CLINICAL PRACTICE

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Severe Covid-19

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 50-year-old, previously healthy man presents to the emergency department with 2 days of worsening dyspnea. He had fever, cough, and fatigue during the week before presentation. He appears acutely ill. The body temperature is 39.5°C (103°F), heart rate 110 beats per minute, respiratory rate 24 breaths per minute, and blood pressure 130/60 mm Hg. The oxygen saturation is 87% while the patient is breathing ambient air. The white-cell count is 7300 per microliter with lymphopenia. Chest radiography shows patchy bilateral opacities in the lung parenchyma. A reverse-transcriptase–polymerase-chain-reaction assay detects the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in a nasopharyngeal swab. How would you evaluate and manage this case?

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THE CLINICAL PROBLEM

The most common initial symptoms of coronavirus disease 2019 (Covid-19) are cough, fever, fatigue, headache, myalgias, and diarrhea.[1] Severe illness usually begins approximately 1 week after the onset of symptoms. Dyspnea is the most common symptom of severe disease and is often accompanied by hypoxemia[2,3] (Fig. 1). Progressive respiratory failure develops in many patients with severe Covid-19 soon after the onset of dyspnea and hypoxemia. These patients commonly meet the criteria for the acute respiratory distress syndrome (ARDS), which is defined as the acute onset of bilateral infiltrates, severe hypoxemia, and lung edema that is not fully explained by cardiac failure or fluid overload.[4] The majority of patients with severe Covid-19 have lymphopenia,[5] and some have thromboembolic complications[6] as well as disorders of the central or peripheral nervous system.[7] Severe Covid-19 may also lead to acute cardiac, kidney, and liver injury, in addition to cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock.[8,9] These organ failures may be associated with clinical and laboratory signs of inflammation, including high fevers, thrombocytopenia, hyperferritinemia, and elevations in C-reactive protein and interleukin-6.[10]

The diagnosis of Covid-19 can be established on the basis of a suggestive clinical history and the detection of SARS-CoV-2 RNA in respiratory secretions. Chest radiography should be performed and commonly shows bilateral consolidations or ground-glass opacities[11] (Fig. 2).

For epidemiologic purposes, severe Covid-19 in adults is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of less than 300 mm Hg, or infiltrates in more than 50%

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KEY CLINICAL POINTS

EVALUATION AND MANAGEMENT OF SEVERE COVID-19

- Patients with severe coronavirus disease 2019 (Covid-19) may become critically ill with acute respiratory distress syndrome that typically begins approximately 1 week after the onset of symptoms.
- Deciding when a patient with severe Covid-19 should receive endotracheal intubation is an essential component of care.
- After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water and with tidal volumes based on the patient's height.
- Prone positioning is a potential treatment strategy for refractory hypoxemia.
- Thrombosis and renal failure are well-recognized complications of severe Covid-19.
- Dexamethasone has been shown to reduce mortality among hospitalized patients with Covid-19 who require oxygen, particularly those receiving mechanical ventilation.
- Remdesivir was recently approved by the Food and Drug Administration for the treatment of Covid-19 in hospitalized patients, on the basis of randomized trials showing that the drug reduces time to clinical recovery; however, more data are needed to inform its role in treating severe Covid-19.

of the lung field.[12] In a large cohort of symptomatic patients with Covid-19 described early in the pandemic, 81% had mild disease, 14% had severe disease, and 5% became critically ill with organ failure; the mortality in the critically ill group was 49%.[12]

Healthy persons of any age may become critically ill with Covid-19. However, age is the most important risk factor for death or critical illness, and the risk increases with each additional decade.[13] People with chronic health conditions such as cardiovascular disease, diabetes mellitus, immunosuppression, and obesity are more likely to become critically ill from Covid-19. Severe disease is more common among men than among women. The risk is also increased among certain racial and ethnic groups such as Black and Hispanic persons in the United States.[14] The social determinants of health probably have a strong influence on the risk of severe disease.[13] A hallmark of the Covid-19 pandemic is the sudden appearance of an unprecedented number of critically ill patients in a small geographic area.[12] This can overwhelm local health care resources, resulting in shortages of trained staff, ventilators, renal-replacement therapy, and intensive care unit beds.

