

## 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<sup>1</sup>
- 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<sup>2</sup>
- 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<sup>2</sup>
- 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,<sup>3</sup> similar to the agents of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)<sup>3</sup>
  - Classified as a member of the species *Severe acute respiratory syndrome–related coronavirus*<sup>4,5</sup>
  - Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2); earlier provisional name was 2019-nCoV<sup>4,5</sup>

## 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)<sup>6</sup>
    - Median time from symptom onset to pneumonia is 5 days; time to severe hypoxemia is 7 to 12 days<sup>7</sup>
  - 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<sup>8,9</sup>
    - 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<sup>10</sup>); be aware that pulse oximetry may be less accurate in dark-skinned persons, in whom the readings may be falsely high (ie, higher than concurrently measured arterial blood oxygen levels)<sup>2</sup>
  - Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever<sup>6</sup>
  - Patients with severe disease may appear quite ill, with tachypnea and labored respirations
  - Tachyarrhythmias may be noted on auscultation or cardiac monitor<sup>11</sup>
  - 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<sup>12</sup>
  - Other reported neurologic findings in severe disease include hyperactive deep tendon reflexes, ankle clonus, and positive Babinski sign<sup>13</sup>
  - Patients may be agitated, confused, or poorly responsive<sup>13</sup>
  - A variety of skin changes have been described, including purpura<sup>14</sup> and petechiae<sup>15</sup> as well as the vesicular<sup>16</sup> and nonspecific erythematous exanthems<sup>17</sup> 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:<sup>10</sup>
    - 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<sup>18</sup> and occurs with close contact,<sup>19</sup> probably largely via respiratory droplets and perhaps in some cases by aerosolization<sup>19</sup>
  - 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<sup>2</sup>
      - 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<sup>20</sup>
  - 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<sup>21</sup>
  - Other risk factors/associations
    - Various underlying medical conditions have been associated with increased risk for severe disease, especially if they are not well controlled:<sup>22</sup>
      - Chronic kidney disease
      - Chronic obstructive pulmonary disease
      - Diabetes type 2
      - Down syndrome
      - Immunosuppression because of previous solid organ transplant
      - Malignancy
      - Pregnancy
      - Severe obesity (BMI of 40 kg/m<sup>2</sup> or higher)
      - Serious cardiac conditions (eg, heart failure, coronary artery disease, cardiomyopathy)
      - Sickle cell disease
      - Smoking
    - Conditions which may be associated with higher risk for severe disease:<sup>22</sup>
      - Asthma (moderate to severe)
      - Cerebrovascular disease
      - Chronic liver disease
      - Cystic fibrosis
      - Diabetes type 1
      - 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
      - Overweight (BMI more than 25 kg/m<sup>2</sup> but less than 30 kg/m<sup>2</sup>)
      - Pulmonary fibrosis
      - Thalassemia
    - Children with medically complex conditions (eg, neurologic, metabolic, genetic, cardiac) are also at higher risk for severe disease<sup>22</sup>

- 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<sup>23</sup>

## DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Polymerase chain reaction tests are the standard for diagnosis; antigen testing<sup>24</sup> has also received emergency use authorization in the United States. Specific test methods and availability vary; public health authorities may assist in arranging diagnostic testing in some areas. Attempts to culture the virus are not recommended. Serologic tests<sup>25</sup> are not recommended for diagnostic purposes in most circumstances<sup>26, 27, 28</sup>
  - WHO<sup>29, 30, 10</sup> and CDC<sup>27</sup> 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 viral testing.<sup>27</sup> 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)<sup>31</sup>
      - Upper respiratory tract
        - Nasopharyngeal, deep nasal (midturbinate), anterior nares, oropharyngeal, or saliva specimens 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. Note that not all tests are designed for use on all specimens
        - 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
        - For tests designed for use on saliva, supervised self-collection of 1 to 5 mL is recommended
      - 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<sup>32</sup>
    - Favor nasopharyngeal, nasal, or midturbinate specimens, saliva specimen, or combined anterior nasal/oropharyngeal swab over oropharyngeal swab alone for SARS-CoV-2 RNA 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
  - A systematic review and meta-analysis compared frequency with which SARS-CoV-2 RNA was detected in sputum, nasopharyngeal swabs, and oropharyngeal swabs in patients with documented COVID-19. Overall positivity was 71% for sputum, 54% for nasopharyngeal swabs, and 43% for oropharyngeal swabs. Earlier testing resulted in higher positivity rates in all specimens<sup>33</sup>
- Serologic testing is not recommended for routine use in diagnosis, but it may be useful under some circumstances (eg, high suspicion for disease with persistently negative results on viral RNA tests; in the diagnosis of multisystem inflammatory syndrome in children; in other situations in which retrospective confirmation of disease is indicated)<sup>25</sup>
- 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 testing<sup>10</sup>
  - Coinfections have been reported, but the frequency is unknown<sup>34, 35, 36</sup>

