CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Severe Covid-19

David A. Berlin, M.D., Roy M. Gulick, M.D., M.P.H., and Fernando J. Martinez, M.D.

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?

From Weill Cornell Medicine, New York. Address reprint requests to Dr. Berlin at Weill Cornell Medicine, Division of Pulmonary and Critical Care, 1300 York Ave., New York, NY 10065, or at berlind@med.cornell.edu.

This article was published on May 15, 2020, at NEJM.org.

DOI: 10.1056/NEJMcp2009575

Copyright © 2020 Massachusetts Medical Society.

THE CLINICAL PROBLEM

The most common initial symptoms of coronavirus disease 2019 (Covid-19) are fever, cough, fatigue, anorexia, 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). A striking feature of Covid-19 is the rapid progression of respiratory failure soon after the onset of dyspnea and hypoxemia. Patients with severe Covid-19 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 disorders of the central or peripheral nervous system.[6] Severe Covid-19 may also lead to acute cardiac, kidney, and liver injury, in addition to cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock.[7-9] These organ failures may be associated with a cytokine release syndrome characterized by high fevers, thrombocytopenia, hyperferritinemia, and elevation of other inflammatory markers.[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%

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

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.
- Data are needed from randomized trials to inform the benefits and risks of antiviral or immunomodulatory therapies for severe Covid-19; as of mid-May 2020, no agents had been approved by the Food and Drug Administration for treatment of these patients.
- Preliminary data from a randomized, placebo-controlled trial involving patients with severe Covid-19 suggest that the investigational antiviral remdesivir shortens time to recovery.

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% of the lung field within 24 to 48 hours from the onset of symptoms.[12] In a large cohort of patients with Covid-19, 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] The majority of critically ill patients with Covid-19 receive prolonged mechanical ventilation.[8]

People with chronic health conditions such as cardiovascular disease, diabetes mellitus, and obesity are more likely to become critically ill from Covid-19. The incidence of critical illness is also higher among men than among women and higher among persons older than 65 years of age than among younger persons.[13-15] However, healthy persons of any age can become critically ill with Covid-19.[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.[12,14] 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.[16] 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 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.[17] 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.[18]

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%.[18] 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 intubation against the risk of sudden respiratory

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

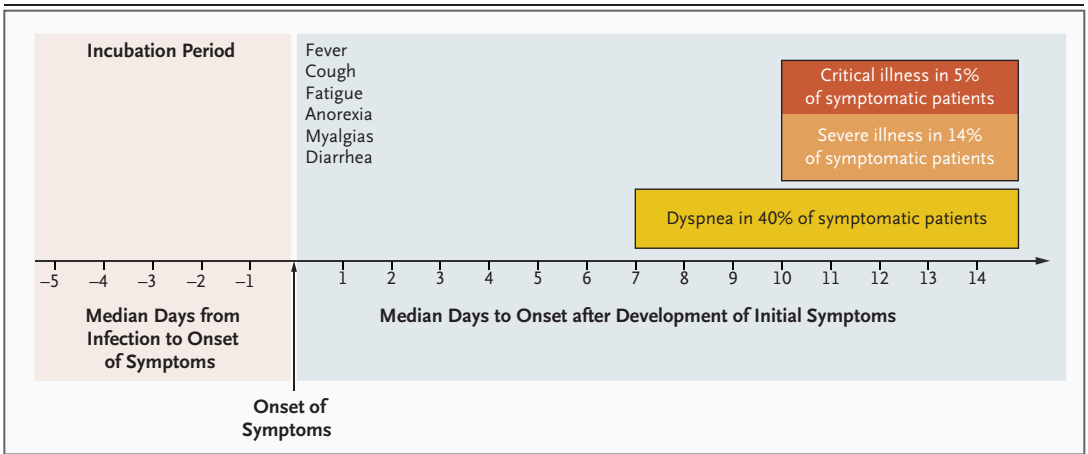


Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

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]

