



Overview of coronavirus disease 2019: Treatment updates and advances

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Abstract: In late December 2019, several cases of pneumonia with unknown cause were reported in Wuhan, China, and this new type of pneumonia spread rapidly to across provinces during the subsequent weeks. The pathogen was identified quickly and was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infectious disease caused by this virus is referred to as coronavirus disease 2019 (COVID-19). Within months, it has caused a global pandemic and posed a major threat to public health worldwide. As of May 23, 2020, 5 252 452 patients have been confirmed to have the disease, and 339 026 deaths have been reported. Multiple therapeutic trials are ongoing, and some promising results have been released. A vaccine would provide the most effective approach to fight the virus by preventing infection, but none are currently available. To control the COVID-19 outbreak, large-scale measures have been applied to reduce human-to-human transmission of SARS-CoV-2. Susceptible populations, including older adults, children, and healthcare providers, warrant particular attention to avoid transmission and infection. This review introduces current understanding of SARS-CoV-2 infection and treatment strategies, emphasizing the relevant challenges associated with prevention, diagnosis, and management.

Keywords: Coronavirus; COVID-19; Severe acute respiratory syndrome coronavirus 2

1. INTRODUCTION

In late December 2019, several pneumonia cases with unknown cause were reported in Wuhan, China. This new type of pneumonia subsequently spread rapidly. A new coronavirus, 2019 novel coronavirus, was quickly identified as the causal pathogen resulting in these outbreaks of severe acute respiratory syndrome-like illness.¹ This was renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO). The disease caused by SARS-CoV-2 infection has been named coronavirus disease 2019 (COVID-19). Initially, this novel coronavirus infection was epidemiologically attributed to exposure in the Huanan seafood wholesale market,¹ and human-to-human transmission of SARS-CoV-2 was then further confirmed by the infection of healthcare practitioners in a Wuhan hospital.¹ As of May 23, 2020, SARS-CoV-2 has infected a total of 5 252 452 people worldwide. The overall mortality rate is approximately 6.5%, with 339 026 deaths occurring among the confirmed cases.² Taiwan is only 130 km from the coast of mainland China; due to its geographical proximity and the frequent travel between these two areas, Taiwan was initially predicted to exhibit the second highest number of

COVID-19 patients.³ However, by May 23, only 441 COVID-19 cases had been documented in Taiwan, representing the 131st highest number of patients among affected countries. Taiwan has provided an example of how a public health system can respond rapidly to a COVID-19 outbreak and prevent a large-scale pandemic. As coronavirus was continuously spreading worldwide with an exponentially increasing number of deaths, the WHO officially announced the COVID-19 outbreak as a pandemic on March 11, 2020. The development of the COVID-19 outbreak has presented an urgent need to thoroughly explore relevant pathogenic information. In this overview, we outline the current understanding and treatment strategies of SARS-CoV-2 infection, emphasizing advances in the therapeutic strategies for augmenting the efficacy of treatment for COVID-19.

2. CLINICAL CHARACTERISTICS OF COVID-19

The typical symptoms of COVID-19 include fever (83%–98%), coughing (59%–82%), dyspnea (19%–55%), and myalgia (11%–44%).^{1,4–7} Some patients may experience a sore throat, headaches, nausea, diarrhea, ageusia, and anosmia a few days before the onset of fever, demonstrating that fever is an important symptom but not the only initial sign of COVID-19.^{6,8} In a clinical report,⁸ 5.6% of patients experienced taste impairment, and 5.1% experienced smell impairment. Therefore, hypogeusia and hyposmia are suggested as early warnings of infection. A small proportion of patients exhibited hemoptysis or headaches,^{7,9} and many patients were found to be relatively asymptomatic.¹⁰ The clinical presentation of COVID-19 pneumonia demonstrates a wide range of progression patterns and severity. Some patients suffered from dyspnea within a median of 7 to 8 days after the onset of ill symptoms (range: 5 to 13 days), and the others may not have the symptoms of respiratory distress.^{7,11} Patients with severe symptoms may have unfavorable disease

