

# COVID-19: An Immunopathologic Assault

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## ABSTRACT

When caring for patients with coronavirus disease 2019 (COVID-19), clinicians have noticed some unusual clinical presentations not observed before, such as profound hypoxia and severe hypotension. Scientists are probing the evidence to explain these issues and many other unanswered questions. Severe acute respiratory syndrome associated with coronavirus 2 presents an uncharted acute and critical care dilemma. Some of the theories and proposed interventions that will improve outcomes for these critically ill patients are explored in this article. Various

testing procedures for COVID-19 are described so valid results can be obtained. Clinical presentations are discussed but continue to evolve as the pandemic ravages our society. The psychological impact of this devastation is also addressed from multiple perspectives. The health care provider is faced with an unprecedented, harrowing situation that has become an internal war that also must be confronted. Professional dedication has provided a formidable response to this destructive virus.  
**Key words:** coronavirus, COVID-19, cytokine release syndrome, SARS-CoV-2

**A** *apocalyptic* was the term used in a *New York Times* article describing the situation in a New York City hospital on March 25, 2020, during the coronavirus pandemic.<sup>1</sup> The United States has never experienced a public health disaster as severe as this pandemic. The impact of this invasive virus challenges every component of our health care system, especially acute and critical care. In this article, we provide critical care clinicians with a pertinent summary of this virus, its characteristics and clinical presentation, as well as care and possible treatment of the devastating disease the virus can cause. The psychological toll on our society also is explored. Knowledge about this virus is constantly evolving, which presents challenges to both readers and authors. It is imperative that health care clinicians stay abreast of current literature.

## Overview of Viral Function and Pathogenesis

The first cluster of pneumonia cases caused by this virus occurred in December 2019 in

Wuhan, China. On January 12, 2020, the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was officially named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).<sup>2</sup> Naming this disease COVID-19 avoids stigmatizing Wuhan, where the virus originated, and helps prevent the use of other

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The authors declare no conflicts of interest. The contents of this article do not necessarily represent the views of the US Department of Health and Human Services. This activity was supported in part by the Intramural Research Program of the National Institutes of Health (NIH), the Critical Care Medicine Department, and the NIH Clinical Center.

DOI: <https://doi.org/10.4037/aacnacc2020802>

names that might be inaccurate. This virus is extremely virulent and in order to better understand its infectivity, we will review basic principles of virology.

### Virology

Viruses are small intracellular parasites that contain either an RNA or DNA genome that can be single or double stranded and is surrounded by a protective protein coat.<sup>3,4</sup> To propagate, viruses enter specialized host cells that supply biochemical and metabolic mechanisms that transcribe and translate the viral genetic material, resulting in the reproduction of the virus.<sup>3,4</sup> Approximately 70% of all viruses are RNA viruses, which can vary in genetic structure. When replicating, RNA viruses have necessary transcription enzymes that are prone to genetic errors and lead to higher mutation rates.<sup>3,4</sup> The higher degree of mutant variations in RNA versus DNA viruses leads to greater adaptability of the viruses to new host cells and, thus, greater infectivity.<sup>3,4</sup>

Viruses enter the body via various portals, including respiratory, gastrointestinal, skin-penetrating, and genital routes. Affinity of viruses for certain tissues depends on factors such as cell receptors, physical barriers, local pH, temperature, and types of secretions.<sup>4,5</sup> Dissemination throughout the human body to target organs is facilitated by travel through the lymph and vascular system. Once entrance to the host is established, the virus needs time to battle host defenses. Depending on the strength of the host defenses, symptoms may be slow to appear or may never materialize.<sup>4,5</sup> The virus will start to control the infected cell's energy mechanisms to replicate and propagate.<sup>4,5</sup> Once the virus has successfully reproduced in the host cell, it will leave the cell and can be released into the circulatory system. This process is referred to as viral shedding and occurs mainly via the respiratory and alimentary tracts. This is considered the most contagious stage.<sup>4,5</sup>

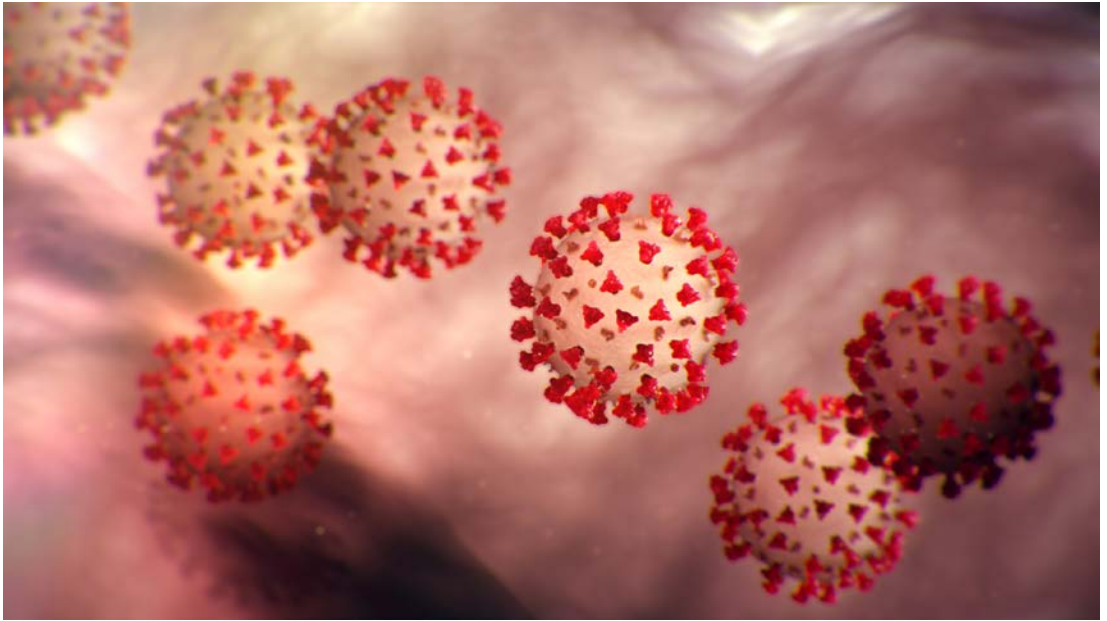
Data are limited on how long individuals shed infectious SARS-CoV-2 RNA after they are infected. According to the Centers for Disease Control and Prevention (CDC),<sup>6</sup> replication-competent SARS-CoV-2 has not been successfully cultured more than 9 days after the onset of COVID-19. In addition, there is no clear correlation between a patient's length of illness and the duration of postrecovery shedding of detectable viral RNA in

