

Coronavirus: novel coronavirus (COVID-19) infection

TERMINOLOGY

CLINICAL CLARIFICATION

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection with a newly recognized coronavirus, SARS-CoV-2, thought to have originated as a zoonotic virus that has mutated or otherwise adapted in ways that allow human pathogenicity
 - Disease was provisionally called 2019-nCoV infection at start of outbreak (2019 novel coronavirus infection)
- Outbreak began in China but has since spread globally; it was officially declared by WHO to be a pandemic¹ on March 11, 2020
- Illness ranges in severity from asymptomatic or mild to severe; a significant proportion of patients with clinically evident infection develop severe disease, which may be complicated by acute respiratory distress syndrome and shock
 - Mortality rate among diagnosed cases (case fatality rate) is generally about 2% to 3% but varies by country; true overall mortality rate is uncertain, as the total number of cases (including undiagnosed persons with milder illness) is unknown²
- 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)
 - 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 that progress (in some cases) to the point of respiratory distress and shock⁶
 - Most common complaints are fever (more than 80%) and cough, which may or may not be productive^{6,7}
 - Myalgia and fatigue are common; fatigue may be profound⁶
 - Alteration in smell and/or taste is increasingly reported, often as an early symptom, and is highly suggestive⁸
 - Patients with moderate to severe disease complain of dyspnea⁶
 - Hemoptysis has been reported in a small percentage of patients⁶
 - Pleuritic chest pain has been reported⁹
 - Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) may be present
 - Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur⁶
 - Patients may or may not report close contact with an infected person
- Physical examination
 - Published case series have not fully detailed physical findings, but clinicians should be particularly attuned to pulmonary and hemodynamic indicators of severe disease
 - Patients in apparent distress require immediate assessment of airway, breathing, and circulation (eg, pulses, blood pressure)
 - Oxygenation should be determined by pulse oximetry¹⁰
 - Patients with severe disease may appear quite ill, with tachypnea and labored respirations
 - Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever⁶
 - Conjunctival secretions, injection, and chemosis have been reported¹¹
 - A variety of skin changes have been described, including erythematous rashes,¹² purpura,¹³ petechiae,¹⁴ and vesicles;¹⁵ acral lesions^{16,17,18} resembling chilblains or Janeway lesions have been seen, particularly in young patients
 - 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

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- Oliguria
- Hyperthermia or hypothermia

CAUSES AND RISK FACTORS

- Causes
 - Infection due to SARS-CoV-2 (2019 novel coronavirus)
 - Person-to-person transmission has been documented⁹ and is presumed to occur by close contact,¹⁹ probably via respiratory droplets²⁰
 - Viral shedding appears to peak 24 to 48 hours before symptom onset,²¹ raising the likelihood of presymptomatic transmission. Several case and cluster reports from various countries^{22,23,24} indicating asymptomatic and presymptomatic transmission have been reported
 - Fomite and fecal-oral transmission, while plausible, have not been established as significant means of transmission
- Risk factors and/or associations
 - Age
 - Most reported cases are in adults of middle age or older,^{6,7} but pediatric infections in adolescents and children^{9,25} have been reported
 - Risk of severe disease increases with age²⁶
 - Sex
 - In published case series, males have been affected more often than females overall^{6,3,9,7}

