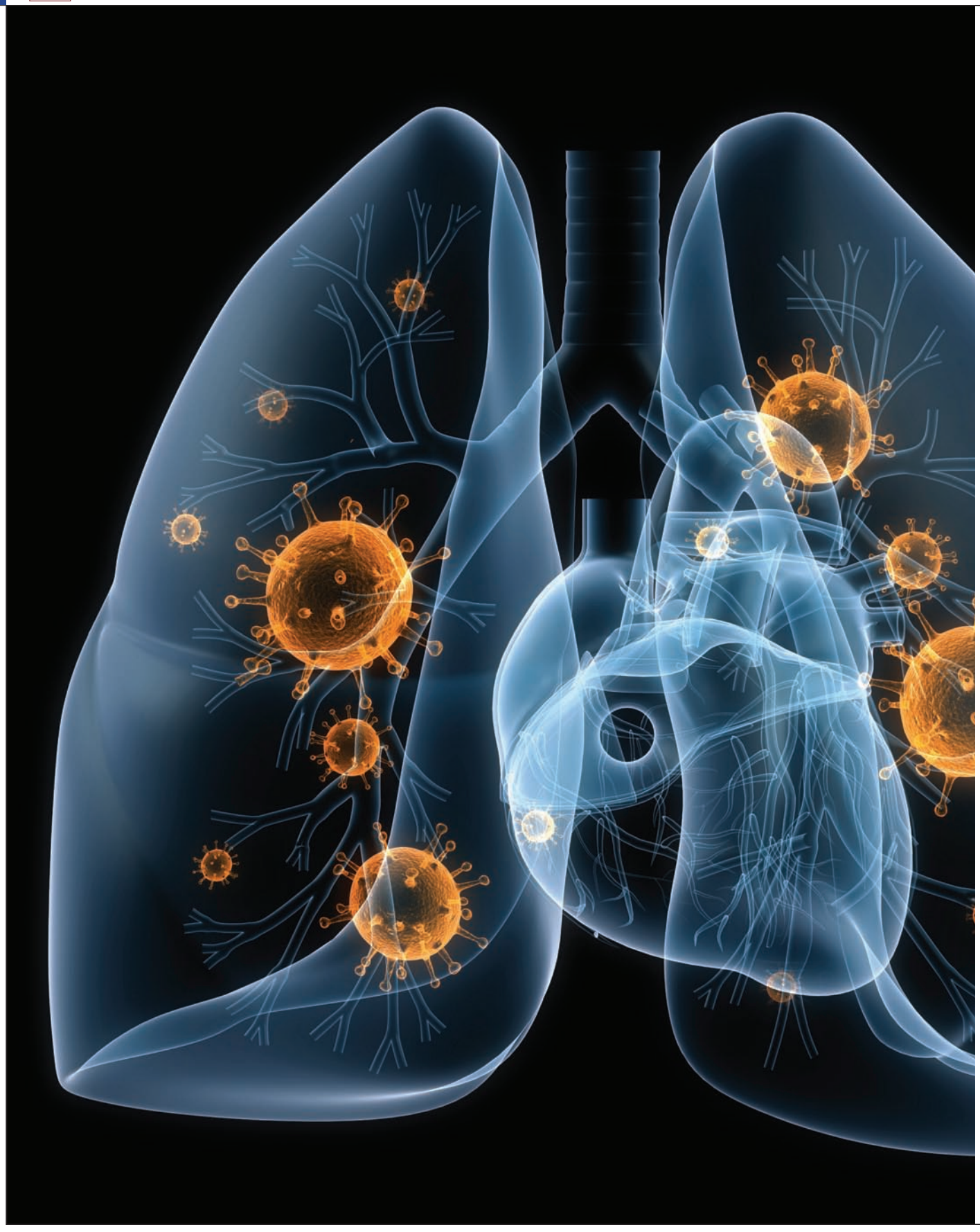

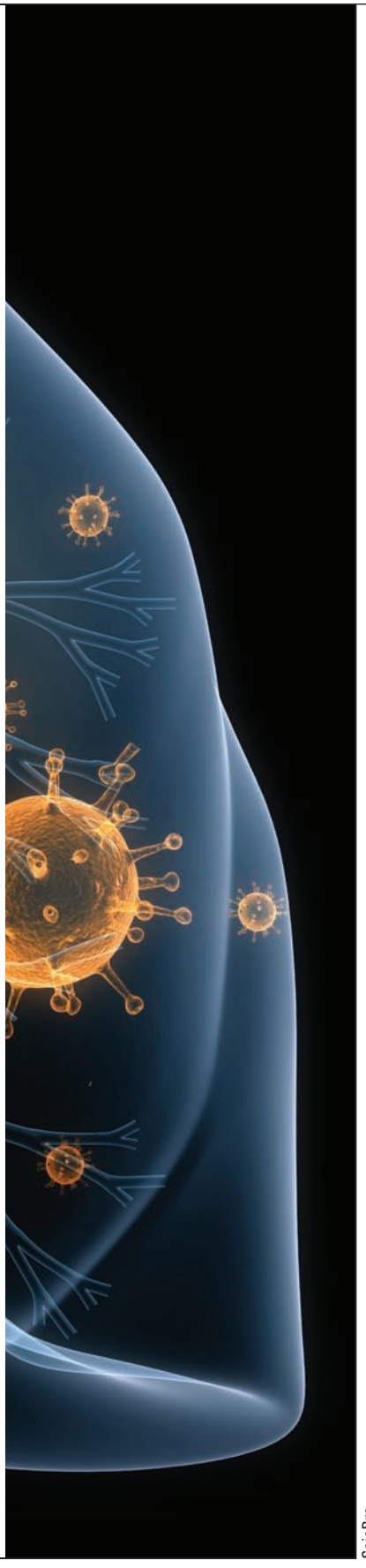
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COVID-19 pneumonia: What APRNs should know

Abstract: *COVID-19-associated pneumonia is a complex acute care diagnosis that requires careful evaluation and management. This article includes pertinent recommendations for management of acutely ill patients with COVID-19 pneumonia.*

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Mr. E, a 55-year-old Hispanic man, presented to the ED with shortness of breath. His symptoms started 4 days prior with a cough, sore throat, and fever of 101° F (38.3° C). Mr. E's primary care provider sent him to the ED. His vital signs during the triage process included temperature of 101.3° F (38.5° C), heart rate of 92 beats/minute, respiratory rate of 24 breaths per minute, BP of 135/85, and oxygen saturation of 94% on room air. His medical history included hypertension, type 2 diabetes mellitus, and gastroesophageal reflux disease. Mr. E's medications included losartan, metformin, and omeprazole. He reported no food or drug allergies, no recent travel, and no sick contacts. Mr. E was alert and oriented and his heart sounds were normal with no murmur; his lung sounds were diminished in both bases, otherwise clear to auscultation. Mr. E's physical exam was significant for a dry cough. He denied nausea, vomiting, diarrhea, abdominal pain, loss of smell or taste, and headaches but complained of intermittent myalgia—especially in the evenings.

