

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 5% to 6% globally^{2,3} but varies by country; true overall mortality rate is uncertain, as the total number of cases (including undiagnosed persons with milder illness) is unknown
- 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,⁴ 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*^{5,6}
 - Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2); earlier provisional name was 2019-nCoV^{5,6}

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 shock⁷
 - Most common complaints are fever (more than 80%) and cough, which may or may not be productive^{8,7}
 - Myalgia and fatigue are common; fatigue may be profound⁷
 - Alteration in smell and/or taste is increasingly reported, often as an early symptom, and is highly suggestive⁹
 - Patients with moderate to severe disease often complain of dyspnea;⁷ however, it has been recognized that many patients with severe hypoxemia due to COVID-19 do not perceive dyspnea¹⁰
 - Hemoptysis has been reported in a small percentage of patients⁷
 - Pleuritic chest pain has been reported¹¹
 - Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) may be present
 - Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur⁷
 - Patients may or may not report close contact with an infected person
- Physical examination
 - Reported case series have not fully detailed physical findings, but clinicians should be particularly attuned to pulmonary and hemodynamic indicators of severe disease
 - 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)¹²
 - Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever⁷
 - Conjunctival secretions, injection, and chemosis have been reported¹³
 - A variety of skin changes have been described, including erythematous rashes,¹⁴ purpura,¹⁵ petechiae,¹⁶ and vesicles;¹⁷ acral lesions^{18,19,20} resembling chilblains or Janeway lesions have been seen, particularly in young patients²¹
 - Hypotension, tachycardia, and cool/clammy extremities suggest shock
 - In children, hypotension plus 2 or more of the following criteria:¹²
 - 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)

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- 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 documented¹¹ and is presumed to occur by close contact,²² probably via respiratory droplets²³
 - Viral shedding appears to peak 24 to 48 hours before symptom onset,²⁴ raising the likelihood of presymptomatic transmission. Several case and cluster reports from various countries^{25, 26, 27} indicating asymptomatic and presymptomatic transmission have been reported
 - 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
 - Most reported cases are in adults of middle age or older,^{7, 8} but pediatric infections in adolescents and children^{11, 28} also occur
 - Risk of severe disease increases with age; in the United States, 94% of deaths occur in people older than 50 years. Percentage of total mortality by age group:^{29, 30}
 - 0 to 49 years: 5.1%
 - 50 to 64 years: 15.3%
 - 65 to 74 years: 21%
 - 75 to 84 years: 26.4%
 - 85 years or older: 32.1%
 - Sex
 - Overall, where sex or gender data are available, it appears that females are more often affected, but disease is more severe in males^{29, 31}
 - Other risk factors/associations
 - Various underlying medical conditions have been associated with increased risk for severe disease, especially if they are not well controlled:³²
 - Chronic kidney disease
 - Chronic obstructive pulmonary disease
 - Immunosuppression because of previous solid organ transplant
 - Malignancy
 - Obesity (BMI of 30 or higher)
 - Serious cardiac conditions (eg, heart failure, coronary artery disease, cardiomyopathy)
 - Sickle cell disease
 - Diabetes type 2
 - Conditions which may be associated with higher risk for severe disease:³²
 - Asthma (moderate to severe)
 - Cerebrovascular disease
 - Cystic fibrosis
 - Hypertension
 - Immunodeficiency from various other causes (eg, bone marrow or hematopoietic stem cell transplant, primary immunodeficiencies, HIV disease, chronic treatment with corticosteroids or other agents with immunosuppressive effects)
 - Neurologic dysfunction
 - Chronic liver disease
 - Pregnancy
 - Pulmonary fibrosis
 - Smoking
 - Thalassemia
 - Diabetes type 1
 - Children with medically complex conditions (eg, neurologic, metabolic, genetic, cardiac) are also at higher risk for severe disease³²

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- 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 status³³

