



# Introduction to Critical Care Management of Adults With COVID-19

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COVID-19 can progress to critical illness, including hypoxemic respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, cardiac dysfunction, thromboembolic disease, hepatic and/or renal dysfunction, central nervous system disease, and exacerbation of underlying comorbidities in both adults and children. In addition, multisystem inflammatory syndrome in adults (MIS-A) can occur several weeks or months after SARS-CoV-2 infection, which can lead to critical illness.

Many of the initial recommendations for the management of critically ill adults with COVID-19 in these Guidelines were extrapolated from experience with other causes of sepsis and respiratory failure.<sup>1</sup> However, there is now a rapidly growing body of evidence regarding the management of critically ill patients with COVID-19.

Treating patients with COVID-19 in the intensive care unit (ICU) often requires managing underlying illnesses or COVID-19-related morbidities. As with any patient who is admitted to the ICU, clinicians also need to focus on preventing ICU-related complications.

## Selected Clinical Manifestations of COVID-19 Critical Illness

### ***Inflammatory Response Due to COVID-19 in Adults***

Patients with COVID-19 may express increased levels of pro-inflammatory cytokines and anti-inflammatory cytokines, which has previously been referred to as “cytokine release syndrome” or “cytokine storm.” However, these terms are both imprecise and misnomers, because the magnitude of cytokine elevation in many patients with COVID-19 is modest compared to that in patients with many other critical illnesses, such as sepsis and ARDS.<sup>2,3</sup> In addition, some patients with elevated cytokine levels have no specific pathology that can be attributed to the elevated levels.

Patients with COVID-19 and severe pulmonary involvement often manifest extrapulmonary disease and exhibit laboratory markers of acute inflammation. Patients with these manifestations of severe pulmonary disease typically progress to critical illness 10 to 12 days after the onset of COVID-19 symptoms.

### ***Multisystem Inflammatory Syndrome in Adults***

There are case reports describing patients who had evidence of acute or recent SARS-CoV-2 infection (confirmed by a nucleic acid amplification test [NAAT] or an antigen or antibody test) with minimal respiratory symptoms but with laboratory markers of severe inflammation (e.g., elevated levels of C-reactive protein [CRP], ferritin, D-dimer, cardiac enzymes, liver enzymes, and creatinine) and various other symptoms, including fever and shock. These patients also had signs of cardiovascular, gastrointestinal, dermatologic, and neurologic disease. This constellation of signs and symptoms has been designated MIS-A.<sup>4</sup> To date, most adults with MIS-A have survived. This syndrome is similar to multisystem inflammatory syndrome in children (MIS-C), which is much more well described.

The current case definition for MIS-A from the [Centers for Disease Control and Prevention](#) states that patients must be aged  $\geq 21$  years, be hospitalized for  $\geq 24$  hours or have an illness that results in death, and meet the clinical and laboratory criteria outlined below. The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition).

## Clinical Criteria

Patients must have a subjective or documented fever ( $\geq 38.0^{\circ}\text{C}$ ) for  $\geq 24$  hours prior to hospitalization or within the first 3 days of hospitalization and at least 3 of the following clinical criteria, which must have occurred prior to hospitalization or within the first 3 days of hospitalization. At least 1 must be a primary clinical criterion.

- Primary clinical criteria:
  - Severe cardiac illness. This includes myocarditis; pericarditis; coronary artery dilatation/aneurysm; or new-onset right or left ventricular dysfunction (left ventricular ejection fraction  $< 50\%$ ), second- or third-degree atrioventricular block, or ventricular tachycardia. Cardiac arrest alone does not meet this criterion.
  - Rash **AND** nonpurulent conjunctivitis
- Secondary clinical criteria:
  - New-onset neurologic signs and symptoms. These include encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome).
  - Shock or hypotension that are not attributable to medical therapy (e.g., sedation, renal replacement therapy)
  - Abdominal pain, vomiting, or diarrhea
  - Thrombocytopenia (platelet count  $< 150,000$  cells/ $\mu\text{L}$ )

## Laboratory Criteria

- The presence of laboratory evidence of inflammation **AND** SARS-CoV-2 infection
- Elevated levels of at least 2 of the following:
  - CRP
  - Ferritin
  - Interleukin (IL)-6
  - Erythrocyte sedimentation rate
  - Procalcitonin
- A positive SARS-CoV-2 test result for current or recent infection using a reverse transcription polymerase chain reaction, serology, or antigen test

These criteria must be met by the end of Day 3 of hospitalization, where the date of hospital admission is Day 0.

Because there is no specific diagnostic test for MIS-A, diagnosis of this inflammatory syndrome is one of exclusion after other causes (e.g., bacterial sepsis) have been eliminated. Although there are currently no controlled clinical trial data in patients with MIS-A to guide treatment of the syndrome, case reports have described the use of intravenous immunoglobulin, corticosteroids, or anti-IL-1 receptor antagonist therapy.<sup>5-7</sup>

## ***COVID-19-Induced Cardiac Dysfunction, Including Myocarditis***

The published literature describes cardiac injury or dysfunction in up to 24% of adults who are hospitalized with COVID-19.<sup>8</sup> COVID-19 may be associated with an array of cardiovascular

complications, including acute coronary syndrome, myocarditis, stress (Takotsubo) cardiomyopathy, arrhythmias, and thromboembolic disease.<sup>9</sup>

### ***Thromboembolic Events and COVID-19***

Critically ill adults with COVID-19 have been observed to have a prothrombotic state and higher rates of venous thromboembolic disease. In some studies, thromboemboli have been diagnosed even in patients who received chemical prophylaxis with heparinoids.<sup>10-12</sup> Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.<sup>13</sup> Some authors have called for routine surveillance of ICU patients for venous thromboembolism.<sup>14</sup> See [Antithrombotic Therapy in Patients With COVID-19](#) for a more detailed discussion.

