

Coronavirus: novel coronavirus (COVID-19) infection

TERMINOLOGY

CLINICAL CLARIFICATION

- COVID-19 (coronavirus disease 2019) is a respiratory tract infection with a newly recognized coronavirus 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 to many other countries; 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
 - Mortality rate among diagnosed cases (case fatality rate) is generally about 2% to 3% but varies by country; true overall mortality rate is uncertain, as the total number of cases (including undiagnosed persons with milder illness) is unknown²
- Knowledge of this disease is incomplete and evolving; moreover, coronaviruses are known to mutate and recombine often, presenting an ongoing challenge to our understanding and to clinical management

CLASSIFICATION

- Pathogen is a betacoronavirus,³ similar to the agents of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)
 - Classified as a member of the species *Severe acute respiratory syndrome–related coronavirus*^{4,5}
 - Designated as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2); earlier provisional name was 2019-nCoV^{5,4}

DIAGNOSIS

CLINICAL PRESENTATION

- History
 - In symptomatic patients, illness may evolve over the course of a week or longer, beginning with mild symptoms that progress (in some cases) to the point of respiratory distress and shock⁶
 - Most common complaints are fever (almost universal) and cough, which may or may not be productive^{7,6}
 - Myalgia and fatigue are common⁶
 - Patients with moderate to severe disease complain of dyspnea⁶
 - Hemoptysis has been reported in a small percentage of patients⁶
 - Pleuritic chest pain has been reported⁸
 - Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) are unusual^{6,7}
 - Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur⁶
 - Patients may report close contact with an infected person; outside of an identified outbreak area, a history of recent travel (within 14 days) to an area with widespread infection⁹ is relevant, although community transmission including cases with no identifiable risk factor¹⁰ also occurs
- Physical examination
 - Reported case series have not detailed physical findings, but clinicians should be particularly attuned to pulmonary and hemodynamic indicators of severe disease
 - Patients with severe disease may appear quite ill, with tachypnea and labored respirations
 - Fever is usual, often exceeding 39 °C. Patients in the extremes of age or with immunodeficiency may not develop fever⁶
 - Hypotension, tachycardia, and cool/clammy extremities suggest shock
 - In children, hypotension plus 2 or more of the following criteria:¹¹
 - 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)

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- Person-to-person transmission has been documented⁸ and is presumed to occur by close contact,¹² probably via respiratory droplets¹³
 - It is not known when in the course of infection a person becomes contagious to others. Community transmission (without apparent contact chains) has raised suspicion that the virus may be transmitted before symptoms develop, and case and cluster reports from various countries^{14, 15, 16} have been published; if such transmission exists, its frequency is not yet known^{16, 13}
- Additional means of transmission have not been ruled out (eg, contact with infected environmental surfaces, fecal-oral)
- Risk factors and/or associations
 - Age
 - Most reported cases are in adults of middle age or older,^{7, 6} but pediatric infections in adolescents and children^{17, 8} have been reported
 - Sex
 - In published case series, males have been affected more often than females overall^{8, 3, 6, 7}
 - Other risk factors/associations
 - Early on, an association was noted between infected persons and a market in Wuhan, Hubei Province, that sold seafood, livestock, and wild game; infection was presumed to have been acquired by exposure to infected animals¹⁸
 - However, although environmental samples from the implicated market showed evidence of the virus, no animal specimens have been positive; a zoonotic origin of the virus remains likely, but the original source and reservoir of infection are unknown¹⁹
 - In the current context of a proclaimed pandemic, identifiable exposures are often absent

DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
 - Infection should be suspected in persons with a compatible respiratory illness and exposure history (if identified)
 - Chest imaging is essential to document presence of pneumonia and to assess severity; plain radiography, CT, and ultrasonography have been used⁷
 - Oxygenation should be assessed by peripheral saturation (eg, pulse oximetry) or by arterial blood gas test¹¹
 - Polymerase chain reaction tests are the standard for diagnosis. Specific methods and availability vary; public health authorities may assist in arranging diagnostic testing in some areas. Attempts to culture the virus are not recommended^{20, 12}
 - CDC¹² and WHO¹¹ have slightly different criteria for whom to test, but the rapid evolution of the pandemic and variable availability of testing render actual practice very fluid. The published criteria apply to patients with clinical features compatible with COVID-19 who are in the following categories; such patients would be considered PUIs (persons under investigation) by CDC:
 - WHO^{21, 22}
 - Any acute respiratory tract illness (fever and at least 1 sign/symptom of respiratory tract disease) **and** no other etiology that fully explains the condition **and** a history of travel to or residence in an area reporting local transmission of COVID-19 during the 14 days preceding symptom onset
 - Any acute respiratory tract illness **and** close contact with a person with confirmed or probable COVID-19 in the 14 days preceding illness onset
 - Severe acute respiratory tract infection requiring hospital admission without an alternative etiologic diagnosis
 - In situations where testing must be prioritized, WHO recommendations prioritizing the following:²³
 - 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
 - CDC¹²
 - Recommends that clinicians use their judgment, informed by knowledge of the patient's travel and/or exposure history, local COVID-19 activity, and other risk factors, to determine the need for testing in persons with a clinically compatible illness
 - Priority levels for testing:
 - Level 1, to ensure optimal care for hospitalized patients, lessen the risk of nosocomial transmission, and maintain the integrity of the health care system
 - Hospitalized patients
 - Symptomatic health care workers
 - Level 2, to ensure identification and triage of those at highest risk of complications from COVID-19
 - Symptomatic patients in long-term care facilities
 - Symptomatic patients aged 65 years or older

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- Symptomatic patients with underlying medical conditions
 - Symptomatic first responders
 - Level 3, in communities experiencing rapidly increasing numbers of hospitalized cases and if resources allow, to decrease community spread and ensure healthy workforce for providing essential services
 - Symptomatic workers in critical infrastructure jobs
 - Health care workers and first responders
 - Other symptomatic persons
- Collection of specimens from upper respiratory tract, lower respiratory tract, and serum is recommended for polymerase chain reaction testing, plus a sputum specimen if productive cough is present.¹² Additional specimens (eg, stool, urine) may be collected and stored for later testing at the discretion of public health authorities. 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 (commercial laboratories and public health laboratories in other jurisdictions may have different requirements):
 - Upper respiratory tract
 - Nasopharyngeal swab is preferred; oropharyngeal swab may be submitted in addition, if obtained. Only synthetic fiber swabs with plastic shafts are acceptable. If both are submitted, they may be placed in the same container
 - For nasopharyngeal specimen, insert swab into nostril parallel to palate. Leave swab in place for a few seconds to absorb secretions
 - For oropharyngeal specimen, swab the posterior pharynx, avoiding tongue and tonsils
 - Nasopharyngeal wash (or aspirate) or nasal aspirate specimens are also acceptable
 - Lower respiratory tract
 - Bronchoalveolar lavage or tracheal aspirate are suitable lower respiratory tract specimens
 - A deep cough sputum specimen (collected after mouth rinse) is also acceptable
 - WHO and CDC advise against attempts to induce sputum, because the process may increase aerosolization and risk of transmission
 - Serum
 - Blood should be collected in a serum separator tube and centrifuged after upright storage for 30 minutes
 - Minimum of 1 mL of whole blood is needed (eg, in pediatric patients)
- Other testing should be performed concurrently, if indicated, to identify alternative pathogens (eg, influenza virus, respiratory syncytial virus, bacterial pathogens); such tests should not delay arrangements for SARS-CoV-2 polymerase chain reaction testing²⁴
- 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)²⁴
- Clinicians should report suspected cases of COVID-19 to appropriate public health authorities, who can facilitate testing if necessary and can undertake contact tracing and monitoring. In the United States, contact local or state health department^{12,25}
- Laboratory
 - Positive identification of SARS-CoV-2 RNA by polymerase chain reaction test is considered confirmation of diagnosis
 - Routine blood work is not diagnostic, but a pattern of typical abnormalities is emerging in case series of hospitalized patients:
 - Leukopenia may be observed and relative lymphopenia is common, especially in patients with more severe illness^{7,8,6}
 - Anemia was noted in about half of patients in one series⁷
 - Both elevated and low platelet counts have been seen^{6,7,8}
 - Prolonged prothrombin time has been reported²⁶
 - Levels of D-dimer and fibrinogen may be elevated^{8,6}
 - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common^{7,6}
 - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection⁶
 - Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate⁷
 - Lactate level of 2 mmol/L or higher suggests presence of septic shock¹¹
- 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^{8,27,7,3,6}