STRATEGIES

INITIAL STEPS

Patients with severe Covid-19 should be hospitalized for careful monitoring. Given the high risk of nosocomial spread,[3] strict infection-control procedures are needed at all times. If able, the patient should wear a surgical mask to limit the dispersion of infectious droplets.[15] Clinicians should don appropriate personal protective equipment (PPE) as defined by their local infection-prevention program, using particular caution when performing procedures that may increase the generation or dispersion of infectious aerosols. These include endotracheal intubation, extubation, bronchoscopy, airway suctioning, nebulization of medication, the use of high-flow nasal cannulae, noninvasive ventilation, and manual ventilation with a bag-mask device.[16] Current guidelines recommend that clinicians wear gowns, gloves, N95 masks, and eye protection at the least and place patients in negative-pressure rooms whenever possible during aerosol-generating procedures.[17]

Patients with severe Covid-19 have a substantial risk of prolonged critical illness and death. Therefore, at the earliest opportunity, clinicians should partner with patients by reviewing advanced directives, identifying surrogate medical decision makers, and establishing appropriate goals of care. Because infection-control measures during the pandemic may prevent families from visiting seriously ill patients, care teams should develop plans to communicate with patients' families and surrogate decision makers.

BASICS OF RESPIRATORY CARE

Patients should be monitored carefully by direct observation and pulse oximetry. Oxygen should be supplemented by the use of a nasal cannula or Venturi mask to keep the oxygen saturation of hemoglobin between 90 and 96%.[17] Deciding whether or not to intubate is a critical aspect of caring for seriously ill patients with Covid-19. Clinicians must weigh the risks of premature

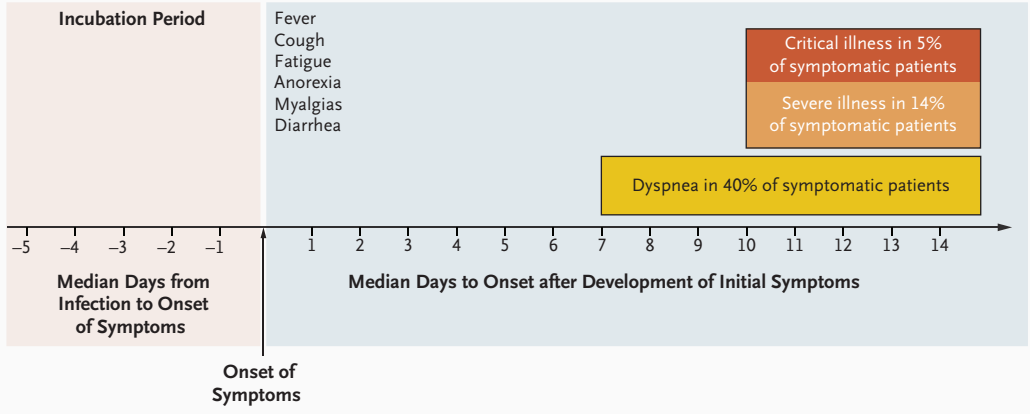

Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

The left border of the colored boxes shows the median time to onset of symptoms and complications. There is wide variation in the duration of symptoms and complications. Adapted from Zhou et al.[2] and the Centers for Disease Control and Prevention.[1]

intubation against the risk of sudden respiratory arrest with a chaotic emergency intubation, which exposes staff to a greater risk of infection. Signs of excessive effort in breathing, hypoxemia that is refractory to oxygen supplementation, and encephalopathy herald impending respiratory arrest and the need for urgent endotracheal intubation and mechanical ventilation. There is no single number or algorithm that determines the need for intubation, and clinicians must consider a variety of factors (Fig. 3A).