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. Serologic tests are not recommended for diagnostic purposes in most circumstances^{22, 34, 35}
 - CDC²² and WHO¹² 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
 - WHO³⁶
 - Any acute respiratory tract illness (fever and at least 1 sign/symptom of respiratory tract disease) *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:³⁷
 - 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
 - CDC²²
 - Recommends that clinicians use their judgment, informed by knowledge of local COVID-19 activity and other risk factors, to determine the need for diagnostic testing in persons with a clinically compatible illness
 - CDC suggests a low threshold for testing persons with extensive or close contact with populations at high risk for severe disease
 - Testing may also be recommended in other circumstances:
 - Any person (even if asymptomatic) with recent close contact with a person known or suspected to have COVID-19
 - Asymptomatic persons without known or suspected exposure in certain settings (eg, close-quarters community, preoperative setting)
 - To document resolution of infection
 - Public health surveillance
 - Specimens from upper or lower respiratory tract are recommended for polymerase chain reaction testing.³⁸ 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)³⁸
 - 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, then remove while gently rotating. It is not necessary to repeat on the other side if the first effort produces a good specimen (ie, swab is saturated)
 - For deep nasal specimen, insert a flocked swab about 2 cm and rotate; repeat on opposite side, using the same swab
 - For anterior nares, insert a flocked swab about 1 cm, rotate in contact with mucus membrane, and leave in place for 10 to 15 seconds; repeat on opposite side, using same swab
 - For oropharyngeal specimen, swab the posterior pharynx, avoiding tongue and tonsils
 - Nasopharyngeal wash (or aspirate) or nasal aspirate specimens (using 1 to 1.5 mL of nonbacteriostatic saline) are also acceptable
 - Because testing methods vary, it is advisable to check with the laboratory to determine which specimens are suitable for the available test

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- 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 negative³⁹
- 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 testing¹²
 - Coinfections have been reported, but the frequency is unknown^{40,41}
- Chest imaging is essential to document presence of pneumonia and to assess severity; plain radiography, CT, and ultrasonography have been used⁸
 - 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 persons⁴²
 - 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 pneumonias⁴³
- 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)¹²
- 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 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^{44,39}
 - 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^{39,44}
 - 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^{11,8,7}
 - Anemia was noted in about half of patients in one series⁸
 - Both elevated and low platelet counts have been seen^{11,8,7}
 - Prolonged prothrombin time has been reported⁴⁵
 - Levels of D-dimer and fibrinogen may be elevated^{11,7}
 - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common^{8,7}
 - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection⁷
 - Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate⁸
 - Lactate level of 2 mmol/L or higher suggests presence of septic shock¹²
- 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^{4,8,46,11,7}

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- CT appears to be more sensitive⁴⁷ than plain radiographs, but normal appearance on CT does not preclude the possibility of COVID-19⁴⁸
- 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^{49,44}

DIFFERENTIAL DIAGNOSIS

- Most common
 - Influenza
 - Presentation includes fever, coryza, sore throat, dry cough, and myalgias; unlike COVID-19, influenza usually has fairly sudden onset
 - Most cases are self-limited, but elderly persons or those with significant comorbidities often require hospitalization
 - Usually occurs in winter months in temperate climates but is less seasonal in equatorial regions
 - Patients with severe disease may have abnormal chest radiographic findings suggesting influenzal pneumonia or secondary bacterial pneumonia
 - Positive result on rapid influenza diagnostic test confirms influenza diagnosis with high specificity during typical season; negative result does not rule out influenza
 - Other viral pneumonias
 - Presentations include fever, dry cough, and dyspnea
 - Physical examination may find scattered rales
 - Chest radiography usually shows diffuse patchy infiltrates
 - Diagnosis is usually clinical. Testing for specific viral causes may be done; multiplex panels can test simultaneously for a number of common viral respiratory pathogens such as respiratory syncytial virus, adenovirus, and others
 - Bacterial pneumonia
 - Presentation includes fever, cough, and dyspnea; pleuritic pain occurs in some cases
 - Physical examination may find signs of consolidation (eg, dullness to percussion, auscultatory rales, tubular breath sounds)
 - Chest radiography usually shows lobar consolidation or localized patchy infiltrate
 - Sputum examination may find abundant polymorphonuclear leukocytes and a predominant bacterial organism
 - Pneumococcal or legionella antigens may be detectable in urine; sputum culture may find those or other pathogens

