

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 3% 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
 - In late 2020 and early 2021, several variants with potential impact on transmission, clinical disease, and immune protection were recognized. Several are characterized as "variants of concern" based on potential for increased transmissibility, greater severity of disease, reduction in protective effect of antibodies generated by previous disease or vaccination, reduced efficacy of available treatments, or reduced sensitivity of testing modalities⁴
 - B.1.1.7: appears to have emerged in the United Kingdom; thought to be more easily transmitted and possibly associated with more severe disease than the original strain
 - B.1.351: first noted in South Africa; may confer some resistance to certain vaccines (eg, Moderna mRNA-1273)
 - P.1: seems to have originated in Brazil; may mitigate the protective effect of antibodies to the original strain
 - B.1.427 and B.1.429: both first detected in California; both associated with slightly increased transmissibility, significant decrease in neutralization effect of some monoclonal antibody treatments, and moderate decrease in neutralization effect of convalescent serum

CLASSIFICATION

- Pathogen is a betacoronavirus,⁵ 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*^{6,7}
 - Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2); earlier provisional name was 2019-nCoV^{7,6}

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 shock⁸
 - Most common complaints are fever (more than 80%) and cough, which may or may not be productive^{9,8}
 - Myalgia and fatigue are common; fatigue may be profound⁸
 - Alteration in smell and/or taste is widely reported, often as an early symptom, and is highly suggestive¹⁰
 - Patients with moderate to severe disease often complain of dyspnea;⁸ however, it has been recognized that many patients with severe hypoxemia due to COVID-19 do not perceive dyspnea¹¹
 - Hemoptysis has been reported in a small percentage of patients⁸
 - Pleuritic chest pain has been reported¹²
 - Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) may be present
 - Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur⁸
 - Patients may or may not report close contact with an infected person
- Physical examination
 - 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)¹³

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- Fever is typical, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever⁸
- Conjunctival secretions, injection, and chemosis have been reported¹⁴
- A variety of skin changes have been described, including erythematous rashes,¹⁵ purpura,¹⁶ petechiae,¹⁷ and vesicles;¹⁸ acral lesions^{19,20,21} resembling chilblains or Janeway lesions have been seen, particularly in young patients²²
- Hypotension, tachycardia, and cool/clammy extremities suggest shock
 - In children, hypotension plus 2 or more of the following criteria:¹³
 - Altered mental status
 - Tachycardia (heart rate more than 160 beats per minute in infants or 150 in older children) or bradycardia (heart rate less than 90 in infants or 70 in older children)
 - Prolonged capillary refill (more than 2 seconds) or warm vasodilation and bounding pulses
 - Tachypnea
 - Mottled skin, petechiae, or purpura
 - Oliguria
 - Hyperthermia or hypothermia

CAUSES AND RISK FACTORS

- Causes
 - Infection due to SARS-CoV-2 (2019 novel coronavirus)
 - Person-to-person transmission has been documented¹² and occurs with close contact,²³ probably largely via respiratory droplets and perhaps in some cases by aerosolization²⁴
 - Viral shedding appears to peak 24 to 48 hours before symptom onset,²⁵ raising the likelihood of presymptomatic transmission. Several case and cluster reports from various countries^{26,27,28} indicating asymptomatic and presymptomatic transmission have been reported
 - A study of viral loads found similar levels in presymptomatic and symptomatic infected persons²⁹
 - 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,^{9,8} but pediatric infections in adolescents and children^{30,12} also occur
 - Risk of severe disease increases with age; in the United States, 94% of deaths occur in people older than 50 years.³¹ Percentage of total mortality by age group:³²
 - 0 to 49 years: less than 5%
 - 50 to 64 years: 14.7%
 - 65 to 74 years: 21.4%
 - 75 to 84 years: 27.6%
 - 85 years or older: 31.7%
 - Sex
 - Overall, where sex or gender data are available, it appears that females are more often affected, but disease is more severe in males³²
 - Other risk factors/associations
 - Various underlying medical conditions have been associated with increased risk for severe disease, especially if they are not well controlled:³³
 - Chronic kidney disease
 - Chronic obstructive pulmonary disease
 - Diabetes type 2
 - Down syndrome
 - Immunosuppression because of previous solid organ transplant
 - Malignancy
 - Pregnancy
 - Severe obesity (BMI of 40 kg/m² or higher)
 - Serious cardiac conditions (eg, heart failure, coronary artery disease, cardiomyopathy)
 - Sickle cell disease
 - Smoking
 - Conditions which may be associated with higher risk for severe disease:³³
 - Asthma (moderate to severe)
 - Cerebrovascular disease

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- Chronic liver disease
- Cystic fibrosis
- Diabetes type 1
- Hypertension
- Immunodeficiency from various other causes (eg, bone marrow or hematopoietic stem cell transplant, primary immunodeficiencies, HIV disease, chronic treatment with corticosteroids or other agents with immunosuppressive effects)
- Neurologic dysfunction
- Overweight (BMI more than 25 kg/m² but less than 30 kg/m²)
- Pulmonary fibrosis
- Thalassemia
- Children with medically complex conditions (eg, neurologic, metabolic, genetic, cardiac) are also at higher risk for severe disease³³
- 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 status³⁴

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - Polymerase chain reaction tests have been the standard for diagnosis; antigen testing³⁵ has also received emergency use authorization in the United States. Specific test methods and availability vary; public health authorities may assist in arranging diagnostic testing in some areas. Attempts to culture the virus are not recommended. Serologic tests³⁶ are not recommended for diagnostic purposes in most circumstances^{23, 37, 38}
 - CDC²³ and WHO¹³ 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
 - WHO^{39, 40}
 - Acute onset of fever and cough *or* acute onset of any 3 or more of a specified list of symptoms (ie, fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status) *plus* one of the following:
 - Living or working in a setting with high risk of transmission of SARS-CoV-2 (eg, closed residential facilities, refugee camps) at any time during the 14 days preceding symptom onset
 - A history of travel to or residence in an area reporting local transmission of COVID-19 during the 14 days preceding symptom onset
 - Working in any health care setting at any time during the 14 days preceding symptom onset
 - Onset within the last 10 days of a severe acute respiratory tract infection requiring hospital admission without an alternative etiologic diagnosis
 - In situations where testing must be prioritized, WHO recommends prioritizing the following:⁴¹
 - 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
 - CDC²³
 - 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 people at high risk for severe disease in their home or employment setting
 - 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 (not routine but may be appropriate in certain circumstances)
 - Public health surveillance

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- Specimens from upper or lower respiratory tract are recommended for viral testing.⁴² 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)⁴²
 - Upper respiratory tract
 - Nasopharyngeal, deep nasal (midturbinate), anterior nares, oropharyngeal, or saliva specimens may be submitted. Only synthetic fiber (eg, polyester) swabs with plastic or wire shafts are acceptable. Flocked swabs are recommended for obtaining deep nasal specimens. If more than one swab is collected, they may be placed in the same container. Nasopharyngeal or nasal washings or aspirates are also acceptable. Note that not all tests are designed for use on all specimens
 - For nasopharyngeal specimen, insert swab into nostril parallel to palate. Leave swab in place for a few seconds to absorb secretions, then remove while gently rotating. It is not necessary to repeat on the other side if the first effort produces a good specimen (ie, swab is saturated)
 - For deep nasal specimen, insert a flocked swab about 2 cm and rotate; repeat on opposite side, using the same swab
 - For anterior nares, insert a flocked swab about 1 cm, rotate in contact with mucus membrane, and leave in place for 10 to 15 seconds; repeat on opposite side, using same swab
 - For oropharyngeal specimen, swab the posterior pharynx, avoiding tongue and tonsils
 - For tests designed for use on saliva, supervised self-collection of 1 to 5 mL is recommended
 - Nasopharyngeal wash (or aspirate) or nasal aspirate specimens (using 1 to 1.5 mL 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
 - 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 negative⁴³
 - Favor nasopharyngeal, nasal, or midturbinate specimens, saliva specimen, or combined anterior nasal/oropharyngeal swab over oropharyngeal swab alone for SARS-CoV-2 RNA testing
 - For patients with high likelihood of disease but negative initial result, repeated testing is recommended; in patients with lower respiratory tract symptoms, sputum or other lower respiratory tract specimen is recommended for repeated testing
 - A systematic review and meta-analysis compared frequency with which SARS-CoV-2 RNA was detected in sputum, nasopharyngeal swabs, and oropharyngeal swabs in patients with documented COVID-19. Overall positivity was 71% for sputum, 54% for nasopharyngeal swabs, and 43% for oropharyngeal swabs. Earlier testing resulted in higher positivity rates in all specimens⁴⁴
- Serologic testing is not recommended for routine use in diagnosis, but it may be useful under some circumstances (eg, high suspicion for disease with persistently negative results on viral RNA tests; in the diagnosis of multisystem inflammatory syndrome in children; in other situations in which retrospective confirmation of disease is indicated)³⁶
- 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 testing¹³
 - Coinfections have been reported, but the frequency is unknown^{45, 46}
 - Influenza may be clinically indistinguishable from COVID-19; additionally, coinfection can occur. Therefore, when influenza and SARS-CoV-2 are both circulating in the community, testing for **both** viruses is recommended for all patients hospitalized with acute respiratory infection. In patients who present with acute respiratory illness but who do not require hospitalization, influenza testing is recommended **in addition to** testing for SARS-CoV-2, if influenza test results would alter management^{47, 48}
 - CDC recommends nucleic acid detection over antigen testing for both pathogens, either by multiplex or individual assay

