TERMINOLOGY

CLINICAL CLARIFICATION

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection with a newly recognized coronavirus; it spread rapidly from the point of origin in China, and was officially declared by WHO to be a pandemic on March 11, 2020[1]
- Illness ranges in severity from asymptomatic or mild to severe; about 5% of diagnosed cases require critical care to manage severe manifestations and complications, including acute respiratory distress syndrome, myocardial dysfunction, and shock[2]
- Most patients with severe COVID-19 seem to have a bimodal illness, where there is initial improvement before severe worsening with critical illness. This may be related to the immunologic role in the sepsis seen with COVID-19
- Among ICU patients with COVID-19, mortality rates of 39% to 72% have been reported[2]
- Knowledge of this disease is incomplete and evolving; moreover, coronaviruses are known to mutate and recombine often, presenting an ongoing challenge to our understanding and to clinical management

CLASSIFICATION

- Pathogen is a betacoronavirus,[3] similar to the agents of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)[3]
  - Classified as a member of the species *Severe acute respiratory syndrome–related coronavirus*[4, 5]
  - Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2); earlier provisional name was 2019-nCoV[4, 5]

DIAGNOSIS

CLINICAL PRESENTATION

- History
  - In symptomatic patients, illness may evolve over the course of a week or longer, beginning with mild symptoms; syndrome is usually dominated by respiratory complaints, but it may include alterations in taste and smell, gastrointestinal symptoms, myalgias, and fatigue (often profound)[6]
    - Median time from symptom onset to pneumonia is 5 days; time to severe hypoxemia is 7 to 12 days[7]
  - In patients with progression to severe disease, deterioration is typically rapid and characterized by progressive hypoxemia which may or may not be associated with symptoms of dyspnea[8, 9]
    - Clinicians should be aware that lack of dyspnea may be misleading, as it has been recognized that many patients with severe hypoxemia due to COVID-19 do not perceive dyspnea
  - Cardiac, vascular, and neurologic manifestations may accompany pulmonary disease, resulting in localized symptoms (eg, pain, including headache) and alterations in cognition and level of consciousness
- Physical examination
  - Reported case series have not fully detailed physical findings, but clinicians should be particularly attuned to pulmonary and hemodynamic indicators of critical illness
    - Patients with severe disease may appear quite ill, with tachypnea and labored respirations
    - Patients in apparent distress require immediate assessment of airway, breathing, and circulation (eg, pulses, blood pressure)
    - Clinicians should be aware of the COVID-19–related phenomenon of silent (or "happy") hypoxemia: absence of signs of respiratory distress may be misleading
    - Oxygenation should be assessed promptly by peripheral saturation (eg, pulse oximetry)[10]
  - Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever[6]
  - Patients with severe disease may appear quite ill, with tachypnea and labored respirations
  - Tachyarrhythmias may be noted on auscultation or cardiac monitor[11]
  - Signs of arterial or deep venous thrombosis may be detected
    - Large-vessel stroke and associated neurologic deficit has been described as the presenting clinical event[12]
  - Other reported neurologic findings in severe disease include hyperactive deep tendon reflexes, ankle clonus, and positive Babinski sign[13]
  - Patients may be agitated, confused, or poorly responsive[13]
  - A variety of skin changes have been described, including purpura[14] and petechiae[15] as well as the vesicular[16] and nonspecific erythematous exanthems[17] typical of viral infections. Typical viral eruptions generally occur early in the disease, but remnants may be apparent in patients presenting with severe disease
  - Hypotension, tachycardia, and cool/clammy extremities suggest shock
    - In children, hypotension plus 2 or more of the following criteria:[10]
      - Altered mental status

- Tachycardia (heart rate more than 160 beats per minute in infants or 150 in older children) or bradycardia (heart rate less than 90 in infants or 70 in older children)
- Prolonged capillary refill (more than 2 seconds) or warm vasodilation and bounding pulses
- Tachypnea
- Mottled skin, petechiae, or purpura
- Oliguria
- Hyperthermia or hypothermia

CAUSES AND RISK FACTORS

- Causes
  - Infection due to SARS-CoV-2 (2019 novel coronavirus)
  - Person-to-person transmission has been documented [18] and is presumed to occur by close contact, [19] probably via respiratory droplets [20]
  - Additional means of transmission are possible but not established (eg, contact with infected environmental surfaces, fomites, fecal-oral route)
- Risk factors and/or associations
  - Age
    - Risk of severe disease increases with age; severe illness is rare in children and adolescents
      - In data from China, case fatality rates were 14.8% for patients aged 80 years or older, 8% for those aged 70 to 79 years, and 3.6% for those aged 60 to 69 years [2]
      - In data from the United States, case fatality rates were 10% to 27% among patients aged 85 years or older, 3% to 11% for those aged 65 to 84 years, and 1% to 3% for those aged 55 to 64 years [21]
  - Sex
    - Male sex may be a risk factor for severe disease; in a series of 5700 hospitalized patients with COVID-19, 60.3% were male; among ICU patients, 66.5% were male [22]
  - Other risk factors/associations
    - Various underlying medical conditions have been associated with increased risk for severe disease, especially if they are not well controlled: [23]
      - Chronic kidney disease
      - Chronic obstructive pulmonary disease
      - Immunosuppression because of previous solid organ transplant
      - Serious cardiac conditions (eg, heart failure, coronary artery disease, cardiomyopathy)
      - Obesity (BMI of 30 or higher)
      - Sickle cell disease
      - Diabetes type 2
    - Conditions which may be associated with higher risk for severe disease: [23]
      - Asthma (moderate to severe)
      - Cerebrovascular disease
      - Cystic fibrosis
      - Hypertension
      - Immunodeficiency from various other causes (eg, bone marrow or hematopoietic stem cell transplant, primary immunodeficiencies, HIV disease, chronic treatment with corticosteroids or other agents with immunosuppressive effects)
      - Neurologic dysfunction
      - Chronic liver disease
      - Pregnancy
      - Pulmonary fibrosis
      - Thalassemia
      - Diabetes type 1
    - Children with medically complex conditions (eg, neurologic, metabolic, genetic, cardiac) are also at higher risk for severe disease [23]
    - Residents of nursing homes and long-term care facilities are at high risk for acquiring infection and for severe disease, probably owing to a combination of heightened transmission in a close-quarters community and prevalence of compromised health status [24]