upper-respiratory-tract specimens. Patients may clear the virus within several days, but some patients may remain positive for weeks after symptom onset.<sup>6</sup> Death from viral disease varies according to the type of virus; SARS-CoV-2 is a coronavirus.

### Pathogenesis of Coronaviruses

Coronaviruses are enveloped, single-stranded RNA viruses that are susceptible to mutation, which can lead to 40 or more variations.<sup>7</sup> These viruses can infect mammals, including humans, bats, and pangolins, and nonmammals, including birds and some reptiles. It has been suggested that the term *coronavirus* comes from the crown-like glycoprotein spike structures these viruses have and use to access the host cell (Figure 1). However, the original group of virologists who discovered coronaviruses in 1968 named these viruses for their resemblance, when viewed under an electron microscope, to the solar corona during an eclipse.<sup>7</sup> The novel coronavirus SARS-CoV-2 that causes COVID-19 belongs to the same species as SARS-CoV, the coronavirus that caused the 2002-2003 outbreak of severe acute respiratory syndrome (SARS). Another related coronavirus, which gained recognition in 2012, is the Middle Eastern respiratory syndrome coronavirus (MERS-CoV); it also caused an acute respiratory syndrome similar to SARS.<sup>7</sup>

Coronaviruses infect humans via the respiratory system. These viruses are thought to be one of the causes of the common cold. However, as these viruses evolved, the signs and symptoms of their infection became more severe. Coronaviruses infect the respiratory macrophage and dendritic cells, which can induce a substantial inflammatory response resulting in cytokine release.<sup>8</sup> The activation of these cells suggests coronaviruses can trigger a marked immunologic response in the body. The 2002-2003 SARS-CoV epidemic in the Guangdong Province of China was thought at the time to be the most severe immunopathologic disease process related to a coronavirus infection. That epidemic led to 8098 cases and 774 associated deaths.<sup>8</sup> From an immunology perspective, some rodent-adapted SARS-CoV models have displayed a decreased T-cell response, further implicating immune dysfunction.<sup>8</sup> The MERS-CoV epidemic emerged in Saudi Arabia in 2012 as another highly pathogenic coronavirus causing



**Figure 1:** Image of severe acute respiratory syndrome coronavirus 2.

<https://www.cdc.gov/media/dpk/diseases-and-conditions/coronavirus/coronavirus-2020.html>.

a respiratory syndrome with a mortality rate of approximately 40%. The epidemic occurred primarily in 2003, and the disease remained limited.<sup>8</sup>

### Pathogenesis of COVID-19

The pathogenesis of COVID-19 is not well understood but is thought to be similar to the disease process associated with SARS-CoV. Both viruses attach to the host cell at the angiotensin-converting enzyme 2 receptor.<sup>8</sup> SARS-CoV-2 specifically binds via the spike, or S, glycoprotein in the crown structure, which leads to alteration in the viral wall envelope. This virus–human cell interaction triggers the release of numerous immune mediators, including cytokines and chemokines aimed at destroying the virus.<sup>2,9</sup> This reaction is a normal function of the immune response of the infected individual to eliminate SARS-CoV-2.<sup>2</sup> It is postulated that nonstructural proteins of coronaviruses may disable this immune response.<sup>10</sup> This process results in a severe immunopathologic cascade, with the release of many proinflammatory cytokines referred to as a *cytokine storm* or cytokine release syndrome (CRS).<sup>2</sup> This abnormal response of the immune system leads to a dual level of pathology for COVID-19: a direct cell injury because of the viral parasitic activity as well

as the unregulated host immune response. Both of these processes can lead to multi-system organ dysfunction.

### Unregulated Immune Response

Our understanding of the CRS associated with COVID-19 continues to evolve. Cytokine release syndrome has been more widely studied in response to adoptive cell therapy toxicity (ie, chimeric antigen receptor [CAR] T-cell therapy).<sup>11</sup> Cytokine release syndrome associated with CAR T-cell therapy has been formally studied and is graded according to the severity of the response, from grade 1, with fever, chills, and myalgias, to grade 4, with refractory shock requiring critical care.<sup>11</sup> The release of proinflammatory cytokines results in hypotension because of capillary leak and hypoxemia, which progresses to shock and acute hypoxemic respiratory failure. Cytokine release syndrome can cause failure in multiple organ systems, including acute kidney injury, acute liver failure, and disseminated intravascular coagulation. Another clinical feature that results from bone marrow suppression during the body's immune response to the viral infection is pancytopenia.<sup>11</sup> Cytokine release syndrome can be suppressed to a certain degree by inhibiting interleukin (IL)-6, which is a major cytokine involved in CRS.