Prior to 2019, the differential diagnosis based on the above presentation and symptoms would have included community-acquired pneumonia, pulmonary embolism, influenza, coronavirus, rhinovirus (common cold), and acute coronary syndrome. Unfortunately, the scenario described above became quite frequent in 2020. Regardless of the causative pathogen or mechanism, pneumonia was a common and manageable acute care diagnosis until COVID-19 originated in late 2019/early 2020. Currently, for patients presenting with the above symptoms, the leading differential diagnosis would be COVID-19. It is important to note that the increased prevalence of COVID-19-associated pneumonia speaks volumes when excluding alternative etiology. With the recent increase in frequency and severity of this disease process, it is important to exclude the diagnosis of COVID-19 first; it has become a diagnosis of inclusion rather than a diagnosis of exclusion. During circumstances of overloaded healthcare systems, Mr. E would likely be tested for COVID-19 and sent home to quarantine and self-monitor for deterioration in oxygenation and worsening symptoms. The biggest challenge with COVID-19-related pneumonia is that patients can deteriorate rapidly despite having minimal symptoms at onset. The chances of the patient presenting back to healthcare institutions after

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deteriorating at home are quite high. Once deterioration occurs, morbidity and mortality trend upward, and often, it becomes a futile situation. The goal of this article is to briefly present the management of COVID-19 pneumonia via acute care advanced practice registered nurses (APRNs) with the collaboration of pharmacy partners and supported by the best-available evidence.

