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The COVID-19 Patient in the Surgical Intensive Care Unit

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Critical care management
• Multiple organ system failure • Respiratory failure • ARDS

KEY POINTS

- The COVID-19 pandemic continues to surge around the globe. Nonintensive care–trained surgeons may be called on to deploy into the critical care unit to care for these complex patients.
- Acute respiratory failure is the most common manifestation of severe COVID-19 infection.
- COVID 19 may be considered an endothelial disease, causing pathologic changes in the brain, heart, lungs, gastrointestinal tract, and kidneys.
- Our understanding of the pathophysiology and treatment of COVID-19 in the critical care setting continues to evolve at a rapid pace.

Coronaviruses, a name derived from their crownlike morphology observed on electron microscope, have been described in literature for over 70 years.[1] They are enveloped, positive single-stranded RNA viruses. These viruses are known to bind to host cells' membrane via a spike protein that facilitates fusion between the virus and host cell. On entry into the cell, their genome is replicated and packaged for delivery to other cells.[1,2]

Coronaviruses are known to cause a variety of symptoms. Many are nonspecific, including fever, cough, and generalized fatigue. They are often responsible for upper and lower respiratory tract infections that can vary from mild to severe, with acute hypoxic respiratory failure and acute respiratory distress syndrome (ARDS) being known sequalae of these respiratory infections.[1,3,4] Enteric, central nervous system (CNS), renal, cardiac, and hematologic diseases can also develop as a result of coronaviruses.[5]

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Within the last 2 decades, multiple variants have been responsible for widespread outbreaks of primarily respiratory infections, including SARS-CoV and MERS-CoV in 2003 and 2012, respectively.[2,3]

In 2019, reports of a new variant called SARS-CoV-2 began circulating, and its resulting disease was named COVID-19.[6] By March 2020, the World Health Organization declared this infection a global pandemic.[7] At the time of this submission, COVID-19 infected more than 230 million people, of which approximately 4.7 million have died.[8] Despite other counties having larger populations, the United States accounts for the greatest number of deaths (more than 43 million).[8]

Because the number of patients with COVID-19 has surged, noncritical care–trained and even junior physicians have been redeployed from their normal area of practice into the intensive care unit (ICU) to mange patients with this complex disease.[9–11] Organizations such as the Society for Critical Care Medicine,[12] The American Thoracic Society,[13] and universities[14] have rushed to fill this educational and experience gap with "just-in-time" training.

There is a high likelihood that surgical intensivists and noncritical care–trained surgeons may be called up to provide critical care for patients who would typically be cared for in a medical ICU. The purpose of this article, therefore, is to provide an overview of the pathophysiology, disease manifestations, and treatment options for patients with COVID-19 admitted to a surgical ICU. To accomplish this, an organ-based, systematic approach will be used. Despite the importance of long-term complications of this infection,[15] the primary focus of this article is critical care.

It is important for the reader to understand that the concepts and strategies presented here are based on the best available current information. Given the rapid evolution of our understanding of this complex disease, updated recommendations may occur between manuscript submission and publication.

THE NEUROLOGIC SYSTEM

During the COVID-19 epidemic, one of the first known neurologic changes was anosmia, leading to a worry in otherwise asymptomatic individuals of an upcoming worse symptomatic infection. With ongoing publications, additional neurologic manifestations have been identified and are still being reported. Anosmia, encephalopathy, and stroke were the most common neurologic syndromes associated with SARS-CoV-2 infection.[16] Dizziness, fatigue, headache, nausea, and confusion have also been reported. Postinfectious complications of acute demyelinating encephalomyelitis, generalized myoclonus, acute transverse myelitis, Guillain–Barré syndromes, and variants have been reported.[17] With the vast array of symptoms reported in lethal and nonlethal COVID-19 infections, an infection with the SARS-CoV-2 virus must be included in the differential diagnosis. Imaging studies of patients with anosmia and COVID-19 revealed hyperintensity and swelling of the olfactory bulb, consistent with inflammation.[18] Biopsy samples of anosmic patients showed SARS-CoV-2 infection in the olfactory epithelium with associated local inflammation.[18]

Theories behind the mechanism of SARS-CoV-2 to cause neurologic changes are ongoing. Entry into the CNS may be due to a "trojan horse" theory, where the SARS-CoV-2 virus directly attaches to inflammatory cells such as lymphocytes, granulocytes, and monocytes, which all express angiotensin-converting enzyme 2 (ACE2). The virus is then picked up by the lungs and transported throughout the body.[19] The virus is then either deposited into the CNS or targets vascular endothelial cells in the CNS causing coagulopathy and vascular endothelial cell dysfunction, with resulting small vessel occlusions and microhemorrhages contributing to subtle neurologic

and neuropsychiatric changes.[20] Postmortem studies on cerebral pathology show that the virus can directly cross the blood-brain barrier, directly infiltrating astrocytes and microglia.[21] With the ACE2 receptor widely expressed in brain microvascular and endothelial cells, the SARS-CoV-2 spike protein can directly bind to the receptor and either damage the blood brain barrier or induce a cytokine storm causing inflammation and neuronal damage.[22,23] The subsequent neurologic changes may also be secondary due to direct retrograde travel of the SARS-CoV-2 virus up the axons to reach the CNS.[24]