DIAGNOSTIC PROCEDURES
- Primary diagnostic tools
  - Polymerase chain reaction tests are the standard for diagnosis. Specific methods and availability vary; public health authorities may assist in arranging diagnostic testing in some areas. Attempts to culture the virus are not recommended [25, 19]
  - WHO [10, 26, 27] and CDC [19] have slightly different criteria for whom to test, and the rapid evolution of the pandemic and variable availability of testing render actual practice very fluid. Both organizations support testing in hospitalized patients with a clinically compatible illness
  - Collection of specimens from upper respiratory tract or lower respiratory tract is recommended for polymerase chain reaction testing. [19] Care must be taken to minimize risks associated with aerosolization during specimen collection
    - CDC provides specific instructions for collection and handling of specimens submitted for testing at CDC laboratories (commercial and institutional laboratories and public health laboratories in other jurisdictions may have different requirements) [28]
      - Upper respiratory tract
        - Nasopharyngeal, deep nasal (midturbinate), anterior nare, or oropharyngeal swab may be submitted. Only synthetic fiber (eg, polyester) swabs with plastic or wire shafts are acceptable. Flocked swabs are recommended for obtaining deep nasal specimens. If more than one swab is collected, they may be placed in the same container
          - For nasopharyngeal specimen, insert swab into nostril parallel to palate. Leave swab in place for a few seconds to absorb secretions, then remove while gently rotating. It is not necessary to repeat on the other side if the first effort produces a good specimen (ie, swab is saturated)
          - For deep nasal specimen, insert a flocked swab about 2 cm and rotate; repeat on opposite side, using the same swab
          - For anterior nares, insert a flocked swab about 1 cm, rotate in contact with mucus membrane, and leave in place for 10 to 15 seconds; repeat on opposite side, using same swab
          - For oropharyngeal specimen, swab the posterior pharynx, avoiding tongue and tonsils
        - Nasopharyngeal wash (or aspirate) or nasal aspirate specimens (using 1 to 1.5 mL nonbacteriostatic saline) are also acceptable in some cases
        - Because testing methods vary, it is advisable to check with the laboratory to determine which specimens are suitable for the available test
      - Lower respiratory tract
        - Bronchoalveolar lavage or tracheal aspirate are suitable lower respiratory tract specimens
        - A deep cough sputum specimen (collected after mouth rinse) is also acceptable
          - WHO and CDC advise against attempts to induce sputum, because the process may increase aerosolization and risk of transmission
    - Infectious Diseases Society of America guidelines provide additional guidance and an algorithm, including indications for repeated testing when suspicion for disease is high but initial test result is negative [29]
      - Favor nasopharyngeal, nasal, or midturbinate specimens over oropharyngeal or salivary specimens for initial testing
      - For patients with high likelihood of disease but negative initial result, repeated testing is recommended; in patients with lower respiratory tract symptoms, sputum or other lower respiratory tract specimen is recommended for repeated testing
  - Other testing should be performed concurrently, if indicated, to identify alternative pathogens (eg, influenza, respiratory syncytial, and other viruses; bacterial pathogens); such tests should not delay arrangements for SARS-CoV-2 polymerase chain reaction testing [10]
    - Coinfections have been reported, but the frequency is unknown [30, 31, 32]
  - In patients with moderate to severe disease, chest imaging is essential to document extent and severity of lung involvement and to serve as a baseline against which to compare should respiratory status worsen; [33] plain radiography, CT, and ultrasonography have been used [34]
    - Recommendations for COVID-19–specific diagnostic use differ regionally, according to availability of testing, prevalence of disease, and public policy
      - During the peak of the outbreak in Wuhan, China, CT scan was considered a surrogate diagnostic modality, based on the following factors: greater sensitivity compared with chest radiographs; the observation that CT may find characteristic abnormalities even in the absence of a positive molecular test result; the high prevalence of COVID-19 in that geographic area; and the public health goal of detecting and isolating all infected persons [33]
      - CDC recommends against using chest radiograph or CT as a specific diagnostic measure for COVID-19; American College of Radiology cautions that findings are not specific to that disease and overlap with other viral pneumonias [35]

- In patients with severe disease, CT may offer an advantage over plain radiographs in distinguishing progression of infection from heart failure due to myocarditis or from pulmonary embolism (both commonly associated with COVID-19) [33]
  - Routine blood work should be ordered initially and repeated as appropriate for clinical management based on disease severity (eg, CBC, coagulation studies, chemistry panel including tests of hepatic and renal function and—if sepsis is suspected—lactate level and blood cultures). Troponin and B-type natriuretic peptide levels may be helpful in assessing the possibility of myocardial involvement [7, 10, 36]
  - Public health reporting requirements vary by jurisdiction; clinicians should consult local authorities. In some regions, public health authorities may be able to facilitate testing and undertake contact tracing and monitoring
- Laboratory
  - Positive identification of SARS-CoV-2 RNA by a polymerase chain reaction test is considered confirmation of diagnosis
    - Clinical performance characteristics of these tests are not well defined. Although high sensitivity and specificity can be achieved in test development, data on accuracy in clinical usage are lacking [29, 7]
    - False-negative results have been reported and may be due to a variety of factors, including inadequate sensitivity, poor or unrepresentative specimen, or time course of disease. Repeated sampling should be considered if suspicion for COVID-19 is high and initial result is negative; in patients with severe pulmonary involvement, lower respiratory tract specimens may provide a higher yield [29, 7]
  - Routine blood work is not diagnostic, but a pattern of typical abnormalities has emerged, particularly in patients with severe illness:
    - Leukopenia may be observed and relative lymphopenia is common, especially in patients with more severe illness [18, 6, 34]
    - Anemia was noted in about half of patients in one series [34]
    - Both elevated and low platelet counts have been seen [18, 34, 6]
    - Prolonged prothrombin time has been reported [37]
    - Levels of D-dimer and fibrinogen may be elevated [18, 6]
    - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common [6, 34]
    - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection [6]
    - Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate [34]
    - Troponin level is commonly elevated, but it does not necessarily signify myocardial infarction in the absence of other indicators (eg, ECG changes); similarly, B-type natriuretic peptide level may be elevated without necessarily indicating presence of heart failure [38]
      - Some experts caution against measuring these biomarkers in the absence of suggestive clinical findings, [38] whereas others note the possibility that elevations suggest noncoronary myocardial involvement that may benefit from early use of vasopressors and inotropes [7]
  - Lactate level of 2 mmol/L or higher suggests presence of septic shock [10]
- Imaging
  - Chest imaging (eg, plain radiography, CT, ultrasonography) has shown abnormalities in most reported patients; it usually shows bilateral involvement, varying from consolidation in more severely ill patients to ground-glass opacities in less severe and recovering pneumonia [39, 3, 34, 18, 6]
  - CT appears to be more sensitive [33, 40] than plain radiographs, but normal appearance on CT does not preclude the possibility of COVID-19 [41]
  - Bedside ultrasonography is widely used to monitor progression of pulmonary infiltrates, and to assess cardiac function and fluid status; it may also be used to detect deep vein or vascular catheter thrombosis, which appear to be common in patients with COVID-19 [42, 7]