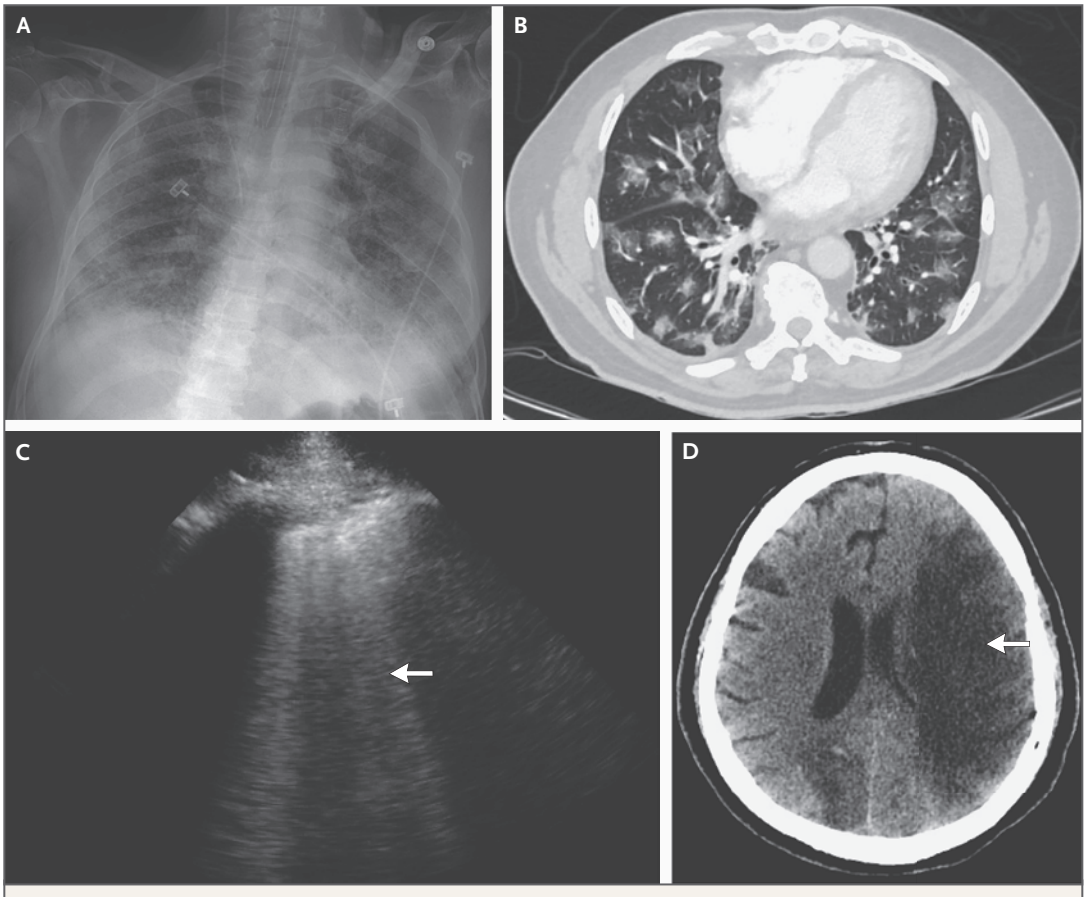


Figure 2. Radiographic and Ultrasonographic Findings of Severe Covid-19.

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).

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

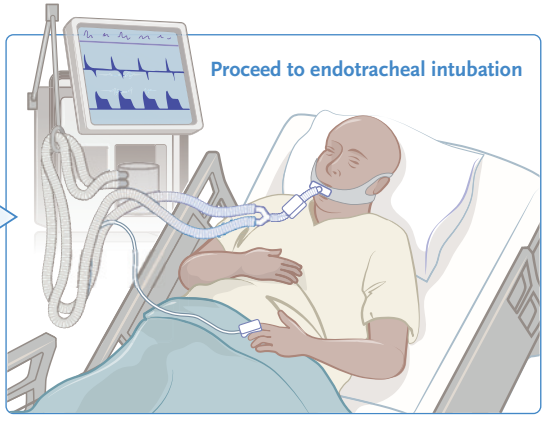
A Determination of Need for Endotracheal Intubation for Covid-19–Related Respiratory Failure

Possible Clinical Indications for Endotracheal Intubation

- Impending airway obstruction
- Signs of unsustainable work of breathing
- Refractory hypoxemia
- Hypercapnia or acidemia
- Encephalopathy or inadequate airway protection

Additional Considerations

- Does illness trajectory predict deterioration?
- Are difficulties in endotracheal intubation anticipated?
- Is there hemodynamic instability?
- Will intubating now improve the safety of a planned procedure or transportation?
- Will intubating now improve infection control and staff safety?