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- Chest imaging is essential to document presence of pneumonia and to assess severity; plain radiography, CT, and ultrasonography have been used⁹
 - 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 at the time; and the public health goal of detecting and isolating all infected persons⁴⁹
 - 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 pneumonias⁵⁰
- 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)¹³
- 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^{43,51}
 - 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^{43,51}
 - Antigen tests are also available for use in diagnosis, and they have the advantage of rapid turnaround
 - In general, these tests are less sensitive than polymerase chain reaction, although specificity is equivalent and may be as high as 100%; therefore, false-positive results are uncommon, but a negative result may warrant retesting (preferably within 2 days) with polymerase chain reaction if there is a high suspicion for infection based on clinical or epidemiologic indicators³⁵
 - A Cochrane review noted wide-ranging sensitivity and specificity of antigen tests (average sensitivity, 56.2%; average specificity, 99.5%), but it concluded that existing published evaluation of these tests has been based largely on application to remnant laboratory samples and thus may not reflect performance in clinical use⁵²
 - A Cochrane review⁵³ notes that antibody tests are most likely to be clinically useful 15 days or more into the course of infection and that data are scarce regarding antibody tests beyond 35 days. For instances when clinicians judge that antibody testing is indicated, Infectious Diseases Society of America³⁶ makes the following recommendations:
 - Testing 3 to 4 weeks after symptom onset maximizes sensitivity
 - Sensitivity at 1 week ranges from 0.23 to 0.63; at 2 weeks, from 0.68 to 0.96
 - Test should measure anti-SARS-CoV-2 IgG or total antibody; a high-specificity test should be used
 - Unlike the usual pattern of antibody production, IgM antibody response to SARS-CoV-2 is somewhat delayed, occurring almost simultaneously with IgG production, so there is no advantage to testing selectively for the IgM fraction
 - Routine blood work is not diagnostic, but a pattern of typical abnormalities has emerged, particularly in patients with severe illness:
 - Leukopenia may be observed and relative lymphopenia is common, especially in patients with more severe illness^{9,8,12}
 - Anemia was noted in about half of patients in one series⁹
 - Both elevated and low platelet counts have been seen^{12,9,8}
 - Prolonged prothrombin time has been reported⁵⁴
 - Levels of D-dimer and fibrinogen may be elevated^{8,12}
 - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common^{8,9}
 - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection⁸
 - Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate⁹
 - Lactate level of 2 mmol/L or higher suggests presence of septic shock¹³
- 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^{8,9,5,12,55}

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- CT appears to be more sensitive⁵⁶ than plain radiographs, but normal appearance on CT does not preclude the possibility of COVID-19⁵⁷
- 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 thrombosis or vascular catheter thrombosis, which appear to be common in patients with COVID-19^{58,51}

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 older adults (eg, those aged 65 years or older) or those with significant comorbidities often require hospitalization
 - Usually occurs in winter months in temperate climates but is less seasonal in equatorial regions
 - Patients with severe disease may have abnormal chest radiographic findings suggesting influenzal pneumonia or secondary bacterial pneumonia
 - Positive result on rapid influenza diagnostic test confirms influenza diagnosis with high specificity during typical season; negative result does not rule out influenza
 - Influenza may be clinically indistinguishable from COVID-19; additionally, coinfection can occur. Therefore, when influenza and SARS-CoV-2 are both circulating in the community, testing for **both** viruses is recommended for all patients hospitalized with acute respiratory infection. In patients who present with acute respiratory illness but who do not require hospitalization, influenza testing is recommended **in addition to** testing for SARS-CoV-2, if influenza test results would alter management^{48,47}
 - CDC recommends nucleic acid detection over antigen testing for both pathogens, either by multiplex or individual assay
 - Other viral pneumonias
 - Presentations include fever, dry cough, and dyspnea
 - Physical examination may find scattered rales
 - Chest radiography usually shows diffuse patchy infiltrates
 - Diagnosis is usually clinical. Testing for specific viral causes may be done; multiplex panels can test simultaneously for a number of common viral respiratory pathogens such as respiratory syncytial virus, adenovirus, and others
 - Bacterial pneumonia
 - Presentation includes fever, cough, and dyspnea; pleuritic pain occurs in some cases
 - Physical examination may find signs of consolidation (eg, dullness to percussion, auscultatory rales, tubular breath sounds)
 - Chest radiography usually shows lobar consolidation or localized patchy infiltrate
 - Sputum examination may find abundant polymorphonuclear leukocytes and a predominant bacterial organism
 - Pneumococcal or legionella antigens may be detectable in urine; sputum culture may find those or other pathogens

TREATMENT

GOALS

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

DISPOSITION

- Admission criteria
 - Nonsevere pneumonia
 - Radiographic evidence of pneumonia; progressive clinical illness; risk factors for severe disease; inadequate care at home^{13,59}
 - 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 measures⁵⁹
 - Criteria for ICU admission
 - WHO provides criteria for critical respiratory tract disease⁶⁰
 - Characterized by tachypnea (respiratory rate greater than 30 breaths or less than 10 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO₂ 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

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- Aged 1 to 12 months: 50 or more breaths per minute *or* 10 or fewer breaths per minute
- Aged 1 year or older: 40 or more breaths per minute
- Presence of severe complications (eg, septic shock, acute respiratory distress syndrome)
- Recommendations for specialist referral
 - All patients should be managed in consultation with public health authorities
 - Consult infectious disease specialist to coordinate diagnosis and management with public health authorities
 - Consult pulmonologist to aid in obtaining deep specimens for diagnosis and managing mechanical ventilation if necessary
 - Consult critical care specialist to manage fluids, mechanical ventilation, and hemodynamic support as needed

TREATMENT OPTIONS

- Standard, contact, and (at least) droplet precautions should be implemented as soon as the diagnosis is suspected; airborne precautions are recommended if resources allow, especially for aerosol-generating procedures⁶¹
 - 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, 1 antiviral agent (remdesivir) is FDA-approved specifically for treatment⁶² of this infection, and emergency use authorization has been granted for monoclonal antibody combinations of bamlanivimab-etesevimab⁶³ and casirivimab-imdevimab;⁶⁴ these target the viral spike protein by which the virus gains entry to human cells. (The emergency use authorization for bamlanivimab alone was revoked because virus variant prevalence has reduced its effectiveness and availability of the combination of bamlanivimab-etesevimab has improved.⁶⁵) Several existing drugs are being used under clinical trial and compassionate use protocols based on in vitro activity (against this or related viruses) and limited clinical experience. One of these (baricitinib⁶⁶), a disease-modifying antirheumatic drug used in refractory rheumatoid arthritis, has received emergency use authorization for administration in conjunction with remdesivir in patients with severe disease. Information on therapeutic trials and expanded access is available at ClinicalTrials.gov⁶⁷
 - A strategy has emerged by which drugs are selected according to the mechanism of action most likely to be effective against the dominant pathophysiology at various stages in the disease process. Thus, antivirals and monoclonal antibodies directed at viral components are most effective when used early in the course of infection to prevent cell entry and viral replication; antiinflammatory drugs (eg, dexamethasone) and immunomodulators are of most benefit during the hyperinflammatory response in later phases of severe disease⁶⁸
 - Remdesivir is an antiviral agent with significant in vitro activity against coronaviruses,^{69,70} some evidence of efficacy in an animal model of MERS,⁷⁰ and some evidence of efficacy in COVID-19⁷¹
 - Remdesivir is approved to treat hospitalized patients with COVID-19. The FDA approval extends to patients aged 12 years or older who weigh 40 kg or more; the earlier emergency use authorization provides continued access for pediatric patients younger than 12 years and/or who weigh less than 40 kg but more than 3.5 kg⁶²
 - Preliminary⁷² and follow-up⁷¹ results of the Adaptive COVID-19 Treatment Trial, a placebo-controlled randomized trial in 1062 patients, showed a statistically significant improvement in time to recovery and a nonsignificant trend in lower mortality; several other trials remain active, as well⁷³
 - On the basis of these and other data from clinical trials, the NIH guideline recommends, and the Infectious Diseases Society of America and Surviving Sepsis Campaign guidelines suggest, remdesivir for hospitalized patients with COVID-19 who require supplemental oxygen^{74, 75, 48, 76}
 - In patients who require oxygen via high-flow device or noninvasive ventilation, NIH offers the option of remdesivir with dexamethasone or dexamethasone alone, because remdesivir appears to confer maximum benefit before onset of more severe disease, in which dexamethasone alone is associated with markedly reduced mortality. NIH does not recommend routine use of remdesivir in patients who require mechanical ventilation or extracorporeal membrane oxygenation
 - Infectious Diseases Society of America recommends use of remdesivir over no antiviral in these patients, but it acknowledges that if shortages occur, this consideration should be taken into account in allocating available drug
 - Surviving Sepsis Campaign guideline suggests that remdesivir not be used in patients with critical COVID-19, outside of clinical trials
 - 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
 - Neither guideline recommends remdesivir for less severely ill patients, even if hospitalized
 - WHO does not recommend remdesivir use outside of clinical trials¹³