DIFFERENTIAL DIAGNOSIS
- Most common
  - Influenza
    - Presentation includes fever, coryza, sore throat, dry cough, and myalgias; unlike COVID-19, influenza usually has fairly sudden onset
    - Most cases are self-limited, but elderly persons or those with significant comorbidities often require hospitalization
    - Usually occurs in winter months in temperate climates but is less seasonal in equatorial regions
    - Patients with severe disease may have abnormal chest radiographic findings suggesting influenzal pneumonia or secondary bacterial pneumonia
    - Positive result on rapid influenza diagnostic test confirms influenza diagnosis with high specificity during typical season; negative result does not rule out influenza
  - Other viral pneumonias
    - Presentations include fever, dry cough, and dyspnea

- – Physical examination may find scattered rales
- – Chest radiography usually shows diffuse patchy infiltrates
- – Diagnosis is usually clinical. Testing for specific viral causes may be done; multiplex panels can test simultaneously for a number of common viral respiratory pathogens such as respiratory syncytial virus, adenovirus, and others
  - ○ Bacterial pneumonia
    - – Presentation includes fever, cough, and dyspnea; pleuritic pain occurs in some cases
    - – Physical examination may find signs of consolidation (eg, dullness to percussion, auscultatory rales, tubular breath sounds)
    - – Chest radiography usually shows lobar consolidation or localized patchy infiltrate
    - – Sputum examination may find abundant polymorphonuclear leukocytes and a predominant bacterial organism
    - – Pneumococcal or legionella antigens may be detectable in urine; sputum culture may find those or other pathogens

TREATMENT

GOALS
- Ensure adequate oxygenation and hemodynamic support during acute phase of illness
- Prevent complications where possible (eg, thromboses); monitor for and treat unavoidable complications (eg, myocardial dysfunction)

DISPOSITION
- Admission criteria
  - ○ Criteria for ICU admission
    - – WHO provides criteria for critical respiratory tract disease [43]
      - □ Characterized by tachypnea (respiratory rate greater than 30 breaths or less than 10 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO$_2$ of less than 92%)
      - □ Pediatric criteria include central cyanosis or SpO$_2$ less than 90%; signs of severe respiratory distress (eg, grunting, chest retractions); inability to drink or breastfeed; lethargy, altered level of consciousness, or seizures; or severe tachypnea defined by age:
        - □ Younger than 1 month: 60 or more breaths per minute *or* 20 or fewer breaths per minute
        - □ Aged 1 to 12 months: 50 or more breaths per minute *or* 10 or fewer breaths per minute
        - □ Aged 1 year or older: 40 or more breaths per minute
    - – Presence of severe complications (eg, septic shock, acute respiratory distress syndrome)
- Recommendations for specialist referral
  - ○ All patients should be managed in consultation with public health authorities
  - ○ Consult infectious disease specialist to coordinate diagnosis and management with public health authorities
  - ○ Consult pulmonologist to aid in obtaining deep specimens for diagnosis and managing mechanical ventilation if necessary
  - ○ Consult critical care specialist to manage fluids, mechanical ventilation, and hemodynamic support as needed

TREATMENT OPTIONS
- Standard, contact, and (at least) droplet precautions should be implemented as soon as the diagnosis is suspected; airborne precautions are recommended if resources allow, especially for aerosol-generating procedures [44]
  - ○ Immediately provide the patient with a face mask (or, if supplies are critically low, at least a cloth face cover) to reduce droplet spread and place the patient in a closed room, ideally one with structural and engineering safeguards against airborne transmission (eg, negative pressure, frequent air exchange)
- Pace of pandemic and severity of illness have necessitated urgent response but have limited the development of evidence-based critical care guidelines specific to this infection, which some experienced clinicians consider to have unique characteristics. Existing published guidelines for management of sepsis and acute respiratory distress syndrome have been modified, and many institutions have created their own protocols
- At present, no specific therapeutic agent is approved for treatment of this infection. Several existing drugs are being used under clinical trial and compassionate use protocols based on in vitro activity (against this or related viruses) and on limited clinical experience
  - ○ Remdesivir is an experimental antiviral agent with significant in vitro activity against coronaviruses [45, 46] and some evidence of efficacy in an animal model of MERS [45]
    - – Although not FDA-approved, remdesivir is in use for the indication; FDA has issued an emergency use authorization for use of IV remdesivir to treat hospitalized patients with severe COVID-19, defined as SpO$_2$ of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [47]
      - □ Preliminary results of the Adaptive COVID-19 Treatment Trial, [48] a placebo-controlled randomized trial in 1063 patients, showed a statistically significant improvement in time to recovery and a nonsignificant trend in lower mortality; several other trials remain active, as well [49]