B Principles of Ventilator Management in ARDS Due to Covid-19

Measure height and calculate predicted body weight

Female predicted body weight (kg)

45.5 + (0.91) (height in cm − 152.4)

Male predicted body weight (kg)

50 + (0.91) (height in cm − 152.4)

Target tidal volume, 6–8 ml/kg of predicted body weight

Set PEEP to prevent lung derecruitment

Monitor hemodynamics, respiratory compliance, and gas exchange at each PEEP setting

If plateau pressure >30 cm of water, consider:

- Reducing tidal volume (minimum, 4 ml/kg of predicted body weight)
- Reducing PEEP
- Allowing higher plateau pressures in patients with obesity or reduced chest-wall compliance

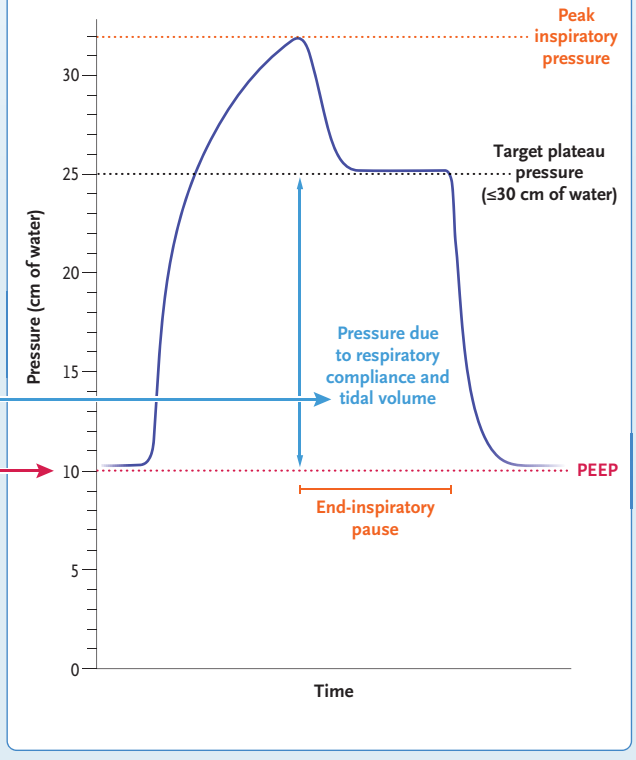


Figure 3. Invasive Mechanical Ventilation for Covid-19–Related Respiratory Failure.

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.

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

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 undergo intubation but remains hypoxemic, a high-flow nasal cannula can improve oxygenation and may prevent intubation in selected patients.[18,19] 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. However, some experts discourage the use of high-flow nasal cannulae and noninvasive ventilation because these treatments may inappropriately delay recognition of the need for endotracheal intubation and expose clinicians to infectious aerosols.[20,21]

Having awake patients turn to the prone position while they breathe high concentrations of supplemental oxygen may improve gas exchange in patients with severe Covid-19. This approach is supported by a case series describing its use in nonintubated patients with ARDS unrelated to Covid-19.[22,23] 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

The most skilled available operator should perform endotracheal intubation in patients with 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.[24] 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.[24] Patients with Covid-19 often become hypotensive soon after intubation owing to positive-pressure ventilation and systemic vasodilation from sedatives.[24] Therefore, intravenous fluids and vasopressors should be immediately available at the time of intubation, and careful hemodynamic monitoring is essential.[24]