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- CT appears to be more sensitive²⁸ than plain radiographs, but normal CT appearance does not exclude COVID-19²⁹

DIFFERENTIAL DIAGNOSIS

- Most common
 - *Because COVID-19 cannot be distinguished clinically from other pneumonias, history of contacts or travel remains an important differentiator, although cases without such history are increasing in frequency*
 - Influenza
 - Presentation includes fever, dry cough, and myalgias; unlike with COVID-19, upper respiratory tract symptoms are common (eg, coryza, sore throat)
 - Most cases are self-limited, but elderly persons or those with significant comorbidities often require hospitalization
 - Usually occurs in winter months in temperate climates but is less seasonal in equatorial regions
 - Patients with severe disease may have abnormal chest radiographic findings suggesting influenzal pneumonia or secondary bacterial pneumonia
 - Positive result on rapid influenza diagnostic test confirms influenza diagnosis with high specificity during typical season; negative result does not rule out influenza
 - Other viral pneumonias
 - Presentations include fever, dry cough, and dyspnea
 - Physical examination may find scattered rales
 - Chest radiography usually shows diffuse patchy infiltrates
 - Diagnosis is usually clinical; testing for specific viral causes (eg, respiratory syncytial virus, adenovirus) may be done
 - Bacterial pneumonia
 - Presentation includes fever, cough, and dyspnea; pleuritic pain occurs in some cases
 - Physical examination may find signs of consolidation (eg, dullness to percussion, auscultatory rales, tubular breath sounds)
 - Chest radiography usually shows lobar consolidation or localized patchy infiltrate
 - Sputum examination may find abundant polymorphonuclear leukocytes and a predominant bacterial organism
 - Pneumococcal or legionella antigens may be detectable in urine; sputum culture may find those or other pathogens

TREATMENT

GOALS

- Ensure adequate oxygenation and hemodynamic support during acute phase of illness

DISPOSITION

- Admission criteria
 - Nonsevere pneumonia
 - Radiographic evidence of pneumonia; progressive clinical illness; risk factors for severe disease; inadequate care at home^{30, 24}
 - 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 measures³⁰
 - Criteria for ICU admission
 - WHO provides criteria for severe pneumonia²⁴
 - Severe pneumonia characterized by tachypnea (respiratory rate greater than 30 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO₂ of 93% or less)
 - Pediatric criteria include central cyanosis or SpO₂ less than 90%; signs of severe respiratory distress (eg, grunting, chest retractions); inability to drink or breastfeed; lethargy, altered level of consciousness, seizures; severe tachypnea defined by age:
 - Younger than 2 months: 60 or more breaths per minute
 - Aged 2 to 11 months: 50 or more breaths per minute
 - Aged 1 to 5 years: 40 or more breaths per minute
 - Presence of severe complications (eg, septic shock, acute respiratory distress syndrome)
- Recommendations for specialist referral
 - All patients should be managed in consultation with public health authorities
 - Consult infectious disease specialist to coordinate diagnosis and management with public health authorities
 - 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