If the patient does not require intubation but remains hypoxemic, a high-flow nasal cannula can improve oxygenation and may prevent intubation in selected patients.[17,18] The use of noninvasive positive-pressure ventilation should probably be restricted to patients with Covid-19 who have respiratory insufficiency due to chronic obstructive pulmonary disease, cardiogenic pulmonary edema, or obstructive sleep apnea rather than ARDS. Patients treated with a high-flow nasal cannula or noninvasive ventilation require careful monitoring for deterioration that would indicate the need for invasive mechanical ventilation.[18]

Having awake patients turn to the prone position while they breathe high concentrations of supplemental oxygen may improve oxygenation in patients with severe Covid-19. This approach is supported by data from prospective cohorts describing its use in nonintubated patients with severe hypoxemia.[19] However, whether prone positioning can prevent intubation in patients with severe Covid-19 is unclear. Because it is difficult to provide rescue ventilation to patients who are prone, this position should be avoided in patients whose condition is rapidly deteriorating.

ENDOTRACHEAL INTUBATION

A skilled operator should perform endotracheal intubation in patients with severe Covid-19. The use of unfamiliar PPE, the risk of infection to staff, and the presence of severe hypoxemia in patients all increase the difficulty of intubation. If possible, intubation should be performed after preoxygenation and rapid-sequence induction of sedation and neuromuscular blockade. An antiviral filter should be placed in line with the airway circuit at all times. Video laryngoscopy may allow the operator to have a good view of the airway from a greater distance.[20] However, operators should choose the technique that is most likely to be successful on the first attempt. Continuous-wave capnography is the best method to confirm tracheal intubation.[20] Patients with severe Covid-19 often become hypotensive soon after intubation owing to positive-pressure ventilation and systemic vasodilation from sedatives.[20] Therefore, intravenous fluids and vasopressors should be immediately available at the time of intubation, and careful hemodynamic monitoring is essential.[20]

VENTILATOR MANAGEMENT

It is unclear whether Covid-19 is associated with a distinct form of ARDS that would benefit from