- On the basis of preliminary data from clinical trials, NIH and IDSA guidelines recommend remdesivir for hospitalized patients with severe COVID-19 (defining criteria as outlined in the emergency use authorization) [50, 51]
- WHO does not recommend use outside of clinical trials [10]
○ Chloroquine and hydroxychloroquine have been used in China and South Korea, reportedly with favorable results, although details are lacking. Initial promise led to an emergency use authorization by FDA in the United States. Subsequent studies have failed to show a significant benefit, but they have highlighted the risk of QT prolongation and cardiac arrhythmias. As a result, FDA emergency use authorization has been withdrawn, [52] although some clinical trials are still in progress [53]
  - Azithromycin has been used in combination with hydroxychloroquine in some protocols; however, azithromycin is also associated with cardiac arrhythmias, and the possible increased risk posed by the combination must be considered [54]
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 states that data are insufficient to make a recommendation on the use of these agents [55]
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends hydroxychloroquine or chloroquine only in the context of a clinical trial, and suggests against combination with azithromycin outside of a clinical trial [51]
  - NIH guidelines recommend against chloroquine or hydroxychloroquine except in the setting of a clinical trial; they recommend against high-dose chloroquine (600 mg twice daily for 10 days) and against the addition of azithromycin to hydroxychloroquine. The guidelines note that when chloroquine or hydroxychloroquine is used, patients must be monitored for adverse effects, particularly prolonged QTc interval [50]
    □ Scoring systems are available to determine risk of arrhythmia [56, 57]
  - WHO recommends against use of chloroquine or hydroxychloroquine with or without azithromycin outside of a clinical trial [10]
  - A systematic review and meta-analysis of studies comparing standard care with and without hydroxychloroquine included 6 studies comprising 1331 patients. There was no difference in mortality between the 2 groups, although a subgroup receiving hydroxychloroquine plus azithromycin experienced significantly higher mortality than the standard care group [58]
○ Lopinavir-ritonavir is FDA-approved for treatment of HIV infection. It has been used in China in conjunction with interferon alfa for treatment of some patients with COVID-19, but reported results have been disappointing
  - A trial in 199 patients with COVID-19 comparing lopinavir-ritonavir with standard care did not show a significant difference in time to improvement or in mortality at 28 days, nor were there differences in duration of viral RNA in oropharyngeal specimens [59]
  - NIH COVID-19 treatment guideline [50] and Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 [55] recommend against use of lopinavir-ritonavir
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against use of recombinant interferons, based on lack of data in COVID-19 and on data from studies on MERS showing lack of efficacy [55]
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends lopinavir-ritonavir only in the context of a clinical trial [51]
  - WHO recommends against use of lopinavir-ritonavir outside of a clinical trial [10]
○ Immunomodulators are also being investigated for mitigation of cytokine release syndrome believed to be a factor in severe acute respiratory distress syndrome and shock in COVID-19 (eg, tocilizumab [55] and sarilumab [60] are both monoclonal antibodies against interleukin-6 receptor)
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 states that data are insufficient to make a recommendation on the use tocilizumab; the guideline did not evaluate other monoclonal antibodies [55]
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends tocilizumab only in the context of a clinical trial, based on evidence of very low certainty [51]
  - NIH COVID-19 treatment guideline states that data are insufficient to recommend for or against use of these agents [50]
  - WHO recommends against use of immunomodulators outside of a clinical trial [10]
○ Studies on the therapeutic efficacy of convalescent plasma are underway in various countries. In the United States, authorization must be obtained through FDA [61]
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 suggests that convalescent plasma not be used on the basis of data in other viral infections, lack of data in COVID-19, and uncertainties about safety [55]
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial [51]

- NIH COVID-19 treatment guideline states that data are insufficient to recommend for or against use of convalescent plasma or hyperimmune immunoglobulin. It recommends against the use of non–SARS-CoV-2 IV immunoglobulin except in a clinical trial or unless there is another indication for it [50]
  - WHO recommends against use of plasma therapy outside of a clinical trial [10]
- Information on therapeutic trials and expanded access is available at ClinicalTrials.gov [62]
- Corticosteroid therapy is not recommended for viral pneumonia but is suggested by some authorities for patients with COVID-19 who have refractory shock or respiratory insufficiency necessitating oxygen administration [10]
  - Preliminary data from a randomized controlled trial in more than 6000 hospitalized patients with COVID-19 found dexamethasone reduced deaths in patients with severe respiratory complications requiring supplemental oxygen [63]
    - Compared with usual care alone, deaths in ventilated patients receiving usual care plus dexamethasone were reduced by a third; among patients receiving oxygen without mechanical ventilation, deaths were cut by 20%
    - Overall 28-day mortality was reduced by 17% in the dexamethasone group
    - Details of the studied regimen have not yet been published
  - Based on these data, NIH COVID-19 treatment guideline recommends use of dexamethasone in patients who require supplemental oxygen with or without mechanical ventilation. It recommends against using dexamethasone in patients who do not require oxygen supplementation [50]
  - Similarly, Infectious Diseases Society of America guideline suggests use of dexamethasone in hospitalized patients with severe COVID-19, defined as SpO_2 of 94% or less on room air or any requirement for supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [51]
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 supports using corticosteroids in mechanically ventilated patients with COVID-19 and acute respiratory distress syndrome (but not those with respiratory failure in the absence of that syndrome) and in patients with COVID-19 and refractory shock; short-course, low-dose regimens are preferred [55]
  - WHO recommends against routine use of corticosteroids for viral pneumonia, but it notes that some clinical circumstances may warrant use (eg, septic shock, moderate to severe acute respiratory distress syndrome, risk of preterm birth associated with COVID-19 in the mother) [10]
- FDA is investigating a controversy that has arisen regarding the use of NSAIDs in patients with COVID-19; however, there is no published evidence connecting the use of NSAIDs with worsening COVID-19 symptoms [64]
  - NIH COVID-19 treatment guideline recommends that use of acetaminophen and NSAIDs in patients with COVID-19 should not differ from that in patients without COVID-19 [50]
  - A retrospective cohort study of acetaminophen and ibuprofen use in 403 patients with confirmed COVID-19 found that 32% of patients used acetaminophen and 22% used ibuprofen, at some point during the week before onset or during the course of illness, and that there were no differences between the 2 groups in mortality or need for respiratory support [65]
- Until a diagnosis of COVID-19 is confirmed by polymerase chain reaction test, appropriate antimicrobial therapy for other viral pathogens (eg, influenza virus) or bacterial pathogens should be administered in accordance with the severity of clinical disease, site of acquisition (hospital or community), epidemiologic risk factors, and local antimicrobial susceptibility patterns [10]
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 supports use of empiric antimicrobial therapy in mechanically ventilated patients with COVID-19 and respiratory failure, with daily consideration for de-escalation [55]
- Based on concerns about the possible role of micro- and macrovascular thrombosis in the pathophysiology of this disease, the use of anticoagulation is being studied. At present, in the absence of a standard indication for it, published guidelines do not recommend therapeutic anticoagulation but do recommend use of prophylactic regimens in any hospitalized patient with COVID-19 [50, 66, 36]
- Otherwise, treatment is largely supportive and includes oxygen supplementation and conservative fluid support; usual measures to prevent common complications (eg, pressure injury, stress ulceration, secondary infection) are applicable [10]
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Surviving Sepsis Campaign,[55] NIH COVID-19 treatment guideline,[50] and WHO[10] provide guidance specific to the treatment of shock in patients with COVID-19
  - In adults, begin with norepinephrine; epinephrine or vasopressin is preferred as second line over dopamine if norepinephrine is unavailable
    - Hemodynamic goal: mean arterial pressure of 60 to 65 mm Hg [55]
  - In patients who do not respond adequately to usual doses of norepinephrine, Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends adding vasopressin rather than further titrating norepinephrine [55]
  - For patients with COVID-19, refractory shock despite fluid and norepinephrine, and evidence of cardiac dysfunction, Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends adding dobutamine rather than further titrating norepinephrine [55]
  - In children, epinephrine is considered the first line agent, and norepinephrine may be added if necessary [10]