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TREATMENT OPTIONS

- Standard, contact, and airborne precautions should be implemented as soon as the diagnosis is suspected³¹
 - Immediately provide the patient with a face mask and place the patient in a closed room (preferably with structural and engineering safeguards against airborne transmission, such as negative pressure and frequent air exchange) pending further evaluation and disposition decisions
- At present, no specific antiviral agent is approved for treatment of this infection. Several existing antiviral agents are being used under clinical trial and compassionate use protocols based on in vitro activity (against this or related viruses) and on limited clinical experience
 - Chloroquine and hydroxychloroquine have been used in China and South Korea, reportedly with favorable results, although details are lacking. Further trials are underway in Europe and the United States. Both are associated with QT prolongation and risk of cardiac arrhythmias³²
 - 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 considered³³
 - In the United States, emergency use authorization for chloroquine and hydroxychloroquine has been issued by FDA to permit use in hospitalized adult and adolescent patients for whom a clinical trial is not available or feasible³⁴
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 states that data are insufficient to make a recommendation on the use of these agents³⁵
 - Remdesivir is an experimental antiviral agent with significant in vitro activity against coronaviruses^{36,37} and some evidence of efficacy in an animal model of MERS³⁶
 - Several clinical trials are in progress, and the drug may be available through expanded access and compassionate use programs³⁸
 - Lopinavir-ritonavir is FDA-approved for treatment of HIV infection. It has been used for other coronavirus infections; it was used empirically for SARS³⁹ and is being studied in the treatment of MERS⁴⁰
 - In China this combination is used in conjunction with interferon alfa for treatment of some patients with COVID-19^{41,42}
 - A trial in 199 patients with COVID-19 comparing lopinavir-ritonavir with standard care did not show a significant difference in time to improvement or in mortality at 28 days, nor were there differences in duration of viral RNA in oropharyngeal specimens⁴³
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against use of lopinavir-ritonavir³⁵
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against use recombinant interferons, based on lack of data in COVID-19 and on data from studies on MERS showing lack of efficacy³⁵
 - 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, tocilizumab³⁵ and sarilumab⁴⁴ are both monoclonal antibodies against interleukin-6 receptor)
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 states that data are insufficient to make a recommendation on the use tocilizumab; the guideline did not evaluate other monoclonal antibodies³⁵
 - Studies on the therapeutic efficacy of convalescent plasma are underway in various countries. In the United States, authorization must be obtained through FDA⁴⁵
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 suggests that convalescent plasma not be used on the basis of data in other viral infections, lack of data in COVID-19, and uncertainties about safety³⁵
 - Information on therapeutic trials and expanded access⁴⁶ is available at ClinicalTrials.gov
- Corticosteroid therapy is not recommended for viral pneumonia but is suggested by some authorities for COVID-19 patients with refractory shock or acute respiratory distress syndrome¹¹
 - Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 supports using corticosteroids in mechanically ventilated patients with COVID-19 and acute respiratory distress syndrome (but not those with respiratory failure in the absence of that syndrome) and in patients with COVID-19 and refractory shock; short-course, low-dose regimens are preferred³⁵
- FDA is investigating a controversy that has arisen regarding the use of NSAIDs in patients with COVID-19; however, there is no published evidence connecting the use of NSAIDs with worsening COVID-19 symptoms. Until additional data are available, acetaminophen may be preferred for temperature control⁴⁷