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^{27,19}
 - Sensitivity of these tests is unknown, but false negative results have been reported; 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 yield²⁸
 - CDC¹⁹ and WHO¹⁰ have slightly different criteria for whom to test, but the rapid evolution of the pandemic and variable availability of testing render actual practice very fluid. The published criteria apply to patients with clinical features compatible with COVID-19 who are in the following categories; such patients would be considered PUIs (persons under investigation) by CDC:
 - WHO
 - Any acute respiratory tract illness (fever and at least 1 sign/symptom of respiratory tract disease) *and* no other etiology that fully explains the condition *and* a history of travel to or residence in an area reporting local transmission of COVID-19 during the 14 days preceding symptom onset
 - Any acute respiratory tract illness *and* close contact with a person with confirmed or probable COVID-19 in the 14 days preceding illness onset
 - Severe acute respiratory tract infection requiring hospital admission without an alternative etiologic diagnosis
 - In situations where testing must be prioritized, WHO recommendations prioritizing the following:²⁹
 - Patients at high risk for severe disease and hospitalization
 - Symptomatic health care workers
 - First symptomatic persons in closed space environment (eg, schools, long-term care facilities, hospitals, prisons), representing possible index cases
 - CDC¹⁹
 - Recommends that clinicians use their judgment, informed by knowledge of local COVID-19 activity and other risk factors, to determine the need for testing in persons with a clinically compatible illness
 - Priority levels for testing:
 - High priority
 - Hospitalized patients
 - Symptomatic workers in health care or congregate living settings and first responders
 - Symptomatic residents in long-term care facilities or other congregate living settings (eg, prisons, shelters)
 - Priority
 - People with symptoms suggesting COVID-19 (eg, fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting, diarrhea, sore throat)
 - Asymptomatic people prioritized by public health authorities or clinicians (eg, for public health monitoring, sentinel surveillance, or screening)

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- Specimens from upper or lower respiratory tract are 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)³⁰
 - Upper respiratory tract
 - Nasopharyngeal deep nasal (midturbinate), anterior nares, 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. Nasopharyngeal or nasal washings or aspirates are also acceptable
 - For nasopharyngeal specimen, insert swab into nostril parallel to palate. Leave swab in place for a few seconds to absorb secretions
 - For oropharyngeal specimen, swab the posterior pharynx, avoiding tongue and tonsils
 - 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
 - Nasopharyngeal wash (or aspirate) or nasal aspirate specimens (using 1 to 1.5 mL of nonbacteriostatic saline) are also acceptable
 - 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 negative³¹
 - 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 testing¹⁰
- Chest imaging is essential to document presence of pneumonia and to assess severity; plain radiography, CT, and ultrasonography have been used⁷
 - Although characteristic features have been described, 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 pneumonias³²
- Routine blood work should be ordered 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)¹⁰
- Clinicians should report suspected cases of COVID-19 to appropriate public health authorities, who can facilitate testing if necessary and can undertake contact tracing and monitoring. In the United States, contact local or state health department^{33,19}
- Laboratory
 - Positive identification of SARS-CoV-2 RNA by polymerase chain reaction test is considered confirmation of diagnosis
 - Routine blood work is not diagnostic, but a pattern of typical abnormalities is emerging in case series of hospitalized patients:
 - Leukopenia may be observed and relative lymphopenia is common, especially in patients with more severe illness^{7,9,6}
 - Anemia was noted in about half of patients in one series⁷
 - Both elevated and low platelet counts have been seen^{9,6,7}
 - Prolonged prothrombin time has been reported³⁴
 - Levels of D-dimer and fibrinogen may be elevated^{6,9}
 - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common^{6,7}
 - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection⁶

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- Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate⁷
- Lactate level of 2 mmol/L or higher suggests presence of septic shock¹⁰
- 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^{6,9,7,3,35}
 - CT appears to be more sensitive³⁶ than plain radiographs, but normal CT appearance does not exclude COVID-19³⁷

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

DISPOSITION

- Admission criteria
 - Nonsevere pneumonia
 - Radiographic evidence of pneumonia; progressive clinical illness; risk factors for severe disease; inadequate care at home^{10,38}
 - CDC provides guidance for determining whether the home is a suitable venue and patient and/or caregiver is capable of adhering to medical care recommendations and infection control measures³⁸
 - Criteria for ICU admission
 - WHO provides criteria for severe pneumonia¹⁰
 - Severe pneumonia characterized by tachypnea (respiratory rate greater than 30 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO₂ of 93% or less)
 - Pediatric criteria include central cyanosis or SpO₂ less than 90%; signs of severe respiratory distress (eg, grunting, chest retractions); inability to drink or breastfeed; lethargy, altered level of consciousness, seizures; severe tachypnea defined by age:
 - Younger than 2 months: 60 or more breaths per minute
 - Aged 2 to 11 months: 50 or more breaths per minute
 - Aged 1 to 5 years: 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

