



Review Article

## COVID-19: A 2020 update

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### ABSTRACT

The 2019 COVID-19 pandemic has thrown the global health-care system into a chaotic flux. Consolidating and reviewing all available knowledge will be crucial to combating the spread of this novel coronavirus. Prevention is paramount, but health care workers are at increased risk, and protective supplies are being limited and being rationed. Common symptoms include fever, cough, and shortness of breath. Hospitalizations are estimated to occur in about 20% of cases and are mostly due to pneumonia.<sup>[1]</sup> While multiple promising treatments are being reported in the medical literature; there is limited, reliable clinical data are available. To minimize exposure of medical staff to contagious patients and to provide rapid escalation of care to these patients, a telehealth strategy could be leveraged. Such a strategy would entail the use of both telemedicine visits for communication and digital health platforms for monitoring.

**Keywords:** Prevention, Diagnosis, Treatment

### INTRODUCTION

A series of viral pneumonia cases linked to a live animal and seafood market in Wuhan, China, was initially reported on December 31, 2019. After the discovery of human-to-human transmission, the virus was isolated and identified as a novel coronavirus.<sup>[2]</sup> After a comparative analysis to the coronavirus causing severe acute respiratory syndrome (SARS-CoV), this novel virus was named SARS CoV-2 and the resultant clinical presentation as coronavirus disease 2019 (COVID-19).<sup>[3]</sup> In comparison to its other counterparts, SARS and Middle-East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV 2 seems to be less lethal, but more communicable. The lower morbidity and mortality of the SARS-CoV-2 virus have led to prolonged patient infectivity, and many carriers are asymptomatic, factors which have enhanced its spread. In the months following the first reported cases, COVID-19 has rapidly spread across the globe. The current pandemic now involves 181 countries and has surpassed 1 million cases worldwide<sup>[4]</sup>. At present, several health-care systems are being pushed to the brink of collapse with a scarcity of hospital and ICU beds. Due to shortages secondary to increased demand and disruption of the global supply chain, rationing of medical supplies, including personal protective equipment (PPE) and ventilators, is now in full effect.<sup>[5]</sup>

### Virology

Coronaviridae (CoV) is a family of positive-sense RNA, phospholipid-enveloped viruses. Alpha and beta-CoV are the sub-classifications that are pathogenic to humans. The SARS-CoV-2 virus was identified as a *Betacoronavirus* after analysis of bronchoalveolar lavage (BAL) fluid

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samples from three early hospitalized patients. There is some homology between SARS CoV-2 and the betacoronaviruses found in bats, subgenus Sarbecovirus. Researchers postulated that all human coronaviruses mutated from an animal host with bats appearing to be the likely reservoir, although there is no evidence of direct transmission.<sup>[6,7]</sup>

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE-2) cell membrane receptors and then translocates into the cell through an activated enzyme pathway, a mechanism common to previous infectious Coronaviridae including SARS-CoV. This knowledge has led to concern for patients on renin-angiotensin-aldosterone system (RAAS) modifying medications. Non-clinical research has demonstrated the upregulation of ACE-2 receptors on cell surfaces under the influence of RAAS inhibitory drugs. However, there is no clinical evidence that these medications increase the risk of COVID-19 infection or precipitate severe disease. Furthermore, these medications reduce morbidity and mortality in patients with cardiovascular disease. They should only be adjusted secondary to clinical judgment with significant regard for hemodynamic status.<sup>[8]</sup>

Viable virus particles were detected at 72 h on most surfaces, with longer viability detected on stainless steel and plastic.<sup>[7,9]</sup> Household disinfectants, particularly those containing ethanol and chlorine, are efficacious in the elimination of virus particles. In addition, ultraviolet radiation is capable of viral inactivation. Stability on surfaces is also comparable. Viability was detected at 72 h on most surfaces, with more favorable durability on stainless steel and plastic.<sup>[7,9]</sup> These data about virus viability and destruction are similar to prior knowledge of other pathogenic coronaviruses – SARS-CoV-2 and MERS-CoV.