Cytokine release syndrome associated with COVID-19 has some unique features. Respiratory symptoms are common and usually begin 7 to 10 days after the onset of other general signs and symptoms (fever, cough, fatigue, myalgia), but presentation can vary.<sup>12,13</sup> Increasing IL-6 levels have been noted as well as lymphopenia, with low CD4+ and CD8+ T-cell counts.<sup>12</sup> These cytokine findings are associated with moderate COVID-19.<sup>12,13</sup> As clinical presentation worsens, dyspnea, hypoxic respiratory failure, and acute respiratory distress syndrome (ARDS) may develop. Substantial elevations in the numbers of IL-6, IL-10, tumor necrosis factor  $\alpha$ , soluble IL-2R receptor (CD25), as well as elevated levels of ferritin, D-dimer, C-reactive protein, lactate dehydrogenase, and procalcitonin have been noted.<sup>13</sup> In addition, a decrease in the levels of CD4+ and CD8+ T cells, natural killer T cells, and interferon- $\gamma$ -expressing CD4+ T cells responsible for modulating the immune responses were noted with an increasing leukocytosis.<sup>12,13</sup> The elevated cytokine levels were associated with patients presenting with severe COVID-19.<sup>12,13</sup>

These classifications of COVID-19 CRS presentations demonstrate the complexity of the inflammatory response to the antigen, SARS-CoV-2, in different hosts. Various T cells, acute phase proteins, and cytokines are intricately involved in the body's protective mechanisms when tissue injury occurs. CD4+ helper T cells and CD8+ cytotoxic T cells launch the response and release interleukins to mobilize more cells. Ferritin is an acute-phase protein produced by the body to help store iron. Pathogens need iron for many cell functions, and the production of ferritin can help disable pathogen function. D-dimer is an acute-phase protein that assists protective coagulation. Interferon- $\gamma$  is a cytokine that inhibits viral replication.<sup>14</sup> The COVID-19 process disrupts all these protective mechanisms and results in critical illness.

### COVID-19 Clinical Presentation

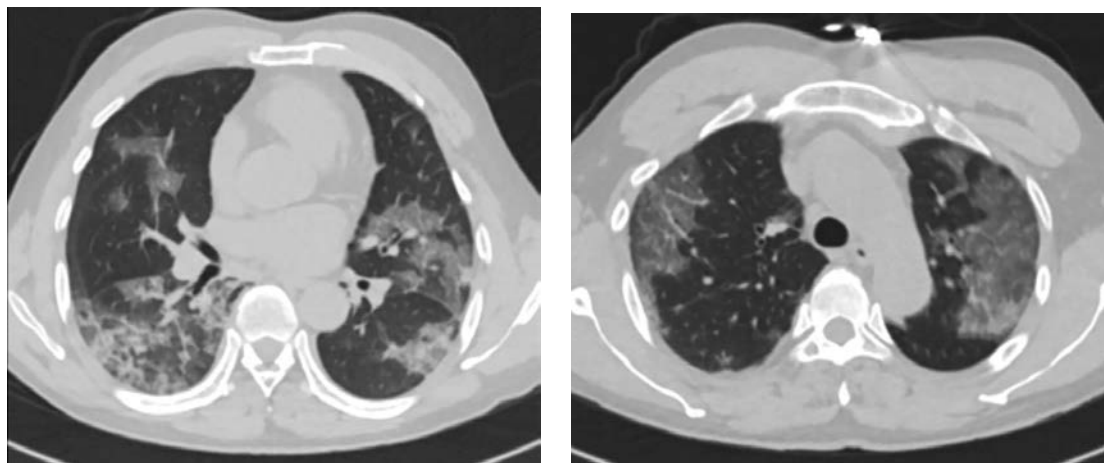
The clinical presentation of COVID-19 is on a continuum from nonspecific signs and symptoms to severe pneumonia and septic shock resulting in multiple organ failure. Common nonspecific signs include fever ranging between 37.7 °C and 38.8 °C (99.9 °F-101.8 °F), dry cough, dyspnea, and myalgias. Less-common symptoms are nausea, vomiting, diarrhea,

and headache.<sup>15</sup> However, the first patient reported in the United States to have COVID-19 was noted to have a 2-day history of nausea and vomiting on admission and then a loose bowel movement on hospital day 2.<sup>16</sup> An increase in observed instances of diarrhea has been noted as more patients have initially presented.<sup>17</sup> Gastrointestinal symptoms are more common in the United States than in China, where gastrointestinal symptoms occurred in only 4% to 5% of patients, which might reflect geographic variation or differential reporting.<sup>18</sup> Thus, gastrointestinal symptoms, although less frequent than other symptoms, should be pursued.

In a retrospective case series of 393 patients with confirmed COVID-19 in New York City, researchers noted that common presenting symptoms were cough (79.4%), fever (77.1%), dyspnea (56.5%), myalgias (23.8%), diarrhea (23.7%), and nausea and vomiting (19.1%).<sup>18</sup> These symptoms contrast with the presentation of syndromes associated with MERS-CoV and SARS-CoV, symptoms of which were commonly a runny nose with occasional gastrointestinal symptoms.<sup>19</sup> The incubation period of SARS-CoV-2 is similar to that of MERS-CoV and SARS-CoV, with time to symptom onset ranging from 2 to 14 days. Whereas with influenza, the onset is usually within a few days.<sup>19,20</sup> There are increasing numbers of reports of altered taste and smell that occur before development of respiratory symptoms.<sup>19,20</sup>

Although patients often present with symptoms, many individuals have limited or no symptoms, and their infections goes undetected. These asymptomatic individuals can expose others to the virus and are thought to contribute substantially to the spread of SARS-CoV-2 infection.