Overview and management

Primary viral pneumonias caused by influenza have been in existence prior to the appearance of COVID-19 pneumonia cases. Challenges related to the management of COVID-19 pneumonia are multifold; novelty, severity, limited resource availability, and contagious nature as well as the speed of progression are critical factors that have overwhelmed healthcare systems.

The worst consequences of COVID-19-associated pneumonias have been seen in older adults and in patients with multiple comorbidities.[1] Factors associated with severe disease requiring mechanical ventilation and increased morbidity and mortality include advanced age, poor baseline health, presence of comorbidities, and racial/ethnic minority status.[2-5]

The severity of pneumonitis that initiates the cascade of acute respiratory distress syndrome (ARDS) of COVID-19 has been at the forefront of the associated morbidity and mortality.[1] Preliminary data on the need for hospitalizations and mechanical ventilation are not conclusive. Richardson et al. reported that 20% of a total 5,700 patients in their sample from New York required mechanical ventilation.[2] In a small study by Arentz et al. (N = 21) in Washington, 71% of those admitted to the ICU required mechanical ventilation.[3] Of course, these studies cannot be compared, but both offer some insight into the problem. By the end of the study period of Richardson et al.'s trial, 24.5% of patients requiring mechanical ventilation had died and a large percentage was still hospitalized.[2]

The definition of severe COVID-19 pneumonia has been outlined by the World Health Organization (WHO) as signs or symptoms of pneumonia such as fever, cough, and shortness of breath, along with tachypnea, respiratory distress, or hypoxia on room air; presence of ARDS is classified as critical disease.[6,7] Chest radiography generally demonstrates evidence of pneumonia and/or ARDS. Exclusion of alternative diagnoses is necessary.[6,7]

According to the WHO, testing for viral RNA with nucleic acid amplification testing, such as reverse transcriptase polymerase chain reaction (RT-PCR), is the recommended diagnostic test for suspected cases of COVID-19.[7] If the test is negative in a patient for whom there is high clinical suspicion of the disease, repeat testing should be considered. SARS-CoV-2 RT-PCR is also considered the gold standard diagnostic test for COVID-19 by the National Institutes of Health (NIH).[8]

Since COVID-19-pneumonia has been known to progress rapidly, it is important to identify patients at risk for deterioration. Although high-quality evidence is currently not available, it is typically recommended to monitor for increased levels of D-dimer (greater than 1,000 ng/mL), C-reactive protein (CRP greater than 100 mg/L), lactate dehydrogenase (greater than 245 U/L), troponin (greater than two times the upper limit), ferritin (greater than 500 mcg/L), and creatine phosphokinase (greater than two times the normal range), as these may be associated with severe disease. A decreased absolute lymphocyte count (less than $0.8x10^9$/L) has also been linked to severe cases.[9-12] Electrolytes and blood urea nitrogen/creatinine should also be monitored to identify kidney function deterioration. In addition to clinical monitoring for vital signs and oxygenation, hospitalized patients should also receive chest radiographs as indicated and ECG to monitor for QT prolongation. Patients with COVID-19 have heightened risk for cardiac arrythmias due to hypoxemia, electrolyte abnormalities, and multiple medications that can further increase the risk for cardiac arrythmias.[3]