# COVID-19 critical care

- Influenza may be clinically indistinguishable from COVID-19; additionally, coinfection can occur. Therefore, when influenza and SARS-CoV-2 are both circulating in the community, testing for **both** viruses is recommended for all patients hospitalized with acute respiratory infection<sup>37, 38</sup>
  - CDC recommends nucleic acid detection over antigen testing for both pathogens, either by multiplex or individual assay
- 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;<sup>39</sup> plain radiography, CT, and ultrasonography have been used<sup>40</sup>
  - 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<sup>39</sup>
    - 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<sup>41</sup>
  - 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)<sup>39</sup>
- 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<sup>10, 42, 7</sup>
- 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<sup>7, 32</sup>
    - 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<sup>7, 32</sup>
  - Antigen tests are also available for use in diagnosis, and they have the advantage of rapid turnaround
    - In general, these tests are less sensitive than polymerase chain reaction, although specificity is equivalent and may be as high as 100%; therefore, false-positive results are uncommon, but a negative result may warrant retesting (preferably within 2 days) with polymerase chain reaction if there is a high suspicion for infection based on clinical or epidemiologic indicators<sup>24</sup>
    - A Cochrane review noted wide-ranging sensitivity and specificity of antigen tests (average sensitivity, 56.2%; average specificity, 99.5%), but it concluded that existing published evaluation of these tests has been based largely on application to remnant laboratory samples and thus may not reflect performance in clinical use
  - A Cochrane review<sup>43</sup> notes that antibody tests are most likely to be clinically useful 15 days or more into the course of infection and that data are scarce regarding antibody tests beyond 35 days. For instances when clinicians judge that antibody testing is indicated, Infectious Diseases Society of America<sup>25</sup> makes the following recommendations:
    - Testing 3 to 4 weeks after symptom onset maximizes sensitivity
      - Sensitivity at 1 week ranges from 0.23 to 0.63; at 2 weeks, from 0.68 to 0.96
    - Test should measure anti-SARS-CoV-2 IgG or total antibody; a high-specificity test should be used
      - Unlike the usual pattern of antibody production, IgM antibody response to SARS-CoV-2 is somewhat delayed, occurring almost simultaneously with IgG production, so there is no advantage to testing selectively for the IgM fraction
  - 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<sup>40, 6, 18</sup>
    - Anemia was noted in about half of patients in one series<sup>40</sup>
    - Both elevated and low platelet counts have been seen<sup>6, 18, 40</sup>
    - Prolonged prothrombin time has been reported<sup>44</sup>
    - Levels of D-dimer and fibrinogen may be elevated<sup>6, 18</sup>

# COVID-19 critical care

- Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common<sup>40, 6</sup>
- Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection<sup>6</sup>
- Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate<sup>40</sup>
- 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<sup>45</sup>
  - Some experts caution against measuring these biomarkers in the absence of suggestive clinical findings,<sup>45</sup> whereas others note the possibility that elevations suggest noncoronary myocardial involvement that may benefit from early use of vasopressors and inotropes<sup>7</sup>
- Lactate level of 2 mmol/L or higher suggests presence of septic shock<sup>10</sup>
- 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<sup>18, 3, 46, 6, 40</sup>
  - CT appears to be more sensitive<sup>39, 47</sup> than plain radiographs, but normal appearance on CT does not preclude the possibility of COVID-19<sup>48</sup>
  - 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<sup>49, 7</sup>