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- 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 procedures³⁹
- 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 pending further evaluation and disposition decisions. The closed room will ideally be one 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)
- 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^{40,41} and some evidence of efficacy in an animal model of MERS⁴¹
 - 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 COVID-19 who have severe disease, defined as SpO₂ of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation⁴²
 - Preliminary results of the Adaptive COVID-19 Treatment Trial,⁴³ 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 well⁴⁴
- Chloroquine and hydroxychloroquine have been used in China and South Korea, reportedly with favorable results, although details are lacking and follow-up studies have been less encouraging. Further trials are underway in Europe and the United States. Both are associated with QT prolongation and risk of cardiac arrhythmias. Scoring systems^{45,46} are available to determine risk of arrhythmia⁴⁷
 - 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 considered⁴⁸
 - In the United States, emergency use authorization for chloroquine and hydroxychloroquine has been issued by FDA to permit use in hospitalized adult and adolescent patients for whom a clinical trial is not available or feasible⁴⁹
 - 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 agents⁵⁰
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends hydroxychloroquine or chloroquine in the context of a clinical trial, and in combination with azithromycin only in the context of a clinical trial, based on evidence of very low certainty⁵¹
 - NIH guidelines do not recommend for or against chloroquine or hydroxychloroquine because of insufficient data; they recommend 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 interval⁵²
 - A large observational study published after the aforementioned guidelines reported data on patients with COVID-19 of whom 58.9% received hydroxychloroquine with or without azithromycin. The authors concluded that hydroxychloroquine was not associated with a significantly higher or lower risk of intubation or death and note the need for an adequately powered randomized controlled trial⁵³
- 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 specimens⁵⁴
 - NIH COVID-19 treatment guideline⁵² and Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19⁵⁰ recommend against use of lopinavir-ritonavir
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends lopinavir-ritonavir only in the context of a clinical trial⁵¹

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- 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, tocilizumab⁵⁰ and sarilumab⁵⁵ 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 of tocilizumab; the guideline did not evaluate other monoclonal antibodies⁵⁰
 - 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 certainty⁵¹
 - NIH COVID-19 treatment guideline states that data are insufficient to recommend for or against use of these agents⁵²
- Studies on the therapeutic efficacy of convalescent plasma are underway in various countries. In the United States, authorization must be obtained through FDA⁵⁶
 - 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 safety⁵⁰
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends convalescent plasma in the context of a clinical trial, based on evidence of very low certainty⁵¹
 - NIH COVID-19 treatment guideline states that data are insufficient to recommend for or against use of convalescent plasma or hyperimmune immunoglobulin⁵²
- Information on therapeutic trials and expanded access⁵⁷ is available at ClinicalTrials.gov
- Corticosteroid therapy is not recommended for viral pneumonia but is suggested by some authorities for patients with COVID-19 who have refractory shock or acute respiratory distress syndrome¹⁰
 - 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 preferred⁵⁰
 - Similarly, Infectious Diseases Society of America suggests against the use of corticosteroids in hospitalized patients with COVID-19 and pneumonia, but it recommends their use in the context of a clinical trial for patients with COVID-19 and acute respiratory distress syndrome⁵¹
 - NIH COVID-19 treatment guideline recommends against routine use in mechanically ventilated patients without acute respiratory distress syndrome, notes insufficient data to recommend for or against it in mechanically ventilated patients with that syndrome, and recommends low-dose corticosteroids in patients with refractory shock⁵²
- 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 symptoms⁵⁸
 - 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-19⁵²
- 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 site of acquisition (hospital or community), epidemiologic risk factors, and local antimicrobial susceptibility patterns¹⁰
 - Additionally, 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-escalation⁵⁰
- Otherwise, treatment is largely supportive and includes oxygen supplementation and conservative fluid support¹⁰
 - Role of anticoagulation is being studied, and some authorities recommend use of prophylactic regimens in all hospitalized patients with COVID-19⁵⁹
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Surviving Sepsis Campaign,⁵⁰ NIH COVID-19 treatment guideline,⁶⁰ and WHO¹⁰ provide guidance specific to the treatment of shock in patients with COVID-19
 - In adults, begin with norepinephrine; epinephrine or vasopressin are preferred as second line over dopamine if norepinephrine is unavailable
 - Hemodynamic goal: mean arterial pressure of 60 to 65 mm Hg⁵⁰
 - 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 norepinephrine⁵⁰
 - 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 norepinephrine⁵⁰
 - In children, epinephrine is considered the first line agent, and norepinephrine may be added if necessary¹⁰