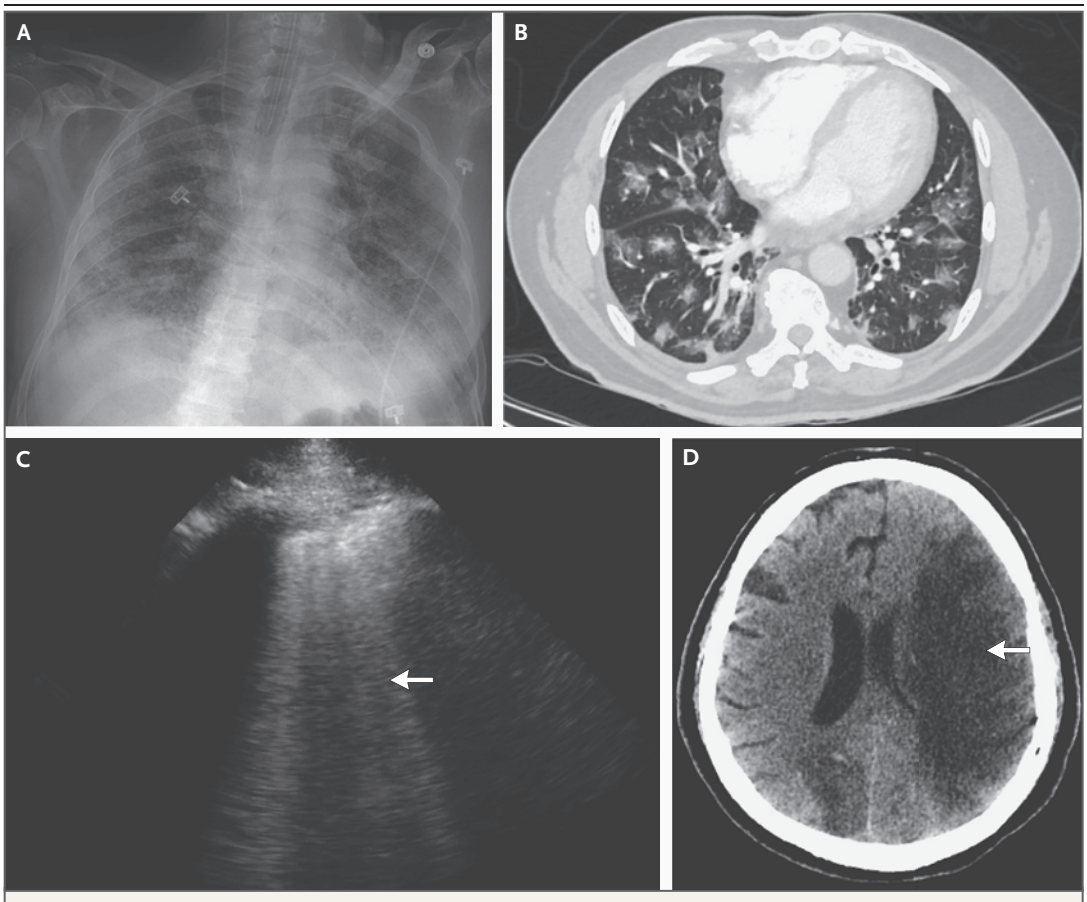

Figure 2. Radiographic and Ultrasonographic Findings of Severe Covid-19.

Chest radiography (Panel A) shows bilateral ground-glass opacities and consolidations. Computed tomography (CT) of the chest (Panel B) shows bilateral ground-glass opacities. Thoracic ultrasonography (Panel C) shows B lines (arrow); this image is courtesy of Dr. Christopher Parkhurst. CT of the head (Panel D) shows left-greater-than-right cerebral infarcts (arrow).

a new strategy of mechanical ventilation. However, most autopsies performed on patients with severe Covid-19 reveal the presence of diffuse alveolar damage, which is the hallmark of ARDS.[21] Moreover, respiratory-system compliance and gas exchange in patients with respiratory failure from severe Covid-19 are similar to those in populations enrolled in previous therapeutic trials for ARDS.[22] Therefore, clinicians should follow the treatment paradigm developed during the past two decades for ARDS (Fig. 3B).[17,18] This strategy aims to prevent ventilator-induced lung injury by avoiding alveolar overdistention, hyperoxia, and cyclical alveolar collapse.

To prevent alveolar overdistention, clinicians should limit both the tidal volume delivered by the ventilator and the maximum pressure in the alveoli at the end of inspiration. To do this, clinicians should set the ventilator to deliver a tidal volume of 6 ml per kilogram of predicted body weight; this approach is termed "lung-protective ventilation." A tidal volume up to 8 ml per kilogram of predicted body weight is allowed if the patient becomes distressed and attempts to take larger tidal volumes. A few times each day, clinicians should initiate a half-second end-inspiratory pause, which allows the pressure in the airway circuit to equilibrate between the patient and the ventilator. The pressure in the airway circuit at the end of the pause — "the plateau pressure" — approximates the alveolar pressure (relative