### ***Renal and Hepatic Dysfunction Due to COVID-19***

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in adults with severe COVID-19.<sup>15</sup> In a 2020 multicenter cohort study of critically ill adults in the United States, 20.6% of patients developed acute kidney injury (AKI) that was treated with renal replacement therapy (RRT).<sup>16</sup> In a cohort of critically ill adults in Brazil, the development of an AKI that required RRT was associated with poor prognosis.<sup>17</sup>

### ***Other Intensive Care Unit-Related Complications***

When treating patients with COVID-19, clinicians also need to minimize the risk of conventional ICU complications. Patients who are critically ill with COVID-19 are at risk for nosocomial infections, such as ventilator-associated pneumonia, hospital-acquired pneumonia, catheter-related bloodstream infections, and other complications of critical illness care.

Critically ill patients with COVID-19 may also experience prolonged delirium and/or encephalopathy. The risk factors that are associated with delirium include the use of mechanical ventilation, restraints, benzodiazepines, opioids, vasopressors, and antipsychotics.<sup>18,19</sup> Neurological manifestations of COVID-19 have been described in a significant proportion of hospitalized patients and are more frequent in patients with severe disease.<sup>20</sup> Autopsy studies have reported both macrovascular and microvascular thrombosis with evidence of hypoxic ischemia.<sup>21</sup> Adequate management of critically ill patients with COVID-19 includes paying careful attention to best sedation practices and monitoring for stroke.

## **Important Considerations in the Care of Critically Ill Patients With COVID-19**

### ***Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Comorbidities***

All ICU patients should be routinely monitored for drug-drug interactions. The potential for drug-drug interactions between investigational medications or medications that are used off-label to treat COVID-19 and concurrent drugs should be considered.

### ***Sedation Management in Adults With COVID-19***

International guidelines provide recommendations on the prevention, detection, and treatment of pain, sedation, and delirium in ICU patients.<sup>22,23</sup> Sedation management strategies, such as maintaining a light level of sedation (when appropriate) and minimizing sedative exposure, have shortened the duration of mechanical ventilation and the length of stay in the ICU for patients without COVID-19.<sup>24,25</sup>

The Society of Critical Care Medicine's (SCCM) ICU Liberation Campaign promotes the ICU Liberation Bundle (A-F) to improve post-ICU patient outcomes. The A-F Bundle includes the following elements:

- A. Assess, prevent, and manage pain;
- B. Both spontaneous awakening and breathing trials;
- C. Choice of analgesia and sedation;
- D. Delirium: assess, prevent, and manage;
- E. Early mobility and exercise; *and*
- F. Family engagement and empowerment.

The A-F Bundle also provides frontline staff with practical application strategies for each element.<sup>26</sup> The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients.<sup>27</sup> Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of SCCM's [PADIS guidelines](#). This puts patients at additional risk for ICU and post-ICU complications.

### ***Post-Intensive Care Syndrome***

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.<sup>28</sup> Patients with PICS may present with varying levels of impairment, including profound muscle weakness (ICU-acquired weakness); problems with thinking and judgment (cognitive dysfunction); and mental health problems, such as problems sleeping, post-traumatic stress disorder (PTSD), depression, and anxiety. ICU-acquired weakness affects 33% of all patients who receive mechanical ventilation, 50% of patients with sepsis, and  $\leq 50\%$  of patients who remain in the ICU for  $\geq 1$  week.<sup>29-31</sup> Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.<sup>32-34</sup> About 50% of ICU survivors do not return to work within 1 year after discharge.<sup>35</sup> Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In 1 study, a third of family members who had major decision-making roles experienced mental health problems, such as depression, anxiety, and PTSD.<sup>36</sup>

Some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.<sup>37</sup> Although specific therapies for COVID-19-induced PICS are not yet available, physicians should maintain a high index of suspicion for cognitive impairment and other related problems in survivors of severe or critical COVID-19 illness.

### ***Advance Care Planning and Goals of Care***

The advance care plans and the goals of care for all critically ill patients must be assessed at hospital admission and regularly thereafter. This is an essential element of care for all patients. Information on palliative care for patients with COVID-19 can be found on the [National Coalition for Hospice and Palliative Care website](#).

To guide shared decision making in cases of serious illness, advance care planning should include identifying existing advance directives that outline a patient's preferences and values. Values and care

preferences should be discussed, documented, and revisited regularly for patients with or without prior directives. Specialty palliative care teams can facilitate communication between clinicians and surrogate decision makers, support frontline clinicians, and provide direct patient care services when needed.

Surrogate decision makers should be identified for all critically ill patients with COVID-19 at hospital admission. Infection-control policies for COVID-19 often create communication barriers for surrogate decision makers, and most surrogates will not be physically present when discussing treatment options with clinicians. Many decision-making discussions will occur via telecommunication.

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