COVID-19 in patients can progress from mild pneumonia to respiratory failure, septic shock, and/or multiple organ dysfunction.<sup>21</sup> If the disease progresses to respiratory failure, it usually does so within a few days from onset of symptoms (range, 2-7 days; average, approximately 5 days).<sup>21,22</sup> Patients who require admission to the intensive care unit are usually older and more likely to have underlying comorbidities, including diabetes, hypertension, malignancy, cardiovascular disease, and cerebrovascular disease.<sup>23</sup> Among 138 patients diagnosed with novel coronavirus-infected pneumonia, the mean Acute Physiology and Chronic Health Evaluation II score was 17



**Figure 2:** Computerized tomography of chests of patients with coronavirus disease 2019.

(range, 14-19).<sup>24</sup> Most patients have multiple system organ failure, including acute cardiac and kidney injury, liver dysfunction, and ARDS. Because progression to ARDS and septic shock can happen rapidly, early identification and timely treatment of critical cases are crucial to decrease risk for death and morbidity.

Patients admitted to the intensive care unit have blood cell counts that typically demonstrate leukopenia, with white blood cell counts less than  $4 \times 10^9/L$  with lymphopenia (lymphocyte count  $< 1.0 \times 10^9/L$ ), suggesting that SARS-CoV-2 consumes many immune cells and inhibits cellular immune function.<sup>25</sup> Leukocytosis develops in other patients. Levels of liver enzymes, D-dimer, ferritin, and prothrombin times are elevated, as is troponin I, noted in patients with cardiac injury. Many patients have thrombocytopenia.

Procalcitonin levels were elevated in patients in whom secondary bacterial infections developed. Secondary infections included but were not limited to carbapenem-resistant *Klebsiella pneumoniae*, *Aspergillus flavus*, *A fumigatus*, extended-spectrum  $\beta$ -lactamase (ESBL)-positive *K pneumoniae*, ESBL-positive *Pseudomonas aeruginosa*, and ESBL-negative *Serratia marcescens*.<sup>21</sup>

### Radiologic Findings

Typical findings on chest computed tomography (CT) images are bilateral, multiple lobular and subsegmental areas of consolidation, similar to what was noted in patients infected with SARS-CoV and MERS-CoV (Figure 2).<sup>26</sup> In a study of 19 patients with COVID-19-associated pneumonia and 15

patients who had pneumonia but not COVID-19, multiple mottling and ground-glass opacities were seen on CT images of patients in the former group.<sup>27,28</sup> According to a meta-analysis, chest radiographic findings of patchy ground-glass shadows can affect a single lung (single or multiple lobes) or both lungs; normal chest radiographic findings are infrequent.<sup>29</sup> A normal chest radiograph, however, does not rule out COVID-19. Among 47 patients with suspected SARS who had normal chest radiographs, 27 had SARS-associated coronavirus infection confirmed by real-time polymerase chain reaction (PCR) and/or positive serologic testing results.<sup>30</sup> Similar to patients with severe influenza (eg, H1N1), inflammation quickly spreads in the lungs of patients with COVID-19. The first 2 patients in Italy with COVID-19 infection who traveled from Wuhan, China, were noted from chest CT scans to have progressive ARDS, similar to previous reports.<sup>31</sup> However, there were also lung patterns in both patients characterized by hypertrophy of the pulmonary vessels, particularly in areas with more pronounced interstitial impairment. This finding differs from those observed in patients with SARS-CoV or MERS-CoV infection, in whom pulmonary vessel vasoconstriction was noted and possibly related to the presence of vasoactive substance within the lesions.<sup>31</sup> Another rare finding with COVID-19 was the presence of mediastinal lymphadenopathy with short-axis oval nodes.

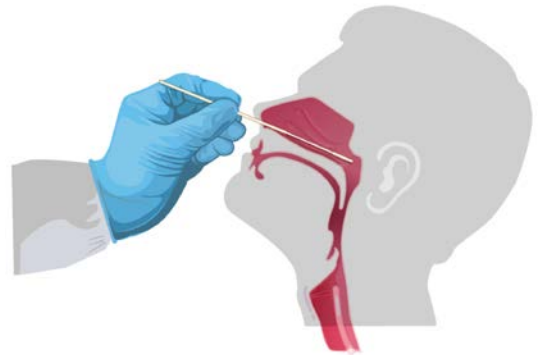
### Diagnosis and Testing

The diagnosis of SARS-CoV-2 infection is made by real-time PCR analysis of respiratory

specimens.<sup>2</sup> Positive results are indicative of active infection with SARS-CoV-2 but do not rule out bacterial infection or coinfection with other viruses. This detection method relies on the presence of sufficient viral genome at the site of sample collection. Incorrect sample collection techniques can limit the usefulness of this assay and allow infected patients to unknowingly spread the infection. Missing the time window of viral replication, that is, obtaining specimens late in the illness, can also provide false-negative results.<sup>32</sup> Among 384 patients hospitalized in Wuhan with negative pharyngeal real-time PCR analysis results, 48 patients (12.5%) were noted to be positive 1 to 2 days later on retesting.<sup>32</sup> Thus, there is a suggestion that real-time PCR test results of pharyngeal swabs should not be considered the only indicator for diagnosis. Repeated testing should be considered for patients who exhibit symptoms suggestive of COVID-19. Some authors recommend using the classic findings of chest CT imaging to make the diagnosis.<sup>30</sup>

**Antibody Testing.** Detection of antibodies, especially Immunoglobulin (Ig) M, that are rapidly produced after SARS-CoV-2 infection can be combined with PCR results to enhance detection, sensitivity, and accuracy of the findings. This would be valuable for patients with symptoms and epidemiology indicative of COVID-19 in the absence of a positive PCR test. However, depending on host factors and the time course of the disease, antibodies may not be present. These issues are especially important where proper diagnosis is essential to limit the spread of this virus.