- Drug therapy
  - Antiviral agent
    - Remdesivir [67]
      - Remdesivir Solution for injection; Neonates weighing 3.5 kg or more requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 9 days suggested by FDA EUA statement.
      - Remdesivir Solution for injection; Neonates weighing 3.5 kg or more NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 4 days suggested by FDA EUA statement. May extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Infants, Children, and Adolescents weighing 3.5 to 39 kg requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 9 days suggested by FDA EUA statement.
      - Remdesivir Solution for injection; Infants, Children, and Adolescents weighing 3.5 to 39 kg NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 5 mg/kg/dose IV once on day 1 then 2.5 mg/kg/dose IV once daily for 4 days suggested by FDA EUA statement. May extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Children and Adolescents weighing 40 kg or more requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 200 mg IV once on day 1 then 100 mg IV once daily for 9 days suggested by FDA EUA statement.
      - Remdesivir Solution for injection; Children and Adolescents weighing 40 kg or more NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 200 mg IV once on day 1 then 100 mg IV once daily for 4 days suggested by FDA EUA statement. May extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Adults requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 200 mg IV once on day 1 then 100 mg IV once daily for 9 days suggested by FDA EUA statement.
      - Remdesivir Solution for injection; Adults NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): The NIH COVID-19 treatment guidelines recommend remdesivir for hospitalized patients with severe COVID-19. 200 mg IV once on day 1 then 100 mg IV once daily for 4 days suggested by FDA EUA statement. May extend treatment for up to 5 additional days if no clinical improvement.
  - Monoclonal antibodies
    - Tocilizumab
      - Tocilizumab Solution for injection; Adults: Available data are limited, and efficacy has not been established. Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not recommend for or against the use of IL-6 receptor inhibitors, such as tocilizumab. 4 to 8 mg/kg/dose (Usual dose: 400 mg; Max dose: 800 mg) IV once is being evaluated in combination with antiviral therapy. A second dose 8 to 12 hours after the first infusion may be considered. One protocol suggests a possible third dose 16 to 24 hours after the first dose.
    - Sarilumab
      - IV dosage
        - Sarilumab Solution for injection; Adults: Efficacy has not been established. Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of IL-6 receptor inhibitors, such as sarilumab. 400 mg IV once in combination with antiviral therapy.
      - Subcutaneous dosage
        - Sarilumab Solution for injection; Adults: Efficacy has not been established. Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of IL-6 receptor inhibitors, such as sarilumab. 200 or 400 mg subcutaneously once in combination with antiviral therapy.
  - Vasopressors
    - Norepinephrine
      - Norepinephrine Bitartrate Solution for injection; Neonates†: 0.1 to 0.5 mcg/kg/minute continuous IV infusion; titrate every 30 minutes to clinical response (Usual Max: 2 mcg/kg/minute).