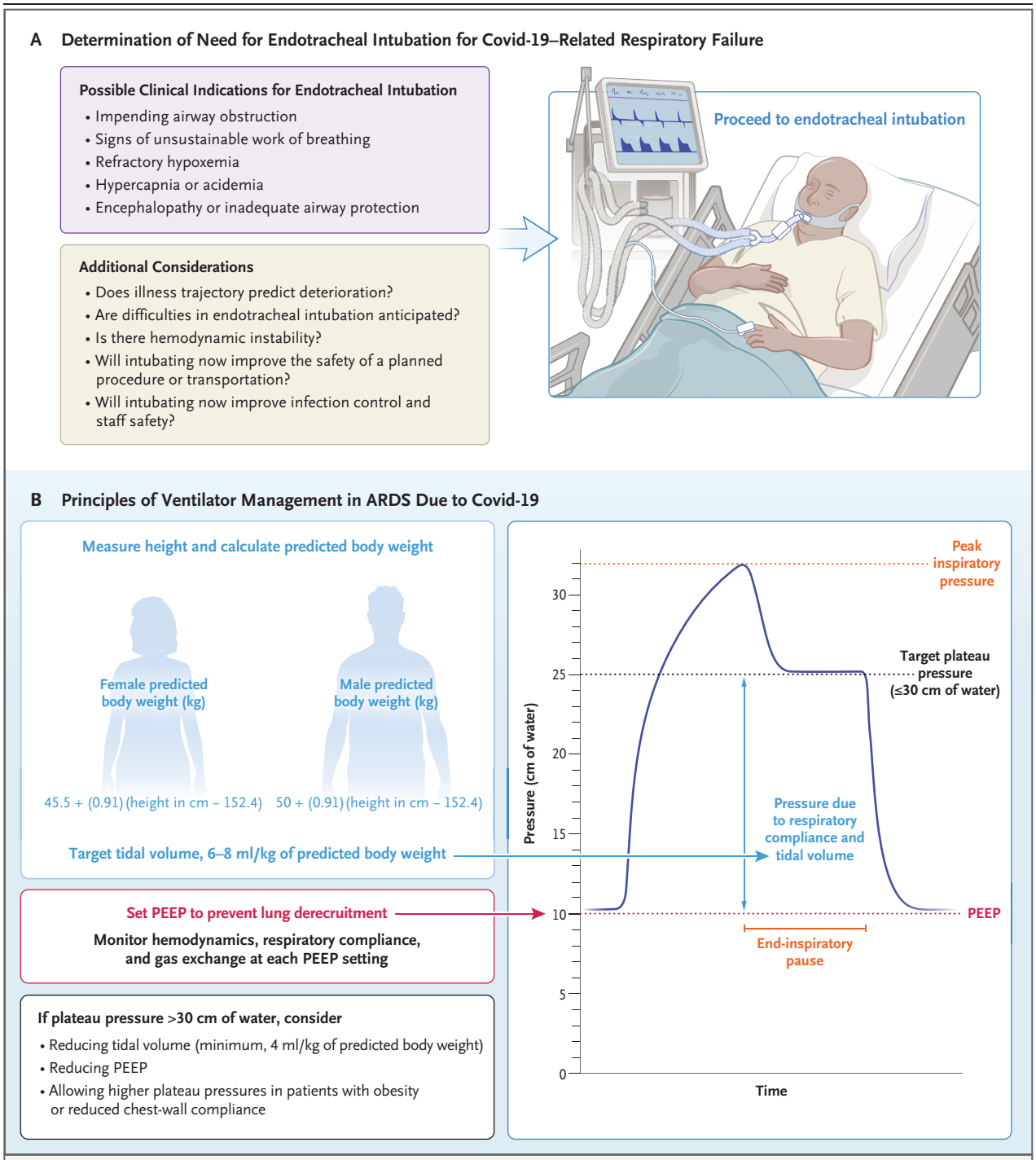

Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.

As shown in Panel A, a life-threatening problem in the purple box or a combination of less severe problems in the purple and tan boxes determines the need for endotracheal intubation. In Panel B, "lung derecruitment" refers to the collapse of alveoli. All pressures are measured in the ventilator circuit and referenced to atmospheric pressure. ARDS denotes acute respiratory distress syndrome, and PEEP positive end-expiratory pressure.

to atmospheric pressure). To prevent alveolar overdistention, the plateau pressure should not exceed 30 cm of water.[23] A higher plateau pressure without the development of ventilator-induced lung injury may be possible in patients with central obesity or noncompliant chest walls.