The long-term sequalae of COVID-19 infections are needing continued evaluation. With the exaggerated response of the CNS to infection leading to meningitis, encephalitis, and meningoencephalitis, continued neurologic manifestations are likely to be associated with a COVID-19 infection if otherwise unexplained.[25] A high proportion of patients with COVID-19 in the ICU develop delirium, suggesting microvascular and inflammatory pathologies to cause neurologic changes.[26] The long recovery of anosmic patients points toward long-term neurologic changes. The more severely affected patients with strokes, microvascular changes, and brain damage may have ongoing chronic issues, and further studies will elucidate associations with the COVID-19 pandemic.

THE CARDIAC SYSTEM

There is an emerging body of evidence to show that cardiac involvement is not uncommon among patients with COVID-19.[27–29] The range of cardiac manifestations of the COVID-19 disease is quite broad and requires a high degree of suspicion in order to diagnose and adequately treat the cardiac manifestations of COVID-19. Here, the authors briefly summarize the proposed pathophysiology of COVID-19 cardiac involvement, discuss the range of cardiac manifestations of the SARS-CoV-2 virus, and briefly discuss potential treatment options relevant to the surgeon caring for patients with COVID-19.

Cardiac Pathophysiology

As described in the pulmonary section of this publication, the SARS-CoV-2 virus binds to ACE2 receptors in type 1 and type 2 pneumocytes as well as other ACE2-expressing cell types, then subsequently enter those ACE2-expressing cells.[30] The ACE2 receptor is found in high amounts in pericytes within adult human hearts, indicating that the heart itself is susceptible to infection by the SARS-CoV-2 virus.[31,32] Indeed, there is evidence to suggest that COVID-19 causes viral myocarditis via direct myocardial cell injury.[33] Compared with patients who have no underlying comorbidities, patients with cardiovascular disease, diabetes, chronic obstructive pulmonary disease, hypertension, and cancer have been shown to have a higher incidence of severe/fatal COVID-19 disease. It has been shown that patients with conditions that result in high levels of activation of the renin-angiotensin system, such as heart failure, hypertension, and atherosclerosis, have higher expression of ACE2 receptors on their cardiac pericytes, possibly predisposing them to more severe manifestations of cardiac disease.[31,32]

In addition to direct infection, COVID-19 is known to cause a systemic inflammatory response in severe disease states, which results in high levels of circulating cytokines that cause injury to a host of tissues, including the reticuloendothelial system as well as cardiomyocytes.[27–30] Endothelial dysfunction is a well-established mechanism of myocardial ischemia and dysfunction, and damage to the endothelial system caused by this cytokine storm may result in increased metabolic demand and decreased

cellular perfusion to the stressed myocardium, depressing cardiac systolic function and inducing myocardial ischemia. The systemic inflammation/endothelial dysregulation seen in COVID-19 has also been linked to plaque rupture and acute coronary syndromes in patients with underlying coronary artery disease.[28,34]

Patients with COVID-19 are also at risk of secondary cardiac complications. Medications used to treat COVID, such as steroids, antivirals, and other immunologic drugs, can have cardiotoxic effects. All patients with severe illness, including patients with COVID-19, are at risk for electrolyte disturbances that may trigger arrythmias. Given the interaction of the SARS-CoV-2 virus with the renin-angiotensin-aldosterone *system* system, hypokalemia is of particular concern and is well known to increase susceptibility to a variety of arrythmias.[28,35]

Cardiac Manifestations and Treatments

Acute coronary syndrome

There have been some studies that have shown an association between COVID-19 and acute coronary syndrome (ACS).[36,37] In some case series, patients presented with classic ST-segment elevation myocardial infarction (STEMI) symptoms without prior COVID-19 symptoms, suggesting that their ACS was not caused by severe systemic inflammation.[38] The pathophysiology of how COVID-19 may lead to ACS is still uncertain; however, it seems to involve endothelial damage with resultant subendocardial microthrombi (in the case of nonepicardial obstruction) or systemic inflammation leading to plaque rupture or coronary spasm (in the case of epicardial coronary vessel obstruction).[39]

The treatment of ACS in the setting of COVID-19 illness is similar to the algorithm for ACS from any other cause. In the case of STEMI presentation, early cardiac catheter laboratory activation and coronary angiography is essential. A thorough workup including electrocardiogram, cardiac biomarkers, coagulation studies, and possibly echocardiography all may be indicated. In patients with demand-induced cardiac ischemia (type II NSTEMI), treatment should focus on optimizing myocardial oxygen delivery and reducing myocardial oxygen demand by treating the underlying disease process. Referral to centers capable of angiography/percutaneous coronary intervention is essential for patients with any history of coronary artery disease who have severe COVID-19 features.