## 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
    - Influenza may be clinically indistinguishable from COVID-19; additionally, coinfection can occur. Therefore, when influenza and SARS-CoV-2 are both circulating in the community, testing for **both** viruses is recommended for all patients hospitalized with acute respiratory infection<sup>37, 38</sup>
      - CDC recommends nucleic acid detection over antigen testing for both pathogens, either by multiplex or individual assay
  - 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<sup>50</sup>
      - Characterized by tachypnea (respiratory rate greater than 30 breaths or less than 10 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO<sub>2</sub> of less than 92%)
      - Pediatric criteria include central cyanosis or SpO<sub>2</sub> 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<sup>51</sup>
  - 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, 1 antiviral agent (remdesivir) is FDA-approved specifically for treatment<sup>52</sup> of this infection. Certain monoclonal antibodies are used in mild to moderate disease (according to risk of progression) but are not used in critical care. Several other existing drugs are being used under clinical trial and compassionate use protocols based on in vitro activity (against this or related viruses) and limited clinical experience. One of these (baricitinib<sup>53</sup>), a disease-modifying antirheumatic drug used in refractory rheumatoid arthritis, has received emergency use authorization for administration in conjunction with remdesivir in patients with severe disease. Information on therapeutic trials and expanded access is available at ClinicalTrials.gov<sup>54</sup>
  - Remdesivir is an antiviral agent with significant in vitro activity against coronaviruses,<sup>55,56</sup> some evidence of efficacy in an animal model of MERS,<sup>56</sup> and some evidence of efficacy in COVID-19<sup>57</sup>
    - Remdesivir is approved to treat hospitalized patients with COVID-19. The FDA approval extends to patients aged 12 years or older who weigh 40 kg or more; the earlier emergency use authorization provides continued access for pediatric patients younger than 12 years and/or who weigh less than 40 kg but more than 3.5 kg<sup>52</sup>
      - Preliminary<sup>58</sup> and follow-up<sup>57</sup> results of the Adaptive COVID-19 Treatment Trial, a placebo-controlled randomized trial in 1062 patients, showed a statistically significant improvement in time to recovery and a nonsignificant trend in lower mortality; several other trials remain active, as well<sup>59</sup>
    - On the basis of these and other data from clinical trials, the NIH guideline recommends, and the Infectious Diseases Society of America and Surviving Sepsis Campaign guidelines suggest, remdesivir for hospitalized patients with COVID-19 who require supplemental oxygen<sup>60,37,61</sup>
      - Because there is less certainty about efficacy in patients who are ill enough to require more aggressive airway assistance methods (eg, high-flow oxygen, noninvasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation), and to mitigate or prevent shortages of remdesivir, NIH suggests that dexamethasone without remdesivir is a reasonable option in those circumstances
      - Infectious Diseases Society of America recommends use of remdesivir over no antiviral in these patients, but it acknowledges that if shortages occur, this consideration should be taken into account in allocating available drug
      - For patients whose condition worsens while they are receiving remdesivir and who require institution of high-flow oxygen, ventilation, or extracorporeal membrane oxygenation, NIH recommends that the treatment course be completed
      - Surviving Sepsis Campaign guideline suggests that remdesivir not be used in patients with critical COVID-19, outside of clinical trials<sup>60</sup>
    - WHO does not recommend remdesivir use outside of clinical trials<sup>10</sup>

# COVID-19 critical care

- 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,<sup>62</sup> although some clinical trials are still in progress<sup>63</sup>
  - 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<sup>64</sup>
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against using hydroxychloroquine<sup>60,65</sup>
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends against hydroxychloroquine or chloroquine and against the combination of either of those drugs with azithromycin<sup>61</sup>
  - NIH guidelines recommend against chloroquine or hydroxychloroquine in hospitalized patients<sup>37</sup>
  - WHO recommends against use of chloroquine or hydroxychloroquine with or without azithromycin outside of a clinical trial<sup>10</sup>
  - 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<sup>66</sup>
  - A subsequently published randomized controlled open-label trial (RECOVERY) of 1561 patients treated with hydroxychloroquine and 3155 treated without showed no survival advantage among patients treated with hydroxychloroquine<sup>67</sup>
- 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
  - 3 randomized placebo-controlled trials have evaluated the effects of lopinavir-ritonavir in the treatment of COVID-19. The combined data<sup>61</sup> did not show significant differences in progression to mechanical ventilation or in mortality
  - NIH COVID-19 treatment guideline,<sup>37</sup> Infectious Diseases Society of America treatment guideline,<sup>61</sup> and Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19<sup>65</sup> 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<sup>65</sup>
  - WHO recommends against use of lopinavir-ritonavir outside of a clinical trial<sup>10</sup>
- Since last guideline updates, interim results of the WHO SOLIDARITY trial have been published. Remdesivir, lopinavir-ritonavir, hydroxychloroquine, and interferon were compared with one another (open label) and with standard care (no placebo) in a total population of over 11,000 patients in over 400 hospitals in 30 countries worldwide<sup>68</sup>
  - End points were in-hospital mortality, initiation of ventilation, and duration of hospital stay. No differences among the groups were noted for any of these parameters. The authors acknowledge that length of stay may have been influenced in some cases by the requirements of antiviral administration (eg, 10 days of IV administration for remdesivir), but they argue that the similarity in percentages of patients in each group remaining in the hospital beyond the course of the study drug indicates a lack of benefit to any treatment arm
    - Full impact of this study on treatment guidelines remains to be seen, but various recommendations against general use of lopinavir-ritonavir and hydroxychloroquine for COVID-19, for example, have evolved
- Studies on the therapeutic efficacy of convalescent plasma are underway in various countries
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 suggests that convalescent plasma not be used outside of clinical trials<sup>60</sup>
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial<sup>61</sup>
  - 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<sup>37</sup>
  - WHO recommends against use of plasma therapy outside of a clinical trial<sup>10</sup>
  - Since the publication of these guidelines, and based on emerging information, FDA has issued an emergency use authorization, citing, among other reasons, the observational safety and efficacy data from 20,000 patients who received convalescent plasma through a program sponsored by the Mayo Clinic:<sup>69</sup>
    - Serious adverse events were uncommon, and they were judged not to exceed the known incidence in transfusion of plasma to critically ill patients