For patients with Covid-19–related ARDS, setting sufficient positive end-expiratory pressure (PEEP) on the ventilator may prevent alveolar collapse and facilitate the recruitment of unstable lung regions. As a result, PEEP can improve respiratory-system compliance and allow for a reduction in the F_{IO_2}. However, PEEP can reduce venous return to the heart and cause hemodynamic instability. Moreover, excessive PEEP can lead to alveolar overdistention and reduce respiratory-system compliance. No particular method of determining the appropriate level of PEEP has been shown to be superior to other methods.[17]

Sedatives and analgesics should be targeted to prevent pain, distress, and dyspnea. They can also be used to blunt the patient's respiratory drive, which improves patient synchrony with mechanical ventilation. Sedation is especially important in febrile patients with high metabolic rates who are treated with lung-protective ventilation. Neuromuscular blocking agents can be used in deeply sedated patients who continue to use their accessory muscles of ventilation and have refractory hypoxemia.[17] These agents can reduce the work of breathing, which reduces oxygen consumption and carbon dioxide production.[24] Moreover, sedatives and neuromuscular blocking agents may help reduce the risk of lung injury that may occur when patients generate strong spontaneous respiratory efforts.

REFRACTORY HYPOXEMIA

Clinicians should consider prone positioning during mechanical ventilation in patients with refractory hypoxemia (P_{aO_2}:F_{IO_2} of <150 mm Hg during respiration and F_{IO_2} of 0.6 despite appropriate PEEP). In randomized trials involving intubated patients with ARDS (not associated with Covid-19), placing the patient in the prone position for 16 hours per day has improved oxygenation and reduced mortality.[18,25] However, prone positioning of patients requires a team of at least three trained clinicians, all of whom require full PPE.[17] Inhaled pulmonary vasodilators (e.g., inhaled nitric oxide) can also improve oxygenation in refractory respiratory failure, although they do not improve survival in ARDS not associated with Covid-19.[17] Extracorporeal membrane oxygenation (ECMO) is a potential rescue strategy in patients with refractory respiratory failure. Clinicians should carefully balance possible benefits with risks (e.g., bleeding) as well as the resources available during the pandemic.[26]

THERAPY

A large, randomized clinical trial involving more than 6400 hospitalized patients with Covid-19 showed that dexamethasone significantly reduced 30-day mortality (17% reduction); benefit was limited to patients who required oxygen supplementation and appeared greater in patients receiving mechanical ventilation.[27] Consequently, dexamethasone (or potentially other glucocorticoids) is now considered the standard of care for patients with severe Covid-19.

Data from a randomized, placebo-controlled trial involving more than 1000 patients with severe Covid-19 showed that the antiviral agent remdesivir reduced time to clinical recovery; the benefit appeared greatest in patients who were receiving supplemental oxygen but were not intubated.[28] The 29-day mortality in that trial was 11.4% with remdesivir and 15.2% with placebo (hazard ratio for death, 0.73; 95% confidence interval, 0.52 to 1.03). These data support the Food and Drug Administration (FDA) approval of remdesivir for the treatment of hospitalized patients with Covid-19 in October 2020. Recent preliminary results of a large, multinational, open-label, randomized trial did not show a reduction in in-hospital mortality with use of remdesivir.[29] The combination of dexamethasone and remdesivir is increasingly used clinically, but its benefit has not been shown in randomized clinical trials. Tocilizumab, an interleukin-6 inhibitor, did not significantly reduce disease progression[30] or death in small randomized trials involving patients with severe Covid-19.[31,32]

SUPPORTIVE CARE

Patients with Covid-19 often present with volume depletion and receive isotonic-fluid resuscitation. Volume repletion helps maintain blood pressure and cardiac output during intubation and positive-pressure ventilation. After the first few days of mechanical ventilation, the goal should be to avoid hypervolemia.[33] Fever and tachypnea in patients with severe Covid-19 often

increase insensible water loss, and careful attention must be paid to water balance. If the patient is hypotensive, the dose of vasopressor can be adjusted to maintain a mean arterial pressure of 60 to 65 mm Hg.[17] Norepinephrine is the preferred vasopressor. The presence of unexplained hemodynamic instability should prompt consideration of myocardial ischemia, myocarditis, or pulmonary embolism.