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- Bamlanivimab and etesevimab are monoclonal antibodies designed to target the SARS-CoV-2 spike protein, disabling viral attachment and entry into human cells; the 2 antibodies target different regions of the spike protein^{63, 65}
 - Preliminary data from clinical trials on bamlanivimab demonstrated a reduction in the incidence of COVID-19–associated emergency department visits and hospital admissions (3% for patients treated with bamlanivimab versus 10% for patients who received placebo)⁷⁷
 - A subsequent trial (BLAZE-1) of bamlanivimab in combination with etesevimab showed a 70% reduction in COVID-19–related hospitalization or death by any cause⁷⁸
 - Based on these data, FDA has issued an emergency use authorization allowing administration of bamlanivimab in combination with etesevimab⁷⁸. (The emergency use authorization for bamlanivimab alone was revoked because virus variant prevalence has reduced its effectiveness and availability of the combination of bamlanivimab-etesevimab has improved.⁷⁷) Use is limited to persons aged 12 years or older who have mild to moderate disease and who are at high risk (by virtue of older age or concomitant conditions) for progression to severe disease and/or hospital admission; the authorizations exclude persons who are already hospitalized or who require supplemental oxygen for COVID-19. The emergency use authorizations define high risk for progression as follows:
 - Persons aged 12 years or older with BMI of 35 or higher, chronic kidney disease, diabetes, or immunocompromise (immunosuppressive disease or treatment)
 - Persons aged 65 years or older
 - Persons aged 55 years or older with cardiovascular disease, hypertension, or chronic respiratory disease including chronic obstructive pulmonary disease
 - Persons aged 12 to 17 years with any of the following:
 - BMI in the 85th percentile or higher for age and gender
 - Sickle cell disease
 - Cardiac disease, congenital or acquired
 - Neurodevelopmental disorders
 - Chronic respiratory disease (including asthma) that requires daily medication to control
 - Dependence on a medical technology such as tracheostomy, gastrostomy, or positive pressure ventilation
 - NIH guideline recommends use of the combination of bamlanivimab with etesevimab for outpatients with COVID-19 at high risk of progressing to severe disease. It recommends against use of the combination in inpatients, except as part of a clinical trial⁴⁸
 - Infectious Diseases Society of America guideline suggests use of bamlanivimab with etesevimab in ambulatory patients at high risk for progression to severe disease⁷⁶
- Monoclonal antibodies casirivimab and imdevimab target the receptor-binding domain of the SARS-CoV-2 spike protein, disabling attachment and entry of the virus into human cells⁶⁴
 - Preliminary clinical studies evaluated effect on viral load and on medically attended illness. In a placebo-controlled trial of 799 patients with mild to moderate COVID-19, reduction in viral load in days 1 through 7 was significantly greater for the monoclonal antibody combination compared with placebo (p less than 0.0001). Treatment was also associated with fewer emergency department visits and hospital admissions (2.8% for patients treated with casirivimab and imdevimab versus 6.5% for patients who received placebo)⁷⁹
 - Based on these data, FDA has issued an emergency use authorization allowing administration of casirivimab and imdevimab in combination to persons aged 12 years or older who have laboratory-confirmed COVID-19 presenting with mild to moderate disease and who are at high risk due to older age or concomitant conditions for progression to severe disease and/or hospital admission; the authorization excludes persons who are already hospitalized or who require supplemental oxygen for COVID-19. The emergency use authorization defines high risk for progression as meeting any of the following criteria:⁷⁹
 - BMI of 35 kg/m² or higher
 - Chronic kidney disease
 - Diabetes
 - Immunosuppression due to disease or treatment
 - Age 65 years or older
 - Age 55 years or older **and** any of the following conditions:
 - Cardiovascular disease
 - Hypertension
 - Chronic respiratory disease including chronic obstructive pulmonary disease
 - Age 12 to 17 years **and** any of the following risks:
 - BMI in 85th percentile or higher
 - Sickle cell disease
 - Congenital or acquired heart disease
 - Neurodevelopmental disorders

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- Chronic respiratory disease (including asthma) that requires daily medication to control
 - Dependence on a medical technology such as tracheostomy, gastrostomy, or positive pressure ventilation
- NIH guidelines recommend using casirivimab and imdevimab in outpatients with mild to moderate COVID-19 who are at high risk for clinical progression. They note that it should not be given to hospitalized patients outside of a clinical trial⁴⁸
- Infectious Diseases Society of America guideline suggests use of casirivimab and imdevimab in ambulatory patients who are at high risk of progression to severe with COVID-19⁷⁶
- Chloroquine and hydroxychloroquine have been used in China and South Korea, reportedly with favorable results,⁸⁰ 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,⁸¹ 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 considered⁸²
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against using hydroxychloroquine⁷⁴
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends against hydroxychloroquine or chloroquine and against the combination of either of those drugs with azithromycin⁷⁶
 - NIH guidelines recommend against chloroquine or hydroxychloroquine in hospitalized patients; in nonhospitalized patients, they recommend against chloroquine or hydroxychloroquine except in a clinical trial. They recommend against high-dose chloroquine (600 mg twice daily for 10 days) and against the addition of azithromycin to hydroxychloroquine except in a clinical trial. The guidelines note that when chloroquine or hydroxychloroquine is used, patients must be monitored for adverse effects, particularly prolonged QTc interval⁴⁸
 - Scoring systems are available to determine risk of arrhythmia^{83, 84}
 - WHO recommends against use of chloroquine or hydroxychloroquine with or without azithromycin outside of a clinical trial¹³
 - 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 group⁸⁵
 - A subsequently published randomized controlled open-label trial (RECOVERY) of 1561 patients treated with hydroxychloroquine and 3155 treated without showed no survival advantage among patients treated with hydroxychloroquine⁸⁶
- Lopinavir-ritonavir is FDA-approved for treatment of HIV infection. It has been used in China in conjunction with interferon alfa for treatment of some patients with COVID-19, but reported results have been disappointing
 - 3 randomized placebo-controlled trials have evaluated the effects of lopinavir-ritonavir in the treatment of COVID-19. The combined data⁷⁶ did not show significant differences in progression to mechanical ventilation or mortality
 - NIH COVID-19 treatment guideline,⁴⁸ Infectious Diseases Society of America guideline on treatment and management of COVID-19,⁷⁶ and Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19⁷⁵ 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 efficacy⁷⁵
 - WHO recommends against use of lopinavir-ritonavir outside of a clinical trial¹³
- Since last guideline updates, interim results of the WHO SOLIDARITY trial have been released in preprint form (not yet peer reviewed). Remdesivir, lopinavir-ritonavir, hydroxychloroquine, and interferon were compared with one another (open-label) and with standard care (no placebo) in a total population of over 11,000 patients in over 400 hospitals in 30 countries worldwide⁸⁷
 - End points were in-hospital mortality, initiation of ventilation, and duration of hospital stay. No differences among the groups were noted for any of these parameters. The authors acknowledge that length of stay may have been influenced in some cases by the requirements of antiviral administration (eg, 10 days of IV administration for remdesivir), but they argue that the similarity in percentages of patients in each group remaining in the hospital beyond the course of the study drug indicates a lack of benefit to any treatment arm. The impact of this study on treatment guidelines remains to be seen
- Studies on the therapeutic efficacy of convalescent plasma are underway in various countries⁸⁸
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 suggests that convalescent plasma not be used outside of clinical trials⁷⁴

