

TERMINOLOGY

CLINICAL CLARIFICATION

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection due to a novel coronavirus, SARS-CoV-2¹
- 5% of diagnosed cases require critical care to manage severe manifestations and complications, with reported mortality rates among ICU patients with COVID-19 ranging from 39% to 72%²
- Most patients with severe COVID-19 experience a bimodal illness, with initial improvement before severe worsening and critical illness. This may be related to the immunologic role in the sepsis seen with COVID-19 ("cytokine storm")

DIAGNOSIS

CLINICAL PRESENTATION

- History
 - In symptomatic patients, median time from symptom onset to pneumonia is 5 days; time to severe hypoxemia is 7 to 12 days³
 - 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^{4,5}
 - Cardiac, vascular, and neurologic manifestations may accompany pulmonary disease, resulting in localized symptoms (eg, pain, including headache) as well as alterations in cognition and level of consciousness
- Physical examination
 - Tachypnea, labored respirations
 - Silent or "happy" hypoxemia: COVID-19-related phenomena of asymptomatic hypoxemia
 - Fever, often exceeding 39 °C⁶
 - Tachyarrhythmias⁷
 - Signs/symptoms of arterial or deep vein thrombosis, including large-vessel stroke, as the presenting clinical event⁸
 - Positive neurologic findings, including hyperactive deep tendon reflexes, ankle clonus, and positive Babinski sign⁹
 - Agitation, confusion, decreased responsiveness⁹
 - Skin changes, including purpura, petechiae, vesicular rashes; nonspecific erythematous exanthems^{10,11,12,13,14}
 - Findings of shock, including hypotension, tachycardia, cool/clammy extremities, altered mental status

CAUSES AND RISK FACTORS

- Risk factors and/or associations
 - Age
 - Risk of severe disease increases with age^{15,2}
 - Sex
 - Male sex may be a risk factor for severe disease¹⁶
 - Other risk factors/associations
 - Medical conditions associated with increased risk for severe disease include chronic kidney disease, chronic obstructive pulmonary disease, type 2 diabetes, cardiovascular disease, severe obesity, immunosuppression, malignancy¹⁷
 - Residents of nursing homes and long-term care facilities are at high risk for acquiring infection and severe disease^{18,19}

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - Polymerase chain reaction tests are the standard for diagnosis; antigen testing has also received emergency use authorization in the United States^{20,21,22,23,3,24,25}
- Laboratory
 - Routine blood work is not diagnostic, but a pattern of typical abnormalities has emerged, particularly in patients with severe illness:^{26,27}
 - Leukopenia and anemia^{6,26,27}
 - Coagulopathy²⁷
 - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common^{27,6}
 - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection⁶
 - Serum levels of acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate²⁷
 - Cardiac biomarkers (troponin, B-type natriuretic peptides) may be elevated²⁸
 - Serum lactate levels are elevated in the setting of shock³

Severe COVID-19 (critical care)

- Imaging
 - Chest imaging (eg, plain radiography, CT, ultrasonography) shows abnormalities with bilateral involvement in most patients; varies from ground-glass opacities to consolidation in more severely ill patients^{26, 27, 29, 30, 6}
 - CT appears to be more sensitive than plain radiographs and can distinguish progression of infection from heart failure due to myocarditis or from pulmonary embolism (both commonly associated with COVID-19)^{31, 32, 33}
 - Bedside ultrasonography is widely used to monitor progression of pulmonary infiltrates, to assess cardiac function and volume status, and to detect deep vein or vascular catheter thrombosis^{3, 34}

TREATMENT

GOALS

- Ensure adequate oxygenation and hemodynamic support, and prevent complications

DISPOSITION

- Admission criteria
 - Criteria for ICU admission
 - Evidence of critical respiratory tract disease: tachypnea, severe respiratory distress, and inadequate oxygenation³⁵
 - 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
 - Consultation of specialists, including infectious disease, pulmonology, and critical care, is recommended