**Specimen Collection.** The CDC recommends collecting and testing a nasopharyngeal swab (Figure 3). For best results, the patient should blow their nose to clear the nasal passages, cough to bring organisms to the nasopharynx, and tilt their head back; the swab then should be passed, gently, approximately 3 to 4 inches into the nasopharynx while keeping the swab near the septum and floor of the nose. The swab should be rotated quickly and removed. Once the swab is placed in a tube that is secured and labeled, it should be stored at 28 °C until it is sent to the appropriate laboratory for testing. Only synthetic-fiber swabs with plastic shafts are to be used. Swabs with cotton or wooden shafts may contain chemicals that could inhibit the virus. Collection of sputum is recommended only for patients



**Figure 3:** Collection of nasopharyngeal swab. <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>.

with productive coughs. Induction of sputum is not recommended.<sup>33</sup> An endotracheal aspirate can be obtained and tested for COVID-19 along with other bacteria and fungi. Oropharyngeal swab collection technique results are not considered as accurate.<sup>33</sup>

At the time of this writing, the Infectious Diseases Society of America has delineated tiers for testing (Table 1).<sup>34</sup> On April 1, 2020, an anti-SARS-CoV-2 rapid test was approved for Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA). It is an assay intended for the presumptive qualitative detection of IgM and IgG antibodies to SARS-CoV-2 in patients with symptoms suspected to be due to COVID-19.<sup>35</sup> The test uses the patient's finger-prick blood, serum, or plasma specimen and has a turnaround time of 15 minutes. As stated on the CDC website, this test has only been approved for EUA. Negative results do not rule out SARS-CoV-2 infection, and the test should not be used as the sole basis for diagnosing SARS-CoV-2 infection nor for screening blood donors. Positive test results may be due, in part, to past or present infections with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E.<sup>36</sup>

**Saliva Testing.** In addition to PCR and antibody testing, the FDA has granted EUA to specific laboratories for saliva testing for SARS-CoV-2. The patient expectorates in a tube and hands the tube back to the health care worker. This test enables broader population screening, decreases the need for testing swabs and for personal protective equipment, and allows for non-health care workers to perform the test.<sup>37</sup> In a recent study of 25 Italian patients positive for SARS-CoV-2

**Table 1: Infectious Diseases Society of America Prioritization Recommendations for COVID-19 Testing<sup>34</sup>**

Priority Level	Population
Tier 1	Critically ill patients with unexplained symptoms Individuals with respiratory symptoms and who have had contact with a patient who has tested positive for COVID-19 or who have recently traveled to areas with high community transmission Individuals with fever or respiratory infections who also are immunocompromised (including those with HIV), elderly, or who have underlying chronic conditions Individuals critical to the pandemic response who have respiratory symptoms, such as health care workers, public health officials, and other essential leaders
Tier 2	Patients who are hospitalized but not in intensive care units and long-term care residents with symptoms
Tier 3	Patients in outpatient settings who meet the criteria for influenza testing, including those with select comorbid conditions such as diabetes, chronic obstructive pulmonary disease, or congestive heart failure Pregnant women Symptomatic children with additional risk factors
Tier 4	Individuals in communities being monitored by health authorities to collect data and ascertain the prevalence of COVID-19

Abbreviation: COVID-19, coronavirus disease 2019.

infection, salivary samples that were analyzed by real-time PCR all tested positive for the presence of SARS-CoV-2.<sup>37</sup>

### COVID-19 Disease Characteristics and Treatment

There is no definitive treatment for this novel SARS-CoV-2. Some of the current treatments are based on previous experience with SARS and MERS outbreaks. Thus far, most treatments are supportive only. The disease can result in multiple system organ failure, including renal, hepatic, and cardiac failure, as well as septic shock. COVID-19, however, has some unique disease characteristics, including pulmonary pathology, associated CRS, and hypercoagulopathy, that are the focus of the discussion in the following sections.

#### Hypoxic Respiratory Failure

Patients with COVID-19 commonly present with hypoxic respiratory failure that can result in severe ARDS. Knowledge about the pathophysiology of ARDS associated with COVID-19 is limited but is thought to be similar to other SARS-CoV disease. The major portal of entry for SARS-CoV-2 is the respiratory system; thus, the virus uniquely affects the function of the alveolar unit and vascular bed of the pulmonary system. Diffuse

alveolar damage occurs as a result of direct tissue injury initiated by SARS-CoV-2, as well as an inappropriate immune host response.<sup>38</sup> The alveolar capillary membrane develops increased permeability that leads to noncardiac pulmonary edema. With typical ARDS, the lung tissue becomes less compliant. However with COVID-19 ARDS, lung compliance can increase, although newer data have not shown this.<sup>39</sup> The released cytokines further increase vascular permeability, leading to the alveolar edema. This normal compliance with vascular congestion may be the cause of significant desaturation without increased work of breathing that has been described anecdotally.