Severe hypoxemia and oxygenation difficulties have been the cornerstone of the challenges associated with morbidity and mortality of COVID-19-pneumonia and ARDS. Extensive damage to the alveoli and large quantities of proinflammatory cytokines causing a cytokine storm have been implicated in the severity of illness in many patients who succumb to this disease.[13,14] Pathophysiology can include interstitial and intra-alveolar edema from the inflammatory response and increased vascular permeability and fibroblast proliferation in alveolar spaces and septa.[13,15,16]

Oxygenation via high-flow nasal cannula (HFNC), noninvasive ventilation, and invasive ventilation are the strategies to support the oxygenation needs of patients with COVID-19-associated pneumonia experiencing hypoxemic respiratory failure on conventional supplemental oxygen.[8,17,18] Preference for HFNC over noninvasive positive pressure ventilation is cited in the Society of Critical Care Medicine (SCCM)'s Surviving Sepsis Campaign Guidelines on the Management of Adults

with COVID-19 in the ICU: First Update.[17] Further, close monitoring for worsening respiratory status and early endotracheal intubation is stressed as well.[17] Therefore, it is imperative to employ strategies for clinical evaluation as well as utilization of objective data to identify patients in need of early endotracheal intubation and mechanical ventilation. For those patients requiring mechanical ventilation with moderate to severe ARDS, high positive end-expiratory pressure (PEEP) over low PEEP is preferred.[17] Close monitoring for barotrauma for patients on high PEEP is important.[17] A strong recommendation for maintaining the oxygen saturation no higher than 96% is also a cornerstone of the SCCM guidelines based on the risk associated with oxygen saturation of higher than 96% while using supplemental oxygen as well as noninvasive and invasive ventilation.[17] Prone positioning with invasive ventilation in patients with moderate-severe ARDS has a mortality benefit and is recommended by the SCCM.[4,8,17] A short trial of inhaled pulmonary vasodilator is also suggested in select patients with COVID-19 who have severe ARDS.[17] Extracorporeal membrane oxygenation can be used for select patients who do not demonstrate improvement with traditional modalities, and this strategy may be beneficial.[19]

Shock related to COVID-19 should be managed to support hemodynamics. Conservative fluid strategy over liberal fluid strategy is recommended for patients with COVID-19 pneumonia with ARDS.[17] Vasopressor support should be applied as it would in septic shock management.[8,19] Monitoring patients for acute kidney injury, acute cardiac injury, cardiac arrythmias, as well as hypercoagulability-related complications is also warranted.

Infection control is key in preventing spread of the virus to healthcare workers as well as other patients and family members. An N95 or higher-level respirator, gown, gloves, and eye protection should be worn by healthcare workers entering the room of a patient with COVID-19.[8,20] Use of a negative-pressure room during aerosol-generating procedures is recommended.[6,17,20]

Pharmacotherapy

APRNs managing the care of patients with COVID-19 pneumonia are faced with unprecedented challenges while navigating the rapidly expanding body of literature. In the last year, researchers raced to identify potential therapies based on theoretical benefits, in vitro studies, or animal model data.[21] Despite tremendous research efforts, currently, few randomized trials are available in the published literature to guide therapeutic decisions, and a limited number of agents have been granted FDA emergency use authorization (EUA) for use to treat COVID-19. At this time, three general medication classes have emerged as primary treatment strategies for COVID-19 pneumonia: antivirals, immunomodulatory agents, and anticoagulation (see *Primary pharmacotherapy for COVID-19 pneumonia*).[8,22] These considerations vary greatly from the treatment of bacterial pneumonia, a disease state in which the standard of care is shaped by years of clinical experience and research.