In case series, approximately 5% of patients with severe Covid-19 have received renal-replacement therapy[34]; the pathophysiology of the renal failure is currently unclear but is probably multifactorial. Because blood clotting in the circuit is common in patients with severe Covid-19,[6] the efficacy of continuous renal-replacement therapy is uncertain.

Abnormalities of the clotting cascade, such as thrombocytopenia and elevation of D-dimer levels, are common in patients with severe Covid-19 and are associated with increased mortality.[3] If there are no contraindications, patients should receive standard thromboprophylaxis (e.g., subcutaneous low-molecular-weight heparin).[35] Some case series of patients with severe Covid-19 have shown clinically significant thrombosis despite the use of thromboprophylaxis.[6] However, the benefits and risks of the routine use of more intense prophylactic anticoagulation in patients are unknown.[35]

Patients hospitalized with severe Covid-19 are often treated empirically with antibiotics.[3,9] However, bacterial coinfection is rare when immunocompetent patients first present to the hospital.[36] Antibiotics can be discontinued after a short course if signs of bacterial coinfection, such as leukocytosis and focal pulmonary infiltrates, are absent.[18] Although Covid-19 itself can cause prolonged fever,[2] clinicians should be vigilant for nosocomial infections.

Performing cardiopulmonary resuscitation in patients with Covid-19 may expose health care workers to infectious droplets and aerosols. Therefore, all the members of the resuscitation team should wear appropriate PPE before performing rescue ventilation, chest compressions, or defibrillation.[37]

Patients with Covid-19 who are receiving mechanical ventilation should receive appropriate nutrition and care to prevent constipation and injury to the skin and corneas. If the condition of a patient has stabilized, clinicians should attempt to withhold continuous sedation each day.[38] Daily awakening may be challenging because an increase in the work of breathing and the loss of synchrony with mechanical ventilation may result in distress and hypoxemia.

During the Covid-19 pandemic, an overwhelming surge of patients presenting to a hospital may temporarily require the rationing of health care resources. Local guidelines and medical ethics consultation can help clinicians navigate these difficult decisions with patients and their families.

AREAS OF UNCERTAINTY

Despite FDA approval of remdesivir for hospitalized patients with Covid-19, more data are needed to inform the role of this drug in severe Covid-19. Numerous randomized trials of many other candidate therapies, including antivirals, antibodies, and immunomodulating agents, are ongoing (Table 1).

Despite observational studies suggesting benefit of interleukin-6 inhibitors,[53,54] small, randomized clinical trials failed to show consistent benefit.[30-32] Other immunomodulating agents currently being evaluated for severe Covid-19 include passive immunotherapy with convalescent plasma, monoclonal antibodies, immunoglobulins, and interleukin-1 pathway inhibitors.[55] Pending final results of randomized trials, the risks and benefits of these approaches are also unknown. Candidate therapies for Covid-19 warrant evaluation separately in patients with established severe disease and in those with milder illness to determine whether they reduce the risk of progression to severe disease.

GUIDELINES

The recommendations in this article are largely concordant with the guidelines for severe Covid-19 from the American Thoracic Society, the Infectious Diseases Society of America, the National Institutes of Health, and the Surviving Sepsis Campaign.[17,18,56,57]

CONCLUSIONS AND RECOMMENDATIONS

For the patient described in the vignette, an important aspect of care is careful monitoring of