- Norepinephrine Bitartrate Solution for injection; Infants†, Children†, and Adolescents†: 0.1 mcg/kg/minute continuous IV infusion; titrate to clinical response (Usual Max: 2 mcg/kg/minute).
- Norepinephrine Bitartrate Solution for injection; Adults: 0.1 mcg/kg/minute (weight-based) or 8 to 12 mcg/minute (flat-dose) continuous IV infusion, initially. Titrate by 0.02 mcg/kg/minute (or more in emergency cases) to clinical response. Usual dosage range: 0.05 to 0.4 mcg/kg/minute (weight-based) or 2 to 4 mcg/minute (flat-dose). Infusion rates up to 3.3 mcg/kg/minute have been used.
  - Epinephrine
    - Epinephrine Hydrochloride Solution for injection; Infants†, Children†, and Adolescents†: 0.1 to 1 mcg/kg/minute continuous IV infusion; titrate to clinical response. Doses up to 5 mcg/kg/minute may be necessary.
    - Epinephrine Hydrochloride Solution for injection; Adults: 0.05 to 2 mcg/kg/minute continuous IV infusion; titrate by 0.05 to 0.2 mcg/kg/minute every 10 to 15 minutes to clinical response.
  - Vasopressin
    - Vasopressin Solution for injection; Adults: 0.01 unit/minute continuous IV infusion; titrate by 0.005 unit/minute every 10 to 15 minutes to clinical response. Max: 0.07 unit/minute.
- Inotrope
  - Dobutamine
    - Dobutamine Hydrochloride Solution for injection; Adults: 0.5 to 1 mcg/kg/minute continuous IV infusion; titrate to clinical response. Usual dosage range: 2 to 20 mcg/kg/minute. Max: 40 mcg/kg/minute.
- Corticosteroid
  - Dexamethasone
    - Dexamethasone Sodium Phosphate Solution for injection; Adults: 6 mg IV once daily for up to 10 days is recommended by the NIH guidelines for use in mechanically ventilated patients and patients who require supplemental oxygen. Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
- Anticoagulants
  - Enoxaparin
    - Enoxaparin Sodium (Porcine) Solution for injection; Neonates and Infants younger than 2 months†: 0.75 mg/kg subcutaneously every 12 hours; adjust dose to maintain an anti-factor Xa concentration of 0.1 to 0.3 International Units/mL.
    - Enoxaparin Sodium (Porcine) Solution for injection; Infants, Children, and Adolescents 2 months to 17 years†: 0.5 mg/kg subcutaneously every 12 hours; adjust dose to maintain an anti-factor Xa concentration of 0.1 to 0.3 International Units/mL.
    - Enoxaparin Sodium (Porcine) Solution for injection; General medical Adult patients with risk factors for DVT due to restrictive mobility during acute illness (e.g., moderate to severe congestive heart failure, severe respiratory disease, or patients who are confined to bed and have 1 or more of the following risk factors: active cancer, history of VTE, sepsis, acute neurological disease, and inflammatory bowel disease): 40 mg subcutaneously once daily for 14 days or less.
- Sedatives (for mechanically ventilated patients)
  - Dexmedetomidine
    - Dexmedetomidine Hydrochloride Solution for injection; Term Neonates†: Limited data available; infusion rates comparable to those used in older populations have been reported in neonates (mean infusion rate: 0.4 mcg/kg/hour). However, decreased plasma clearance and prolonged half-life may warrant relatively lower doses in neonates. 0.05, 0.1, or 0.2 mcg/kg IV loading dose, followed by 0.05, 0.1, or 0.2 mcg/kg/hour continuous IV infusion adequately sedated mechanically-ventilated neonates (n = 24) for 6 to 24 hours in an open-label trial. Retrospective reviews including term neonates have reported no loading doses and higher infusion rates ranging from 0.1 to 1.5 mcg/kg/hour (mean: 0.4 mcg/kg/hour) continuous IV infusion for a median duration of 78 hours (range: 40 to 290 hours). Mean maximum infusion rate was 0.8 mcg/kg/hour (range: 0.3 to 2 mcg/kg/hour). A median maximum infusion dose of 1.8 mcg/kg/hour has been reported in a phase I pharmacokinetic trial (n = 20).
    - Dexmedetomidine Hydrochloride Solution for injection; Infants†, Children†, and Adolescents†: 0.5 to 1 mcg/kg IV loading dose over 10 minutes, followed by 0.2 to 0.7 mcg/kg/hour continuous IV infusion; titrate by 0.1 to 0.2 mcg/kg/hour every 20 to 30 minutes to clinical response. Loading dose is optional. Doses up to 2.5 mcg/kg/hour have been used.
    - Dexmedetomidine Hydrochloride Solution for injection; Adults: 1 mcg/kg IV loading dose over 10 minutes, followed by 0.2 to 0.7 mcg/kg/hour continuous IV infusion for up to 24 hours; titrate to clinical response. Loading dose may not be required. May increase infusion rate up to 1.5 mcg/kg/hour as tolerated.

- Propofol
    - Propofol Emulsion for injection; Adolescents 17 years: 5 mcg/kg/minute continuous IV infusion, initially; titrate by 5 to 10 mcg/kg/minute every 5 to 10 minutes to clinical response. Usual dose: 5 to 50 mcg/kg/minute. Do not exceed 4 mg/kg/hour unless the benefits outweigh the risks. May use 10 to 20 mg IV bolus if needed to rapidly increase sedation depth in patients where hypotension is unlikely to occur.
    - Propofol Emulsion for injection; Adults: 5 mcg/kg/minute continuous IV infusion, initially; titrate by 5 to 10 mcg/kg/minute every 5 to 10 minutes to clinical response. Usual dose: 5 to 50 mcg/kg/minute. Do not exceed 4 mg/kg/hour unless the benefits outweigh the risks. May use 10 to 20 mg IV bolus if needed to rapidly increase sedation depth in patients where hypotension is unlikely to occur.
  - Neuromuscular blockers (for mechanically ventilated patients)
    - Rocuronium
        - Intermittent IV dosage
            - Rocuronium Bromide Solution for injection; Neonates: 0.45 to 0.6 mg/kg IV once, followed by 0.075 to 0.6 mg/kg/dose IV as needed; adjust dose and interval to patient's twitch response. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
            - Rocuronium Bromide Solution for injection; Infants, Children, and Adolescents: 0.45 to 0.6 mg/kg IV once, followed by 0.075 to 0.6 mg/kg/dose IV as needed; adjust dose and interval to patient's twitch response. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
            - Rocuronium Bromide Solution for injection; Adults: 0.6 to 1 mg/kg IV once, followed by 0.1 to 1 mg/kg/dose IV as needed; adjust dose and interval to patient's twitch response. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
        - Continuous infusion IV dosage
            - Rocuronium Bromide Solution for injection; Neonates: 0.6 mg/kg IV bolus, followed by 5 to 10 mcg/kg/minute continuous IV infusion; titrate to patient's twitch response. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
            - Rocuronium Bromide Solution for injection; Infants, Children, and Adolescents: 0.6 mg/kg IV bolus, followed by 5 to 10 mcg/kg/minute continuous IV infusion; titrate to patient's twitch response. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
            - Rocuronium Bromide Solution for injection; Adults: 0.6 to 1 mg/kg IV bolus, followed by 8 to 12 mcg/kg/minute continuous IV infusion; titrate to patient's twitch response. Usual dosage range: 4 to 16 mcg/kg/minute. Coadministration of certain drugs may need to be avoided or dosage adjustments may be necessary; review drug interactions.
- Nondrug and supportive care
  - Excellent supportive care is the only treatment to date that appears to be consistently helpful in COVID-19
  - WHO,[10] NIH,[50] and Surviving Sepsis Campaign[55] provide specific guidance for oxygenation, ventilation, and fluid management in COVID-19
    - Patients with severe respiratory distress, obstructed or absent breathing, central cyanosis, shock, seizures, or coma require aggressive airway management (which may include intubation) and oxygen
        - Assess severity of respiratory distress using the PaO_2/FIO_2 ratio; some guidelines and protocols use this ratio to direct management of oxygenation and ventilation
            - Mild acute respiratory distress syndrome: 300 mm Hg or less, but greater than 200 mm Hg
            - Moderate acute respiratory distress syndrome: 200 mm Hg or less, but greater than 100 mm Hg
            - Severe acute respiratory distress syndrome: 100 mm Hg or less
    - Oxygenation and ventilation
        - Begin supplemental oxygen therapy when oxygen saturation falls below 90% to 92%[55]
        - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute[10]
            - Titrate to reach SpO_2 of 94% or more initially
            - Once stable, target SpO_2 of 90% or higher in nonpregnant adults; 92% or higher in pregnant patients
            - In most children the target SpO_2 is 90% or greater; for those who require urgent resuscitation (eg, those with apnea or obstructed breathing, severe respiratory distress, central cyanosis, shock, seizures, or coma), a target SpO_2 of 94% or higher is recommended
        - High-flow nasal oxygen or noninvasive ventilation has been used to achieve adequate oxygenation in some patients[68]
            - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign[55] and NIH[50] for patients with COVID-19 who develop hypoxemic respiratory failure despite conventional oxygen therapy; there is some evidence that it averts the need for intubation and mechanical ventilation. Noninvasive positive pressure ventilation may be used if high-flow nasal oxygen is not available