## COVID-19 critical care

- There was some evidence of improved survival in the subset of patients treated with convalescent plasma containing higher titers of neutralizing antibody compared with patients who received plasma with lower levels (ie, there appeared to be a dose-response gradient)
- Early administration (eg, before mechanical ventilation is required) appeared more likely to be beneficial, but the possibility of benefit even to intubated patients could not be excluded
- FDA has produced a fact sheet<sup>70</sup> for providers that includes labeling criteria (high versus low titer), suggested dosing and infusion practices, and potential adverse effects. It suggests starting with a single unit (about 200 mL), taking care to avoid fluid overload in patients with impaired cardiac function; additional doses may be administered based on the patient's response and clinician's judgment
- 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<sup>65</sup> and sarilumab,<sup>71</sup> both monoclonal antibodies against interleukin-6 receptor; baricitinib<sup>53</sup> and other Janus kinase inhibitors)
  - Baricitinib, a Janus kinase inhibitor currently approved for use in refractory rheumatoid arthritis owing to its antiinflammatory effect, has received emergency use authorization for treatment in combination with remdesivir for severely ill patients on oxygen supplementation (including mechanical ventilation or extracorporeal membrane oxygenation)<sup>53</sup>
    - FDA reviewed data from the ACTT-2 trial (Adaptive COVID-19 Treatment Trial 2), which compared remdesivir plus baricitinib (515 patients) against remdesivir plus placebo (518 patients) in patients with documented SARS-CoV-2 infection and either pulmonary infiltrates, O<sub>2</sub> saturation less than 94%, or requirement for some degree of oxygen supplementation. Patients who received baricitinib were more likely to have better clinical status (based on an 8-point score) at day 15 than those who did not. Median time to recovery was 7 days in the baricitinib arm versus 8 days in the placebo group. The odds of dying or progressing to noninvasive/high-flow oxygen or invasive ventilation were significantly lower for patients in the baricitinib group<sup>53</sup>
    - NIH guidelines find data to be insufficient to recommend for or against use of baricitinib with remdesivir in hospitalized patients when corticosteroids can be used; in circumstances in which corticosteroids cannot be used, they recommend use of baricitinib with remdesivir in hospitalized nonintubated patients. They recommend against the use of baricitinib without remdesivir except in clinical trials, and they caution that use of baricitinib with corticosteroids increases the risk of superinfection versus use of a single immunosuppressive agent<sup>37</sup>
    - Infectious Diseases Society of America guidelines recommend baricitinib plus remdesivir in hospitalized patients with severe COVID-19 when corticosteroids cannot be used, and they note uncertain benefits in patients who require mechanical ventilation. They recommend use of baricitinib in addition to remdesivir plus steroids only in the context of a clinical trial<sup>61</sup>
  - 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 tocilizumab; the guideline did not evaluate other monoclonal antibodies<sup>65</sup>
  - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America suggests against the routine use of tocilizumab, based on evidence of low certainty, although it does recommend tocilizumab in addition to standard care (steroids) for patients with progressive severe or critical COVID-19 who have elevated levels of markers of systemic inflammation<sup>61</sup>
  - NIH COVID-19 treatment guideline recommends tocilizumab in combination with dexamethasone (with or without remdesivir) in recently hospitalized patients who are showing rapid respiratory decompensation. This class includes (1) those who require invasive or noninvasive mechanical ventilation or high-flow oxygen and (2) those with rapidly increasing oxygen needs requiring noninvasive ventilation or high-flow nasal cannula and who have significantly increased levels of inflammatory markers<sup>37</sup>
    - Current version of the guideline does not comment directly on sarilumab; previous versions indicated that data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an ICU and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (more than 0.4 FIO<sub>2</sub>/30 L/minute); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guideline recommends against use of sarilumab outside clinical trials
    - NIH guideline recommends against use of siltuximab (another monoclonal antibody against interleukin-6 activity) outside of a clinical trial
    - NIH guideline notes that data are insufficient to recommend for or against use of interleukin-1 inhibitors (eg, anakinra) or interferon beta (the latter in mild to moderate infection); it recommends against use of interferons in severe or critical infection and against use of kinase inhibitors
  - WHO recommends against use of immunomodulators outside of a clinical trial<sup>10</sup>
  - A systematic review and meta-analysis of retrospective trials with data from 240 patients who received tocilizumab and 352 controls concluded that the low-quality evidence available did not demonstrate clear benefit from tocilizumab<sup>72</sup>