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course with rapid progression to multiple organ failure and death;^{5,7} dyspnea and hypoxemia can rapidly deteriorate into respiratory failure, acute respiratory distress syndrome (ARDS), severe sepsis with septic shock, and even multiple organ failure within 1 week.^{9,12} A total of 3% to 29% patients may require the intensive care; 17–29% of hospitalized patients were reported to have ARDS about 8 days after the onset of symptoms, and the global mortality rate of COVID-19 is approximately 6.5%.^{2,7}

Moreover, normal or lower white blood cell counts, lymphopenia or thrombocytopenia, and an increased level of C-reactive protein have been noted in patients with COVID-19.^{5-7,9} People presenting with fever and upper respiratory tract symptoms accompanied with leukopenia or lymphopenia should be vigilant for COVID-19, particularly those who have travelled to an endemic region or had close contact with others who have done so. Human-to-human transmission of SARS-CoV-2 has caused the international spread and lethality, similar to SARS-CoV, and it poses a major challenge to global public health system.¹³

The incubation period after exposure to SARS-CoV-2 has been reported as approximately 4 to 8 days, and this highly contagious virus can survive for approximately 2 hours in air.⁵⁻⁷ Asymptomatic patients with COVID-19 are a major source of viral transmission during the incubation period, which has presented a critical obstacle in relation to disease control and epidemic prevention.¹⁴ Respiratory droplets are recognized as the main route of transmission. In addition, transmission through the ocular surface requires special attention because the epithelium of conjunctiva is vulnerable to respiratory droplets and body fluids carrying viruses.¹⁵ SARS-CoV-2 has also been identified in the stools of patients with COVID-19 presenting with abdominal symptoms, suggesting that the fecal-oral route is another transmission route.¹⁶ Angiotensin-converting enzyme 2 (ACE2), the main cellular receptor of SARS-CoV-2, is expressed on the gastrointestinal epithelial cells, so the gastrointestinal symptoms may be due to the direct viral injury to the intestine rather than the immune response to the pulmonary infection in the patients. Therefore, the viral shedding at the gastrointestinal tract may lead to fecal-oral transmission.¹⁷ In addition, positive test results for SARS-CoV-2 were reported in a newborn aged 30 hours, indicating vertical transmission between mothers and infants. Thus far, various contagious periods of SARS-CoV-2 have been reported, and the incidental host of this virus remains unclear. As a result, the potentially underestimated contagious period and zoonotic transmission of unconfirmed incidental hosts may greatly hinder epidemic prevention.⁴ Human-to-human transmission of SARS-CoV-2 on a massive scale in communities and among family members has indicated the rapid spread of this pathogen before the onset of symptoms. Some patients with COVID-19 have reportedly had positive real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test results after recovery.¹⁸ COVID-19 can be contagious before the onset of symptoms and after complete treatment. Therefore, the development of optimal strategies for the discontinuance of quarantine and hospital discharge is warranted to enhance disease control.

Chest X ray (CXR) and chest computed tomography (CT) scans are valuable tools for early detection and follow-up of COVID-19 pneumonia.¹⁹ The imaging findings for COVID-19 pneumonia are similar to those for influenza, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) pneumonia.²⁰⁻²⁴ CXR for patients with COVID-19 pneumonia may show bilateral, peripheral, and patchy opacities. Although CXR is not sensitive for the detection ground-glass opacity (GGO) in the early stages of COVID-19 pneumonia,¹⁹ bilateral multiple consolidation can be identified in severely ill patients. Chest CT scans can detect the early stages of COVID-19 pneumonia more efficiently than CXR.²⁵ It has been reported that pulmonary opacities on chest CT scans were identified in around

two-thirds (61%) of COVID-19 patients and negative finding on CT scans was found in 20% of symptomatic patients.²⁶ The imaging findings of COVID-19 pneumonia in chest CT scans are various and nonspecific, such as multiple GGOs, patchy consolidations, peripherally subpleural distribution, and predisposition of dependent part/lower lobe involvement.²⁷⁻²⁹ The most common patterns of COVID-19 pneumonia in chest CT scans consist of multiple GGOs (56.4%) and bilateral patchy opacities (51.8%); other patterns include local patchy opacities (28.1%) and interstitial lesions (4.4%). Patients with severe symptoms tend to demonstrate more prominent radiologic findings in chest CT scans, such as more bilateral patchy opacities (82%), more multifocal GGOs (60%), and more local patchy opacities (55.1%) compared with nonsevere cases.^{5-7,9,30-33}