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- In patients admitted to hospital with COVID-19, Infectious Diseases Society of America recommends against convalescent plasma; in ambulatory patients, it recommends convalescent plasma only in the context of a clinical trial⁷⁶
- 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 it⁴⁸
- WHO recommends against use of plasma therapy outside of a clinical trial
- Since the publication of these guidelines, and based on emerging information, FDA has issued an emergency use authorization, citing, among other reasons, the observational safety and efficacy data from 20,000 patients who received convalescent plasma through a program sponsored by the Mayo Clinic:⁸⁸
 - Serious adverse events were uncommon, and they were judged not to exceed the known incidence in transfusion of plasma to critically ill patients
 - There was some evidence of improved survival in the subset of patients treated with convalescent plasma containing higher titers of neutralizing antibody compared with patients who received plasma with lower levels (ie, there appeared to be a dose-response gradient)
 - Early administration (eg, before mechanical ventilation is required) appeared more likely to be beneficial, but the possibility of benefit even to intubated patients could not be excluded
- FDA has produced a fact sheet⁸⁹ for providers that includes labeling criteria (high versus low titer), suggested dosing and infusion practices, and potential adverse effects. It suggests starting with a single unit (about 200 mL), taking care to avoid fluid overload in patients with impaired cardiac function; additional doses may be administered based on the patient's response and clinician's judgment
- Immunomodulators are also being investigated for mitigation of cytokine release syndrome believed to be a factor in severe acute respiratory distress syndrome and shock in COVID-19 (eg, tocilizumab⁷⁵ and sarilumab,⁹⁰ both monoclonal antibodies against interleukin-6 receptor; baricitinib⁶⁶ and other Janus kinase inhibitors)
 - Baricitinib, a Janus kinase inhibitor currently approved for use in refractory rheumatoid arthritis owing to its antiinflammatory effect, has received emergency use authorization for treatment in combination with remdesivir for severely ill patients on oxygen supplementation (including mechanical ventilation or extracorporeal membrane oxygenation)⁶⁶
 - FDA reviewed data from the ACTT-2 trial (Adaptive COVID-19 Treatment Trial 2), which compared remdesivir plus baricitinib (515 patients) against remdesivir plus placebo (518 patients) in patients with documented SARS-CoV-2 infection and either pulmonary infiltrates, O₂ saturation less than 94%, or requirement for some degree of oxygen supplementation. Patients who received baricitinib were more likely to have better clinical status (based on an 8-point score) at day 15 than those who did not. Median time to recovery was 7 days in the baricitinib arm versus 8 days in the placebo group. The odds of dying or progressing to noninvasive/high-flow oxygen or invasive ventilation were significantly lower for patients in the baricitinib group⁶⁶
 - NIH guidelines find data to be insufficient to recommend for or against use of baricitinib with remdesivir in hospitalized patients when corticosteroids can be used; in circumstances in which corticosteroids cannot be used, they recommend use of baricitinib with remdesivir in hospitalized nonintubated patients. They recommend against the use of baricitinib without remdesivir except in clinical trials, and they caution that use of baricitinib with corticosteroids increases the risk of superinfection versus use of a single immunosuppressive agent⁴⁸
 - Infectious Diseases Society of America guidelines recommend baricitinib plus remdesivir in hospitalized patients with severe COVID-19 when corticosteroids cannot be used, and they note uncertain benefits in patients who require mechanical ventilation. They recommend use of baricitinib in addition to remdesivir plus steroids only in the context of a clinical trial⁷⁶
 - 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 antibodies⁷⁵
 - In patients admitted to hospital with COVID-19, Infectious Diseases Society of America suggests against the routine use of tocilizumab, based on evidence of low certainty, although it does recommend tocilizumab in addition to standard care (steroids) for patients with progressive severe or critical COVID-19 who have elevated levels of markers of systemic inflammation⁷⁶

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- NIH COVID-19 treatment guideline recommends tocilizumab in combination with dexamethasone (with or without remdesivir) in recently hospitalized patients who are showing rapid respiratory decompensation. This class includes (1) those who require invasive or noninvasive mechanical ventilation or high-flow oxygen and (2) those with rapidly increasing oxygen needs requiring noninvasive ventilation or high-flow nasal cannula and who have significantly increased levels of inflammatory markers⁴⁸
 - Current version of the guideline does not comment directly on sarilumab; previous versions indicated that data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an ICU and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (more than 0.4 FIO₂/30 L/minute); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guidelines recommend against the use of sarilumab outside clinical trials
 - NIH guideline recommends against use of siltuximab (another monoclonal antibody against interleukin-6 activity) outside of a clinical trial
 - NIH guideline notes that data are insufficient to recommend for or against use of interleukin-1 inhibitors (eg, anakinra) or interferon beta (the latter in mild to moderate infection); it recommends against use of interferons in severe or critical infection and against use of kinase inhibitors
- WHO recommends against use of immunomodulators outside of a clinical trial¹³
- A systematic review and meta-analysis of retrospective trials with data from 240 patients who received tocilizumab and 352 controls concluded that the low-quality evidence available did not demonstrate clear benefit from tocilizumab⁹¹
- A review of data from 5 randomized controlled trials comparing tocilizumab to usual care (with or without placebo) did not show a 28-day mortality benefit, but it did show a lower relative risk of clinical deterioration (ie, ICU admission, mechanical ventilation, death), although evidence was of low certainty⁷⁶
- 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 administration¹³
 - 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^{92,93}
 - Compared with usual care alone, deaths in ventilated patients receiving usual care plus dexamethasone were reduced by a third; among patients receiving oxygen without mechanical ventilation, deaths were cut by 20%
 - Overall 28-day mortality was reduced by 17% in the dexamethasone group
 - Based on these data, NIH COVID-19 treatment guideline recommends use of dexamethasone in patients who require supplemental oxygen with or without mechanical ventilation (optional for patients who require oxygen supplementation only, that is, without high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation). It recommends against using dexamethasone in patients who do not require oxygen supplementation⁴⁸
 - In the absence of dexamethasone, another glucocorticoid (eg, prednisone, methylprednisolone, hydrocortisone) may be used
 - Similarly, Infectious Diseases Society of America guideline suggests use of dexamethasone in hospitalized patients who are severely or critically ill with COVID-19, defined as SpO₂ of 94% or less on room air or any requirement for supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation, or with other end-organ dysfunction resulting from COVID-19⁷⁶
 - Guideline provides equivalent doses of alternative glucocorticoids if dexamethasone is unavailable
 - Infectious Diseases Society of America recommends against the use of steroids in patients who are not hypoxemic
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 strongly recommends using corticosteroids (preferably dexamethasone) for up to 10 days in patients with severe or critical COVID-19^{74,75}
 - 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)¹³
 - 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 end point: transfer to ICU, need for mechanical ventilation, and mortality. Guidelines do not currently support administration of steroids early in the disease course⁹⁴
- 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 symptoms⁹⁵
 - 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-19⁴⁸
 - 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 support⁹⁶

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- Until a diagnosis of COVID-19 is confirmed by polymerase chain reaction or antigen test, appropriate antimicrobial therapy for other viral pathogens (eg, influenza virus) or bacterial pathogens should be administered in accordance with the severity of clinical disease, site of acquisition (hospital or community), epidemiologic risk factors, and local antimicrobial susceptibility patterns¹³
- Based on concerns about the possible role of micro- and macrovascular thrombosis in the pathophysiology of this disease, the use of anticoagulation is being studied. At present, in the absence of a standard indication for it, published guidelines do not recommend therapeutic anticoagulation but do suggest or recommend use of usual prophylactic regimens in any hospitalized patient with COVID-19, including pregnant patients^{48, 97, 98, 13, 99, 74, 100}
 - Some experts recommend risk assessment and consideration of continued prophylaxis for up to 45 days after discharge^{101, 97, 98}
- 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 applicable¹³
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Surviving Sepsis Campaign,⁷⁵ NIH COVID-19 treatment guideline,⁴⁸ and WHO¹³ provide guidance specific to treatment of shock in patients with COVID-19
- Drug therapy
 - Antiviral agent
 - Remdesivir
 - For patients NOT requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation
 - Remdesivir Solution for injection; Hospitalized Neonates weighing 3.5 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)†: 5 mg/kg/dose IV once on day 1 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; Hospitalized Infants, Children, and Adolescents weighing 3.5 to 39 kg NOT requiring invasive mechanical ventilation 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.
 - Remdesivir Solution for injection; Hospitalized Children and Adolescents 12 years and older and weighing 40 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1 then 100 mg IV once daily for 4 days. May extend treatment for up to 5 additional days if no clinical improvement.
 - Remdesivir Solution for injection; Hospitalized Adults NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO): 200 mg IV once on day 1 then 100 mg IV once daily for 4 days. May extend treatment for up to 5 additional days if no clinical improvement.
 - Dosages for patients who require mechanical ventilation or extracorporeal membrane oxygenation have been established^{102, 103}
 - Monoclonal antibodies (antiviral)
 - Bamlanivimab
 - NOTE: Bamlanivimab and etesevimab MUST be administered in combination. Neither drug is authorized for administration as a single agent (i.e., monotherapy).
 - For patients aged 12 years or older, weighing 40 kg or more, with mild to moderate disease (not requiring supplemental oxygen and not hospitalized) at risk for progression
 - Bamlanivimab Solution for injection; Children and Adolescents 12 years and older weighing 40 kg or more: 700 mg of bamlanivimab and 1,400 mg of etesevimab together in a single IV infusion. Give as soon as possible after the positive SARS-CoV-2 test and within 10 days of symptom onset. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the routine use of these antibodies in pediatric patients. The NIH recommends the use of these antibodies be considered on a case-by-case basis in consultation with a pediatric infectious diseases specialist.
 - Bamlanivimab Solution for injection; Adults weighing 40 kg or more: 700 mg of bamlanivimab and 1,400 mg of etesevimab together in a single IV infusion. Give as soon as possible after the positive SARS-CoV-2 test and within 10 days of symptom onset.
 - Casirivimab-imdevimab
 - For patients aged 12 years or older, weighing 40 kg or more, with mild to moderate disease (not requiring supplemental oxygen and not hospitalized) at risk for progression
 - Casirivimab-imdevimab; Children, Adolescents, and Adults weighing 40 kg or more: The optimal dosing regimen has not yet been established, and the recommended dose may be updated as data from clinical trials become available. Administer 2400 mg (1200 mg of casirivimab and 1200 mg of imdevimab) as a single IV infusion over at least 60 minutes. Administer infusion as soon as possible after the positive test result for SARS-CoV-2 and within 10 days of symptom onset.