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- Until a diagnosis of COVID-19 is confirmed by polymerase chain reaction test, appropriate antiviral or antimicrobial therapy for other viral pathogens (eg, influenza virus) or bacterial pathogens should be administered in accordance with the site of acquisition (hospital or community) and epidemiologic risk factors¹¹
 - Additionally, Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 supports use of empiric antimicrobial therapy in mechanically ventilated patients with COVID-19 and respiratory failure, with daily consideration for de-escalation³⁵
- Otherwise, treatment is largely supportive and includes oxygen supplementation and conservative fluid support²⁴
 - Role of low-molecular-weight heparin (beyond standard prophylaxis indications) is being studied, and some authorities recommend use in any patient with COVID-19 and blood markers indicating coagulopathy (eg, marked elevation of D-dimer level, prolonged prothrombin time, platelet count of 100,000 cells/mm³ or lower, fibrinogen level less than 2 g/L)⁴⁸
- Management of septic shock includes use of vasopressors if fluid administration does not restore adequate perfusion. Both Surviving Sepsis Campaign³⁵ and WHO provide guidance specific to the treatment of shock in patients with COVID-19²⁴
 - In adults, begin with norepinephrine; epinephrine or vasopressin are preferred as second line over dopamine if norepinephrine is unavailable
 - Hemodynamic goal: mean arterial pressure of 60 to 65 mm Hg³⁵
 - In patients who do not respond adequately to usual doses of norepinephrine, Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends adding vasopressin rather than further titrating norepinephrine³⁵
 - For patients with COVID-19, refractory shock despite fluid and norepinephrine, and evidence of cardiac dysfunction, Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends adding dobutamine rather than further titrating norepinephrine³⁵
 - In children, epinephrine is considered the first line agent, and norepinephrine may be added if necessary¹¹
- Drug therapy
 - Antimalarial agents
 - Chloroquine
 - Infants, Children, and Adolescents weighing less than 50 kg : Efficacy and optimal dosing not established; however, based on extrapolation from pediatric dosing for other indications and comparative doses to the adult dosing regimen suggested for COVID-19, 8.3 mg (5 mg base)/kg/dose PO twice daily [Max: 500 mg/dose (300 mg base/dose)] is being used in limited pediatric dosing protocols; a 10-day course is being used in adult patients.
 - Adolescents weighing 50 kg or more : Data are limited; efficacy has not been established. 1000 mg PO on day 1 then 500 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Based on extrapolation from pediatric dosing for other indications and comparative doses to the adult dosing regimen suggested for COVID-19, 8.3 mg (5 mg base)/kg/dose PO twice daily [Max: 500 mg/dose (300 mg base/dose)] is being used in limited pediatric dosing protocols; a 10-day course is being used in adult patients.
 - Adults weighing less than 50 kg : Data are limited; efficacy has not been established. 500 mg PO twice daily for 10 days is being evaluated alone and in combination.
 - Adults weighing 50 kg or more : Data are limited; efficacy has not been established. 1000 mg PO on day 1 then 500 mg PO daily for 4 to 7 days suggested by FDA EUA statement. 500 mg PO twice daily for 10 days is also being evaluated alone and in combination.
 - Hydroxychloroquine
 - Infants, Children, and Adolescents weighing less than 50 kg : Efficacy and optimal dosing not established; however, based on extrapolation from pediatric dosing for other indications and comparative doses to adult dosing regimens suggested for COVID-19, doses of 6.5 mg (5 mg base)/kg/dose PO every 12 hours [Max: 400 mg/dose (310 mg base/dose)] for 2 doses, then 3.25 mg (2.5 mg base)/kg/dose every 12 hours [Max: 200 mg/dose (155 mg base/dose)] are being used in limited pediatric dosing protocols; a 5- to 20-day course is being used in adult patients.
 - Adolescents weighing 50 kg or more : Data are limited; efficacy has not been established. 800 mg PO on day 1 then 400 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Based on extrapolation from pediatric dosing for other indications and comparative doses to adult dosing regimens suggested for COVID-19, doses of 6.5 mg (5 mg base)/kg/dose PO every 12 hours [Max: 400 mg/dose (310 mg base/dose)] for 2 doses, then 3.25 mg (2.5 mg base)/kg/dose every 12 hours [Max: 200 mg/dose (155 mg base/dose)] are being used in limited pediatric dosing protocols; a 5- to 20-day course is being used in adult patients.
 - Adults weighing less than 50 kg : Data are limited; efficacy has not been established. Dosing regimens, alone and in combination, are being evaluated, including 400 mg PO twice daily on day 1 then 200 mg PO twice daily for 4 days; 200 mg PO twice daily for 5 to 20 days; and 200 mg PO three times daily for 10 days. Additional clinical evaluation is needed.