The important difference in the pathogenesis of COVID-19 is that the pulmonary vascular bed, due to alveolar hypoxia, is not able to react with the expected vasoconstriction. There has been discussion in the critical care community about the COVID-19 ARDS presentation. Gattinoni et al<sup>39</sup> have proposed that there are 2 phenotypes of lung pathology: type L, with low elastance (high compliance), reduced lung weight, low ventilation-to-perfusion ratio, and reduced lung recruitability; and type H, with high elastance (low compliance), increased lung weight, high right-to-left shunt, and increased lung recruitability. Consideration

of this theory may alter clinical interventions with ventilator management.

### Pulmonary and Ventilator Management

Supportive care remains the primary treatment strategy for treating respiratory failure with COVID-19. Supplemental oxygen should be considered when oxygen saturation measured by pulse oximetry ( $\text{SpO}_2$ ) is less than 92% on room air and initiated if  $\text{SpO}_2$  is less than 90%; the optimal oxygenation goal is an  $\text{SpO}_2$  of 92% to 96%.<sup>40,41</sup> These  $\text{SpO}_2$  goals are the recommendation in the current guidelines after analysis of several studies.<sup>41</sup> A standard nasal cannula can be tried; however, a high-flow nasal cannula may provide more comfort for the patient. There has been some concern about disease dispersion of aerosolized particles with high-flow nasal cannulas, but this issue has not been supported in current research.<sup>40,41</sup> Noninvasive ventilation is another option, although a full face mask is recommended and patient tolerance is variable. All patients with COVID-19 should be placed in negative-flow rooms when any aerosolized treatments or procedures are to be performed.<sup>40,41</sup>

The decision to intubate the patient with COVID-19 is made after close clinical monitoring of oxygen saturation. Every effort should be made to intubate under controlled conditions. The provider should (1) be experienced with intubation; (2) use video rather than direct laryngoscopy; (3) minimize use of manual bag ventilation to minimize aerosolization of secretions; (4) use rapid sequence intubation; and (5) use full personal protective equipment.<sup>40</sup> Once intubated, low tidal-volume ventilation is recommended using 4 to 8 mL/kg of predicted body weight and a plateau pressure goal of less than 30 cm  $\text{H}_2\text{O}$ .<sup>40,41</sup> This strategy for respiratory support for patients with COVID-19 is currently being studied. Recruitment maneuvers can be used to improve alveolar ventilation, but staircase recruitment maneuvers should be avoided because of possible increased barotrauma.<sup>40,41</sup> Because of vasodilation of pulmonary vasculature associated with COVID-19 CRS, inhaled nitric oxide is not recommended for routine use.<sup>40,41</sup>

Prone positioning can be used with moderate to severe ARDS. The recommended duration in the prone position is 12 to 16 hours. An institutional protocol for proning should be

followed, and the patient should be assessed for pressure injuries and endotracheal tube stability and patency.<sup>40,41</sup> There are anecdotal experiences of “self-proning” with more stable patients who are not intubated; this positioning could be considered using an institutional protocol.<sup>42</sup> Ventilator synchrony has been difficult with some of these patients and has required intermittent dosing of neuromuscular blockade with higher doses of sedation.<sup>40,41</sup> Frequent monitoring via measurement of arterial blood gases and calculating the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen can aid treatment decisions. With refractory hypoxemia, extracorporeal membrane oxygenation could be another intervention, but it is not available in all institutions. The decision to implement venovenous extracorporeal membrane oxygenation should be made early in the treatment course so safe transport to an extracorporeal membrane oxygenation center can be arranged efficiently.<sup>40,41</sup> With evolving clinical evidence, additional caution must be used with all standard ARDS interventions.

### Cytokine Release Syndrome

Although immunologic aspects of COVID-19 are not well identified, it has been established that SARS-CoV-2 causes an immunopathologic response that features proinflammatory cytokine release similar to secondary hemophagocytic lymphohistiocytosis, as well as CRS, after CAR T-cell therapy.<sup>43</sup> Trending of cytokines and acute-phase proteins including IL-6, ferritin, C-reactive protein, triglycerides, fibrinogen, and D-dimer results are being monitored in patients with COVID-19. Tocilizumab is a humanized monoclonal antibody that blocks IL-6 receptors. This drug is used clinically in the treatment of autoimmune diseases but has been approved to treat CRS after CAR T-cell therapy.<sup>11</sup> Given the similarly elevated IL-6 levels seen in COVID-19, tocilizumab has been used. Data from formal clinical trials are pending. Steroids have also been used to minimize the inflammatory response, although their use is not recommended in current guidelines as standard of care.<sup>40,41</sup> Remdesivir is an antiviral agent that terminates viral replication by binding to RNA-dependent RNA polymerase. Results from the recent randomized, controlled Adaptive COVID-19 Treatment Trial demonstrated that remdesivir accelerates recovery from



advanced COVID-19; the drug has received emergency FDA approval.<sup>44</sup> Combination lopinavir and ritonavir is another antiviral agent that reduces viral replication but is not recommended for use in treating COVID-19.<sup>40,41</sup> Convalescent plasma, or plasma that has been collected from patients who have recovered from COVID-19 and is presumed to have antibodies, may inactivate the virus. It is infused into critically ill patients with COVID-19 and some anecdotal success has been reported. The current evidence is not sufficient to recommend this as a routine intervention.<sup>40,41</sup>