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- Etesevimab
 - Etesevimab Solution for injection; Children and Adolescents 12 years and older weighing 40 kg or more: 700 mg of bamlanivimab and 1,400 mg of etesevimab together in a single IV infusion. Give as soon as possible after the positive SARS-CoV-2 test and within 10 days of symptom onset. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the routine use of these antibodies in pediatric patients. The NIH recommends the use of these antibodies be considered on a case-by-case basis in consultation with a pediatric infectious diseases specialist.
 - Etesevimab Solution for injection; Adults weighing 40 kg or more: 700 mg of bamlanivimab and 1,400 mg of etesevimab together in a single IV infusion. Give as soon as possible after the positive SARS-CoV-2 test and within 10 days of symptom onset.
- Immunomodulators
 - Baricitinib
 - Baricitinib Oral tablet; Children 2 to less than 9 years: 2 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the use of baricitinib with remdesivir in pediatric patients.
 - Baricitinib Oral tablet; Children and Adolescents 9 years of age and older: 4 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. According to the NIH COVID-19 guidelines, there are insufficient data to recommend either for or against the use of baricitinib with remdesivir in pediatric patients.
 - Baricitinib Oral tablet; Adults: 4 mg PO once daily for 14 days or until hospital discharge, whichever comes first. Baricitinib is to be taken in combination with remdesivir. The NIH COVID-19 guidelines recommend baricitinib plus remdesivir only in rare circumstances where a corticosteroid cannot be used.
 - Tocilizumab
 - Tocilizumab Solution for injection; Adults: The NIH COVID-19 treatment guidelines recommend a single 8 mg/kg (actual body weight, up to 800 mg) IV dose given with dexamethasone (or equivalent corticosteroid) to treat recently hospitalized adults with rapid respiratory decompensation due to COVID-19 who meet the following criteria: admitted to the ICU within the prior 24 hours and require mechanical ventilation or high-flow nasal canula oxygen (more than 0.4 FiO₂/30 L/min) OR not in the ICU but have rapidly increasing oxygen needs requiring noninvasive mechanical ventilation or high-flow nasal canula AND have significantly increased markers of inflammation. Some Panel members also support use of the drug in patients who don't yet require mechanical ventilation or high-flow nasal canula but have rapidly increasing oxygen needs while on dexamethasone AND have a CRP of at least 75 mg/L.
 - Sarilumab
 - IV dosage
 - Sarilumab Solution for injection; Adults: According to the NIH COVID-19 treatment guidelines, data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an intensive care unit (ICU) and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (greater than 0.4 FiO₂/30 L/min); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guidelines recommend against the use of sarilumab outside clinical trials. 400 mg IV once in combination with antiviral therapy is being evaluated.
 - Subcutaneous dosage
 - Sarilumab Solution for injection; Adults: According to the NIH COVID-19 treatment guidelines, data are insufficient to recommend either for or against the use of sarilumab to treat COVID-19 in patients who are within 24 hours of admission to an intensive care unit (ICU) and require mechanical ventilation (invasive or noninvasive) or high-flow oxygen (greater than 0.4 FiO₂/30 L/min); efficacy of sarilumab in these patients has not been determined. For patients not requiring ICU-level care or who are in the ICU but do not meet the above criteria, the NIH guidelines recommend against the use of sarilumab outside clinical trials. 200 or 400 mg subcutaneously once in combination with antiviral therapy is being evaluated.
- Corticosteroid
 - Dexamethasone
 - Dexamethasone Sodium Phosphate Solution for injection; Adults: 6 mg IV once daily for up to 10 days or until hospital discharge (whichever comes first) is recommended by the NIH guidelines for use in hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The WHO strongly recommends systemic corticosteroids for 7 to 10 days in patients with severe or critical COVID-19. Before starting therapy, review the patient's medical history and assess the potential risks and benefits.

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- Various guidelines provide recommendations for alternative glucocorticoids if dexamethasone is not available:^{76, 48}
 - Methylprednisolone
 - Methylprednisolone Sodium Succinate Solution for injection; Adults: 8 mg IV every 6 hours or 16 mg IV every 12 hours for 7 to 10 days. The WHO strongly recommends systemic corticosteroids in patients with severe or critical COVID-19. The NIH recommends methylprednisolone as an alternative corticosteroid for hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The NIH recommends 32 mg IV once daily (or in 2 divided doses) for up to 10 days or until hospital discharge (whichever comes first). Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
 - Prednisone
 - Prednisone Oral tablet; Adults: 40 mg PO daily for 7 to 10 days. The WHO strongly recommends systemic corticosteroids in patients with severe or critical COVID-19. The NIH recommends prednisone as an alternative corticosteroid for hospitalized patients who require supplemental oxygen, including those on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO. The NIH recommends 40 mg PO once daily (or in 2 divided doses) for up to 10 days or until hospital discharge (whichever comes first). Before starting therapy, review the patient's medical history and assess the potential risks and benefits.
- Nondrug and supportive care
 - Excellent supportive care remains the mainstay of treatment to date in COVID-19
 - WHO,¹³ NIH,⁴⁸ and Surviving Sepsis Campaign⁷⁵ 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%⁷⁵
 - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute¹³
 - 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 patients¹⁰⁴
 - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign⁷⁵ and NIH⁴⁸ 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 provided⁷⁵
 - 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)⁵¹
 - Although optimal technique has not been fully defined, COVID-19–specific recommendations are emerging
 - Extracorporeal membrane oxygenation has been used⁸ 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 respond¹⁰⁵
 - 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^{8, 12}

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- 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 so¹⁰⁶
 - 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^{107, 108, 109, 110, 111, 112}
 - A prospective cohort study based on routinely collected data from more than 8 million persons enrolled in general practices in England identified more than 19,000 persons with COVID-19. Use of ACE inhibitors or angiotensin receptor blockers was associated with reduced risk of COVID-19 disease and was not associated with increased risk of requiring intensive care. The reduction in risk was less for Black people of Caribbean and African descent¹¹³
- Special populations
 - Pregnant patients
 - WHO guidelines¹³ 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 the mode of delivery be determined based on obstetric indications and patient preference; cesarean delivery is recommended only for the usual medically justified indications¹³
 - There is little evidence to suggest vertical transmission; ^{114, 13} however, an infected woman may transmit the virus by the airborne route to her neonate. CDC and WHO differ in their recommendations¹¹⁵
 - 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 caregiver¹¹⁵
 - 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 care¹³
 - Patients with HIV
 - 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 not well defined (limited study data)¹¹⁶
 - 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 guideline¹¹⁶ 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 more¹¹⁷ into the course of illness and may be quite abrupt¹¹⁸
- For patients receiving chloroquine or hydroxychloroquine, monitoring of QTc is recommended⁸⁴
 - 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 Tisdale⁸³ 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 apart¹¹⁹

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Most common complication is acute respiratory distress syndrome; other reported complications include:^{8, 9}
 - Septic shock
 - Acute kidney injury
 - Myocardial injury