It is now known that the clinical course of a patient infected with SARS-CoV-2 follows two distinct phases: a viral infection and replication phase and an inflammatory phase. Remdesivir, a nucleotide analogue prodrug that interrupts viral replication, is the most pertinent agent with antiviral activity.[23] Remdesivir was approved by the FDA in October 2020 for the treatment of COVID-19 requiring hospitalization in adults and children age 12 and older weighing at least 40 kg.[24] Results from the Adaptive COVID-19 Treatment Trial (ACTT-1) revealed remdesivir decreased time to recovery from 15 to 10 days compared with placebo.[25] However, these results contrasted from the interim results from the WHO's Solidarity trial, which demonstrated no difference in mortality compared with placebo.[26] There is a lack of consensus regarding the optimal place in therapy of this agent among major organizations, as these studies differed in study design and clinical outcomes. Remdesivir has been associated with renal and hepatic dysfunction and should be avoided in patients with severe impairments.[23]

Several immunomodulatory and anti-inflammatory agents have been proposed as therapeutic modalities. These agents can benefit patients in the inflammatory phase of their disease by mitigating the development of the cytokine storm phenomenon, which can result in multiorgan failure and death.[27] Some agents that gained significant international attention initially have not been found to be beneficial, such as hydroxychloroquine.[28] However, corticosteroids, which exert a broad-spectrum anti-inflammatory effect, demonstrated impressive results in randomized trials that have led to widespread implementation globally.[28,29] In the Randomised Evaluation of COVID-19 Therapy trial, 6 mg per day of dexamethasone for up to 10 days led to a decreased mortality in patients receiving invasive mechanical ventilation and those receiving oxygen without invasive ventilation but offered no benefit for patients not receiving oxygen.[27,29]

Primary pharmacotherapy for COVID-19 pneumonia*

Medication class	Medication	Indications	Side notes
Antivirals[8,23-25]	Remdesivir[8,23-25]	Patients with hypoxia requiring supplemental oxygen. Add dexamethasone with clinical deterioration and increased oxygen requirements[8]	Avoid remdesivir in patients with severe renal or hepatic dysfunction
Immuno-modulatory agents[8,27,28,30,31]	Dexamethasone[8,17,27] (corticosteroid)	Severely ill patients requiring higher concentration of oxygen and those on mechanical ventilation[8,17,27]	Recommended for up to 10 days
	Either tocilizumab^ (interleukin-6 inhibitor) or baricitinib^ (Janus kinase inhibitor) in combination with dexamethasone or dexamethasone+ remdesivir [8,28,30,31]	Severely ill patients with decompensation[8†]	- Tocilizumab: Investigational use - Baricitinib: under Emergency Use Authorization for use in combination with remdesivir[33]
Anticoagulants[7,8,17]	Prophylactic doses[7,8,17]	Hospitalized patients	Standard of care
	Empiric therapeutic doses	Severely ill patients with rapidly increasing D-dimer	Not currently recommended but being advocated for
Monoclonal antibodies[8,33]	Bamlanivimab+Etesevimab[8,33]	Outpatients with mild-moderate disease at high risk of progression	Not for hospitalized patients
	Casirivimab+Imdevimab[8,33]	Outpatients with mild-moderate disease at high risk of progression	Not for hospitalized patients
	Sotrovimab[33]	Outpatients with mild-moderate disease at high risk of progression	Not for hospitalized patients

*Information based on evidence available at the time of writing. Not a complete list of all recommendations and clinical considerations. Refer to relevant guidelines.
^NIH guideline recommends against use of baricitinib in combination with tocilizumab for COVID-19 treatment[8]
†baricitinib in combination with remdesivir is recommended if corticosteroids cannot be used[8]

Other targeted immunomodulatory agents are also being used in some institutions, such as inhibitors of the cytokines interleukin (IL)-6 (tocilizumab) and IL-1 (anakinra), and Janus kinase inhibitors (baricitinib).[8,27] Of note, some have demonstrated inconsistent results in trials and some have insufficient data. Although early studies of tocilizumab produced conflicting results, these studies were limited by heterogenous study designs and patient populations, as well as constantly evolving standards of care. Recently, two major studies provide support of tocilizumab in hospitalized patients requiring noninvasive or invasive ventilation.[8,30,31] The REMAP-CAP trial was an international, multifactorial, adaptive platform randomized trial of IL-6 inhibitors in hospitalized patients within 24 hours of requiring invasive or noninvasive ventilation or an I.V. vasopressor or inotrope in the ICU.[30] Importantly, the vast majority of patients received concurrent corticosteroids, which reflects the current standard of care. Compared with placebo, these patients experienced more organ support-free days (10 days for tocilizumab, 11 days for sarilumab, and 0 days for placebo) and reduced mortality.[30] These results were confirmed in the RECOVERY trial.[31] This study evaluated tocilizumab in patients with an elevated CRP of at least 75 mg/L and hypoxia and also demonstrated improved survival.[31]

It is important to note that these immunomodulatory therapies have not yet been compared with each other in clinical trials or studied in combination, and more randomized controlled studies in peer-reviewed publications are necessary to better understand their place in therapy in relation to each other.