Table 1. Selected Candidate Therapies for Coronavirus Disease 2019 (Covid-19).*

Class	Availability	Rationale	Clinical Data
Antiviral agents			
Hydroxychloroquine	FDA-approved for lupus, malaria, rheumatoid arthritis; FDA emergency-use authorization for certain hospitalized patients with Covid-19 was revoked	In vitro activity against SARS-CoV-2[39]	Randomized, controlled trials showed no benefit in hospitalized patients[40,41]
Lopinavir–ritonavir	FDA-approved for HIV infection	In vitro activity against SARS-CoV-2[42]	Randomized, controlled trials showed no benefit in hospitalized patients[43,44]
Remdesivir	FDA-approved for hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[42,45]	Randomized, placebo-controlled trials showed faster time to recovery with remdesivir in hospitalized patients[28,46]; preliminary results from a large, multinational, open-label randomized trial showed no mortality benefit[29]
Antibodies			
Convalescent plasma	Investigational; FDA emergency-use authorization for hospitalized patients with Covid-19	Use in other viral illnesses, including H1N1 influenza, SARS, and MERS	Small, uncontrolled cohort studies suggested benefit[47,48]; small randomized, controlled trials did not suggest benefit[49,50]; large uncontrolled study showed preliminary safety[51]; additional randomized, controlled trials in progress
Monoclonal antibodies	Investigational; FDA emergency-use authorization for nonhospitalized patients with Covid-19	Use in other viral illnesses, including Ebola and HIV	One randomized clinical trial showed that a single dose of bamlanivimab (LY-CoV555) reduced viral load in outpatients with Covid-19[52]; role in inpatients unclear
Immune-based agents			
BTK inhibitors (acalabrutinib, ibrutinib, rilzabrutinib)	FDA-approved for some hematologic cancers	Immunomodulation-targeting cytokines	Clinical trials in progress
Dexamethasone (and other glucocorticoids)	FDA-approved for multiple indications	Broad immunomodulation	Large randomized, controlled trial showed mortality benefit with dexamethasone in hospitalized patients requiring oxygen[27]
Interleukin-1 inhibitors (anakinra, canakinumab)	FDA-approved for some autoimmune diseases	Immunomodulation; activity in macrophage activation syndrome	Clinical trials in progress
Interleukin-6 inhibitors (sarilumab, siltuximab, tocilizumab)	FDA-approved for some autoimmune diseases and cytokine release syndrome (tocilizumab)	Immunomodulation; activity in cytokine release syndrome	Small randomized, controlled trials have not shown benefit[30-32]; additional clinical trials in progress
JAK inhibitors (baricitinib, ruxolitinib)	FDA-approved for rheumatoid arthritis (baricitinib) and myelofibrosis and polycythemia vera (ruxolitinib); FDA emergency-use authorization for baricitinib in combination with remdesivir for hospitalized patients with Covid-19 requiring oxygen	Broad immunomodulation	Clinical trials in progress

* Selected references are provided for rationale and clinical data. ARDS denotes acute respiratory distress syndrome, BTK Bruton's tyrosine kinase, FDA Food and Drug Administration, HIV human immunodeficiency virus, IND investigational new drug, JAK Janus kinase, MERS Middle East respiratory syndrome, SARS severe acute respiratory syndrome, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

his respiratory status to determine whether endotracheal intubation is appropriate. If mechanical ventilation is initiated, the clinician should adhere to a lung-protective ventilation strategy by limiting the plateau pressure and tidal volumes. Deep sedation with neuromuscular blocking agents and prone positioning should be considered if refractory hypoxemia develops. Prophylactic anticoagulants should be administered to prevent thrombosis. Dexamethasone should be started, because data from a randomized clinical trial show a reduction in mortality. Although more data are needed to inform benefits of treatment with both remdesivir and dexamethasone, we would also give remdesivir given its antiviral mechanism of action and data from randomized clinical trials showing that it shortens time to clinical recovery. Rigorous adherence to infection-control practices is essential at all times. Given the high risk of complications from severe Covid-19, clinicians should work with patients and families to establish appropriate goals of care at the earliest possible time.

Given the uncertainties regarding effective treatment, clinicians should discuss available clinical trials with patients. In addition, clinicians should discuss the value of autopsies with the families of patients who do not survive.

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