Mechanisms of human transmission are currently being investigated, with the prevailing thought favoring droplet transmission and surface fomites. High viral loads are detected in the nasopharynx. Although viral loads are higher when patients are symptomatic, they are still significant in those that are asymptomatic, potentially clarifying how asymptomatic people are capable of transmitting virus.<sup>[10]</sup> Aerosolized particles are implicated as an instrument of transmission, particularly during intubation.<sup>[9,11]</sup> SARS-CoV-2 has also been found in the stool samples of infected patients, but it is unclear to what extent fecal material is contagious. Early research demonstrates that even after patients recover and repeat testing is negative, the virus remains detectable in pharyngeal, urine, and fecal samples.<sup>[12]</sup> At this time, it is difficult to say with any degree of certainty if those patients remain contagious through persistent viral shedding.

**Clinical manifestations**

Approximately 80% of patients are asymptomatic or present with mild symptoms. The most common symptoms observed

are fever, cough, and shortness of breath. Although fever was reported in over 90% of symptomatic individuals, some studies report only 50% with fever at the time of hospital presentation.<sup>[13]</sup> Other frequent symptoms include headache, sore throat, sinus and nasal congestion, myalgias, and fatigue. Less common symptoms reported are anosmia and ageusia, which in some individuals may be the only presenting symptoms.<sup>[3,6,14]</sup> Dermatologic findings have been reported from Italian cohorts and describe urticarial, vesicular, and truncal erythematous patterns.<sup>[15]</sup> Gastrointestinal (GI) manifestations are reported as well. These include anorexia, diarrhea, abdominal pain, nausea, and vomiting [Table 1]. There is some evidence that those whose initial presentation is restricted to GI symptoms may have a worse outcome.<sup>[16]</sup>

Viral pneumonia is the most prevalent presentation in hospitalized patients and is often complicated by secondary acute hypoxic respiratory failure. A subset of patients proceeds to develop acute respiratory distress syndrome (ARDS) and require mechanical ventilation and ICU level care. As is the course with severe infections, septic shock and multiorgan failure may occur during ICU admission with a corresponding increased risk of mortality.<sup>[17]</sup>

Myocardial damage has additionally been reported in the literature. This is not surprising in people with pre-existing cardiovascular disease as the physiologic strain of systemic inflammatory responses and hypoxemic states are well known as potential causes of demand ischemia in these patients. However, myocardial injury is seen, albeit to a lesser extent, in previously healthy critically ill patients which may be attributable to either acute plaque rupture secondary to severe inflammation or viral myocarditis.<sup>[18]</sup> Clinically significant neurological manifestations are still limited to case reports but have included altered consciousness, cerebrovascular accident, and encephalitis.<sup>[19,20]</sup>

**Risk stratification**

Review of the epidemiologic data has identified a specific subset of patients who are at high risk for poor outcomes should they be infected. This vulnerable population includes patients who are elderly (>65 years old), actively smoking, or have pre-existing cardiovascular disease, chronic lung disease (including asthma, COPD, and cystic fibrosis),

**Table 1:** Clinical symptoms.

Frequent	Common	Uncommon
Fever	Headache	Anorexia
Cough	Myalgias	Diarrhea
Dyspnea	Pharyngitis	Nausea/vomiting
	Fatigue	Abdominal pain
	Sinus and nasal congestion	Rash
		Anosmia/ageusia

end-stage renal disease, end-stage liver disease, diabetes, morbid obesity, bone marrow or solid organ transplant recipients, active chemotherapy, any immunosuppressed state [Table 2].<sup>[21]</sup> Familiarity with these categories would allow for more effective triage and monitoring for those who are COVID-19 positive.

### Pregnancy

At present, healthy pregnant patients are not considered to be at high risk for severe COVID-19 disease, but they are often a vulnerable population during pandemics. There is no conclusive evidence of vertical transmission; therefore, a cesarean section should not be recommended solely based on COVID-19 positive status. Notable obstetric complications occur in a small proportion of COVID-19-positive mothers and include intrauterine growth retardation, miscarriages, and pre-term delivery. SARS-CoV-2 has not been detected in breast milk or amniotic fluid, so the Centers for Disease Control (CDC) have recommended that COVID-19-positive mothers continue breastfeeding, as breast milk contributes significantly to the immune system of infants. As always, shared decision-making should take place between patients, obstetricians, and pediatricians.<sup>[22,23]</sup>

### Pediatrics

Reports from infected pediatric populations suggest that they do not appear to be at increased risk for severe illness and often have a milder disease course in comparison to adults. As with adults, special consideration and precautions should be recommended to those with multiple comorbidities and immunocompromised states, as this population was at significantly higher risk of hospitalization and ICU admission.<sup>[24]</sup>