Heart failure

Multiple studies that have emerged over the last 18 months have described a link between COVID-19 and new-onset heart failure. Studies have shown that among patients with severe COVID-19, 23% to 33% of patients developed new-onset cardiomyopathy, depressed ejection fraction, or cardiogenic shock.[40–42]

In some of the early studies out of Wuhan, China, nearly 50% of the patients who died of COVID-19 developed heart failure.[42] COVID-19 is well known to cause hypoxia and acute lung injury, resulting in significant pulmonary hypertension, and this can lead to development of right heart failure, and the clinician caring for COVID-19 patient must maintain a high degree of suspicion for developing right ventricular failure.

Workup for potential COVID-19–induced heart failure consists of obtaining a congestive heart failure peptide, troponin biomarkers, transthoracic or transesophageal echocardiography, and in some cases cardiac MRI. For patients with suspected right ventricular failure, hemodynamic monitoring via a pulmonary arterial catheter may be indicated.

Treatment of COVID-19–induced heart failure is similar to that of other types of acute heart failure. Limiting preload as well as reducing afterload, particularly in

patients with right heart failure, is essential. Inotropic agents such as epinephrine or dobutamine can be used to increase the contractile function of the myocardium. In patients with right ventricular failure, particularly due to pulmonary hypertension, milrinone seems to be an effective medication at reducing the pulmonary vasoconstriction while significantly increasing the contractile force of the right ventricle. Inhaled vasodilators such as epoprostenol may also be used to reduce the afterload experienced by the right heart. In severe cases, venoarterial extracorporeal membranous oxygenation (ECMO) may be used to provide both hemodynamic and ventilatory support; however, the indications for initiation of VA-ECMO in patients with COVID-19 are highly individualized and beyond the scope of this publication.

Arrythmia/sudden cardiac death

As described earlier, COVID-19 can cause injury to the heart via several mechanisms, including hypoxia, exacerbation of underlying coronary artery disease, direct cellular damage, and systemic inflammation.[36] All types of cardiac injury can induce an arrythmia within the cardiac conduction system. Patients with COVID-19 are particularly prone to deviations in serum potassium levels due to the interaction of the SARS-CoV-2 virus with the renin-angiotensin-aldosterone pathway.[36]

Various types of arrhythmias have been seen in patients with COVID-19, including high-grade atrioventricular blocks, supraventricular tachyarrythmias, and ventricular tachyarrhythmias.[43] It is imperative that clinicians be mindful of the proclivity for patients with COVID-19 to develop arrythmias, particularly in light of the various QT-prolonging medications that may be given to these patients. Cardiac monitoring with telemetry is essential, and regular assessment of the QTc is imperative.

Treatment of these cardiac arrythmias is no different than if they were to arise in a non–COVID-19 patient. Correction of underlying electrolyte derangements, hemodynamic stabilization, and possibly correction of the arrythmia are all warranted.

Thromboembolism/hypercoagulability

Studies have shown that COVID-19 tends to cause a hypercoagulable state in affected patients.[44] The hypercoagulability is likely caused by a combination of severe systemic inflammation, extensive cytokine release, and endothelial damage, all of which produce additive effects in patients with baseline hypercoagulable comorbidities.[45,46] This hypercoagulable state can lead to multiple pulmonary emboli and subsequent right heart failure and can even lead to microthrombi within the myocardium itself, presenting as an acute STEMI.[44]

There is some early evidence to suggest that early anticoagulation is of benefit in patients with COVID-19.[47] Retrospective studies have suggested that use of enoxaparin or other low-molecular-weight heparins was associated with increased survival in patients with clinical coagulopathy or elevated D-dimer.[48] Recent studies are still mixed with regard to the optimal anticoagulation strategy. One recent study showed no benefit to intermediate-dose enoxaparin (1 mg/kg daily) compared with standard prophylactic dosing (40 mg daily),[49] whereas other observational studies have suggested a mortality benefit to treatment-dose anticoagulation, particularly in patients with more severe disease.[47] The European Heart Journal has proposed an algorithmic approach to the level of anticoagulation based on severity of disease, serum biomarkers, level of care, and presence of thromboembolism on point-of-care ultrasound.[50] In general, more severe cases of COVID-19 seem to necessitate higher levels of anticoagulation; however, the optimal strategy is still yet to be determined.[51,52]

THE PULMONARY SYSTEM

Pathophysiology of COVID-19–Induced Lung Injury

The role of angiotensin-converting enzyme 2 in the lung

ACE2 has been repeatedly demonstrated to be the host receptor of SARS-CoV-2. ACE2 is an essential component of the renin-angiotensin system (RAS). ACE is the enzyme responsible for catalyzing the conversion of angiotensin I to angiotensin II, which promotes the synthesis of aldosterone, vasoconstriction, and increased sodium reabsorption in the kidney's nephrons.[2,53] Meanwhile, ACE2 inactivates angiotensin II and cleaves it into angiotensin I. Therefore, ACE2 provides a counterbalance to ACE, thus regulating the effect of the RAS system on the body. ACE/ACE2 also play a role in the inflammation process, and a careful balance between proinflammatory and antiinflammatory pathways is maintained in healthy patients.[53] In contrast to its proinflammatory counterpart, the antiinflammatory responsibility of ACE2 provides necessary protection to the lung against injury.

