, direct cardiovascular toxicities may be possible. For example, one patient who was treated with remdesivir developed hypotension and subsequent cardiac arrest [105], though remdesivir's role is unclear.

Nirmatrelvir-ritonavir (Paxlovid)

Nirmatrelvir inhibits viral replication through inhibition of SARS-CoV-2 main protease, and is copackaged with ritonavir, an HIV-1 protease inhibitor. The combination was granted EUA by the FDA on December 22, 2021 for the treatment of mild to moderate COVID-19 in adults and pediatric patients at high risk for progression to severe COVID-19, and is recommended by the IDSA guideline for this use as it may demonstrate reduced all-cause mortality [93]. Its use is subject to significant drug interactions and is contraindicated in drugs that are dependent on CYP3A for clearance - particularly CV medications such as ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, lovastatin, simvastatin, and sildenafil [106].

Molnupiravir

Molnupiravir is an oral antiviral that is a pro-drug converted into a substrate for RNA-dependent polymerase, ultimately incorporating into viral RNA and reducing viral replication of SARS-CoV-2. In ambulatory patients, molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with COVID-19 [107], and it received EUA for use in mild-to-moderate COVID-19 in adults at high-risk for progression to severe COVID and is recommended by the IDSA for use in ambulatory patients 18 years and above [93].

As we look to the future, the COVID-19 pandemic will require significant societal cooperation and further scientific advancement to ultimately achieve containment. This is a process that many experts feel will take months, if not years. On a governmental level, social distancing rules and public health initiatives are changing by the day, but such interventions will ultimately dictate how effectively the spread of the virus can be mitigated.

Multiple clinical trials are currently underway to evaluate various medications and vaccinations in the hope to ultimately provide an effective treatment for COVID-19, however final approval of medications and distribution of vaccinations will take many months. Additionally, time will tell if a vaccine will prove effective enough to induce effective immunity, especially in the most vulnerable populations.

The healthcare system is rapidly adapting to the pandemic in order to further decrease the spread of the virus and ultimately prevent overwhelming the healthcare system. Globally, telemedicine has become increasingly important in mitigating spread and whether or not such a virtual platform will become a more permanent reality is yet to be seen.

Author's viewpoint

Through our experience with COVID-19 within the United States since its onset, we have noted a rapid shift in attitude and practice patterns, largely influenced by our understanding of the virus. Prior to its spread within the US, we noted conflicting beliefs surrounding the transmission patterns and the likelihood of the virus spreading globally. Ultimately, COVID-19 did become a global pandemic. Early within the clinical sphere, optimal treatment strategies had yet to be elucidated and practitioners were without clinical society guidelines for treatment. Increasing incidence of thrombotic events such as VTE, stroke, and coronary occlusions led to heterogeneous thrombotic prophylaxis strategies based on inflammatory markers and/or D-dimer levels. Various antivirals and immunomodulators were utilized with cautious optimism. Preventive visits and management of chronic medical comorbidities were deferred in hopes to mitigate spread of the virus in the healthcare setting. Once viral spread was temporarily ameliorated and vacci-

nation rates rose, patients resumed care of chronic comorbidities but frequently had complications as a result of temporarily unmanaged disease. The advent of telemedicine allowed patients to maintain interface with the healthcare system while limiting exposure to the virus, and practitioners felt more comfortable managing patients remotely. Clinical trial data, rapid developments in therapeutics, and professional society statements provided guidance for practitioners for both COVID-related management and management of non-COVID conditions in the era of COVID. At present, the healthcare system and the public have gained more experience with prevention and management of COVID. However, opportunities remain to further prevent spread of COVID in light of emerging variants and increasing incidence of the disease, and all members of society must capitalize on our ability to rapidly develop and adopt prevention modalities such as vaccines that may target newer variants and direct antiviral therapies. We hope that preventive strategies highlighted in this manuscript also provide better understanding of the virus and serve as guidance for further reduction of COVID-related morbidity and mortality.

Limitations and strengths

Although we have attempted to give a broad overview of the ever-increasing literature related to COVID-19, the rapid evolution of the various topics covered, and high publication output makes a complete review challenging. Additionally, many topics related to COVID-19, including treatment and prevention, are informed largely by observational data while larger RCTs are still underway. We believe that our review does give an updated broad compilation of the relevant literature to date. Given the high volume of publications related to COVID-19, summaries and reviews such as these are needed, and more reviews will be needed in the future as the scientific literature expands related to SARS-COV-2.

Conclusion

The COVID-19 pandemic remains ever-evolving. With emergence of new viral variants with altered protein structures, treatments and preventative measures (i.e. vaccines) must have continued reassessment. Fortunately, emergence of variants and detection of disease related to SARS-CoV-2 are now readily recognized, allowing for prompt action. With this pandemic, we have tested our capabilities in numerous ways, highlighting our ability to develop novel therapeutics (i.e. Paxlovid) and apply new technologies (e.g. mRNA, ferroparticle vaccine technology) while also exposing shortcomings in our medical systems. With a wide array of clinical effects, specific manifestations of COVID-19 and their treatments must be further explored. Prompt recognition of the side effects or misapplication of preventative and therapeutic modalities, such as thrombosis risks and erroneous antiparasitic use, is prudent. Further exploration of the cardiovascular impacts of acute and chronic infection and of targeted therapeutics is warranted. With viral tropism for cardiomyocytes and with emergence of new viral structures, it is unclear whether newer cardiac manifestations will materialize.

The management decisions involved in COVID-19 patients should be discussed by an interdisciplinary team including the patient, primary team, infectious disease, and critical care team. Regular exercise, optimal nutrition, and sleep hygiene and social distancing should be recommended. Health systems and government must continue to strategically minimize unnecessary exposures and support healthcare workers with critical medical supplies needed for an effective response, while the private sector can aid in the production of critically needed medical supplies. The need for global research and rigorous clinical trial collaboration for COVID-19 treatment and vaccine development has never been so urgently needed.

Disclosure of conflict of interest

Dr. Krittanawong discloses the following relationships - Member of the American College of Cardiology Solution Set Oversight Committee, the American Heart Association Committee of the Council on Genomic and Precision Medicine, and the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Performance Measures, The Lancet Digital Health (Advisory Board), European Heart Journal Digital Health (Editorial board), Journal of the American Heart Association (Editorial board), JACC: Asia (Section Editor), The Journal of Scientific Innovation in Medicine (Associate Editor), and Frontiers in Cardiovascular Medicine (Associate Editor).

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