### Hypercoagulopathy

The intersection of unregulated immune response and hemostatic abnormalities (embolic events) associated with COVID-19 has recently been observed in the clinical setting. It is not clear if the hemostatic abnormality mechanism is caused by SARS-CoV-2 itself or by the immune response to the virus via endothelial injury.<sup>45</sup> The most common coagulation-related laboratory abnormalities include thrombocytopenia and increased D-dimer levels. Coagulation studies may also demonstrate prolongation in international normalized ratio or prothrombin time and activated partial thromboplastin time. Some patients meet the criteria for disseminated intravascular coagulation.<sup>45</sup> Patients with COVID-19–associated respiratory failure are also at risk for venous thrombotic embolism. It is recommended that patients with COVID-19 receive prophylactic anticoagulation with either daily low-molecular-weight heparin or twice-daily unfractionated heparin dosing, as well as mechanical prevention devices.<sup>45</sup> Embolic events such as pulmonary embolism are thought to contribute to the severity of the respiratory failure associated with COVID-19. These patients also experienced acute coronary syndrome as well as vascular embolisms leading to limb or digit compromise or loss.<sup>45</sup> Some centers are now routinely using therapeutic anticoagulation in patients with elevated D-dimer level, on the basis of preliminary study results from China.<sup>43</sup> Formal trials are ongoing. Although discussion of all clinical or in-depth treatment options is not feasible for this article, there are references that provide that information (Table 2).<sup>45</sup>

### Psychological Impact of COVID-19 General Public

Beyond the physiological impact of the COVID-19 pandemic, there is significant

psychological impact on the general public, on patients, and on health care workers caring for infected patients. In fact, there is an urgent call for mental health care related to the COVID-19 outbreak, in part based on the mental health problems that occurred during and after the 2003 SARS outbreak.<sup>46</sup> This call specifies care for those with COVID-19 as well as contacts, family and friends in isolation, health care professionals caring for infected patients, and the general public.<sup>46</sup>

The impact on the general public includes fear of the consequences of infection, along with boredom, loneliness, and anger experienced during isolation.<sup>46</sup> Reports of high death rates and uncertainty regarding the adequacy of the health care system's response may intensify fear and anxiety. Other stressors related to widespread social distancing may include loss of income and increased home responsibilities. Preexisting abuse and neglect may intensify. The culmination of these effects include increased rates of depression, anxiety, insomnia, substance use, and suicide in the short-term. Long-term impacts include ongoing depression, anxiety, and insomnia, along with the potential for post-traumatic stress symptoms. Compounding the situation is lack of access to mental health care services as a result of overwhelmed medical care facilities and locally enforced social distancing.

Increased suicide rates are predicted after the pandemic, based in part on an increase that occurred after the SARS outbreak in 2009 but also on the intensity of risk factors in the current situation.<sup>47</sup> It is noteworthy that the national suicide rate in the United States was at an all-time high in the most recent data available for 2018.<sup>48</sup> Added to that backdrop is the current increase in economic, psychosocial, and health-associated risk factors, as already discussed, but also including a reported surge in the purchase of firearms, which is independently associated with an increase in the suicide rate.<sup>49</sup> Reger et al<sup>47</sup> also note that the suicide rate typically peaks in late spring and early summer in the northern hemisphere, which increases concern regarding the suicide rate in the months after the pandemic initiation in the United States.

### Impact on Patients With COVID-19

Patients infected with the virus experience the same mental stressors as the general public.

**Table 2: Brief Summary of Additional General Critical Care Interventions<sup>a</sup>**

Topic	Interventions
Infection control	<p>Use of negative-pressure rooms</p> <p>When performing aerosol-generating procedures, fitted N95 masks recommended, as well as additional PPE if available</p> <p>When performing nonaerosol-generating procedures, general surgical mask recommended</p> <p>CDC offers guidance for managing PPE shortages at <a href="https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html">https://www.cdc.gov/coronavirus/2019-ncov/hcp/ppe-strategy/index.html</a></p>
Shock (adults)	<p>Monitor clinical status using dynamic parameters (eg, skin temperature, capillary refill time, serum lactate levels)</p> <p>Use conservative fluid-resuscitation strategy with buffered or balanced crystalloids</p> <p>First-line vasoactive agent: norepinephrine</p> <p>Second-line vasoactive agent: vasopressin or epinephrine</p> <p>Titrate vasoactive agents for MAP goal of 60-65 mm Hg (vs a higher MAP goal)</p> <p>Avoid routine use of colloids</p> <p>If cardiac dysfunction is possible despite fluid resuscitation and vasoactive agents, consider using dobutamine</p> <p>If refractory shock, consider low-dose steroid therapy</p>
Acute kidney injury	<p>Consider initiation of continuous venovenous hemofiltration</p> <p>Discuss dialysate disposal with institutional infection control resources</p>

Abbreviations: CDC, Centers for Disease Control and Prevention; MAP, mean arterial pressure; PPE, personal protective equipment.

<sup>a</sup>Data were derived from Alhazzani et al<sup>40</sup> and Centers for Disease Control and Prevention.

In addition, they must also cope with stress of the illness and the associated treatments, which may worsen their anxiety and mental distress.<sup>46</sup> With contact tracing and quarantine measures, patients may suffer from increased anxiety and guilt regarding the potential for infecting others.<sup>46</sup> These additional stressors, along with the pathophysiological impact of the infection itself, increase the likelihood of long-term mental health effects for patients who survive COVID-19.