In the lungs, ACE2 is expressed in the alveolar epithelial cells. It has mainly been detected in type II alveolar cells. The role of these cells includes surfactant production, movement of water across the epithelium, and restoration and regeneration of damaged lung alveolar epithelium.[54] The lung's substantial surface area and large concentration of ACE2 contribute to the lung's significant vulnerability to COVID-19 in comparison to other organs.

Sars-CoV-2 and receptor binding

The interaction between ACE2 and SARS-CoV-2 has been thoroughly investigated. Research into its binding kinetics show a 10 to 20x higher receptor preference for SARS-CoV-2 in comparison to SARS-CoV-1, which may provide insight into why the virus is so easily transmissible.[53] Similar to how other coronaviruses bind to host cells, it is thought the spike protein of SARS-CoV-2 interacts with ACE2, which initiates the release of viral RNA into the epithelial cells.[55]

Hyperinflammation, the cytokine storm, and fibrosis

Once SARS-CoV-2 binds to ACE2, the virus is replicated and cell apoptosis occurs. Consequently, proinflammatory cytokines are released, which upregulate the inflammatory reaction.[55,56] ACE2 is also downregulated, reducing its antiinflammatory capabilities in the lung. This local emission of cytokines, including tumor necrosis factor alpha, interleukin-1 (IL-1), IL-6, IL-8, and *monocyte chemoattractant protein 1*, is then released into systemic circulation. Homeostasis is progressively lost between proinflammatory and antiinflammatory pathways, which leads to widespread release of cytokines and damage to tissues, including the lung.[55,56] In addition, this cytokine storm also produces a collapse of T cells, and cellular-mediated adaptive immune response fails to produce meaningful protection for patients with COVID-19.[55] In the lung, ARDS is a common sequela after this widespread cytokine storm. Downregulation of ACE2 also leads to an increase in angiotensin II. Angiotensin II is proinflammatory and profibrotic, thus contributing to the development of pulmonary fibrosis.

Pathophysiologic Modulators of COVID-19 Severity in the Lungs

Age

Age is the strongest predictor of severity of COVID-19 disease in patients.[53] One study found that patients with COVID-19 younger than 60 years had a 1.38% mortality rate compared with 6.4% for those aged 60 years and older[57]; this may occur for a few reasons. First, ACE2 expression may increase with age, thus creating a greater susceptibility to COVID-19 in the elderly population.[58] Moreover, it is widely acknowledged

that innate and adaptive immune responses weaken with aging, predisposing older populations to a more severe COVID-19 infection.

OBESITY

Evidence supports an association between obesity and higher mortality from COVID-19, with obese patients having 3.4-fold greater odds of developing severe COVID-19.[59] ACE2 is widely expressed in adipocytes. As a result, when SARS-CoV-2 binds to ACE2, the adipocytes release proinflammatory mediators that are then released systemically andaffect other organs, including the lungs. Furthermore, it is thought that ACE2 also downregulates pulmonary fibrosis, thus pulmonary fibrosis tends to develop more often in obese patients.[59,60]

Diabetes Mellitus

Diabetic patients have a 2.95x higher risk of mortality from COVID-19 in comparison with patients without diabetes, and they are more likely to develop a severe COVID-19 infection, with an odds ratio of 2.58 compared with nondiabetic patients.[61] Diabetes mellitus is known to involve a constant low-grade proinflammatory state that consequently compounds inflammatory damage on the lungs. Furthermore, hyperglycemia associated with diabetes mellitus promotes dysregulation of innate and adaptive immune responses. Studies have demonstrated a higher prevalence of ARDS in patients with hyperglycemia.[62]

Immunosuppression

Intuitively immunosuppression would be predicted to increase the risk of developing COVID-19. A recent metanalysis did not show any significant increased risk of COVID-19 infection for chronically immunosuppressed patients.[63] The pathophysiology of COVID-19 involves upregulation of proinflammatory pathways. However, with immunosuppressed patients, immunosuppressants modulate the proinflammatory pathways, which then limits the damage that COVID-19 can have on the lungs and the rest of the body. Although, the investigators did admit that their study may have been susceptible to selection bias, as immunosuppressed patients are more likely to adhere to precautions to limit transmission of SARS-CoV-2.[63]

MANAGEMENT OF COVID-19–INDUCED RESPIRATORY FAILURE

Management of acute respiratory failure due to COVID-19 may be thought of as a therapeutic pyramid,[64] staring with conventional oxygen therapy, progressing to high-flow nasal canula, noninvasive mechanical ventilation, intubation, conventional and if needed advanced mechanical ventilation, and ultimately extracorporeal membrane oxygenation.