Anticoagulation is another important aspect in the management of COVID-19. Early autopsy reports

demonstrated extensive vascular microthrombi within the pulmonary circulation of severely ill patients with COVID-19, which may contribute to the profound hypoxia these patients experience.[22,32] In addition, various studies highlighted higher-than-expected rates of arterial and venous thrombosis in patients with COVID-19, even weeks to months after their diagnosis.[8] Patients should receive standard prophylactic doses of anticoagulants while hospitalized.[7,8,17] Although not currently recommended, many institutions advocate for higher than prophylactic doses of anticoagulation for hospitalized patients especially those with significantly elevated or rapidly increasing D-dimer levels. More studies are anxiously awaited to further clarify whether certain patient populations may benefit from higher-dose prophylactic or empiric therapeutic anticoagulation in COVID-19 pneumonia.

Other agents have been granted an EUA via the FDA, such as the combination of bamlanivimab plus etesevimab, or casirivimab plus imdevimab.[33] These agents are monoclonal antibody cocktails that were rapidly developed as other agents to fight COVID-19. However, these agents should only be used in patients with mild to moderate COVID-19 who are at high risk of progression to severe COVID-19 or hospitalization and do not have a role for patients admitted to the hospital due to COVID-19.[8] Many other medications continue to be proposed and studied at a record pace, including agents under development as well as agents currently approved for other indications that are being repurposed for COVID-19. It is imperative that all APRNs caring for patients with COVID-19 pneumonia remain vigilant in providing evidence-based care and modifying treatment protocols according to the results of high-quality clinical trials.

In patients with severe ARDS, supportive care strategies are recommended that mimic recommendations for non-COVID-19 ARDS.[8] Specifically, in addition to lung protective ventilation strategies and prone positioning, patients should receive adequate sedation to allow for safe delivery of ventilation strategies. Although lighter levels of sedation are generally recommended when appropriate, sedation and analgesia requirements in critically ill patients with COVID-19 may be higher than expected.[8,34] This phenomenon may be explained by an increased incidence of ICU delirium in this population, which may be the result of encephalopathy presenting as delirium.[34] Other contributing factors include less personalized attention, staff shortages, and less family support at the bedside.[34] For patients with moderate to severe ARDS, intermittent, as-needed administration of neuromuscular blocking agents is recommended.[17] Those with persistent ventilator dyssynchrony despite optimal ventilator settings may require continuous administration of neuromuscular blocking agents for up to 48 hours.[8,17] Pulmonary vasodilators, such as inhaled epoprostenol, can also be considered as a rescue therapy for refractory hypoxia.[8,17]

Conclusion

Management of COVID-19 pneumonia is complex due to ARDS resulting from this phenomenon. Supportive care to manage hemodynamics and to optimize oxygenation are imperative for improving outcomes in patients with COVID-19 pneumonia. Even though much more is known now than at its onset in 2019, much work is needed in identifying evidence-based strategies for prevention, early identification, and treatment. APRNs managing patients diagnosed with COVID-19 pneumonia must stay up-to-date with the guidelines from the SCCM, the Infectious Diseases Society of America, the WHO, and the CDC.

Disclaimer: The information presented in this article is based on evidence available at the time of writing. Given the novelty of the situation, information is subject to change and may be different by the time of publication. Additionally, this article is not inclusive of all considerations of management of patients with COVID-19 pneumonia. Readers are encouraged to consult relevant guidelines.

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