3. TREATMENT OF COVID-19

Reports have shown that more than half of patients with COVID-19 (58%–97.5%) received intravenous antibiotic treatments, and 35.8% to 84.6% of patients underwent antiviral therapies, including oseltamivir, ganciclovir, remdesivir, and lopinavir or ritonavir.^{9,34-38} Reports of the success of antiviral therapies against COVID-19 are currently limited. At the convalescent stage of COVID-19, prolonged viral shedding in the respiratory tract and feces has been observed,^{39,40} leading to increased duration of isolation and heavy burden on public health systems. Effective antiviral agents are essential for decreasing the viral load and the duration of virus shedding to control the COVID-19 epidemic. Potent antiviral agents are reviewed in the following section.

No sufficient evidence has been provided for effective treatment of COVID-19 infection. Numerous clinical trials are currently testing a wide range of potential treatments by targeting the coronavirus life cycle or modulating the human immune system. Virus entry is the first step in and a crucial target for viral infection. The virus binds to host receptors, forming the virus–receptor complex. ACE2 cell-surface protein was confirmed to be a virus receptor for SARS-CoV-2. In subsequent endocytosis, the host cell kinase AP2-associated protein kinase 1 (AAK1) plays a regulatory role. Disruption of AAK1 might prevent the passage of the virus into host cells and inhibition of the intracellular assembly of virus particles.⁴¹ The Janus kinase (JAK) inhibitor, baricitinib, inhibits AAK1 with high affinity and binds the cyclin G-associated kinase, which is also a regulator of endocytosis.⁴² In addition, selective therapies with JAK inhibitors could impair the infection-induced inflammation responses of hosts. Clinical trials on baricitinib demonstrated at least some effects in selective patient populations with COVID-19 acute respiratory disease.⁴² Chloroquine phosphate was reported to demonstrate superiority in mitigating the exacerbation of pneumonia, thus facilitating a negative conversion rate in virus tests, and shortening the disease course compared with the control group.⁴³ Chloroquine effectively inhibited the replication of SARS-CoV in vitro by interfering with the glycosylation of the cellular receptor ACE2 and increasing endosomal pH to avoid membrane fusion between the virus and host cells.⁴⁴ Its in vivo antiviral activity is now undergoing clinical trials. Moreover, hydroxychloroquine, which has the same mechanism of action as chloroquine but fewer side effects, was found to yield more impressive results than chloroquine did. In a study published in China, hydroxychloroquine was shown to be more potent than chloroquine for the inhibition of SARS-CoV-2 in vitro.⁴⁵ However, both hydroxychloroquine and chloroquine were associated with concerns of cardiac toxicity, particularly characterized by QT interval prolongation triggering ventricular arrhythmia.⁴⁶ In a multinational study, hydroxychloroquine or chloroquine with a macrolide was related to decreased in-hospital survival, so the benefits of these regimens were unable to be confirmed.⁴⁷ Umifenovir (Arbidol)