High-Flow Nasal Cannula and Noninvasive Mechanical Ventilation

High-flow nasal cannula has emerged as treatment of hypoxic respiratory failure due to COVID-19. Although data continue to evolve, this technique seems to be an effective alternative to noninvasive mechanical ventilation, delay or reduce the need for intubation, and reduce mortality.[65,66]

Noninvasive ventilation, including continuous positive airway pressure and bilevel positive airway pressure, has been successfully and safely used to treat moderate-to-severe acute hypoxemic respiratory failure and ARDS.[67,68] Preventing the need for invasive ventilation and its potential complications, including ventilator associated pneumonia and lung injury, is undoubtedly beneficial. In patients with acute

hypoxemic respiratory failure treated with noninvasive ventilation, only 28% of patients required eventual endotracheal intubation.[67] Meanwhile, noninvasive ventilation was successful in 48.1% of patients with ARDS secondary to COVID-19.[68]

Invasive Mechanical Ventilation

The next step up in the management of respiratory failure in patients with COVID-19 is intubation and conventional mechanical ventilation. Similar to other types of patients with ARDS, it is recommended that patients with CVOID-19 undergo traditional lung protective ventilation, as outlined in the ARDS net study published in 2000.[69] This type of ventilation is characterized by low tidal volume (4–8 mL/kg), high and individualized positive end-expiratoty pressure, and plateau pressures less than 30 cm H_2O.[69–71] It should be noted that although this approach is commonly used, some data suggest that it may also have detrimental effects.[72]

Extracorporeal Membrane Oxygenation

Should invasive mechanical ventilation failure occur, ECMO may be an option. However, evidence on the utilization of ECMO to treat the pulmonary complications of COVID-19 is inconclusive. A recent meta-analysis of 25 peer-reviewed journal articles on the subject showed that further research needs to be performed to determine the effectiveness of ECMO on COVID-19 pulmonary complications because a most of the available research are case reports or case series.[73]

Venovenous (VV) ECMO is the most common form of ECMO used in reported studies. Indications that were used to initiate VV-ECMO included refractory hypoxia and hypercapnia or single organ failure. Meanwhile, venoarterial ECMO was very rarely used in reported studies. Indications that were used included cardiogenic shock due to cardiac injury.[73] Because of the limited amount of data available, the investigators of the meta-analysis recommended caution with using ECMO in the setting of COVID-19 until studies with larger sample sizes are performed to investigate its efficacy.

FLUID MANAGEMENT IN PATIENTS WITH COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME

In ARDS, regardless of cause, fluid overload can detrimentally affect patients' outcomes, and, consequently, conscientious fluid management is essential. Positive pressure ventilation is known to contribute to pulmonary vasoconstriction, which produces fluid retention and interstitial edema.[70,71] As a result, restrictive fluid management is recommended, as it is associated with greater ventilator-free days.[74] Unfortunately, fluid management in patients with ARDS secondary to COVID-19 has not been thoroughly investigated.

PRONE POSITIONING

Prone positioning has long been used for ARDS and acute hypoxic respiratory failure.[75,76] Over the years, when and how to use this strategy has been refined.[77] Prone positioning has now been implemented as a treatment of COVID-19 respiratory sequelae.

Prone positioning is thought to improve oxygenation through several means. First, lung recruitment and perfusion are optimized. Second, the functional lung size is greatly improved. Third, evidenced on echocardiography, right heart strain is significantly reduced by decreasing overall pulmonary resistance.[70]

For awake, nonintubated patients, it has been demonstrated that simply giving these patients supplemental oxygen in the emergency department and placing them in prone position increases oxygen saturation from a median of 80% to 94%.[78] However, studies have shown that on resupination the increased oxygenation continues in only approximately one-half of patients.[79] Even more, studies have not demonstrated a significant difference in rates of intubation when comparing prone awake patients with supine awake patients, although a delay to intubation has been noted.[80,81] Also, significant changes in 28-day mortality were not evidenced when comparing proned versus supine patients.[81]

Prone positioning has also been used for intubated patients with COVID-19.[82] In ventilated patients, timing of initiating prone positioning is essential. If patients are placed into prone position early in the disease course, then they are less likely to experience in-hospital mortality.[83] Use of early use of the prone position seems to lead to better oxygenation and an earlier pulmonary recovery.