VENTILATOR MANAGEMENT

It is unclear whether Covid-19 is associated with a distinct form of ARDS that would benefit from a new strategy of mechanical ventilation.[25] However, available data suggest that respiratory-system compliance in patients with severe Covid-19 is similar to that in populations enrolled in previous therapeutic trials for ARDS.[8,26] Therefore, present guidelines recommend that clinicians follow the treatment paradigm developed during the past two decades for ARDS (Fig. 3B).[18,19] 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 to atmospheric pressure). To prevent alveolar overdistention, the plateau pressure should not exceed 30 cm of water.[19,27] A higher plateau pressure without the development of ventilator-induced lung injury may be possible in patients with central obesity or noncompliant chest walls.

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

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.[18]

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.[18] These agents can reduce the work of breathing, which reduces oxygen consumption and carbon dioxide production.[28] 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.[18,29] However, prone positioning of patients requires a team of at least three trained clinicians, all of whom require full PPE.[18] 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.[18] Extracorporeal membrane oxygenation (ECMO) is a potential rescue strategy in patients with refractory respiratory failure. However, ECMO may not be effective owing to the cytokine storm and hypercoagulability of Covid-19, and its use will probably be limited as the pandemic strains resources.[30,31]

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.[32] 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.[18] 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[15,33]; 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, the efficacy of continuous renal-replacement therapy is uncertain.[34]

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.[3,35,36] Prophylactic low-dose heparin should be used to reduce the risk of venous thrombosis.[37] However, in one series of critically ill patients with Covid-19, one third had clinically significant venous or arterial thrombosis despite thromboprophylaxis.[38] Life-threatening thrombosis has also occurred despite full-dose anticoagulation with heparins.[34] The benefits and risks of more intense anticoagulation or of using direct thrombin inhibitors in patients with severe Covid-19 are unknown.

Patients hospitalized with severe Covid-19 are often treated empirically with antibiotics.[3,9] However, bacterial coinfection is rare when patients first present to the hospital.[8,39,40] Antibiotics can be discontinued after a short course if signs of bacterial coinfection, such as leukocytosis and focal pulmonary infiltrates, are absent. Although

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

Covid-19 itself can cause prolonged fever, clinicians should be vigilant for nosocomial infections.[2]

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.[41]

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.[42] 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

Little is known about the pathogenesis and treatment of this new disease. Preliminary data from a randomized, placebo-controlled trial involving more than 1000 patients with severe Covid-19 suggest that the investigational antiviral agent remdesivir reduces time to recovery,[43] and the Food and Drug Administration (FDA) has granted it emergency-use authorization. No agent is currently FDA-approved for the treatment of severe Covid-19. Numerous randomized trials of many other candidate therapies are ongoing (Table 1).

The delayed onset of critical illness in patients with Covid-19 suggests a maladaptive host response to infection.[10] Therefore, there is intense interest in the effects of immunomodulating therapies. Glucocorticoids have been used widely for cytokine storm and respiratory failure in patients with Covid-19; however, there is concern that they may prolong viral shedding and lead to secondary infections.[58-60] Current guidelines offer conflicting advice on the use of glucocorticoids. The Surviving Sepsis Campaign suggests a short course of glucocorticoids for moderate-to-severe ARDS related to Covid-19,[18] whereas the Infectious Diseases Society of America recommends their use only in the context of a clinical trial.[62] For reversal of vasopressor-dependent shock in patients with Covid-19, the Surviving Sepsis Campaign recommends low-dose glucocorticoids (hydrocortisone at a dose of 200 mg daily by means of infusion or with intermittent dosing).[18]

Other immunomodulating agents currently being evaluated for severe Covid-19 include passive immunotherapy with convalescent plasma,[56,57] intravenous immunoglobulin, and interleukin-1 and interleukin-6 pathway inhibition.[63] Pending 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.[10]

GUIDELINES

The recommendations in the present 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.[18,62,64,65]

CONCLUSIONS AND RECOMMENDATIONS

For the patient described in the vignette, the most important aspect of care is careful monitoring of 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. Anticoagulants should be administered to prevent thrombosis. Preliminary data support the use of remdesivir if available. Rigorous adherence to infection-control practices is essential at all times. Given the