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- Drug therapy
 - Antiviral agent⁶¹
 - Remdesivir
 - Neonates, Infants, Children, and Adolescents weighing 3.5 to 39 kg requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 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.
 - Neonates, Infants, Children, and Adolescents weighing 3.5 to 39 kg NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 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.
 - Children and Adolescents weighing 40 kg or more requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1 then 100 mg IV once daily for 9 days suggested by FDA EUA statement.
 - Children and Adolescents weighing 40 kg or more NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 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.
 - Adults requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1 then 100 mg IV once daily for 9 days suggested by FDA EUA statement.
 - Adults NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO): Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of remdesivir. 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.
 - Antimalarial agents
 - Chloroquine
 - Infants, Children, and Adolescents weighing less than 50 kg : Efficacy and optimal dosing not established; however, based on extrapolation from pediatric dosing for other indications and comparative doses to the adult dosing regimen suggested for COVID-19, 8.3 mg (5 mg base)/kg/dose PO twice daily [Max: 500 mg/dose (300 mg base/dose)] is being used in limited pediatric dosing protocols; a 10-day course is being used in adult patients.
 - Adolescents weighing 50 kg or more : Data are limited; efficacy has not been established. 1000 mg PO on day 1 then 500 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Based on extrapolation from pediatric dosing for other indications and comparative doses to the adult dosing regimen suggested for COVID-19, 8.3 mg (5 mg base)/kg/dose PO twice daily [Max: 500 mg/dose (300 mg base/dose)] is being used in limited pediatric dosing protocols; a 10-day course is being used in adult patients.
 - Adults weighing less than 50 kg : Data are limited; efficacy has not been established. 500 mg PO twice daily for 10 days is being evaluated alone and in combination.
 - Adults weighing 50 kg or more : Data are limited; efficacy has not been established. 1000 mg PO on day 1 then 500 mg PO daily for 4 to 7 days suggested by FDA EUA statement. 500 mg PO twice daily for 10 days is also being evaluated alone and in combination.
 - Hydroxychloroquine
 - Infants, Children, and Adolescents weighing less than 50 kg : Efficacy and optimal dosing not established; however, based on extrapolation from pediatric dosing for other indications and comparative doses to adult dosing regimens suggested for COVID-19, doses of 6.5 mg (5 mg base)/kg/dose PO every 12 hours [Max: 400 mg/dose (310 mg base/dose)] for 2 doses, then 3.25 mg (2.5 mg base)/kg/dose every 12 hours [Max: 200 mg/dose (155 mg base/dose)] are being used in limited pediatric dosing protocols; a 5- to 20-day course is being used in adult patients.
 - Adolescents weighing 50 kg or more : Data are limited; efficacy has not been established. 800 mg PO on day 1 then 400 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Based on extrapolation from pediatric dosing for other indications and comparative doses to adult dosing regimens suggested for COVID-19, doses of 6.5 mg (5 mg base)/kg/dose PO every 12 hours [Max: 400 mg/dose (310 mg base/dose)] for 2 doses, then 3.25 mg (2.5 mg base)/kg/dose every 12 hours [Max: 200 mg/dose (155 mg base/dose)] are being used in limited pediatric dosing protocols; a 5- to 20-day course is being used in adult patients.
 - Adults weighing less than 50 kg : Data are limited; efficacy has not been established. Dosing regimens, alone and in combination, are being evaluated, including 400 mg PO twice daily on day 1 then 200 mg PO twice daily for 4 days; 200 mg PO twice daily for 5 to 20 days; and 200 mg PO three times daily for 10 days. Additional clinical evaluation is needed.
 - Adults weighing 50 kg or more : Data are limited; efficacy has not been established. 800 mg PO on day 1 then 400 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Other dosing regimens, alone and in combination, are being evaluated, including 400 mg PO twice daily on day 1 then 200 mg PO twice daily for 4 days; 200 mg PO twice daily for 5 to 20 days; and 200 mg PO three times daily for 10 days. Additional clinical evaluation is needed.