### Diagnostics

#### Laboratory findings

Lymphopenia is a commonly reported abnormality in the complete blood count of COVID-19 patients. Elevated liver enzymes were recorded in a number of cases, suggestive of viral hepatitis. D-Dimer, prothrombin time (PT), serum

creatinase kinase, ferritin, lactate dehydrogenase (LDH), and interleukin-6 (IL-6) were found to be elevated in hospitalized patients, correlating with increased mortality.<sup>[17]</sup> As mentioned previously, myocardial injury has been reported and is detected through elevated high-sensitivity troponin T, C-reactive protein, and N-terminal pro-B type natriuretic peptide.<sup>[18]</sup>

### Radiological features

Consensus findings on chest radiographs and chest CT images from viral pneumonia in COVID-19-positive patients include ground-glass opacification, which is principally bilateral and multilobar in nature. In contrast, SARS-CoV and MERS-CoV presented typically with unilateral radiographic features.<sup>[25]</sup> These imaging findings have also been noted in asymptomatic individuals.<sup>[26]</sup>

A growing body of evidence suggests that point of care ultrasound (POCUS) is clinically useful for patients who test positive. B lines seen on ultrasound representing edema, effusion, or ground-glass opacities may represent worsening disease. A lines, seen on healthy lung tissue, appear as lung disease resolves. Improvement may be monitored with serial POCUS assessment of the pleural space and lung parenchyma. The advantages of this method of surveillance include its portability, rapidity of assessment, and its low cost makes it applicable and accessible in resource-scarce settings.<sup>[27]</sup>

### Diagnostic testing

The most widespread testing methodology is currently real-time polymerase chain reaction (RT-PCR). Samples for screening are typically obtained from the nasopharynx or oropharynx, as these anatomic regions have demonstrated the highest viral loads. The yield of the nasopharyngeal (NP) swabs (63% detection rate) is significantly higher and is the standard procedure. If oropharyngeal swabs (32% detection rate) are performed, they should be combined with NP swabs. RT-PCR may also be performed on sputum and BAL samples when indicated.<sup>[28,29]</sup> A combined approach of testing on upper and lower respiratory samples would theoretically achieve the highest accuracy, but sputum induction and BAL collection methods generate aerosolized particles that pose an increased transmission risk to medical staff. Cell culture methods have not been proven to be efficacious. Serology testing will be of lower diagnostic utility but may have a role in determining immunity. Rapid antigen testing methods are currently under development and being prepared for release.<sup>[28]</sup>

### Treatments

#### Prevention

Social distancing as a means to “flatten the curve” is on the minds of most people in the current setting and for good

**Table 2:** High-risk categories.

Age > 65
Diabetes
Chronic lung disease
Active smoker
Cardiovascular disease
Obesity with BMI > 40
Bone marrow transplant
Solid organ transplant
Any immunocompromised state

reason. We have identified the presence of asymptomatic carriers who pose a considerable risk of disease propagation. Limiting large social gatherings and the frequency of close contact are an essential measure to halt the exponential growth of cases.<sup>[30,31]</sup> In addition to this, the quarantine of known and suspected positive patients is vital to prevention. Ubiquitous testing and efficient triaging of positive patients are crucial to sustaining the health-care infrastructure.<sup>[32]</sup> Strict hand hygiene and proper use of PPE reduce the risk of infectious disease, including SARS-CoV, among health care workers.<sup>[33]</sup>

### Supportive care

For most patients, antipyretics such as acetaminophen and over-the-counter cold medications are recommended for symptom management. Observational studies, including one of four COVID-19 patients in France, treated with ibuprofen with subsequent poor outcomes, led to controversy about the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen in COVID-19 patients. The proposed mechanism purports that pro-inflammatory upregulation occurs as a consequence of NSAID administration, but has not been substantiated scientifically. Current guidelines recommend acetaminophen as the first line for fever treatment but do not recommend advising against NSAIDs if clinically indicated.<sup>[34,35]</sup> Additional conservative measures that should be employed include frequent handwashing and adequate oral fluid and nutritional intake complemented with proper rest.

Hospitalized patients with moderate disease will benefit from intravenous fluids and supplemental oxygen as clinically indicated.<sup>[32]</sup> Decompensated patients will require intubation to manage ARDS and vasopressors for shock. Prone positioning has been proven beneficial in intubated patients with ARDS, and as the supply of ventilators dwindles, consideration should be given to the prone positioning of non-intubated patients who require oxygen as well.<sup>[36]</sup> Cardiopulmonary and renal support devices such as extracorporeal membrane oxygenation (ECMO) and dialysis may be required depending on hemodynamic and renal status.