TREATMENT

GOALS

- Ensure adequate oxygenation and hemodynamic support during acute phase of illness
- Prevent complications where possible (eg, thromboses)

DISPOSITION

- Admission criteria
 - Nonsevere pneumonia
 - Radiographic evidence of pneumonia; progressive clinical illness; risk factors for severe disease; inadequate care at home^{50,12}
 - 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 measures⁵⁰
 - Criteria for ICU admission
 - WHO provides criteria for critical respiratory tract disease⁵¹
 - Characterized by tachypnea (respiratory rate greater than 30 breaths or less than 10 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO₂ of less than 92%)
 - 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, 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

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- 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 procedures⁵²
- 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^{53,54} and some evidence of efficacy in an animal model of MERS⁵⁴
 - Although not FDA-approved, remdesivir is in use for the indication; FDA has issued an emergency use authorization for use of IV remdesivir to treat hospitalized patients with severe COVID-19, defined as SpO₂ of 94% or less on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation⁵⁵
 - Preliminary results of the Adaptive COVID-19 Treatment Trial,^{56,57} 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 well⁵⁸
 - On the basis of preliminary data from clinical trials, NIH and IDSA guidelines recommend remdesivir for hospitalized patients with severe COVID-19 (defining criteria as outlined in the emergency use authorization)^{59,60}
 - Because there is less certainty about efficacy in patients who are ill enough to require the more aggressive airway assistance methods (ie, high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation), and because there is a shortage of remdesivir, NIH recommends prioritization for patients requiring supplemental oxygen but not those methods
 - NIH currently does not make a recommendation for or against starting remdesivir in patients who require high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation, but it does recommend starting remdesivir for patients who require oxygen and can be adequately oxygenated without those methods
 - 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
 - WHO does not recommend use outside of clinical trials¹²
 - Chloroquine and hydroxychloroquine have been used in China and South Korea, reportedly with favorable results,⁶¹ 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,⁶² although some clinical trials are still in progress
 - 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 considered⁶³
 - 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 agents⁶⁴
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends hydroxychloroquine or chloroquine only in the context of a clinical trial, and suggests against combination with azithromycin outside of a clinical trial⁵⁹
 - NIH guidelines recommend against chloroquine or hydroxychloroquine except in the setting of a clinical trial; they recommend against high-dose chloroquine (600 mg twice daily for 10 days) and against the addition of azithromycin to hydroxychloroquine. The guidelines note that when chloroquine or hydroxychloroquine is used, patients must be monitored for adverse effects, particularly prolonged QTc interval⁶⁰
 - Scoring systems are available to determine risk of arrhythmia^{65,66}
 - WHO recommends against use of chloroquine or hydroxychloroquine with or without azithromycin outside of a clinical trial¹²
 - 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 group⁶⁷

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- 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 specimens⁶⁸
 - NIH COVID-19 treatment guideline⁶⁰ and Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19⁶⁴ 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 efficacy⁶⁴
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends lopinavir-ritonavir only in the context of a clinical trial⁵⁹
 - WHO recommends against use of lopinavir-ritonavir outside of a clinical trial¹²
- 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, tocilizumab⁶⁴ and sarilumab⁶⁹ are both monoclonal antibodies against interleukin-6 receptor)
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 states that data are insufficient to make a recommendation on the use tocilizumab; the guideline did not evaluate other monoclonal antibodies⁶⁴
 - 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 certainty⁵⁹
 - NIH COVID-19 treatment guideline states that data are insufficient to recommend for or against use of these agents, 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 inhibitors⁶⁰
 - WHO recommends against use of immunomodulators outside of a clinical trial¹²
- Studies on the therapeutic efficacy of convalescent plasma are underway in various countries. In the United States, authorization must be obtained through FDA⁷⁰
 - 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 safety⁶⁴
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends convalescent plasma only in the context of a clinical trial⁵⁹
 - 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 it⁶⁰
 - WHO recommends against use of plasma therapy outside of a clinical trial
- Information on therapeutic trials and expanded access is available at ClinicalTrials.gov⁷¹
- 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 administration¹²
 - 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^{72,73}
 - 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. It recommends against using dexamethasone in patients who do not require oxygen supplementation⁶⁰
 - Similarly, Infectious Diseases Society of America guideline suggests use of dexamethasone in hospitalized patients with severe COVID-19, defined as SpO₂ of 94% or less on room air or any requirement for supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation⁵⁹
 - 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 preferred⁶⁴
 - 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)¹²