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 procedures³⁶
- Drug therapy
 - Remdesivir, an antiviral agent, is the only FDA-approved antiviral drug recommended specifically for treatment of hospitalized COVID-19 patients who require supplemental oxygen^{37, 38, 39, 40, 41}
 - Corticosteroid therapy is recommended for patients with COVID-19 who have refractory shock or respiratory insufficiency necessitating oxygen administration⁴²
 - Dexamethasone has shown efficacy in patients with severe disease and hypoxemia^{27, 32, 43}
 - Typical duration up to 10 days in patients with severe or critical COVID-19^{39, 40}
 - In the absence of dexamethasone, another glucocorticoid (eg, prednisone, methylprednisolone, hydrocortisone) may be used
 - Studies on the therapeutic efficacy of convalescent plasma are underway in various countries
 - Early administration (eg, before mechanical ventilation is required) appears more likely to be beneficial
 - FDA fact sheet for providers includes labeling criteria, suggested dosing/infusion practices, and potential adverse effects⁴⁴
 - Immunomodulators for the mitigation of cytokine release syndrome ("cytokine storm") in severe acute respiratory distress syndrome and shock in COVID-19 are being investigated (eg, tocilizumab and sarilumab, both monoclonal antibodies against interleukin-6 receptor; baricitinib and other Janus kinase inhibitors)^{40, 45, 46}
 - Baricitinib may be added to remdesivir in severely ill patients, under emergency use authorization⁴⁵
 - Surviving Sepsis Campaign, Infectious Diseases Society of America, and NIH COVID-19 treatment guidelines do not recommend tocilizumab at this time for routine use, although it may be considered in patients with progressive severe or critical COVID-19 who have elevated levels of markers of systemic inflammation^{42, 37, 47, 38, 40}
 - Appropriate antimicrobial therapy should be administered until a diagnosis of COVID-19 is confirmed in accordance with the severity of clinical disease, site of acquisition (hospital or community), epidemiologic risk factors, and local antimicrobial susceptibility patterns^{40, 42}
 - NIH and Infectious Diseases Society of America recommend against hydroxychloroquine or chloroquine and against the combination of either of these drugs with azithromycin in hospitalized patients for the treatment of COVID-19 due to risk of QT prolongation and cardiac arrhythmias^{40, 48, 39, 49, 37}
 - Published guidelines do not recommend therapeutic anticoagulation for hospitalized patients with COVID-19 (unless there is documented thrombosis or other accepted indication) but do recommend usual prophylactic regimens in any hospitalized patient with COVID-19, including pregnant patients^{50, 51, 52, 39, 38}
 - Pharmacologic (vasopressor) support may be necessary in patients with COVID-19 and evidence of septic shock whose hemodynamic parameters do not respond to initial fluid support and oxygen supplementation^{38, 42, 3, 40}
- Nondrug and supportive care
 - Oxygenation and ventilation
 - High-flow nasal oxygen or noninvasive positive pressure ventilation has been used to achieve adequate oxygenation in some COVID-19 patients who develop hypoxemic respiratory failure despite conventional oxygen therapy⁵³

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- For patients with persistent hypoxemia but without other indications for intubation, awake prone positioning can be attempted as a means to improve oxygenation³⁸
- 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, PaO₂/FiO₂ ratio of less than 300 mm Hg)³. Most published recommendations are based on the ARDSNet protocol⁵⁴
 - 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 patients
 - Mechanical ventilation may be required for a prolonged period, necessitating tracheostomy
- Fluid management
 - In patients with shock, administration of crystalloids (eg, lactated Ringer solution) is recommended; solutions such as hydroxyethyl starches, gelatins, dextrans, and albumin are not recommended
 - Volume overload should be avoided as it may precipitate or exacerbate acute respiratory distress syndrome⁵⁵
- Procedures
 - Extracorporeal membrane oxygenation
 - General explanation
 - Heart-lung bypass technique that allows transmembrane exchange of oxygen and carbon dioxide by circulation of the blood through a bypass machine; also supports arterial blood pressure^{39, 40}
 - Indication
 - Refractory hypoxemia with or without hemodynamic compromise despite standard supportive measures

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Most common ICU complications: acute respiratory distress syndrome (60%-70%), shock (30%), myocardial injury (20%-30%), arrhythmias (44%), and acute kidney injury (10%-30%)³
- Secondary bacterial and fungal infections and multiorgan failure are also commonly cited³
- Thrombotic events, both venous and arterial, have become increasingly recognized³

PROGNOSIS

- Patients who require hospital admission often require prolonged inpatient stay (longer than 20 days), which may result in profound deconditioning^{6, 27}
- Laboratory markers associated with increased mortality include high D-dimer levels, high C-reactive protein levels, and low lymphocyte counts³
- Reported mortality rates in critically ill patients are high (40% or more)^{3, 2}

SYNOPSIS

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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