THE ENTERIC SYSTEM

The Gastrointestinal System and Nutrition

Although known primarily as a respiratory ailment, COVID-19 infection has been implicated in the dysfunction of every major organ system, and the gastrointestinal (GI) organs are no exception. An estimated 4% of patients with COVID infection present solely with GI complaints,[84] including diarrhea, abdominal pain, nausea and vomiting, and loss of appetite. Large meta-analyses with thousands of subjects have shown that prevalence of gastrointestinal symptoms among patients with COVID-19 ranged from 10% to 17.6%,[85] and one study found that patients who did present with GI symptoms (nausea, vomiting, or diarrhea) had significantly more severe symptoms of fever, fatigue, and shortness of breath[86] as well as delayed presentation.[87] These gastrointestinal symptoms begin to make sense when examining the pathophysiology of infection; ACE2 is a known cellular attachment receptor for the COVID-19 virion, and transmembrane protease serine 2 (TMPRSS2) has been shown to cleave the spike protein of COVID-19, together facilitating entry into the cell.[88,89] These effects are marked in the lung tissue, whose high expressions of ACE-2 and TMPRSS2 are likely responsible for the characteristic pulmonary symptoms of the disease. High expressions of ACE-2 and TMPRSS2 are also found throughout the gastrointestinal tract, especially in the small intestine and colon,[89] and may be the culprit behind the GI effects of COVID-19.

COVID-19 virions are known to be shed in stool, creating a potential reservoir of infectious virus particle.[90] Seventy percent of those with fecal RNA shedding testing fecal positive after their respiratory specimens cleared the virus,[88] leading to concerns that patients who test negative on a nasopharyngeal swab could still expose others to active disease through fecal-oral transmission. The Centers for Disease Control and Prevention recommends using separate bathrooms for COVID-19–positive patients.[91] COVID has been shown to replicate virus in enterocytes,[85] adding to the concern that endoscopies could be high-risk aerosolizing procedures. All major GI societies have recommended to delay any nonurgent endoscopies during the height of the pandemic.[92] Internationally, upper endoscopy and colonoscopy rates decreased by 85%,[84] concerning for delayed diagnoses or progression of cancer. It has been suggested that alternatives to endoscopy, such as FIT testing for colorectal cancer screening or calprotectin for inflammatory bowel disease (IBD) diagnosis, be used to reduce risk during the pandemic while minimizing harm from delaying endoscopic procedures. Modeling has found that widespread FIT testing would prevent 90% of life

years lost due to cancer diagnosis delay.[84] Coronaviruses are known to be transmittable through a fecal-oral routes; one study in mice found exaggerated symptoms and pathology in infected mice that had been treated with a proton pump inhibitors. This group of mice demonstrated increased pulmonary inflammation histologically,[93] raising questions about proton pump inhibitor usage and infectivity in humans but further research is needed. ACE2 and TMPRSS2 both are key receptors involved in cellular entry of COVID-19 virions; ACE2 is overexpressed in states of bowel inflammation,[94] and TMPRSS2 is overexpressed in the ileal inflammation,[84] possibly increasing the likelihood of cellular entry and infection. Direct absorptive enterocyte injury due to COVID-related inflammation can lead to malnutrition and secretory diarrhea.[87] Malnutrition, whether from enterocyte injury or from poor oral intake during acute illness, can lead to atrophied lymphoid tissue and increased bacterial translocation.[95] Loss of appetite is noted to be common (~26%)[94] during COVID infections with a high prevalence of gustatory dysfunction, which may contribute to this[90]; early enteral nutrition is recommended in patients with COVID by the American and European Societies for Parental and Enteral Nutrition, even in proned patients.[95] There are multiple cytokines released in the course of infection that are known to alter gut microbiota[94]; some patients demonstrate decreased intestinal probiotics[92] and increased opportunistic gut bacteria that have been known to cause bacteremia, changes that were shown to persist even after clearance of COVID-19.[85]

GI bleeding does not seem to be increased among patients with COVID but a study among New York patients with GI bleeds found that they tended to have significantly poorer outcomes during the pandemic, possibly related to patient's reluctance to present to hospital during an outbreak along with an increased threshold to perform endoscopy in the setting of widespread COVID-19.[84]

A special population to consider in the COVID era is patients with IBD. ACE2 expression has been shown to be elevated during active IBD.[94] An analysis of patients on the SECURE-IBD registry found that in patients with IBD, steroid and mesalamine use has been shown to be associated with higher rates of mortality from COVID-19, with almost 20% of patients with COVID who require steroid use for their IBD experiencing ICU admission, mechanical ventilation, or death as part of their clinical course of COVID-19.[84] In contrast, only 2% to 3% of patients on biological monotherapy for their IBD experienced these adverse events.