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- A smaller study comparing standard care with and without a 3-day course of methylprednisolone early in the disease course showed an association between corticosteroid use and a reduction in the 3 components of the composite endpoint: transfer to ICU, need for mechanical ventilation, and mortality. Guidelines do not currently support administration of steroids early in the disease course⁷⁴
- 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 symptoms⁷⁵
 - 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-19⁶⁰
 - 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 support⁷⁶
- Until a diagnosis of COVID-19 is confirmed by polymerase chain reaction test, appropriate antimicrobial therapy for other viral pathogens (eg, influenza virus) or bacterial pathogens should be administered in accordance with the severity of clinical disease, site of acquisition (hospital or community), epidemiologic risk factors, and local antimicrobial susceptibility patterns¹²
- Based on concerns about the possible role of micro- and macrovascular thrombosis in the pathophysiology of this disease, the use of anticoagulation is being studied. At present, in the absence of a standard indication for it, published guidelines do not recommend therapeutic anticoagulation but do recommend use of prophylactic regimens in any hospitalized patient with COVID-19^{77, 78, 60, 79, 12, 80}
 - Some experts recommend risk assessment and consideration of continued prophylaxis for up to 45 days after discharge^{80, 77, 78}
- 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 applicable¹²
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Surviving Sepsis Campaign,⁶⁴ NIH COVID-19 treatment guideline,⁶⁰ and WHO¹² provide guidance specific to treatment of shock in patients with COVID-19
- Drug therapy
 - Antiviral agent⁸¹
 - Remdesivir
 - For patients NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation
 - Remdesivir Solution for injection; Neonates weighing 3.5 kg or more who require supplemental oxygen BUT NOT on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO): The NIH recommends remdesivir be prioritized for hospitalized patients with severe COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or 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.
 - Remdesivir Solution for injection; Infants, Children, and Adolescents weighing 3.5 to 39 kg who require supplemental oxygen BUT NOT on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO): The NIH recommends remdesivir be prioritized for hospitalized patients with severe COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or 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.
 - Remdesivir Solution for injection; Children and Adolescents weighing 40 kg or more who require supplemental oxygen BUT NOT on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO): The NIH recommends remdesivir be prioritized for hospitalized patients with severe COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or 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.
 - Remdesivir Solution for injection; Adults requiring supplemental oxygen BUT NOT on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO): The NIH recommends remdesivir be prioritized for hospitalized patients with severe COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or 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.

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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
 - IV dosage
 - Sarilumab Solution for injection; Adults: Efficacy has not been established. Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of IL-6 receptor inhibitors, such as sarilumab. 400 mg IV once in combination with antiviral therapy.
 - Subcutaneous dosage
 - Sarilumab Solution for injection; Adults: Efficacy has not been established. Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of IL-6 receptor inhibitors, such as sarilumab. 200 or 400 mg subcutaneously once in combination with antiviral therapy.
- Corticosteroid
 - Dexamethasone
 - Dexamethasone Sodium Phosphate Solution for injection; Adults: 6 mg IV once daily for up to 10 days is recommended by the NIH guidelines for use in mechanically ventilated patients and patients who require supplemental oxygen. Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
- Nondrug and supportive care
 - Excellent supportive care is the only treatment to date that appears to be consistently helpful in COVID-19
 - WHO,¹² NIH,⁶⁰ and Surviving Sepsis Campaign⁶⁴ 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 therapy when oxygen saturation falls below 90% to 92%⁶⁴
 - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute¹²
 - 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 patients⁸²
 - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign⁶⁴ 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 provided⁶⁴
 - 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)⁴⁴
 - Although optimal technique has not been fully defined, COVID-19–specific recommendations are emerging
 - Extracorporeal membrane oxygenation has been used⁷ 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 respond⁸³