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- 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
 - Sarilumab Solution for injection; Adults: Efficacy has not been established. 200 mg IV or subcutaneously once or 400 mg IV once is being evaluated in combination with antiviral therapy.
- Nondrug and supportive care
 - WHO,¹⁰ NIH,⁶⁰ and Surviving Sepsis Campaign⁵⁰ 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
 - Oxygenation and ventilation
 - Begin supplemental oxygen when O₂ saturation falls below 90% to 92%⁵⁰
 - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute¹⁰
 - Titrate to reach SpO₂ of 94% or more initially
 - Once stable, target SpO₂ of 90% or higher in nonpregnant adults; 92% or higher in pregnant patients
 - In most children the target SpO₂ 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 SpO₂ of 94% or higher is recommended
 - High-flow nasal oxygen or noninvasive ventilation has been used to achieve adequate oxygenation in some patients⁶²
 - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign⁵⁰ and NIH⁶⁰ 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 provided⁵⁰
 - 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
 - Recommended settings are tidal volume of 4 to 8 mL/kg (predicted body weight) and inspiratory pressures less than 30 cm H₂O
 - 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 H₂O
 - Use of PEEP may be necessary in patients with acute respiratory distress syndrome. Optimal regimen is not clearly defined, although guidelines^{10,50} suggest higher pressures (eg, more than 10 cm H₂O) rather than lower pressures. A protocol is available from ARDSnet⁶³
 - 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
 - Extracorporeal membrane oxygenation has been used⁶ 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
 - 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. WHO¹⁰ 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 Hg⁵⁰ (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

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- 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)
- 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^{9, 6}
 - 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 so⁶⁴
 - Several retrospective 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^{65, 66, 67, 68}
- Special populations
 - Pregnant patients
 - WHO guidelines¹⁰ suggest that pregnant patients receive supportive care as recommended for nonpregnant adults, with accommodations as dictated by the physiologic changes of pregnancy (eg, expanded volume of distribution, elevated diaphragm)
 - WHO recommends that mode of delivery be determined based on obstetric indications and patient preference; cesarean delivery is recommended only for the usual medically justified indications¹⁰
 - There is little evidence to suggest vertical transmission;¹⁰ however, an infected woman may transmit the virus by the airborne route to her neonate. CDC and WHO differ in their recommendations⁶⁹
 - Because of concerns for transmission, CDC has recommended that separation of neonates from mothers known or suspected to have COVID-19 be considered until isolation can be discontinued per usual protocol. Under such circumstances, breast milk may be pumped and fed to the infant by another caregiver⁶⁹
 - Focusing on ensuring successful initiation of breastfeeding, WHO advises that postpartum women and their neonates room in (cohabit), including the practice of skin-to-skin and kangaroo care¹⁰
 - Patients with HIV⁷⁰
 - It does not appear that HIV infection per se alters risk for infection or disease process. Whether advanced HIV infection (eg, CD4 count less than 200 cells/mm³) increases the risk for severe disease or complications is unknown
 - It is recommended that patients continue their current antiretroviral regimen; specifically, empiric addition of lopinavir-ritonavir (for possible efficacy against or protection from SARS-CoV-2) is not recommended outside of a clinical trial
 - A guideline⁷⁰ by the US Department of Health and Human Services offers strategies for ensuring continuity of antiretroviral medication
 - Recommendations for management of patients with HIV who develop COVID-19 do not differ from standard recommendations; it is recognized that the potential for drug interactions may complicate eligibility for enrollment in a clinical trial for COVID-19