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

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

Class	Availability	Rationale	Clinical Data
Antiviral agents			
Chloroquine	FDA-approved for extraintestinal amoebiasis, malaria; FDA emergency-use authorization from Strategic National Stockpile for certain hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[44]	Limited: small randomized trial showed limited benefit[45]; small trial stopped early because of increased mortality with higher dose[46]; randomized, controlled trials in progress
Hydroxychloroquine	FDA-approved for lupus, malaria, rheumatoid arthritis; FDA emergency-use authorization from Strategic National Stockpile for certain hospitalized patients with Covid-19	In vitro activity against SARS-CoV-2[47]	Limited: small randomized trials and retrospective case series with inconsistent results[48-51]; randomized, controlled trials in progress
Lopinavir–ritonavir	FDA-approved for HIV infection	In vitro activity against SARS-CoV-2[52]	Small randomized clinical trial failed to show clinical benefit[53]; other randomized, controlled trials in progress
Remdesivir	Investigational; FDA emergency-use authorization for hospitalized patients with severe Covid-19; compassionate-use program for pregnant women and children with severe Covid-19; expanded-access program for persons unable to participate in clinical trials (ClinicalTrials.gov number, NCT04323761)	In vitro activity against SARS-CoV-2[44]	Small, single-group, uncontrolled study showed clinical benefit in a majority of patients[54]; underenrolled and underpowered randomized, placebo-controlled trial involving hospitalized patients showed no significant differences in clinical or virologic outcomes[55]; randomized, placebo-controlled trial involving hospitalized patients showed faster time to recovery with remdesivir[43]; additional clinical trials in progress
Immune-based agents			
BTK inhibitors (acalabrutinib, ibrutinib, rilzabrutinib)	FDA-approved for some hematologic cancers	Immunomodulation-targeting cytokines	Clinical trials in progress
Convalescent plasma	Investigational; FDA single-patient emergency IND; expanded-access program for persons ineligible for or unable to participate in clinical trials	Use in other viral illnesses, including H1N1 influenza, SARS, and MERS	Limited: small, uncontrolled cohort studies suggested benefit, but confirmation required[56,57]; randomized, controlled trials in progress
Glucocorticoids	FDA-approved for multiple indications	Broad immunomodulation	Limited: retrospective, nonrandomized cohort study showed association with lower mortality among patients with severe Covid-19 and ARDS,[39] but concern for survivor treatment bias; randomized clinical trials involving patients with influenza, MERS, or SARS did not show benefit and suggested possible harm (increased viral shedding and increased mortality)[58-60]
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	Limited: in a small cohort study, a majority of patients who received siltuximab had an improved or stabilized condition[61]; randomized, controlled trials in progress
JAK inhibitors (baricitinib, ruxolitinib)	FDA-approved for rheumatoid arthritis (baricitinib) and myelofibrosis and polycythemia vera (ruxolitinib)	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.

Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

The New England Journal of Medicine

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.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the nurses, respiratory therapists, social workers, therapists, chaplains, custodial staff, consultants, and all the other members of the intensive care unit team for their extraordinary courage and professionalism during this pandemic.