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- 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^{7,11}
 - 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 so⁸⁴
 - 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^{85, 86, 87, 88, 89, 90}
- Special populations
 - Pregnant patients
 - WHO guidelines¹² 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 indications¹²
 - There is little evidence to suggest vertical transmission;^{91,12} however, an infected woman may transmit the virus by the airborne route to her neonate. CDC and WHO differ in their recommendations⁹²
 - 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 caregiver⁹²
 - 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 care¹²
 - Patients with HIV⁹³
 - 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 guideline⁹³ 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 more⁹⁴ into the course of illness and may be quite abrupt⁹⁵
- For patients receiving chloroquine or hydroxychloroquine, monitoring of QTc is recommended⁶⁵
 - 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 Tisdale⁶⁶ or similar score, may consider no further monitoring
- In hospitalized patients with confirmed COVID-19, repeated testing may be done to document clearance of virus, defined as 2 consecutive negative results on polymerase chain reaction tests at least 24 hours apart⁹⁶

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Most common complication is acute respiratory distress syndrome; other reported complications include:^{8,7}
 - Septic shock
 - Acute kidney injury
 - Myocardial injury
 - Secondary bacterial and fungal infections
 - Multiorgan failure

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- Thrombotic events⁸⁰
- Guillain-Barré syndrome⁹⁷
- Clinicians in Europe and the United States have reported emergence in children of an inflammatory syndrome resembling Kawasaki disease, and thought to be associated with COVID-19. Presentation may follow a diagnosis of or exposure to COVID-19^{98, 99, 100, 101}
 - Characteristic features include:^{101, 98}
 - Persistent fever
 - Hypotension, syncope, confusion
 - Headache
 - Sore throat, neck swelling
 - Cough, hypoxemia
 - Abdominal pain, vomiting and diarrhea
 - Rash, conjunctival injection, mucosal inflammation
 - Swelling of hands and feet
 - Lymphadenopathy
 - Laboratory markers of inflammation (eg, elevated erythrocyte sedimentation rate; elevated levels of C-reactive protein, ferritin, D-dimer, fibrinogen, procalcitonin, lactate dehydrogenase, interleukin-6, and interleukin-10; low level of serum albumin)
 - Abnormal blood cell counts: anemia, thrombocytopenia, neutrophilia
 - Indicators of multiorgan involvement: increased levels of creatinine, BUN, urine protein, transaminases, creatine kinase, troponins, and lactate dehydrogenase
 - Imaging
 - Chest radiograph or CT scan: bilateral patchy pulmonary infiltrates, pleural effusions
 - Echocardiogram: pericardial effusion, myocardial dysfunction, valvulitis, coronary artery dilatation
 - Abdominal ultrasonography: ascites, colitis, ileitis, hepatosplenomegaly, lymphadenopathy
 - Diagnosis is based on clinical presentation and absence of an alternative explanation; CDC⁹⁸ and WHO¹⁰² provide case definitions for reporting
 - In the absence of laboratory documentation of SARS-CoV-2, it may be difficult to distinguish this syndrome from Kawasaki disease or toxic shock syndrome; bacterial sepsis must also be considered and appropriate cultures obtained (including blood cultures)
 - Several professional organizations provide guidance on management^{103, 101, 104}
 - Cardiac (telemetry) and blood pressure monitoring; continuous pulse oximetry
 - Prompt ECG and echocardiogram, with serial follow-up studies
 - Close clinical and laboratory monitoring for progressive inflammation and cardiac involvement, including levels of C-reactive protein, troponin, and B-type natriuretic peptide
 - Empiric antibiotic coverage pending culture results
 - Consideration may be given to treating for Kawasaki syndrome or toxic shock syndrome
 - Consideration may be given to antiviral and/or immunomodulatory therapy
 - Low-dose aspirin should be administered to patients with Kawasaki-like features unless contraindicated (eg, thrombocytopenia); patients with aneurysms and a z score of 10 or higher, documented thrombosis, or an ejection fraction less than 35% should receive therapeutic anticoagulation in addition