### Corticosteroids

The use of corticosteroids for the sole treatment of COVID-19 may prolong viral shedding, worsen active disease from immunosuppression, and predispose to bacterial superinfection. Those patients in critical care with ARDS, shock, and multiorgan failure may, however, benefit from stress dose steroid administration.<sup>[37]</sup> Inhaled and systemic steroids should be continued for the management of asthma as clinically indicated.<sup>[38]</sup>

### Chloroquine and hydroxychloroquine

Prior experience during the SARS epidemic suggested that the anti-malarial drugs chloroquine and hydroxychloroquine

(HCQ) may be clinically beneficial. They are currently being investigated as potential treatment or prophylaxis for COVID-19. Their mechanism of action is unclear but may involve glycosylation of ACE 2 receptors. In addition, the immunomodulatory properties of these compounds may play a role in the improvement of COVID-19 disease. Non-randomized trials in China and France suggested clinical improvement and decreased length of stay in conjunction with a decrease in viral load.<sup>[39]</sup> A small study that prescribed a treatment regimen of HCQ in combination with azithromycin implied a synergistic response. The side effect profile of HCQ, while not insignificant, is preferable to chloroquine [Table 3]. These drugs are known to be QT prolonging agents and should be used with extreme caution, especially in patients with known cardiovascular disease. While results are promising, higher-quality studies must continue before strong endorsements are universal.

### Antiviral agents

Remdesivir is a nucleotide analog antiviral medication that has activity against SARS-CoV and MERS-CoV, as well as other RNA viruses. It is a broad-spectrum agent which is an ideal starting therapy. *In vitro* studies demonstrate inhibitory activity toward cell entry of SARS-CoV-2.<sup>[39,40]</sup> A few research protocols are looking at drug cocktails, including remdesivir and chloroquine. Another nucleotide analog, ribavirin, has shown *in vitro* activity against novel coronaviruses. Ribavirin also has indirect anti-viral properties that may be beneficial. T-helper cell activity seems to increase in the presence of this medication.<sup>[41]</sup>

The protease inhibitor, ritonavir, which is typically used in HIV treatment, has also inhibited SARS-CoV *in vitro*. Ritonavir can be combined with lopinavir to boost serum levels through inhibition of cytochrome P450 enzymes effectively. Lopinavir had previously been shown in animal models to have efficacy against MERS-CoV. However, when the combination of ritonavir-lopinavir underwent a randomized controlled trial in China for COVID-19, the treatment regimen was deemed ineffective.<sup>[42]</sup>

### Anti-parasitic agents

Nitazoxanide is an anti-parasitic drug initially purposed for the elimination of protozoal organisms. However, this medication has demonstrated broad-spectrum activity against respiratory

**Table 3:** Prospective treatments.

Anti-malarial	Antiviral	Anti-parasitic	Immunomodulatory
Chloroquine	Remdesivir	Nitazoxanide	Tocilizumab
Hydroxy chloroquine	Ribavirin	Ivermectin	Convalescent plasma
	Ritonavir/ lopinavir		BCG vaccine

viruses, including influenza and MERS-CoV, which may be mediated by its metabolite, tizoxanide. Tizoxanide may interfere with viral replication and downregulate host release of cytokines, which makes it an appealing candidate for further investigation.<sup>[43]</sup> Existing data from trials evaluating the treatment of influenza-like diseases did not demonstrate a change in the length of hospital stay<sup>[44]</sup> and to date clinical data regarding efficacy against COVID-19 are not available.

Similarly, ivermectin is an anti-parasitic with demonstrable antiviral activity. *In vitro* studies report a decrease in viral replication of SARS-CoV-2 which is postulated to occur through the inhibition of nuclear import proteins.<sup>[45]</sup> Both of these medications have a studied safety profile for use in humans, given their prior indications. Nevertheless, proper clinical data are still needed before any consensus recommendation.