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- Secondary bacterial and fungal infections
- Multiorgan failure
- Thrombotic events⁹⁷
- Guillain-Barré syndrome¹²⁰
- 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.^{121, 122, 123, 124, 125} Presentation may follow a diagnosis of or exposure to COVID-19. More recently, a number of adults¹²⁶ have been reported with similar clinical findings and recent history of diagnosed COVID-19 or serologic evidence of recent infection
 - Characteristic features include:^{122, 124}
 - 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; CDC¹²² and WHO¹²⁷ 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^{128, 124, 129, 130}
 - 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
 - Hospitalized children and those who fulfill criteria for Kawasaki syndrome should be treated with IV immunoglobulin 2 g/kg based on ideal body weight; glucocorticoids may be given in conjunction
 - Volume associated with IV immunoglobulin requires careful monitoring in patients with cardiac dysfunction
 - Low-dose aspirin should be administered to patients with Kawasaki-like features unless contraindicated (eg, thrombocytopenia); patients with aneurysms and a zscore 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) and experience significant deconditioning^{9, 8}
- Otherwise, short-term and long-term prognosis (eg, recovery of pulmonary function) remains to be seen with time
- It is increasingly recognized that a substantial proportion of patients, including some who did not have severe manifestations of the acute infection, experience persistent symptoms and prolonged recovery. "Long COVID" or "postacute COVID-19" is most commonly characterized by the following symptoms persisting more than 3 weeks from onset of COVID-19:^{131, 132}
 - Low-grade fever, which may come and go
 - Fatigue, which may be profound and may be sharply exacerbated by even mild exertion
 - Joint and/or muscle pain
 - Chest pain
 - Cough

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- Headache
- Cognitive dysfunction
- It is not yet known whether recovery from infection is associated with protective immunity; reinfection has been documented, and the risk of reinfection may be increased with exposure to variant strains that have emerged in the United Kingdom, South Africa, and Brazil, although data are limited^{133, 117}
- Mortality rate of diagnosed cases is generally about 3% but varies by country^{2, 3}
- Case fatality rates are higher for patients in older age groups and with certain comorbidities
 - Case fatality rates by age in the United States:³¹
 - 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:¹¹⁷
 - 10.5% for cardiovascular disease
 - 7.3% for diabetes
 - 6.3% for chronic respiratory disease
 - 5.6% 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^{13, 61}
 - 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-19⁶¹
 - 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)⁶¹
 - Guidelines released by Infectious Diseases Society of America also recommend testing of asymptomatic persons in the following circumstances, given sufficient testing supplies:⁴³
 - Known exposure to COVID-19
 - Admission to hospital for unrelated condition, if community prevalence is high
 - Immunosuppression, about to undergo immunosuppressive treatment, and on hospital admission (for any reason)
 - About to undergo major surgery that is time-sensitive
 - About to undergo aerosol-generating procedure that is time-sensitive and personal protective equipment is lacking; but if protective gear is adequate, then the guidelines recommend against routine testing in asymptomatic persons who are not known to have been exposed to COVID-19
 - About to undergo transplant (hematopoietic stem cell or solid organ)
 - 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:^{23, 134, 13, 61}
 - 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)

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- Many hospitals have instituted frequent screening of temperature and symptoms in health care workers (eg, at beginning of each shift)⁶¹
- 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 patients⁴³
- The role of antigen tests for screening is not as clearly defined. In the United States, the emergency use authorization for antigen tests extends only to diagnostic testing. CDC acknowledges that the rapid turnaround may nevertheless offer an advantage in certain circumstances and provides guidance on interpretation of results and considerations for confirmatory testing³⁵
- 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 or antigen tests (to detect current infection) and antibody tests (to detect history of infection) may evolve as 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^{135, 38, 136}
 - Furthermore, the details of how and when presence of antibodies confers immunity (as well as duration) are still not entirely known (although it is clear that nearly all immunocompetent persons develop some adaptive immune response after SARS-CoV-2 infection)¹³⁶
 - CDC provides guidance¹³⁶ 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)
 - FDA¹³⁷ provides information on interpreting antibody testing results and on the estimated performance characteristics of the tests available under emergency use authorization

PREVENTION

- Vaccines
 - Several vaccines against SARS-CoV-2 have entered use in various countries, and more are in development
 - After analyses of data from phase 3 trials, the vaccines in use have received emergency or temporary authorizations from various national regulatory authorities under the emergency conditions of the pandemic, and future authorizations in more countries are pending
 - BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) has received use authorization in the United States,¹³⁸ the United Kingdom,¹³⁹ Canada,¹⁴⁰ the European Union, and elsewhere
 - Moderna COVID-19 vaccine (mRNA-1273) has received use authorization in the United States,¹⁴¹ the United Kingdom, Canada, the European Union, and elsewhere
 - Oxford-AstraZeneca COVID-19 vaccine has received authorization for temporary supply in the United Kingdom¹⁴² and similar authorizations in other countries. Pauses to investigate rare clotting events have occurred in various countries; vaccination has resumed in some areas based on public health risk-benefit assessments (ie, the apparent rarity of the adverse effect versus the relatively higher risk posed by COVID-19)¹⁴³
 - Janssen COVID-19 vaccine (Johnson and Johnson) has received use authorization in the United States;¹⁴⁴ use was briefly paused but resumed¹⁴⁵ with warnings about rare occurrences of cerebral venous sinus thrombosis and thrombocytopenia after administration. Authorizations elsewhere are pending
 - Various other vaccines are in use in many other countries (eg, BBIBP-CorV, CoronaVac, Sputnik V) but may not have authorizations from agencies that WHO designates with stringent regulatory authority status
 - WHO has issued emergency use listing for BNT162b2¹⁴⁶ and the AstraZeneca COVID-19 vaccine,¹⁴⁷ supporting the possibility of regulatory approval and distribution in countries that do not have the resources for an independent evaluation process
 - BNT162b2 (tozinameran)
 - Evaluated in a randomized placebo-controlled trial of more than 43,000 participants; at time of submission for authorization in the United Kingdom, safety and efficacy data were available for 19,067 patients evenly distributed in vaccine and placebo groups. Overall efficacy was about 95%¹³⁹
 - Among subgroups, results were similar in older age groups (older than 65 years) and in persons with comorbidities associated with increased risk for severe disease

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- Data evaluated for US emergency use authorization included 36,621 persons, aged 12 years or older, equally divided between vaccine group and placebo group (18,242 versus 18,379, respectively), with wide ethnic and age diversity, and incorporating a large percentage of persons with comorbidities. At time of analysis, participants had been followed for a median of 2 months after the second dose¹³⁸
 - Vaccine efficacy was greater than 94.6% in all groups including all ages and with or without evidence of prior SARS-CoV-2 infection
- At time of data analysis for these authorizations, 8 cases of COVID-19 had occurred in the vaccine group compared with 162 cases in the placebo group^{138, 139}
- Adverse events
 - Common adverse effects included pain at injection site, fatigue, headache, myalgia, chills, arthralgia, and fever; these were largely mild to moderate and resolved within a few days^{139, 138}
 - Appendicitis was reported in 8 vaccine recipients and 4 persons who received placebo. Bell palsy was reported in 4 vaccine recipients. Although both of these adverse events are reported as "imbalances" between vaccine and placebo populations, data are insufficient to determine a causal relationship¹³⁸
 - Severe allergic reactions have been described, and facilities at which vaccine is administered must have the ability to treat such reactions (including anaphylaxis)¹³⁸
- Although the study population included persons as young as 12 years, Pfizer is releasing the vaccine for use only in persons aged 16 years or older, pending further study in younger patients^{138, 139}
 - Trial data were published after release of the emergency use authorization; total numbers of patients in both vaccine and placebo groups were slightly larger, but results (including efficacy calculations) were unchanged¹⁴⁸
- Moderna COVID-19 vaccine (mRNA-1273)¹⁴⁹
 - Safety data evaluated for US emergency use authorization (and subsequently published¹⁵⁰) included 30,351 persons, aged 18 years or older, equally divided between vaccine group and placebo group (15,185 versus 15,166, respectively); efficacy data was available for 14,134 vaccine recipients and 14,073 persons who received placebo. Participants included wide ethnic and age diversity; persons with stable comorbidities were included. At time of analysis, participants had been followed for a median of 9 weeks after the second dose
 - Overall efficacy was 94.1% (95.6% for persons aged 18 through 64 years and 86.4% for persons aged 65 or older)
 - Common adverse effects included pain at injection site, fatigue, headache, myalgia, chills, arthralgia, and fever; these were largely mild to moderate and resolved within a median of 2 to 3 days
 - Bell palsy was reported in 3 vaccine recipients (1 case classed as serious) and 1 placebo recipient; a causal relationship has not been established. Two patients who had previously received facial injection of dermatologic fillers experienced severe facial swelling considered likely vaccine-related. One patient developed intractable vomiting requiring hospital admission, deemed a result of vaccine
 - Severe allergic reactions have been described, and facilities at which vaccine is administered must have the ability to treat such reactions (including anaphylaxis)
 - CDC provides guidance on anaphylaxis to aid vaccine providers in preparing for and managing such events¹⁵¹, and for post-anaphylaxis laboratory assessment¹⁵²
- AstraZeneca COVID-19 vaccine (ChAdOx1-S [recombinant])¹⁴²
 - Safety data considered in the UK authorization for temporary use came from 23,745 persons who were enrolled in a clinical trial. The most common adverse effects included injection site tenderness (more than 60%) and injection site pain, headache, or fatigue (more than 50%). Less common adverse effects included myalgia or malaise (more than 40%), fever or chills (more than 30%), and arthralgia or nausea (more than 20%). Most of these symptoms resolved within a week. Adverse reactions were less common after the second dose and were less common overall in older recipients
 - Authorizing body considered efficacy data from 11,636 persons enrolled in a multinational trial: 5,807 patients received the COVID-19 vaccine and 5,829 received meningococcal vaccine (placebo). Vaccine efficacy measured at least 22 days after the first dose was 73%, and it was similar for patients with comorbidities compared with those without
 - Use of the vaccine has been interrupted in several regions while reports of unusual clotting disorders after administration were investigated; vaccination has resumed in some areas based on public health risk-benefit assessments¹⁵³ (ie, the apparent rarity of the disorder versus the relatively higher risk posed by COVID-19). About 30 cases have been reported among about 5 million persons receiving this vaccine in Europe¹⁵⁴
 - Characterized by venous thrombosis and thrombocytopenia associated with high levels of platelet factor 4–polyanion complexes (ie, similar to heparin-induced thrombocytopenia, but in the absence of heparin exposure; thus termed vaccine-induced immune thrombotic thrombocytopenia)
 - One published series reported 5 cases (in persons aged 32 to 54 years) in a population of more than 130,000 vaccine recipients; patients experienced onset of severe thromboses (some with embolization), associated with thrombocytopenia (some with hemorrhage), occurring 7 to 10 days after vaccination¹⁵⁵