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, 8}
- 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 immunity⁹⁴
- Mortality rate of diagnosed cases is generally about 5% to 6% but varies by country^{3, 2}
- Case fatality rates are higher for patients in older age groups and with certain comorbidities
 - Case fatality rates by age in the United States:³⁰
 - 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:⁹⁴
 - 10.5% for cardiovascular disease
 - 7.3% for diabetes
 - 6% for chronic respiratory disease

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- 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^{12, 52}
 - 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-19⁵²
 - 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)⁵²
 - Guidelines released by Infectious Diseases Society of America also recommend testing of asymptomatic persons in the following circumstances, given sufficient testing supplies:³⁹
 - 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
 - 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:^{52, 105, 12, 22}
 - 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 have instituted frequent screening of temperature and symptoms in health care workers (eg, at beginning of each shift)⁵²
 - Polymerase chain reaction screening of asymptomatic persons is recommended in some other medical settings (eg, in persons with certain conditions or who must undergo certain medical or surgical procedures). Other circumstances (eg, high local prevalence, low availability of personal protective equipment) may lower the threshold for wider screening of hospitalized patients³⁹
 - 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
 - Numerous antibody testing methods have been developed; however, performance (sensitivity and specificity) in laboratory testing of known positive and negative specimens does not correlate with performance in clinical testing in populations with relatively low prevalence, in which the positive predictive value is low and the rate of false-positives is high^{106, 34, 107}
 - Furthermore, it is not yet known whether presence of antibodies confers immunity¹⁰⁷
 - CDC provides guidance¹⁰⁷ for antibody testing, including appropriate clinical and epidemiologic situations in which testing may be of value, and it suggests measures to optimize positive predictive value (eg, orthogonal testing algorithm in which a positive result is followed by retesting with a different method)

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- FDA¹⁰⁸ provides information on interpreting antibody testing results and on the estimated performance characteristics of the tests available under emergency use authorization

PREVENTION

- There is no vaccine against COVID-19. At present, neither pre- nor postexposure prophylaxis is recommended outside of a clinical trial⁶⁰
- 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 doctor¹⁰⁹
 - 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)¹⁰⁹
 - 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)¹⁰⁹
 - 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 handwashing¹⁰⁹
 - Cover coughs. Use tissue and throw it away; second choice is sleeve, not hand¹⁰⁹
 - Avoid touching face¹⁰⁹
- 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 members¹¹⁰
 - 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
 - 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^{111, 52}
 - CDC provides preparedness checklists¹¹² 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 droplet or 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; WHO¹¹¹ suggests using 70% ethyl alcohol

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- Criteria for discontinuation of isolation precautions^{113, 114, 96}
 - CDC recommends that a symptom-based strategy should be used to determine when to discontinue isolation in most patients. Two sets of criteria have been established based on observations¹¹⁴ showing that duration of shedding of infective virus varies from less than 10 days in milder cases to less than 20 days in more severe infections and in immunocompromised persons
 - Mild to moderate illness, no immunocompromise:
 - At least 10 days have passed since symptom onset *and*
 - At least 24 hours have passed since last fever without use of antipyretics *and*
 - Symptoms have improved
 - If illness has been entirely asymptomatic, 10 days from first positive specimen is acceptable criterion
 - Severe or critical illness, or immunocompromising condition:
 - At least 20 days have passed since symptom onset *and*
 - At least 24 hours have passed since last fever without use of antipyretics *and*
 - Symptoms have improved
 - For severely immunocompromised persons whose infection has been entirely asymptomatic, precautions may be discontinued 20 days from first positive specimen
 - For persons not severely immunocompromised whose infection has been entirely asymptomatic, 10 days from first positive specimen is acceptable criterion
 - A 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 symptomatic patients
 - 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
 - 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 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 catastrophic⁷
- 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;⁵⁷ 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
- A significant proportion of clinically evident cases are severe; the mortality rate among diagnosed cases is generally about 5% to 6% but varies by country^{2, 3}
- 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 at least droplet 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

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- 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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