## COVID-19 critical care

- A review of data from 5 randomized controlled trials comparing tocilizumab to usual care (with or without placebo) did not show a 28-day mortality benefit, but it did show a lower relative risk of clinical deterioration (ie, ICU admission, mechanical ventilation, death), although evidence was of low certainty<sup>61</sup>
- 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<sup>10</sup>
  - A randomized controlled trial in more than 6000 hospitalized patients with COVID-19 found that dexamethasone reduced deaths in patients with severe respiratory complications requiring supplemental oxygen<sup>73</sup>
    - 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
  - Based on these data, NIH COVID-19 treatment guideline recommends use of dexamethasone in patients who require supplemental oxygen with or without mechanical ventilation (optional for patients who require oxygen supplementation only, that is, without high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation). It recommends against using dexamethasone in patients who do not require oxygen supplementation<sup>37</sup>
    - In the absence of dexamethasone, another glucocorticoid (eg, prednisone, methylprednisolone, hydrocortisone) may be used
  - Similarly, Infectious Diseases Society of America guideline suggests use of dexamethasone in hospitalized patients who are severely or critically ill with COVID-19, defined as SpO<sub>2</sub> of 94% or less on room air or any requirement for supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation<sup>61</sup>
    - Guideline provides equivalent doses of alternative glucocorticoids if dexamethasone is unavailable
    - Infectious Diseases Society of America recommends against the use of steroids in patients who are not hypoxemic
  - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 strongly recommends using corticosteroids (preferably dexamethasone) for up to 10 days in patients with severe or critical COVID-19<sup>65, 60</sup>
  - 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)<sup>10</sup>
- 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<sup>74</sup>
  - 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<sup>37</sup>
  - 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<sup>75</sup>
- Until a diagnosis of COVID-19 is confirmed by polymerase chain reaction or antigen 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<sup>10</sup>
  - 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<sup>65</sup>
- 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 suggest or recommend use of usual prophylactic regimens in any hospitalized patient with COVID-19, including pregnant patients<sup>37, 42, 60, 76, 77</sup>
- 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<sup>10</sup>
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Surviving Sepsis Campaign,<sup>65</sup> NIH COVID-19 treatment guideline,<sup>37</sup> and WHO<sup>10</sup> provide guidance specific to 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<sup>60</sup>
  - 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<sup>60</sup>
  - For adults with refractory septic shock, NIH guideline recommends addition of low-dose corticosteroids if corticosteroids are not already being administered for other indications<sup>37</sup>