### IL-6 modulators

Severe, systemic inflammation that results in ARDS, septic shock, coagulopathies, and organ failure is caused on a molecular level by cytokine release. IL-6 is identified as a critical intermediary in this pathophysiologic process. Inhibition of this molecule may ameliorate inflammatory states that precipitate critical illness. Tocilizumab is an IL-6 receptor antagonist used in autoimmune disease, which is being investigated for the treatment of moderate-to-severe presentations of COVID-19. Credibility is derived from the approval to use tocilizumab for cytokine release syndrome in patients undergoing chimeric antigen receptor T-cell immunotherapy (CAR-T).<sup>[46]</sup> Other medications that share congruous pharmacodynamics are also being considered. A case study in a patient with multiple myeloma and COVID-19 reported resolution of symptoms after initiation of tocilizumab.<sup>[47]</sup>

### Convalescent plasma

Use of convalescent plasma has been used in medical practice for decades, but more recently, during the SARS, Ebola, and the 2009 H1N1 influenza epidemics. The underlying principle is to harvest donor plasma from patients who have recovered from viral infection and demonstrate the presence of neutralizing antibodies. This plasma is then transfused into critically ill infected patients with the aim of neutralizing and clearing viral particles with donor antibodies. A trial of five critically ill, COVID-19-positive patients (who were also receiving ritonavir/lopinavir) demonstrated an improved clinical course after convalescent plasma transfusion.<sup>[48]</sup> This is a promising modality and is undergoing widespread clinical trials.

### Zinc

The concept of zinc as antiviral therapy is not novel. There is evidence in cell culture and *in vitro* of blunting RNA viral

replication, but this has not parlayed into clinical practice. Trials on zinc preparations for common cold viruses claimed reduction in symptom duration with the main adverse effects being anosmia and dysgeusia.<sup>[49,50]</sup>

### BCG vaccine

The Bacille Calmette-Guerin (BCG) vaccine for mycobacterium tuberculosis is one of the most widely used vaccines across the globe. Several studies have demonstrated a decrease in non-tuberculous respiratory infections in vaccinated populations. Epigenetic effects on monocytes and T-lymphocytes might be responsible for this observation.<sup>[51]</sup> In addition, the BCG vaccine has immunomodulatory properties that are clinically effective.<sup>[52]</sup> Clinical trials to determine effectiveness against COVID-19 are commencing.

### Vaccine development

Vaccine development is a prolonged and expensive process, which traditionally requires multiple phase trials. This process is not feasible in a pandemic, so fast-tracked models need to be considered, and the simultaneous development of multiple vaccine candidates is likely necessary. This method is best suited to run in parallel with the traditional model.<sup>[53]</sup>

### Telehealth response

The non-face-to-face remote delivery of health-care resources to patients, or telehealth, presents unique value in pandemics. The great majority of COVID-19-positive patients can be safely managed in an outpatient setting through telemedicine as these patients are low risk and mildly symptomatic. Additional benefits include being able to deliver care to patients under quarantine while reducing infectivity to medical staff and others in the community. Medical staff can also triage patient concerns and thus decrease activation of EMS and ED visits. This can be augmented by the utilization of remote patient monitoring (RMP) services, which provide patient vital signs and can facilitate direct admission in appropriate cases without ED utilization.<sup>[54,55]</sup> Measuring oxygen saturation through RMP is often valuable for early detection of respiratory decompensation from acute hypoxic respiratory failure. Mobile health, access to health information through mobile device apps, also offers benefits in times of pandemic. Mobile devices can transmit data from RMP equipment, communicate with physicians, and contribute to contact tracing, which would be a significant public health asset. Artificial intelligence algorithms could tap into data obtained from the electronic health record and identify clusters and predict hot spots before extensive outbreaks to allow local health-care systems to prepare in advance and implement strategies to minimize growth.<sup>[56]</sup>

The digital age of medicine, which was in its infancy before the COVID-19, pandemic is poised to cement its position in our delivery of health care.

## CONCLUSION

The COVID-19 pandemic will leave its mark on contemporary medical history. While we are still in the midst of it, we need to ensure that all available evidence are critically analyzed and appropriately distributed. While proposed treatments will attract significant media attention and processes will be accelerated and circumvented to streamline treatment development and delivery, optimal delivery of clinical care should be based on the latest scientific data. At present, while many treatment options show some clinical promise, there is no clear scientific guidance as to therapy for COVID-19 disease. The COVID pandemic and the need for social distancing and quarantine have thrust telemedicine to the forefront. Leveraging telecommunication technology and artificial intelligence to decrease risk to the health-care workforce should be paramount in the management of this pandemic.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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## Conflicts of interest

There are no conflicts of interest.

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