An additional concern regarding the psychological well-being of COVID-19 survivors is the effect on their neurologic status. In a study of 214 patients, some of whom had severe COVID-19 and others with nonsevere symptoms, 36% had neurologic manifestations, including acute cardiovascular disease and impaired consciousness.<sup>50</sup> More concerning are preliminary findings of other neurologic damage in survivors. Helms et al<sup>51</sup> reported not only confusion but also a dysexecutive syndrome that includes disattention, disorientation, and poorly organized movements in patients discharged from the hospital after having COVID-19. At this point, it is not clear whether the symptoms of encephalopathy, including prominent agitation and confusion with corticospinal tract signs, are related to a generalized encephalopathy, the effect of

withdrawal of medications, or are specific to the SARS-CoV-2 infection.<sup>51</sup> This additional burden of impaired neurologic functioning further complicates the psychological response to and recovery from SARS-CoV-2 infection.

Based on results of studies of survivors of the SARS outbreak in 2003, patients with COVID-19 will experience continued symptoms of stress. In a study of such survivors 1 year after the 2003 SARS outbreak, patients continued to report increased levels of stress as well as depression, anxiety, and posttraumatic stress symptoms including intrusion, avoidance, and hyperarousal.<sup>52</sup> In addition, 64% of patients reported such levels of distress as to indicate significant negative mental health status.<sup>52</sup> These findings are also consistent with a study of Legionnaires disease in which 15% of survivors had posttraumatic stress disorder 17 months after recovery.<sup>53</sup> Another study of survivors of ARDS showed that 23.9% still had posttraumatic stress disorder at the 8-year follow-up assessment.<sup>54</sup> It is reasonable to predict that survivors of COVID-19-related pneumonia potentially will suffer long-term psychological consequences of this event.

### Impact on Health Care Workers

Health care workers treating patients with COVID-19 face a more complicated picture

in coping psychologically with the pandemic. These health care workers, particularly those working in hospitals, face stress from their increased risk of infection, inadequate protection from contamination, overwork, frustration, fear of spreading the virus to family and friends, and isolation from family when in quarantine or when traveling for work.<sup>46,55</sup> However, what has emerged thus far is an unclear picture of the psychological effect on health care workers, with denial of psychological symptoms, potentially fear of stigmatization, and the importance of altruism as a coping mechanism.

Information from China, where the outbreak began, may be useful in examining this phenomenon. Second Xiangya Hospital of Central South University, in the Hunan Province, the largest top-class tertiary hospital in the region, attempted to provide psychological interventions to medical staff in the midst of the pandemic. These interventions were met with resistance.<sup>56</sup> Despite obvious agitation, unwillingness to rest, and clear signs of psychological distress, nurses refused any psychological help and denied mental health problems. Likewise, physicians declined group and individual help.<sup>56</sup> Additional investigation revealed that medical workers were concerned about their patients and the patients' families. In lieu of psychological interventions, health care workers requested they be given adequate uninterrupted sleep, sufficient protective equipment, and for the mental health workers to use their services to help their patients cope with their illness.<sup>56</sup>

Lai et al<sup>57</sup> conducted a survey of 1257 health care workers (61% nurses, 39% physicians) in 34 hospitals in China, caring for patients with COVID-19. A considerable portion reported symptoms of depression (50%), anxiety (45%), insomnia (34%), and general distress (71%). Frontline workers, women, and those working in the city of Wuhan were more likely to experience all 4 symptoms. The concern with these findings is not only the long-term mental health implications for the individual but the individual's ability to function during the crisis—that is, the impact on their decision-making, attention, and understanding.<sup>55</sup>

Data gathered after the SARS outbreak in 2003 may again be useful in predicting and understanding the impact on health care workers. Wu et al<sup>58</sup> conducted a follow-up study of

549 employees from a hospital that had been affected by the 2003 SARS outbreak. They found a persistence rate of 40% for severe posttraumatic stress symptoms 3 years after the outbreak. Results of other studies indicate symptoms that persist for longer than 6 months after an event are likely to persist over the long term, indicating a poorer prognosis.<sup>58</sup> Researchers also found that having a family member or friend contract SARS was a predictor for higher levels of posttraumatic stress symptoms, as was concern about future outbreaks. More encouragingly, having an altruistic belief system, in which the health care worker accepts the risk of infection in order to do his or her work, provided a buffer and decreased the rate of posttraumatic stress symptoms.<sup>58</sup> It appears that the psychological impact of pandemic events is more complex for health care workers than for the general public.

## Conclusion

Writing this article has been a humbling experience. COVID-19 is a massive assault on our society physically and psychologically; however, the outbreak has confirmed the dedication of all critical care clinicians. This disease has produced many innovations in the care of these critically ill patients. COVID-19 causes an immunopathologic human response that leads to multiple system organ dysfunction. Although health care clinicians are accustomed to dealing with multiple organ failure syndromes, COVID-19 has unique aspects that affect clinical decision-making. The CRS and hypercoagulopathy associated with COVID-19 seem to be responses of more substantial magnitude. The hypoxic respiratory failure presents with significant hypoxemia without the expected initial symptoms.

Clinical experience with this disease is increasing; fortunately, science continues to advance at phenomenal speed. Current guidelines cannot generate evidence to support use of many interventions at this time. Experts seem to agree that successful treatment of COVID-19 will be a sequence of interventions rather than a single agent. Hopefully, with time, we will be able to conquer COVID-19 and successfully improve care of affected patients.

## ACKNOWLEDGMENT

The authors would like to thank Dr Janhavi Athale, a colleague in the Critical Care Medicine Department at the National Institutes of Health, for her willingness to share her expertise in immunology and hematology in reviewing this article.

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