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- Adults weighing 50 kg or more : Data are limited; efficacy has not been established. 800 mg PO on day 1 then 400 mg PO daily for 4 to 7 days suggested by FDA EUA statement. Other dosing regimens, alone and in combination, are being evaluated, including 400 mg PO twice daily on day 1 then 200 mg PO twice daily for 4 days; 200 mg PO twice daily for 5 to 20 days; and 200 mg PO three times daily for 10 days. Additional clinical evaluation is needed.
- Macrolide
 - Azithromycin
 - Azithromycin Oral tablet; Adults: Data are limited and efficacy has not been established. Risk of adverse events must be weighed against potential benefit. Azithromycin 500 mg PO on day 1 then 250 mg PO once daily for 5 days with hydroxychloroquine has been used.
- Monoclonal antibodies
 - Tocilizumab
 - Tocilizumab Solution for injection; Adults: Available data are limited, and efficacy has not been established. 4 to 8 mg/kg/dose (Usual dose: 400 mg; Max dose: 800 mg) IV once is being evaluated in combination with antiviral therapy. A second dose 8 to 12 hours after the first infusion may be considered. One protocol suggests a possible third dose 16 to 24 hours after the first dose.
 - Sarilumab
 - Sarilumab Solution for injection; Adults: Efficacy has not been established. 200 mg IV or subcutaneously once or 400 mg IV once is being evaluated in combination with antiviral therapy.
- Nondrug and supportive care
 - WHO²⁴ and Surviving Sepsis Campaign³⁵ provide specific guidance for oxygenation, ventilation, and fluid management in COVID-19
 - Patients with severe respiratory distress, obstructed or absent breathing, central cyanosis, shock, seizures, or coma require aggressive airway management (which may include intubation) and oxygen
 - Oxygenation and ventilation
 - Begin supplemental oxygen when O₂ saturation falls below 90% to 92%.³⁵
 - Nasal cannula at 5 L/minute or face mask with reservoir bag at 10 to 15 L/minute¹¹
 - 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 patients⁴⁹
 - High-flow nasal oxygen is recommended by Surviving Sepsis Campaign³⁵ for COVID-19 patients 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 provided³⁵
 - Mechanical ventilation may become necessary for patients in whom oxygenation targets cannot be met with less invasive measures or who cannot maintain the work of breathing
 - Recommended settings are tidal volume of 4 to 8 mL/kg (predicted body weight) and inspiratory pressures less than 30 cm H₂O
 - In children, tidal volumes of 5 to 8 mL/kg (predicted body weight) for preserved lung compliance and 3 to 6 mL/kg for poor compliance; inspiratory pressures should be less than 28 cm H₂O
 - Use of PEEP may be necessary in patients with acute respiratory distress syndrome. Optimal regimen is not clearly defined, although guidelines^{11,35} suggest higher pressures (eg, more than 10 cm H₂O) rather than lower pressures. A protocol is available from ARDSnet⁵⁰
 - For patients with moderate to severe acute respiratory distress syndrome, prone positioning for 12 to 16 hours/day is recommended
 - Lateral decubitus position for pregnant women
 - Extracorporeal membrane oxygenation has been used⁶ in severely ill patients, and it can be considered if resources and expertise are available
 - Fluid management
 - Overhydration should be avoided, because it may precipitate or exacerbate acute respiratory distress syndrome

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- In patients with shock:
 - Administration of crystalloids is recommended (preferably buffered/balanced; eg, lactated Ringer solution); solutions such as hydroxyethyl starches, gelatins, dextrans, and albumin are not recommended according to Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19. WHO¹¹ provides the following guidance:
 - Adults: administer 250 to 500 mL over the first 15 to 30 minutes; goal is mean arterial pressure of 60 to 65 mm Hg³⁵ (if invasive pressure monitoring is available)
 - Children: 10 to 20 mL/kg bolus over the first 30 to 60 minutes
 - If there is no response to fluid bolus or if signs of fluid overload exist, discontinue or reduce fluid administration
 - For patients who respond to initial bolus and are without evidence of fluid overload, titrate continued fluid to achieve improvement in clinical signs (capillary refill, heart rate, tactile temperature of extremities, palpable pulses), urine output (0.5 mL/kg/hour in adults, 1 mL/kg/hour in children), and hemodynamic parameters (mean arterial pressure more than 65 mm Hg in adults)
- 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^{8,6}
 - Owing to the role of the ACE2 receptor in the pathogenesis of COVID-19, controversy has arisen over the positive or negative effects that ACE inhibitors and angiotensin receptor blockers may have on the disease. A joint statement by the American College of Cardiology, American Heart Association, and Heart Failure Society of America recommends that persons who are currently taking these medications for appropriate indications should continue to do so⁵¹
- Special populations
 - Pregnant patients
 - WHO guidelines²⁴ suggest that pregnant patients receive supportive care as recommended for nonpregnant adults, with accommodations as dictated by the physiologic changes of pregnancy (eg, expanded volume of distribution, elevated diaphragm)
 - WHO recommends that mode of delivery be determined based on obstetric indications and patient preference; cesarean delivery is recommended only for the usual medically justified indications²⁴
 - There is little evidence to suggest vertical transmission;²⁴ however, an infected woman may transmit the virus by the airborne route to her neonate. CDC and WHO differ in their recommendations⁵²
 - 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 caregiver⁵²
 - 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 care²⁴
 - Patients with HIV⁵³
 - It does not appear that HIV infection per se alters risk for infection or disease process. Whether advanced HIV infection (eg, CD4 count less than 200 cells/mm³) increases the risk for severe disease or complications is unknown
 - It is recommended that patients continue their current antiretroviral regimen; specifically, empiric addition of lopinavir-ritonavir (for possible efficacy against or protection from SARS-CoV-2) is not recommended outside of a clinical trial
 - A guideline⁵³ 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 more⁵⁴ into the course of illness and may be quite abrupt¹¹
- In hospitalized patients with proven COVID-19, repeated testing is recommended to document clearance of virus, defined as 2 consecutive negative results on polymerase chain reaction tests at least 24 hours apart¹¹