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- Another series reported 11 cases in Germany and Austria (total number of vaccinations administered was not given); 9 of 11 patients were female, and the mean age was 36 years. Patients experienced severe and multiple venous thromboses (cerebral, splanchnic, pulmonary, other) associated with thrombocytopenia and, in some cases, disseminated intravascular coagulation
- Janssen COVID-19 vaccine¹⁵⁶
 - A replication-deficient adenovirus vector vaccine that generates immunity to the SARS-CoV-2 spike protein. The vaccine is administered as a single 1-time dose
 - A multinational trial enrolled 44,325 persons randomized to receive the Janssen COVID-19 vaccine or saline placebo; a preliminary efficacy analysis of 39,321 was presented to the FDA, of whom 19,630 received vaccine and 19,691 received placebo. The populations were similar and represented diverse racial and ethnic backgrounds, and patients were distributed across all age ranges 18 years and older. Persons with stable underlying medical conditions (including HIV infection) were included
 - At 14 days after vaccine administration, efficacy against severe/critical COVID-19 was 76.7%, rising to 85.4% at 28 days; for moderate to severe/critical COVID-19, efficacy rates at 14 and 28 days were 66.9% and 66.1%, respectively. At 28 days, efficacy rates did not differ between populations aged 18 to 59 years and those aged 60 years or older
 - Common adverse reactions (reported in more than 10% of participants) included headache, fatigue, myalgia, and nausea; they were reported in 13.1% of vaccine recipients and 12% of placebo patients; other adverse events included urticaria in 5 vaccine recipients (including 1 with angioedema) and 1 placebo recipient
 - 2 unique serious adverse events thought to be related to the vaccine occurred, as follows: 1 patient experienced severe pain in the injected arm unresponsive to analgesics and persistent to 74 days of follow-up, and another patient had fever, headache, and generalized weakness that resolved within 3 days
 - Several events occurred more frequently in vaccine recipients than in placebo recipients, but a causal relationship to the vaccine could not be determined, due to confounding effects of existing underlying conditions: deep vein thrombosis (6 vaccine recipients versus 2 placebo recipients); pulmonary embolus (4 vaccine recipients versus 2 placebo recipients); transverse sinus thrombosis (single case, in a vaccine recipient); seizures (4 vaccine recipients versus 1 placebo recipient); tinnitus (in 6 vaccine recipients only)
 - On April 12, 2021, CDC and FDA recommended that practitioners in the United States suspend use of this vaccine while reports of an unusual clotting disorder associated with administration of this vaccine were investigated¹⁵⁷
 - Characterized by cerebral venous thrombosis with thrombocytopenia occurring 6 to 13 days after administration
 - Initial data included 6 cases among more than 6.8 million persons immunized with this vaccine in the United States; all were in women aged 18 to 48 years
 - On April 23, 2021, CDC and FDA recommended that use of this product could resume because occurrence of the observed clotting disorder is extremely rare and benefit of vaccination against COVID-19 is felt to outweigh risk¹⁵⁸
 - Collection and analysis of further data included 9 more cases, for a total of 15 affected persons, all of whom were women aged between 18 and 59 years
 - Specific risk factors for this complication have not been identified¹⁴⁵
- CDC¹⁵⁹ and the European Medicines Agency¹⁶⁰ have recommended that clinicians maintain a high index of suspicion for thrombotic events and thrombocytopenia among persons who have received the Janssen or AstraZeneca vaccines
 - Symptoms may include severe headache, blurred vision, back pain, abdominal pain, chest pain, dyspnea, leg edema, petechiae, or easy bruising; overt bleeding has occurred in some cases^{160, 159}
 - American Society of Hematology recommends the following workup for suspected vaccine-induced immune thrombotic thrombocytopenia:¹⁶¹
 - CBC and platelet count; range in reported cases has been 9000 to 107,000 cells/mm³
 - Imaging guided by presentation (eg, CT or MRI venogram of brain, thorax, abdomen, or other clinically indicated site)
 - D-dimer level (markedly elevated in reported cases)
 - Fibrinogen level (may be low)
 - Platelet factor 4/heparin ELISA assay; all reported cases have been positive
 - Platelet factor 4 platelet activation assay if platelet factor 4/heparin ELISA result is low positive or if the diagnosis is otherwise uncertain
 - Treatment recommendations from the American Society of Hematology include:¹⁶¹
 - IV immunoglobulin 1 g/kg daily for 2 days
 - Anticoagulation with 1 of the following heparin alternatives (avoid heparin):
 - Parenteral direct thrombin inhibitors (argatroban or bivalirudin if baseline value for activated partial thromboplastin time is normal)
 - Direct oral anticoagulants
 - Fondaparinux
 - Danaparoid

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- Low fibrinogen level or bleeding do not absolutely preclude anticoagulation, especially if platelet count exceeds 20,000 cells/mm³
- Avoid platelet transfusion
- Patients with isolated thrombocytopenia without thrombosis or positive test result for platelet factor 4/heparin may have idiopathic thrombocytopenic purpura, not vaccine-induced thrombotic thrombocytopenia¹⁶¹
 - Immune thrombocytopenia has been reported following the AstraZeneca, Janssen, Moderna and Pfizer vaccines
 - Treatment includes IV immunoglobulin and/or steroids; platelet transfusions may be required for bleeding
- Vaccine contraindications and use in special populations
 - Contraindications include:^{156, 159}
 - Severe allergic reaction (eg, anaphylaxis) after a previous dose of a COVID-19 vaccine or any of its components
 - Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol) or to polysorbate (because of possible cross-reacting immune response against polyethylene glycol)
 - Safety and efficacy of these vaccines in pregnant patients has not been determined; whether vaccine is excreted in breast milk is unknown^{149, 142, 139, 138}
 - Based on mRNA vaccine data only, American College of Obstetricians and Gynecologists recommends that patients eligible for a COVID-19 vaccine be offered a vaccine regardless of pregnancy status. Patients planning to become pregnant who are eligible for a COVID-19 vaccine are encouraged to complete their vaccination series before conception to ensure maximal protection before pregnancy. If a patient becomes pregnant after the first dose, administer the second dose as indicated. If a patient becomes pregnant within 30 days of receipt of vaccine, encourage participation in CDC's V-safe program¹⁶² (a mobile phone-based monitoring and reminder system for recipients of COVID-19 vaccines)¹⁶³
 - Although safety and efficacy have not been studied specifically in patients with cancer, National Comprehensive Cancer Network has issued a recommendation that cancer patients should receive vaccine when available; this recommendation is based on the extra risk for COVID-19 complications conferred by malignancy, as well as on the absence of any clear-cut known or theoretical vaccine-associated risks unique to cancer patients¹⁶⁴
 - Exceptions include recent recipients of hematopoietic cell transplant or cellular therapy (who should delay vaccination for 3 months) and patients with hematologic malignancies who are neutropenic (who should await recovery of absolute neutrophil count). Patients who require major surgical procedures should time vaccination for several days before or after the surgery
 - Other immunocompromised persons may receive COVID-19 vaccine, although safety and efficacy data are limited; in particular, they should be counseled that they may not develop a robust immune response. This CDC recommendation is currently specific to mRNA vaccines but will likely be generalized¹⁵⁹
 - History of COVID-19 is not a contraindication to vaccine; in fact, guidelines recommend that such persons be offered vaccine, although not until after recovery from the acute illness. Persons who received treatment with convalescent plasma or COVID-specific monoclonal antibodies should defer vaccination for 90 days¹⁵⁹
 - Little clinical information exists on the use of vaccine in persons with autoimmune disease, but no unusual responses were noted in vaccine trial participants with autoimmune conditions, and current recommendations do not advise against vaccination of persons with autoimmune diseases¹⁵⁹
 - History of Guillain-Barré syndrome (postinfectious polyneuritis) is not considered to be a contraindication¹⁵⁹
 - A small number of cases of Bell palsy have been reported after COVID-19 vaccination, but the incidence is not considered significantly different from that in the general population, and history of Bell palsy is not a contraindication¹⁵⁹
 - A small number of patients who have received cosmetic injections with dermal fillers have experienced mild inflammation at the filled site(s) after COVID-19 vaccination, but a history of such procedures is not considered to be a contraindication¹⁵⁹
- Until vaccine is widely available, some jurisdictions have developed stratified distribution schemes based on likelihood of exposure (health care workers, first responders) and risk for severe disease (older age, comorbidities)^{165, 166, 167, 168}
- Authorizations in different jurisdictions may differ in details; practitioners should consult the specific authorization issued in their jurisdiction for indications, requirements for patient education and consent, and mandated reporting (eg, adverse events)
 - In the United States, emergency use authorizations require health care providers to communicate to the patient, parent, or caregiver information consistent with the vaccine-specific (manufacturer-specific) fact sheet for recipients and caregivers^{169, 170, 171} before each patient receives the vaccine; such information includes the following:¹³⁸
 - Alternatives to receiving the vaccine
 - Option to accept or refuse the vaccine
 - Significant known and potential risks and benefits of the vaccine, and the extent to which such potential risks and benefits are unknown