The Liver

In the setting of patients without preexisting liver disease, COVID-19–associated liver injury tends to be mild in most cases. Elevated aspartate transaminase/alanine aminotransferase has been found to be the most common hepatic manifestation of the disease at an estimated rate of 20% to 30%.[92]. However, Hajifathalian and colleagues[96] reported that an association between risk of ICU admission/mortality and the presence of acute liver injury on admission. Potential mechanisms to explain this process include drug-induced liver injury, direct COVID-induced hepatitis/myositis, and ACE2-mediated binding and damage. ACE2 receptors were found to be high in cholangiocytes,[97] and although normally were low in hepatocytes their expression has been shown to be inducible by hypoxia and inflammation or preexisting liver disease,[98] hypoxic injury, indirect injury due to systemic inflammation and cytokines, ventilator-associated hepatic congestion, and aggravation of preexisting viral hepatitis.[99] Remdesivir has been found in a large trial (n = 1073) to increase liver enzymes[88] with 2.5% and 3.6% of patients in the 5- and 10-day courses, respectively, discontinuing treatment due to these elevated liver enzymes.[100]

Other drugs commonly used in the off-label treatment of COVID-19 such as hydroxychloroquine, corticosteroids, and acetaminophen also have known hepatotoxic potential.[98] Systemic inflammatory response syndrome–induced markers of cholestasis, such as bile duct proliferation, bile plugs, and inflammatory infiltrates, have been found in autopsy studies of patients with COVID.[98] Beyond the frequently encountered mild acute liver injury, COVID-19 can have severe implications for patients with preexisting liver problems. Chronic liver disease was associated with a 60% increased risk of mortality from COVID-19, and frequent hepatic decompensation has been reported among this population during acute infection.[84]

Chronic liver disease can also affect COVID treatment options for patients; for example, patients with decompensated cirrhosis are recommended to not receive remdesivir, one of the only antivirals approved to treat COVID-19.[84]

The pandemic has also affected liver transplant programs around the globe; for prospective transplant candidates, it is recommended that transplant be limited to high MELD score patients or those with high risk of decompensation/hepatocellular carcinoma progression, especially given the decreased number of organs procured during the pandemic.[101] It is also unanimously recommended to continue immunosuppressive therapy in postliver transplant patients throughout the COVID pandemic, given the increased risk for rejection.[101]

The Pancreas

Pancreatic acinar cells do express ACE2 receptors, and it was theorized that this could lead to direct viral-mediated pancreatic damage, but despite several early reports of COVID-associated acute pancreatitis, acute pancreatitis seems to be a rare finding in people infected with COVID. One retrospective study of 63,000 patients with COVID in Spain found an incidence of only 0.07% of acute pancreatitis among these patients.[102] However, patients with COVID were much more likely to be diagnosed with idiopathic pancreatitis versus gallstone or alcoholic pancreatitis (69% compared with 21%), although this was thought to be related to pancreatitis due to widespread multiorgan failure. Many early studies did not use uniform definitions of pancreatitis but instead used elevated serum amylase as an indicator even in the absence of abdominal symptoms.[103] Amylase was found to be elevated in 17.9% of severe COVID cases versus only 1.9% of nonsevere COVID-19 cases, although most of these had no other signs of pancreatitis[104]; elevated amylase is not specific for pancreatitis and could be elevated due to cytokine storm or multiorgan failure that can be seen in severe COVID infection. Lung injury and increased intestinal permeability seen in the setting of COVID infection both could also cause increased serum amylase levels. Pancreatic cancer has been associated with increased ACE2 expression, possibly raising the baseline risk for infection among patients with pancreatic adenocarcinoma.[104] Similar to other cancers, the immunosuppressive effects of chemotherapy can worsen the effects of COVID; one study found a 40% rate of severe adverse events, including death, associated with pancreatic cancer among patients with COVID-19 as opposed to just 8% among those without cancer.[105]

THE RENAL SYSTEM

Acute kidney injury in the setting of COVID-19 may be the result of direct viral injury to the kidney[106] and/or dysfunctions in other organ systems that secondarily affect the kidney.[107] Although exact pathophysiologic mechanisms remain

controversial,[108] the development of acute kidney injury or worsening of chronic kidney disease is associated with a worse prognosis.[109] Treatment approaches used for acute kidney injury in patients with COVID-19 are similar to those used in non–COVID-19 patients.[110]