REFERENCES

1. Centers for Disease Control and Prevention. Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). 2020 (https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html).
2. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-62.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
4. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
5. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020 April 22 (Epub ahead of print).
6. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020 April 10 (Epub ahead of print).
7. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020 March 27 (Epub ahead of print).
8. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region — case series. N Engl J Med. DOI: 10.1056/NEJMoa2004500.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
10. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4.
11. Wong HYF, Lam HYS, Fong AH-T, et al. Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology 2019 March 27 (Epub ahead of print).
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020 February 24 (Epub ahead of print).
13. CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019 — United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020;69:382-6.
14. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020;323:1574-81.
15. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. N Engl J Med. DOI: 10.1056/NEJMc2010419.
16. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med 2020 April 3 (Epub ahead of print).
17. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7(4):e35797.
18. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med 2020;46:854-87.
19. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 2020;8:433-4.
20. Ñamendys-Silva SA. Respiratory support for patients with COVID-19 infection. Lancet Respir Med 2020;8(4):e18.
21. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA 2020 March 26 (Epub ahead of print).
22. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020;24:28.
23. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. Ann Intensive Care 2020;10:33.
24. Cook TM, El-Boghdadly K, McGuire B, McNarry AF, Patel A, Higgs A. Consensus guidelines for managing the airway in patients with COVID-19: guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists. Anaesthesia 2020;75:785-99.
25. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. Covid-19 does not lead to a "typical" acute respiratory distress syndrome. Am J Respir Crit Care Med 2020 March 30 (Epub ahead of print).
26. Ziehr DR, Alladina J, Petri CR, et al. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. Am J Respir Crit Care Med 2020 April 29 (Epub ahead of print).
27. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.
28. Manthous CA, Hall JB, Kushner R, Schmidt GA, Russo G, Wood LD. The effect of mechanical ventilation on oxygen consumption in critically ill patients. Am J Respir Crit Care Med 1995;151:210-4.
29. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159-68.
30. Ramanathan K, Antognini D, Combes A, et al. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med 2020;8:518-26.
31. Zeng Y, Cai Z, Xianyu Y, Yang BX, Song T, Yan Q. Prognosis when using extracorporeal membrane oxygenation (ECMO) for critically ill COVID-19 patients in China: a retrospective case series. Crit Care 2020;24:148.
32. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
33. Guan W, Ni Z, Hu Y, et al. Clinical

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.

characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
34. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020 May 4 (Epub ahead of print).
35. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020 March 21 (Epub ahead of print).
36. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
37. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18:1094-9.
38. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020 April 10 (Epub ahead of print).
39. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020 March 13 (Epub ahead of print).
40. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA 2020 April 15 (Epub ahead of print).
41. Resuscitation Council UK statement on COVID-19 in relation to CPR and resuscitation in healthcare settings. London: Resuscitation Council UK, 2020.
42. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.
43. National Institutes of Health. NIH trial shows remdesivir accelerates recovery from advanced COVID-19. April 29, 2020 (https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19).
44. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30: 269-71.
45. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. J Mol Cell Biol 2020 April 1 (Epub ahead of print).
46. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open 2020;3(4):e208857.
47. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 2020; 6:16.
48. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. April 23, 2020 (https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2). preprint.
49. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) 2020 March 6 (Epub ahead of print).
50. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. April 10, 2020 (https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v3). preprint.
51. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 March 20 (Epub ahead of print).
52. Choy K-T, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtononine inhibit SARS-CoV-2 replication in vitro. Antiviral Res 2020 April 3 (Epub ahead of print).
53. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382:1787-99.
54. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007016.
55. Wang Y, Zhang D, Guanhua D, et al. Remdesivir in adults with severe Covid-19: a randomized, double-blind, placebo-controlled, multicentre trial. Lancet. April 29, 2020 (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31022-9.pdf).
56. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020;117:9490-6.
57. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582-9.
58. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East Respiratory Syndrome. Am J Respir Crit Care Med 2018;197:757-67.
59. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473-5.
60. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev 2016; 3:CD010406.
61. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. April 15, 2020 (https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v2). preprint.
62. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Arlington, VA: Infectious Diseases Society of America, 2020 (https://www.idsociety.org/COVID19guidelines).
63. Cron RQ, Chatham WW. The rheumatologist's role in COVID-19. J Rheumatol 2020;47:639-42.
64. Wilson KC, Chotirmall SH, Bai C, Rello J. Covid-19: Interim guidance on management pending empirical evidence: from an American Thoracic Society-led international task force. April 3, 2020 (https://www.thoracic.org/covid/covid-19-guidance.pdf).
65. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. 2020 (https://covid19treatmentguidelines.nih.gov/).

Copyright © 2020 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at SAN FRANCISCO (UCSF) on June 9, 2020. For personal use only. No other uses without permission.
Copyright © 2020 Massachusetts Medical Society. All rights reserved.