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- Available alternative preventive vaccines in clinical trials or approved for use under other emergency use authorizations
- In the United States, emergency use authorizations require health care providers to report^{149, 156, 138} all vaccine administration errors, exposures during pregnancy, and serious adverse events to VAERS (Vaccine Adverse Event Reporting System)¹⁷² and to the manufacturer (via Pfizer online report form,¹⁷³ email to ModernaPV@modernatx.com,¹⁴⁹ or at the Janssen COVID-19 vaccine website¹⁷⁴) within 7 calendar days from onset of event. Additionally, they must report cases of COVID-19 resulting in hospitalization or death and cases of multisystem inflammatory syndrome that occur in vaccinated patients
- In the United Kingdom, a site has been established to report suspected adverse events related to vaccines, diagnostic tests, and therapies for COVID-19: Coronavirus Yellow Card reporting site¹⁷⁵
- It is recommended that vaccine recipients be given a card containing information about the type of vaccine given, the date of administration, and (if applicable) the interval at which a booster dose should be administered^{149, 138, 162}
 - For the mRNA vaccines, CDC advises that second doses that are administered up to 4 days early are considered valid, as are doses that are administered later than the prescribed interval but within 42 days after the first dose¹⁵⁹
 - There are no data available on the interchangeability of the COVID-19 vaccines to complete the vaccination series. Patients who receive the first dose of any of the vaccines should receive a second dose of the same vaccine to complete the vaccination series¹⁵⁹
 - 14-day interval is recommended between administration of COVID-19 vaccine and other immunizations unless the need for the other vaccine is deemed urgent (eg, tetanus or rabies prophylaxis)¹⁵⁹
- Vaccine recipients are encouraged to participate in CDC's V-safe monitoring and reminder system,¹⁶² available as a mobile phone app¹⁴⁹

Vaccines against SARS-CoV-2 that have reached authorization status in some jurisdictions.

Product name	Manufacturer	Active ingredient	Age range for use	Dose and route	Dosing interval	Comments
BNT162b2 (tozinameran)	Pfizer-BioNTech	Nucleoside-modified mRNA of SARS-CoV-2	16 years or older	30 mcg (0.3 mL) intramuscular injection (deltoid) × 2 doses	21 days	Investigational; under EUA in the United States and temporary authorization in the United Kingdom
Moderna COVID-19 vaccine (mRNA-1273)	ModernaTX	Synthetic mRNA of SARS-CoV-2	18 years or older	100mcg (0.5 mL) intramuscular injection	1 month	Investigational; under EUA in the United States and temporary authorization in the United Kingdom
Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1-S recombinant)	AstraZeneca	Recombinant, replication-deficient chimpanzee adenovirus vector encoding SARS-CoV-2 spike glycoprotein (S protein)	18 years or older	0.5 mL intramuscular injection	4 to 12 weeks	Investigational; under temporary authorization in the United Kingdom
Janssen COVID-19 vaccine	JanssenBiotech, Inc (a Janssen Pharmaceutical Company of Johnson and Johnson)	Recombinant, replication-deficient adenovirus26 vector expressing SARS-CoV-2 spike glycoprotein (S protein)	18 years or older	0.5 mL intramuscular injection	Not applicable (single dose only)	Investigational; under EUA in the United States (use in the United States was paused then resumed in April 2021)

EUA, emergency use authorization.

- Standard infection control measures, including isolation of infected patients, remain essential. Quarantine may be imposed on asymptomatic exposed persons deemed by public health authorities to be at high risk

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- For the general public, avoidance of ill persons and diligent hand and cough hygiene are recommended, and physical distancing should be used as much as possible
 - Advise public as follows:
 - If sick, stay home and call doctor¹⁷⁶
 - 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)¹⁷⁶
 - 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)¹⁷⁶
 - 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 handwashing¹⁷⁶
 - Cover coughs. Use tissue and throw it away; second choice is sleeve, not hand¹⁷⁶
 - Avoid touching face¹⁷⁶
 - These precautions continue to apply even to persons who have already had COVID-19 and/or have already been vaccinated against COVID-19, owing to uncertainties about durations of naturally acquired immunity, the impact of new variants, and the fact that while the vaccines are very effective in preventing *severe* disease, they may not prevent mild disease that could be inadvertently transmitted to others^{133, 177, 159}
- 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 members¹⁷⁸
 - 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
- Patients managed in health care facilities (outpatient or inpatient)^{61, 179}
 - CDC provides preparedness checklists¹⁸⁰ 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; WHO¹⁷⁹ suggests using 70% ethyl alcohol

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- Criteria for discontinuation of isolation precautions^{119, 181, 133}
 - 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 observations¹³³ 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 10 days and up to 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 when at least 10 days and up to 20 days have passed since first positive specimen
 - 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 (eg, in immunocompromised patients)
 - 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 a respiratory tract infection due to a novel coronavirus, SARS-CoV-2; global pandemic is ongoing
- 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 catastrophic⁸
- 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; antigen testing is also available and has equivalent specificity but is slightly less sensitive
- Treatments and treatment strategies are emerging; available drugs are administered at different stages of disease based on the pharmacologic mechanism of action and the dominant pathophysiology of the disease phase
 - Bamlanivimab⁶⁵ (alone or in combination with etesevimab⁶³) and casirivimab-imdevimab⁶⁴ are monoclonal antibodies that prevent viral entry into human cells; they may be used under emergency use authorization in persons with mild to moderate infection at risk of progressing to severe disease
 - Remdesivir is an FDA-approved antiviral drug⁶² specifically for treatment of COVID-19; it is recommended for hospitalized patients with COVID-19 who require supplemental oxygen^{48, 76}
 - Dexamethasone also has been associated with significant reduction in mortality rates of patients requiring supplemental oxygen⁹²
 - Baricitinib¹⁸², a Janus kinase inhibitor, may also be used in conjunction with remdesivir in severely ill patients, under emergency use authorization
 - Compassionate use and trial protocols⁶⁷ for several other agents are underway. 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 3% but varies by country^{2, 3}
- Various vaccines are available through use authorizations and clinical trials, with good efficacy and safety to date. Infection control measures remain essential (ie, hand and cough hygiene; physical distancing; face coverings in public; 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

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- 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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Reviewed on April 27, 2020 by:

John C. O'Horo, MD, MPH, FACP

Consultant, Division of Infectious Diseases

Joint Appointment, Division of Pulmonary & Critical Care Medicine

Associate Professor of Medicine, Mayo Clinical College of Medicine

Reviewed on May 5, 2020 by:

Raphael Dolin, MD

Professor of Medicine, Beth Israel Deaconess Medical Center