# COVID-19 critical care

- 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<sup>60</sup>
- In children, epinephrine is considered the first line agent, and norepinephrine may be added if necessary<sup>10</sup>
- Drug therapy
  - Antiviral agent
    - Remdesivir<sup>78, 79</sup>
      - Remdesivir Solution for injection; Neonates weighing 3.5 kg or more requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)†: 5 mg/kg/dose IV once on day 1, followed by 2.5 mg/kg/dose IV once daily for 9 days.
      - Remdesivir Solution for injection; Neonates weighing 3.5 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)†: 5 mg/kg/dose IV once on day 1, followed by 2.5 mg/kg/dose IV once daily for 4 days; may extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Infants and Children 1 to 11 years weighing at least 3.5 kg requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)†: 5 mg/kg/dose (Max: 200 mg/dose) IV once on day 1, followed by 2.5 mg/kg/dose (Max: 100 mg/dose) IV once daily for 9 days.
      - Remdesivir Solution for injection; Infants and Children 1 to 11 years weighing at least 3.5 kg NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)†: 5 mg/kg/dose (Max: 200 mg/dose) IV once on day 1, followed by 2.5 mg/kg/dose (Max: 100 mg/dose) IV once daily for 4 days; may extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Children and Adolescents 12 to 17 years weighing 40 kg or more requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1, followed by 100 mg IV once daily for 9 days.
      - Remdesivir Solution for injection; Children and Adolescents 12 to 17 years weighing 40 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1, followed by 100 mg IV once daily for 4 days; may extend treatment for up to 5 additional days if no clinical improvement.
      - Remdesivir Solution for injection; Adults requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1, followed by 100 mg IV once daily for 9 days.
      - Remdesivir Solution for injection; Adults NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1, followed by 100 mg IV once daily for 4 days; may extend treatment for up to 5 additional days if no clinical improvement.
    - Immunomodulators
      - Baricitinib
        - Baricitinib Oral tablet; Children 2 to less than 9 years: 2 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the use of baricitinib with remdesivir in pediatric patients.
        - Baricitinib Oral tablet; Children and Adolescents 9 years of age and older: 4 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the use of baricitinib with remdesivir in pediatric patients.
        - Baricitinib Oral tablet; Adults: 4 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. The NIH COVID-19 guidelines recommend baricitinib plus remdesivir only in rare circumstances where a corticosteroid cannot be used.
      - Tocilizumab
        - Tocilizumab Solution for injection; Adults: The NIH COVID-19 treatment guidelines recommend a single 8 mg/kg (actual body weight, up to 800 mg) IV dose given with dexamethasone (or equivalent corticosteroid) to treat recently hospitalized adults with rapid respiratory decompensation due to COVID-19 who meet the following criteria: admitted to the ICU within the prior 24 hours and require mechanical ventilation or high-flow nasal canula oxygen (more than 0.4 FiO<sub>2</sub>/30 L/min) OR not in the ICU but have rapidly increasing oxygen needs requiring noninvasive mechanical ventilation or high-flow nasal canula AND have significantly increased markers of inflammation. Some Panel members also support use of the drug in patients who don't yet require mechanical ventilation or high-flow nasal canula but have rapidly increasing oxygen needs while on dexamethasone AND have a CRP of at least 75 mg/L.

# COVID-19 critical care

- Sarilumab
  - IV dosage
    - Sarilumab Solution for injection; Adults: According to the NIH COVID-19 treatment guidelines, data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an intensive care unit (ICU) and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (greater than 0.4 FiO<sub>2</sub>/30 L/min); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guidelines recommend against the use of sarilumab outside clinical trials. 400 mg IV once in combination with antiviral therapy is being evaluated.
  - Subcutaneous dosage
    - Sarilumab Solution for injection; Adults: According to the NIH COVID-19 treatment guidelines, data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an intensive care unit (ICU) and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (greater than 0.4 FiO<sub>2</sub>/30 L/min); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guidelines recommend against the use of sarilumab outside clinical trials. 200 or 400 mg subcutaneously once in combination with antiviral therapy is being evaluated.
- 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
  - For treatment of severe COVID-19 in patients requiring supplemental oxygen
    - Dexamethasone
      - Dexamethasone Sodium Phosphate Solution for injection; Adults: 6 mg IV once daily for up to 10 days or until hospital discharge (whichever comes first) is recommended by the NIH guidelines for use in hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The WHO strongly recommends systemic corticosteroids for 7 to 10 days in patients with severe or critical COVID-19. Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
    - Methylprednisolone
      - Methylprednisolone Sodium Succinate Solution for injection; Adults: 8 mg IV every 6 hours or 16 mg IV every 12 hours for 7 to 10 days. The WHO strongly recommends systemic corticosteroids in patients with severe or critical COVID-19. The NIH recommends methylprednisolone as an alternative corticosteroid for hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The NIH recommends 32 mg IV once daily (or in 2 divided doses) for up to 10 days or until hospital discharge (whichever comes first). Before starting therapy, review the patient's medical history and assess the potential risks and benefits.