- □ However, there is concern that these techniques may result in higher risk of aerosolization of the virus. Additionally, sudden deterioration may require emergent intubation, which is associated with more risk to both patient and provider. Therefore, some authorities reserve these options for settings in which airborne precautions can be taken and close monitoring provided [55]
  - □ Mechanical ventilation may become necessary for patients in whom oxygenation targets cannot be met with less invasive measures or who cannot maintain the work of breathing (eg, PaO_2/FIO_2 ratio of less than 300 mm Hg) [7]
    - □ Recommended settings are tidal volume of 4 to 8 mL/kg (predicted body weight) and inspiratory pressures less than 30 cm H_2O
    - □ In children, tidal volumes of 5 to 8 mL/kg (predicted body weight) for preserved lung compliance and 3 to 6 mL/kg for poor compliance; inspiratory pressures should be less than 28 cm H_2O
    - □ Use of PEEP may be necessary in patients with acute respiratory distress syndrome (especially with PaO_2/FIO_2 ratio less than 200 mm Hg). [7] Optimal regimen is not clearly defined, although guidelines [10, 55] suggest higher pressures (eg, more than 10 cm H_2O) rather than lower pressures. A protocol is available from ARDSNet [69]
    - □ Routine use of inhaled nitric oxide is not recommended by either Surviving Sepsis Campaign or NIH guidelines; both note that a trial may be reasonable as a rescue strategy in patients who remain hypoxemic despite all other measures [50, 55]
    - □ For patients with moderate to severe acute respiratory distress syndrome, prone positioning for 12 to 16 hours/day is recommended
      - □ Lateral decubitus position for pregnant women
    - □ Sedation with or without neuromuscular blockade may be necessary for comfort and optimal ventilation; Society of Critical Care Medicine offers guidance on appropriate agents [70] (eg, propofol, dexmedetomidine) and monitoring; shortages are occurring and American Society of Health-System Pharmacists offers guidance on substitutions [71]
      - □ If neuromuscular blockade (eg, rocuronium) is needed (eg, for ventilator dyssynchrony), Surviving Sepsis Campaign guideline suggests intermittent boluses rather than continuous infusion [55]
    - □ Mechanical ventilation may be required for a prolonged period, necessitating tracheostomy
  - □ Extracorporeal membrane oxygenation has been used [6] in severely ill patients, and it can be considered if resources and expertise are available
- – Fluid management
  - □ Overhydration should be avoided, because it may precipitate or exacerbate acute respiratory distress syndrome
  - □ An assessment of likely fluid responsiveness may be made by measuring the change in cardiac output (by echocardiography or transpulmonary thermodilution) on passive leg raise; an increase in cardiac output after 1 minute of passive leg raise has been shown to be a reliable predictor of response and helps to avoid overhydration in patients unlikely to respond [72]
  - □ In patients with shock:
    - □ Administration of crystalloids is recommended (preferably buffered/balanced; eg, Lactated Ringer solution); solutions such as hydroxyethyl starches, gelatins, dextrans, and albumin are not recommended according to Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19. WHO [10] provides the following guidance:
      - □ Adults: administer 250 to 500 mL over the first 15 to 30 minutes; goal is mean arterial pressure of 60 to 65 mm Hg [55] (if invasive pressure monitoring is available)
      - □ Children: 10 to 20 mL/kg bolus over the first 30 to 60 minutes
      - □ If there is no response to fluid bolus or if signs of fluid overload exist, discontinue or reduce fluid administration
      - □ For patients who respond to initial bolus and are without evidence of fluid overload, titrate continued fluid to achieve improvement in clinical signs (capillary refill, heart rate, tactile temperature of extremities, palpable pulses), urine output (0.5 mL/kg/hour in adults, 1 mL/kg/hour in children), and hemodynamic parameters (mean arterial pressure more than 65 mm Hg in adults)
- ○ Procedures
  - – Extracorporeal membrane oxygenation
    - □ General explanation
      - □ Heart-lung bypass is a technique in which blood is circulated from patient through bypass machine, where transmembrane exchange of oxygen and carbon dioxide occurs before blood is returned to patient; can also be used to support arterial blood pressure
    - □ Indication
      - □ Refractory hypoxemia with or without hemodynamic compromise despite standard supportive measures
      - □ May be helpful if resources and expertise are available [55]
    - □ Contraindications
      - □ Neurologic impairment

□ Severe preexisting disease
□ Complications
□ Limb ischemia distal to vascular access catheters
- Comorbidities
  ○ Severe COVID-19 has been associated with chronic conditions such as diabetes, hypertension, and other cardiovascular conditions; existing published guidance on COVID-19 management does not address issues specific to these comorbidities [6, 18]
  ○ Owing to the role of the ACE2 receptor in the pathogenesis of COVID-19, controversy has arisen over the positive or negative effects that ACE inhibitors and angiotensin receptor blockers may have on the disease. A joint statement by the American College of Cardiology, American Heart Association, and Heart Failure Society of America recommends that persons who are currently taking these medications for appropriate indications should continue to do so [73]
    − Several analyses of data from large numbers of patients with COVID-19 have shown no association between ACE inhibitors or angiotensin receptor blockers and either acquisition of COVID-19 or severity of infection [74, 75, 76]