manifested broad-spectrum antiviral capability in vitro through inhibition of virus–cell membrane fusion between the virus and target host cells.⁴⁸ Clinical trial of umifenovir for COVID-19 pneumonia has been initiated. The most promising pharmacological management approach in clinical trials is currently remdesivir, which directly targets the life cycle of SARS-CoV-2. It did not demonstrate impressive activity against Ebola virus, but its safety for humans was confirmed in a trial.⁴⁹ Notably, remdesivir also exhibits wide-ranging antiviral properties against other single-stranded ribonucleic acid (RNA) viruses in vitro and in vivo, including SARS-CoV and MERS-CoV. In a clinical trial of patients with severe COVID-19, the compassionate use of remdesivir elicited clinical improvement in 36 of 53 patients (68%), suggesting promising efficacy for remdesivir.^{50,51} China launched two randomized phase III clinical trials with remdesivir. A global randomized phase III trial showed that remdesivir can significantly shorten the time to recovery in patients with COVID-19 pneumonia.⁵² Favipiravir, an approved influenza drug with a mechanism of action similar to that of remdesivir, was developed by a Japanese company. It not only suppresses viral replication but also synergistically interacts with interferon- α to enhance the immune system, which will be studied in a future clinical trial. On March 17, 2020, the National Medical Products Administration of China approved favipiravir as the first coronavirus drug with evidence from clinical trials showing efficacy for the treatment of COVID-19 infection.

In addition, several effective therapies other than targeting the entry or the lifecycle of coronavirus have been explored. Coronavirus expresses its genome through the synthesis of polyproteins which were subsequently processed to different functional proteins such as replicase, nucleoprotein, spikes, envelope, and membrane of the viruses. Hence, during viral reproduction, viral proteinase plays a crucial role in the cleavage of coronavirus polyproteins. Lopinavir inhibits the cleavage of viral Gag-Pol polyprotein precursors through binding to the site of HIV-1 protease activity, leading to the production of noninfectious and immature viral particles. The synergistic effect of ritonavir increases the plasma level of lopinavir by prohibiting the CYP3A metabolism of lopinavir. Accordingly, a coformulation of lopinavir and ritonavir was shown to exhibit antiviral activity against SARS-CoV in vitro⁵³ and against MERS-CoV in animal studies;⁵⁴ it has been administered to humans to treat COVID-19,¹ and some case reports have shown some effects for the treatment of COVID-19.^{55–57} However, a randomized, controlled trial indicated no benefits in patients with severe COVID-19 receiving lopinavir–ritonavir treatment compared with standard care.⁵⁸ Ivermectin, an anthelmintic agent, also demonstrated antiviral activities against HIV and dengue virus.⁵⁸ It inhibits viral replication by dissociating preformed importin α / β 1 heterodimer responsible for nuclear import of viral protein cargos.^{58,59} An in vivo study reported that the treatment of ivermectin reduced viral RNA up to 5000 fold after 48 hours in cells infected with SARS-CoV-2. Multiple clinical trials are undergoing to evaluate the efficacy of ivermectin.⁵⁹ Drug repositioning is another widely explored strategy for the development of COVID-19 treatment. Teicoplanin, an antibiotic, was demonstrated to exhibit antiviral activity against previous coronavirus and SARS-CoV-2 in vitro. Future in vivo study is required to confirm its activity against SARS-CoV-2.⁶⁰ In March 2020, Moderna's messenger RNA-1273 (mRNA-1273) which encodes the spike protein of SARS-CoV-2 is the first vaccine that proceeded with clinical trials on human subjects.⁶¹ The recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine has demonstrated tolerability and immunogenicity at 28 days post-vaccination.⁶² After the vaccine's safety is verified, subsequent evaluation of its efficacy will be conducted.

In conclusion, this review summarizes the status of the COVID-19 pandemic and the potential therapeutic options.

Although SARS-CoV-2 is characterized by relatively low lethality compared with SARS-CoV and MERS-CoV, it has demonstrated a wider range of clinical presentation and notably higher contagion. In addition to supportive treatment (such as empirical antibiotics and neuraminidase inhibitors for influenza), numerous antiviral drugs designed for other RNA viruses have been reintroduced and applied in clinical studies, such as hydroxychloroquine, favipiravir, and remdesivir. To prevent recurrent outbreaks of COVID-19, a safe and effective vaccine is urgently required. Some vaccine designs have been developed. In March 2020, the first clinical trial for the mRNA-based vaccine (mRNA-1273) from Moderna was initiated. The Ad5 vectored COVID-19 vaccine has demonstrated tolerability and immunogenicity. Further clinical investigation and intensive development of antiviral therapies are ongoing to establish superior treatment strategies against the constantly changing nature of deadly SARS-CoV-2.

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