# COVID-19 critical care

- Prednisone
  - Prednisone Oral solution; Adults: 40 mg PO daily for 7 to 10 days. The WHO strongly recommends systemic corticosteroids in patients with severe or critical COVID-19. The NIH recommends prednisone as an alternative corticosteroid for hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The NIH recommends 40 mg PO once daily (or in 2 divided doses) for up to 10 days or until hospital discharge (whichever comes first). Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
- For treatment of COVID-19–related septic shock refractory to vasopressors and fluids
  - Hydrocortisone
    - Hydrocortisone Sodium Succinate Solution for injection; Adults: 50 mg IV every 6 hours or 200 mg/day continuous IV infusion. Taper dose once vasopressors are no longer required.
- 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†: 0.05 to 0.5 mcg/kg IV, then 0.05 to 0.6 mcg/kg/hour continuous IV infusion, initially. Titrate until target level of sedation is attained. Loading doses are often bypassed. Max: 2.5 mcg/kg/hour.
    - Dexmedetomidine Hydrochloride Solution for injection; Infants†: 0.5 to 1 mcg/kg IV, then 0.1 to 0.5 mcg/kg/hour continuous IV infusion, initially. Titrate by 0.1 to 0.2 mcg/kg/hour every 20 to 30 minutes until target level of sedation is attained. Loading doses are often bypassed. Usual maintenance dose: 0.3 to 0.7 mcg/kg/hour. Max: 2.5 mcg/kg/hour.
    - Dexmedetomidine Hydrochloride Solution for injection; Children† and Adolescents†: 0.5 to 1 mcg/kg IV, then 0.1 to 0.5 mcg/kg/hour continuous IV infusion, initially. Titrate by 0.1 to 0.2 mcg/kg/hour every 20 to 30 minutes until target level of sedation is attained. Loading doses are often bypassed. Usual maintenance dose: 0.3 to 0.7 mcg/kg/hour. Max: 2.5 mcg/kg/hour.
    - Dexmedetomidine Hydrochloride Solution for injection; Adults: 1 mcg/kg IV, then 0.2 to 0.7 mcg/kg/hour continuous IV infusion, initially. Titrate until target level of sedation is attained. Loading doses are often bypassed. Max: 1.5 mcg/kg/hour.
  - 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.

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- 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 remains the mainstay of treatment to date in COVID-19
  - WHO,<sup>10</sup> NIH,<sup>37</sup> and Surviving Sepsis Campaign<sup>65</sup> 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<sub>2</sub>/FIO<sub>2</sub> 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%<sup>60</sup>
      - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute<sup>10</sup>
        - Titrate to reach SpO<sub>2</sub> of 94% or more initially
        - Once stable, target SpO<sub>2</sub> of 90% or higher in nonpregnant adults; 92% or higher in pregnant patients
        - In most children the target SpO<sub>2</sub> 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<sub>2</sub> of 94% or higher is recommended
      - High-flow nasal oxygen or noninvasive ventilation has been used to achieve adequate oxygenation in some patients<sup>80</sup>
        - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign<sup>65</sup> and NIH<sup>37</sup> 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<sup>65</sup>
      - For patients with persistent hypoxemia but without other indications for intubation, awake prone positioning can be tried as a means to improve oxygenation; it is not recommended as a means of averting the need for mechanical ventilation in patients who otherwise require it (eg, respiratory distress, hemodynamic instability)<sup>37</sup>
      - 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<sub>2</sub>/FIO<sub>2</sub> ratio of less than 300 mm Hg)<sup>7</sup>
        - Recommended settings are tidal volume of 4 to 8 mL/kg (predicted body weight) and inspiratory pressures less than 30 cm H<sub>2</sub>O
        - 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<sub>2</sub>O
        - Use of PEEP may be necessary in patients with acute respiratory distress syndrome (especially with PaO<sub>2</sub>/FIO<sub>2</sub> ratio less than 200 mm Hg).<sup>7</sup> Optimal regimen is not clearly defined, although guidelines<sup>10,60</sup> suggest higher pressures (eg, more than 10 cm H<sub>2</sub>O) rather than lower pressures. A protocol is available from ARDSNet<sup>81</sup>
        - 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<sup>37,60</sup>