MONITORING
- Standard critical care monitoring, including oxygen saturation and hemodynamic measures, is appropriate
- For patients receiving chloroquine or hydroxychloroquine, monitoring of QTc is recommended [56]
  ○ Perform ECG at baseline, 2 to 3 hours after second dose of drug, and daily thereafter
  ○ If QTc increases by more than 60 milliseconds or absolute QTc is greater than 500 milliseconds (or greater than 530 to 550 milliseconds if QRS exceeds 120 milliseconds), reduce dose and (if applicable) discontinue azithromycin
- Patients who are undergoing a trial of high-flow oxygen or noninvasive ventilation require especially close attention pending sustained improvement or decision to intubate

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS
- Among ICU patients, the following complications have been noted most frequently: [7]
  ○ Acute respiratory distress syndrome (60% to 70%)
  ○ Shock (30%)
  ○ Myocardial injury (20% to 30%) and arrhythmias (44%)
  ○ Acute kidney injury (10% to 30%)
- Secondary bacterial and fungal infections and multiorgan failure have also been commonly cited; thrombotic events are being recognized with increasing frequency

PROGNOSIS
- Patients who require hospital admission often require prolonged inpatient stay (more than 20 days), although duration of stay may be inflated by need for isolation until documentation of sustained absence of fever and serial negative results on polymerase chain reaction test [34, 6]
  ○ Deconditioning may be profound
- Laboratory markers associated with mortality include high D-dimer levels, high C-reactive protein levels, and low lymphocyte counts [7]
- Reported mortality rates in critically ill patients are high (on the order of 40% or more) [2, 7]

SCREENING AND PREVENTION

PREVENTION
- In the critical care setting, infection control strategies are essential to prevent infection of staff and other patients; this includes standard, contact, and (at least) droplet precautions [44]
  ○ Patients should be placed in a single room, with the door closed, and ideally with structural and engineering safeguards against airborne transmission (eg, negative pressure, frequent air exchange); *but*, in the high-prevalence stages of the pandemic (with crowded hospitals), reserve negative pressure isolation rooms for the greatest needs (ie, aerosol-generating procedures; tuberculosis, measles, and varicella)
  ○ Source control should be applied whenever possible; this consists of a face mask or cloth covering for nonintubated patients and measures to reduce leakage around oxygen masks and from ventilator tubing
  ○ Limit transport of patient from the room (eg, for studies or procedures). Arrange for portable studies and procedures if feasible; during aerosol-generating procedures, limit number of workers in room to those necessary
  ○ Persons entering the room should wear gloves, gowns, eye protection, and surgical/procedural mask with adherence to hospital donning and doffing protocols, including aggressive hand hygiene. For aerosol-generating procedures, a respirator at least as effective as an N95 should be used in place of a surgical/procedural mask
  ○ Equipment used for patient care should be single-use (disposable) or should be disinfected between patients; WHO [77] suggests using 70% ethyl alcohol

- Criteria for discontinuation of isolation precautions may vary depending on resources. In patients who have had symptomatic illness, precautions should be maintained until the following conditions are met: [78]
  - Test-based
    - Demonstration of negative results of molecular assays for SARS-CoV-2 RNA on nasopharyngeal swabs obtained at least 24 hours apart (a single specimen suffices for each test), *and*
    - Subjective and objective evidence of clinical improvement, including absence of fever without use of antipyretic medication
  - Symptom-based
    - Subjective and objective evidence of improvement in respiratory symptoms and absence of fever without use of antipyretic medication for 72 hours, *and*
    - At least 10 days since onset of symptoms

SYNOPSIS

KEY POINTS
- COVID-19 (coronavirus disease 2019) is respiratory tract infection due to a novel coronavirus, SARS-CoV-2 (initially called 2019-nCoV); as of March 11, 2020, extent of infection was declared pandemic by WHO [1]
- About 5% of diagnosed cases require critical care to manage severe manifestations and complications. [2] Among patients with COVID-19 who are critically ill, mortality rates of 39% to 72% are reported [2]
- There is no specific antiviral therapy, although compassionate use and trial protocols for several agents are underway. At present, remdesivir appears most promising, based on preliminary reports of a large prospective randomized controlled trial. [48]Dexamethasone has also shown efficacy in patients with severe disease and hypoxemia [63]. Otherwise, treatment is largely supportive, consisting of supplemental oxygen and conservative fluid administration
- In patients with increasing hypoxemia, a cautious trial of high-flow oxygen or noninvasive ventilation may be undertaken. If significant improvement does not occur over a period of several hours, intubation and mechanical ventilation is indicated; optimal ventilatory strategy has not been clearly established, but most published recommendations are based on the ARDSNet protocol [10, 69, 7, 55]
- Pharmacologic support may be necessary in patients with shock whose hemodynamic parameters do not respond to fluids and oxygen; most guidelines favor norepinephrine as the initial agent for adults, and epinephrine in children [55, 7, 10]
- The most common complications, after acute respiratory distress syndrome and shock, are myocardial and renal dysfunction. Thrombotic events, both venous and arterial, are increasingly recognized [7]
- There is no vaccine available to prevent this infection; infection control measures are the mainstay of prevention (ie, standard, contact, and at least droplet precautions, with strict attention to proper donning and doffing of personal protective equipment)

URGENT ACTION
- Patients with respiratory distress require prompt administration of supplemental oxygen; patients with respiratory failure require intubation and mechanical ventilation
- Patients in shock require urgent fluid resuscitation and administration of empiric antimicrobial therapy to cover possible bacterial pathogens and/or influenza

PITFALLS
- Knowledge of this disease is incomplete and evolving; moreover, coronaviruses are known to mutate and recombine often, presenting an ongoing challenge to our understanding and to clinical management

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Reviewed on May 17, 2020 by:
John C. O'Horo, MD, MPH, FACP Consultant
Division of Infectious Diseases
Joint Appointment Divsion of Pulmonary & Crictical Care Medicine
Associate Professor of Medicine
Mayo Clinical College of Medicine