MONITORING

- Patients who do not require admission should self-monitor temperature and symptoms, and they should return for reevaluation if symptoms worsen; deterioration may occur a week or more⁷¹ into the course of illness and may be quite abrupt¹⁰
- For patients receiving chloroquine or hydroxychloroquine, monitoring of QTc is recommended⁴⁶
 - In hospitalized patients, 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
 - In outpatients, perform ECG at baseline, and on day 3, at 2 to 3 hours after dose is taken
 - If QTc increases by more than 30 to 60 milliseconds or absolute QTc is greater than 500 milliseconds (or greater than 530 to 550 milliseconds if QRS exceeds 120 milliseconds), consider discontinuing therapy
 - In patients deemed to be at low risk by Tisdale⁴⁵ or similar score, may consider no further monitoring
- In hospitalized patients with proven COVID-19, repeated testing is recommended to document clearance of virus, defined as 2 consecutive negative results on polymerase chain reaction tests at least 24 hours apart¹⁰

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Most common complication is acute respiratory distress syndrome; other reported complications include:^{6,7}
 - Septic shock
 - Acute kidney injury
 - Myocardial injury
 - Secondary bacterial and fungal infections
 - Multiorgan failure
 - Thrombotic events

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.^{7,6}
- Otherwise, short-term and long-term prognosis (eg, recovery of pulmonary function) remains to be seen with time
- It is not yet known whether recovery from infection is associated with protective immunity⁷¹
- Mortality rate of diagnosed cases is generally about 2% to 3% but varies by country²
- Case fatality rates are higher for patients in older age groups and with certain comorbidities
 - Case fatality rates by age in the United States:²⁶
 - 10% to 27% for those aged 85 years or older
 - 3% to 11% for those aged 65 to 84 years
 - 1% to 3% for those aged 55 to 64 years
 - Less than 1% for those aged 0 to 54 years
 - Case fatality rates for disease in Chinese patients with common comorbidities:⁷¹
 - 10.5% for cardiovascular disease
 - 7.3% for diabetes
 - 6% for chronic respiratory disease
 - 6% for hypertension
 - 6% for cancer

SCREENING AND PREVENTION

SCREENING

- At-risk populations
 - In health care settings
 - Patients presenting for care
 - Triage screening is recommended at points of medical care to identify patients with symptoms and exposure history that suggest the possibility of COVID-19, so that prompt isolation measures can be instituted.^{39,10}
 - At least during high-prevalence phases of the pandemic, the following principles apply to the isolation areas:
 - Set up separate, well-ventilated triage areas; place patients with suspected or confirmed COVID-19 in private rooms with the door closed and with private bathrooms (as possible); many hospitals designate building wings to be dedicated to probable COVID-19.³⁹
 - Reserve airborne infection isolation rooms for patients with COVID-19 undergoing aerosol-generating procedures and for care of patients with pathogens transmitted by airborne route (eg, tuberculosis, measles, varicella)³⁹
 - Guidelines released by Infectious Diseases Society of America also recommend testing of asymptomatic persons in the following circumstances, given sufficient testing supplies:³¹
 - Known exposure to COVID-19
 - Admission to hospital for unrelated condition, if community prevalence is high
 - Immunosuppression, or about to undergo immunosuppressive treatment
 - About to undergo major surgery that is time-sensitive
 - About to undergo aerosol-generating procedure that is time-sensitive
 - Health care workers
 - At increased risk because of occupational exposure; in turn, undetected infection in health care worker poses risk for nosocomial transmission to patients and coworkers