# COVID-19 critical care

- 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; the Society of Critical Care Medicine offers guidance on appropriate agents<sup>82</sup> (eg, propofol, dexmedetomidine) and monitoring; shortages are occurring and the American Society of Health-System Pharmacists offers guidance on substitutions<sup>83</sup>
    - If neuromuscular blockade (eg, rocuronium) is needed (eg, for ventilator dyssynchrony), Surviving Sepsis Campaign guideline suggests intermittent boluses rather than continuous infusion<sup>65</sup>
  - Mechanical ventilation may be required for a prolonged period, necessitating tracheostomy
- Extracorporeal membrane oxygenation has been used<sup>6</sup> 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<sup>84</sup>
  - 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 the Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19. WHO<sup>10</sup> 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<sup>60</sup> (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<sup>60</sup>
    - 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<sup>6, 18</sup>
  - 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<sup>85</sup>
    - 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<sup>86, 87, 88</sup>

# COVID-19 critical care

- A prospective cohort study based on routinely collected data from more than 8 million persons enrolled in general practices in England identified more than 19,000 persons with COVID-19. Use of ACE inhibitors or angiotensin receptor blockers was associated with reduced risk of COVID-19 disease and was not associated with increased risk of requiring intensive care. The reduction in risk was less for Black people of Caribbean and African descent<sup>89</sup>
- Special populations
  - American College of Rheumatology has issued guidance pertaining to children with severe COVID-19 and hyperinflammation. It recommends that immunomodulatory therapy be considered in children with COVID-19 and acute respiratory distress syndrome; shock or cardiac dysfunction; elevated levels of L-lactate dehydrogenase, D-dimer, interleukin-6, interleukin-2 receptor, and/or ferritin; or low albumin level, low platelet count, and/or low lymphocyte count<sup>90</sup>
  - IV immunoglobulin is considered first line therapy; glucocorticoids should be used adjunctively in patients with severe disease. Anakinra may be considered in patients whose condition does not respond to these agents

## MONITORING

- Standard critical care monitoring, including oxygen saturation and hemodynamic measures, is appropriate
- 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:<sup>7</sup>
  - 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), and resulting deconditioning may be profound<sup>6, 40</sup>
- Laboratory markers associated with mortality include high D-dimer levels, high C-reactive protein levels, and low lymphocyte counts<sup>7</sup>
- Reported mortality rates in critically ill patients are high (on the order of 40% or more)<sup>7, 2</sup>

## SCREENING AND PREVENTION

### SCREENING

### PREVENTION

- Several vaccines against SARS-CoV-2 have entered use in various countries, and more are in development
- In the critical care setting, infection control strategies are essential to prevent infection of staff and other patients (ie, standard, contact, and at least droplet precautions, with strict attention to proper donning and doffing of personal protective equipment)<sup>51</sup>
  - 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<sup>91</sup> suggests using 70% ethyl alcohol
- Criteria for discontinuation of isolation precautions may vary depending on resources. CDC recommends that a symptom-based strategy should be used to determine when to discontinue isolation in most patients<sup>92, 93</sup>
  - For patients with severe or critical illness the following criteria apply:
    - At least 10 days and up to 20 days have passed since symptom onset *and*

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- At least 24 hours have passed since last fever without use of antipyretics *and*
- Symptoms have improved
- Test-based strategy is no longer advised in most cases, because many persons have prolonged positivity reflecting detection of noninfective viral particles. It may be used at discretion of provider in patients who have had severe disease or who are immunocompromised

## SYNOPSIS

### KEY POINTS

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection due to a novel coronavirus, SARS-CoV-2; global pandemic is ongoing
- About 5% of diagnosed cases require critical care to manage severe manifestations and complications.<sup>2</sup> Among patients with COVID-19 who are critically ill, mortality rates of 39% to 72% are reported<sup>2</sup>
- Remdesivir is the only FDA-approved antiviral drug<sup>52</sup> specifically for treatment of COVID-19; it is recommended for hospitalized patients with COVID-19 who require supplemental oxygen.<sup>61, 37</sup> Dexamethasone has also shown efficacy in patients with severe disease and hypoxemia.<sup>73</sup> Baricitinib<sup>53</sup>, a Janus kinase inhibitor, may also be added to remdesivir in severely ill patients, under emergency use authorization. Compassionate use and trial protocols for several other agents are underway. 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<sup>81, 10, 65, 7</sup>
- 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<sup>10, 65, 7</sup>
- 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<sup>7</sup>
- Several vaccines against SARS-CoV-2 have entered use in various countries, and more are in development. In the critical care setting, infection control strategies are essential to prevent infection of staff and other patients (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 Division of Pulmonary & Critical Care Medicine

Associate Professor of Medicine, Mayo Clinical College of Medicine