THE VASCULAR AND HEMATOLOGICAL SYSTEMS

During normal times of health, the vascular endothelium has many roles: immune competence, inflammatory equilibrium, maintaining tight junctional barriers, and aiding in hemodynamic stability. It is well known that the vascular endothelium also plays a significant role in the thrombotic and fibrinolytic pathways. During the COVID-19 epidemic, studies have been able to elucidate many vascular complications associated with infection with this novel virus apart from the known respiratory problems. Thromboembolic complications have been reported affecting not just the vasculature of the lungs[111] but also the brain,[112] heart,[113] and extremities.[114] The incidence of thrombotic complications in the ICU ranges from 16% to 69%.[114] Current clinical data indicate both deep vein thrombosis and pulmonary embolisms are the most frequent thrombotic events.[115,116] The mechanisms by which this occurs is related to the damage caused by virus on endothelial cells and subsequent inflammatory reaction and activation of the coagulation cascade. The vascular endothelial cells have vast expression of ACE2, including alveolar cells of the lung.[117] Entry of the SARS-CoV-2 virus into the endothelial cell occurs by binding of the spike (S) protein to the ACE2 receptors, where the SARS-CoV-2 virus has a nearly 10-fold greater affinity for ACE2 versus its SARS-CoV-1, also known as severe acute respiratory syndrome.[118] This entry into the endothelial cell then triggers activation of the immune system followed by cytokine release and subsequent activation of macrophages. This hyperinflammatory state leads to expression of IL-1, IL-6, damage-associated molecular patterns, and recruitment of macrophages to the infected cells leading to endothelial injury. Damaged endothelial cells increase vascular permeability and activate the coagulation cascade.[119] In patients with COVID-19, this heightened innate immune system creates a prothrombotic state and endothelial cell injury. Injury then leads to plasminogen activator inhibitor-1 upregulation, which inhibits fibrinolysis. Tissue factor is increased, leading to procoagulation, as well as release of von Willebrand factor creating intraluminal thrombus. Studies have demonstrated an increase in fibrinogen levels as well.[120,121] D-dimer levels have been elevated, as well as fibrin degradation products increased.[122,123]

Autopsy reports in patients with COVID-19 revealed increased pulmonary endothelial inclusions and increased capillary microthrombi.[124,125] Questions on how to best treat this hypercoagulative state remain active. An observational study found a lower mortality and risk of intubation in patients with COVID-19 with either therapeutic or prophylactic anticoagulation compared with no anticoagulation.[126] No benefit was seen comparing prophylactic with therapeutic anticoagulation. A recent recommendation for patients with COVID-19 recommends prophylactic low-molecular-weight heparin given for all patients with COVID-19 in the absence of active bleeding, low platelet counts less than 25,000, and fibrinogen levels less than 0.5 g/L.[127]

Other hematologic issues may also occur in patients with COVID-19. Lymphopenia does develop in more than 50% of patients with COVID-19 infection.[128] The O and Rh blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness. However, the reasons why and the significance of this association have yet to be determined.[129]

PHARMACOLOGIC TREATMENTS AND CONVALESCENT PLASMA

Lopinavir-Ritonavir

Lopinavir-ritonavir is a protease inhibitor and nucleoside analogue combination medication primarily used to treat human immunodeficiency virus. It was theorized that its dual antiviral nature would be effective in treating COVID-19. However, a systematic risk-benefit analysis of 7 peer reviewed journal articles did not demonstrate a clear benefit to using this medication for severe COVID-19 infection. Dangerous side effects include prolonged QT interval and inhibitor of cytochrome P450.[130]

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are medications that have multiple antiviral mechanisms, including inhibition of viral entry and release of virus into the cell, along with immunomodularity activities.[130] Despite its increase in popularity in 2020 as a treatment of COVID-19, data are inconclusive in terms of its potential benefit. Dangerous side effects include prolonged QT interval and hypoglycemia.[130–132]

Dexamethasone

Dexamethasone is a corticosteroid that has been used to treat COVID-19. A 10-day course has been demonstrated by multiple studies and trials, including the RECOVERY and CoDEX trials, to have a significant decrease in 28-day mortality, number of ventilator-free days, and incidence of hypoxia.[133,134] As a result, dexamethasone has become standard of care in the treatment of COVID-19.[135] Despite its benefit in the treatment of COVID-19, dexamethasone is also associated with several complications including glaucoma, hyperglycemia, and hypertension.[136]

Remdesivir

Remdesivir is an antiviral nucleoside analogue known to inhibit RNA polymerase that has also been used to treat COVID-19. It has been shown to significantly reduce recovery time and has been associated with higher odds of clinical improvement.[137–140] Side effects are generally mild, but more severe ones include hypotension and cardiac arrythmias.

CONVALESCENT PLASMA

Convalescent plasma treatment of infectious diseases is characterized by immediate immunity through the administration of passive antibodies.[141] A systematic report of 5 studies on convalescent plasma and COVID-19 demonstrated there may be clinical benefit, and it seems to be safe. Almost all patients who were administered convalescent plasma had symptomatic improvement, and zero mortality was reported.[142] However, a recommendation was made for a large multicenter clinical trial to provide stronger evidence. Recommendations for ideal plasma donors include donors who donate 28 days after the onset of symptoms and had fevers for more than 3 days.[143]

SUMMARY

COVID-19 continues to ebb and flow, as waves, across the globe. During times of surge, nonintensive care–trained surgeons may be deployed into a critical care setting, to care for patients who would normally be treated in a medical ICU. Although primarily a pulmonary disease, COVID-19 has many extrapulmonary manifestations. The interaction between different organ systems and COVID-19's effect on each create difficulty in managing these patients. This difficulty is further exacerbated by

our incomplete understanding and constantly evolving guidelines. The authors wish health for our patients and safety for those who provide care at this historically challenging time.

CONFLICT OF INTEREST

None of the authors have any conflicts of interest related to this article.

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