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- Screening tests
 - In health care settings
 - Screening and subsequent triage to isolation and testing with polymerase chain reaction is based on clinical presentation and exposure history:^{10, 72, 19, 39}
 - Presence of respiratory symptoms (cough, dyspnea) and fever (CDC, WHO)
 - Close contact with a person with known or suspected COVID-19 while that person was ill (WHO, CDC)
 - Work in a health care setting in which patients with severe respiratory illnesses are managed, without regard to place of residence or history of travel (WHO)
 - Unusual or unexpected deterioration of an acute illness despite appropriate treatment, without regard to place of residence or history of travel, even if another cause has been identified that fully explains the clinical presentation (WHO)
 - Many hospitals are instituting frequent temperature screening of health care workers (eg, at beginning of each shift)³⁹
 - In public places
 - Screening in public places with infrared thermometers (to detect fever) is used in some regions but has limited sensitivity as a screening tool for infection
 - Wider use of screening with polymerase chain reaction tests (to detect current infection) and antibody tests (to detect history of infection) is expected to evolve once testing capacities improve

PREVENTION

- There is no vaccine against COVID-19. Prevention depends on standard infection control measures, including isolation of infected patients. Quarantine may be imposed on asymptomatic exposed persons deemed by public health authorities to be at high risk
- For the general public, avoidance of ill persons and diligent hand and cough hygiene are recommended. Physical distancing should be used as much as possible. Advise public as follows:
 - If sick, stay home and call doctor⁷³
 - Avoid large gatherings and unnecessary gatherings; stay home except for critical needs (eg, to resupply food and medicines) during acceleration phase of pandemic or subsequent regional flare-ups
 - Telecommute if nature of job makes it possible
 - When going out in public is unavoidable, cover mouth and nose with a cloth face cover (not with a mask meant for health care workers)⁷³
 - Greet others without touching; nod or wave instead of shaking hands or hugging. Try to maintain physical distance: at least 1 m (3 ft), preferably 2 m (6 ft)⁷³
 - Psychological and emotional toll of physical distancing from family and friends can be mitigated with nonphysical interaction (eg, phone calls, texting, video chats)
 - Wash hands often and thoroughly. Soap and water are best. High-alcohol hand sanitizers are acceptable until next possible handwashing⁷³
 - Cover coughs. Use tissue and throw it away; second choice is sleeve, not hand⁷³
 - Avoid touching face⁷³
- Patients managed at home
 - Patient is encouraged to stay at home except to seek medical care, to self-isolate to a single area of the house (preferably with a separate bathroom), to practice good hand and cough hygiene, and to wear a cloth face cover during any contact with household members⁷⁴
 - Patients should be advised that if a need for medical care develops, they should call their health care provider in advance so that proper isolation measures can be undertaken promptly on their arrival at the health care setting
 - Household members/caregivers should:
 - Ideally, wear face mask, gown, and gloves when caring for patient, and remove and discard all when leaving the room (do not reuse); however, if some of these supplies are absent, wear cloth face cover and scrupulously wash hands and laundry
 - Dispose of disposable items in a container lined with a trash bag that can be removed and tied off or sealed before disposal in household trash
 - Wash hands for at least 20 seconds after all contact; an alcohol-based hand sanitizer is acceptable if soap and water are not available
 - Not share personal items such as towels, dishes, or utensils before proper cleaning
 - Wash laundry and high-touch surfaces frequently
 - Wear disposable gloves to handle dirty laundry and use highest possible temperatures for washing and drying, based on washing instructions on the items
 - Clean surfaces with diluted bleach solution or an EPA-approved disinfectant

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- Restrict contact to minimum number of caregivers and, in particular, ensure that persons with underlying medical conditions are not exposed to the patient
- In health care settings^{75, 39}
 - CDC provides preparedness checklists⁷⁶ for outpatient and inpatient health care settings
 - 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 pending further evaluation and disposition decisions. The closed room will ideally be one 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)
 - Persons entering the room should follow standard, contact, and airborne precautions
 - Gloves, gowns, eye protection, and respirator (N95 or better) with adherence to hospital donning and doffing protocols
 - In circumstances in which supplies of N95 respirators and other protective equipment are short, their use should be prioritized for aerosol-generating procedures; standard surgical face masks should be used for other situations
 - Equipment used for patient care should be single-use (disposable) or should be disinfected between patients; WHO⁷⁵ suggests using 70% ethyl alcohol
- Criteria for discontinuation of isolation precautions^{77, 78}
 - CDC offers several strategies depending on whether the patient was symptomatic *at any time* or was asymptomatic *throughout*. These apply to patients who were cared for in hospital or at home. Note that if patients are discharged from hospital before they meet these criteria, appropriate precautions must be maintained in the setting to which they are discharged (eg, other healthcare facility or home)
 - In symptomatic patients, precautions should be maintained until the following conditions are met:
 - 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
 - Test-based
 - Subjective and objective evidence of clinical improvement, including absence of fever without use of antipyretic medication, *and*
 - Demonstration of negative results of molecular assays for SARS-CoV-2 RNA on 2 consecutive respiratory specimens obtained at least 24 hours apart (a single specimen suffices for each test)
 - In asymptomatic patients precautions should be maintained until the following conditions are met:
 - Time-based
 - At least 10 days since first positive COVID-19 molecular test result was obtained
 - Test-based
 - Demonstration of negative results of molecular assays for SARS-CoV-2 RNA on 2 consecutive respiratory specimens obtained at least 24 hours apart (a single specimen suffices for each test)

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 the WHO¹
- Infection ranges from asymptomatic to severe; symptoms usually include fever, cough, and (in moderate to severe cases) dyspnea. Disease may evolve over the course of a week or more from mild to severe; deterioration may be sudden and catastrophic⁶
- Infection should be suspected based on presentation with a clinically compatible history (eg, fever, upper or lower respiratory tract symptoms); alterations in smell and taste are particularly suggestive
- Chest imaging in symptomatic patients almost always shows abnormal findings, usually including bilateral infiltrates; laboratory findings are variable but typically include lymphopenia and elevated lactate dehydrogenase and transaminase levels
- Diagnosis is confirmed by detection of viral RNA on polymerase chain reaction test of upper or lower respiratory tract specimens
- 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;⁴³ otherwise, treatment is largely supportive, consisting of supplemental oxygen and conservative fluid administration
- Most common complications are acute respiratory distress syndrome and septic shock; myocardial, renal, and multiorgan failure have been reported

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- A significant proportion of clinically evident cases are severe; the mortality rate among diagnosed cases is generally about 2% to 3% but varies by country²
- There is no vaccine available to prevent this infection; infection control measures are the mainstay of prevention (ie, hand and cough hygiene; physical distancing; standard, contact, and airborne precautions in health care)

URGENT ACTION

- Triage screening is recommended at registration for medical care to identify patients with symptoms and exposure history that suggest the possibility of COVID-19, and to promptly institute isolation measures
- Patients with respiratory distress require prompt administration of supplemental oxygen; patients with respiratory failure require intubation
- Patients in shock require urgent fluid resuscitation and administration of empiric antimicrobial therapy to cover possible bacterial pathogens and/or influenza

PITFALLS

- Persons with prodromal or asymptomatic infection may spread infection, making effective prevention more challenging; regardless, physical distancing is vital to slowing transmission enough to avoid overwhelming health systems
- 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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