COMPLICATIONS AND PROGNOSIS

COMPLICATIONS

- Most common complication is acute respiratory distress syndrome; other reported complications include:^{7,6}
 - Septic shock

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- Acute kidney injury
- Myocardial injury
- Secondary bacterial and fungal infections
- Multiorgan failure

PROGNOSIS

- Patients who require hospital admission often require prolonged inpatient stay (more than 20 days), although duration of stay may be inflated by need for isolation until documentation of sustained absence of fever and serial negative results on polymerase chain reaction test^{7,6}
- Otherwise, short-term and long-term prognosis (eg, recovery of pulmonary function) remains to be seen with time
- Mortality rate of diagnosed cases is generally about 2% to 3% but varies by country²

SCREENING AND PREVENTION

SCREENING

- At-risk populations
 - Screening of travelers from affected areas is being done under the guidance of public health authorities at airports to assure that persons who are ill are referred for medical evaluation, and to educate those who are not ill but at risk for infection about self-monitoring
 - 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^{31,11}
- Screening tests
 - Screening and triage to isolation and testing with polymerase chain reaction are based on clinical presentation and exposure history:^{12,11,31}
 - Presence of respiratory symptoms (cough, dyspnea) and fever (CDC, WHO)
 - Recent (within 14 days) travel to or residence in any geographic areas with widespread COVID-19 (WHO, CDC)
 - 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)

PREVENTION

- There is no vaccine against COVID-19. Prevention depends on standard infection control measures, including isolation of infected patients. Quarantine may be imposed on asymptomatic exposed persons deemed by public health authorities to be at high risk
- For the general public, avoidance of ill persons and diligent hand and cough hygiene are recommended. Physical distancing should be used as much as possible. Advise public as follows:
 - If sick, stay home and call doctor⁵⁵
 - 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)⁵⁵
 - 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)⁵⁵
 - 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 handwashing⁵⁵
 - Cover coughs. Use tissue and throw it away; second choice is sleeve, not hand⁵⁵
 - Avoid touching face⁵⁵
- 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 face mask during any contact with household members⁵⁶
 - 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

Coronavirus: novel coronavirus (COVID-19) infection

- Duration of infectious potential and need for precautions has not been fully established; CDC offers 2 strategies based on test-based or non-test-based criteria:⁵⁷
 - Test-based
 - Demonstration of negative results of molecular assays for SARS-CoV-2 RNA on nasopharyngeal swabs obtained at least 24 hours apart (a single specimen suffices for each test), *and*
 - Subjective and objective evidence of clinical improvement, including absence of fever without use of antipyretic medication
 - Non-test-based
 - Subjective and objective evidence of clinical improvement, including absence of fever without use of antipyretic medication for 72 hours, *and*
 - At least 7 days since onset of symptoms
 - Persons who have tested positive but have had no symptoms may discontinue home isolation 7 days after the date of the first positive test
- Household members/caregivers should:
 - Wear face masks, gowns, and gloves when caring for patient; remove and discard all when leaving the room (do not reuse)
 - Dispose of these items in a container lined with a trash bag that can be removed and tied off or sealed before disposal in household trash
 - Wash hands for at least 20 seconds after all contact; an alcohol-based hand sanitizer is acceptable if soap and water are not available
 - Not share personal items such as towels, dishes, or utensils before proper cleaning
 - Wash laundry and high-touch surfaces frequently
 - Wear disposable gloves to handle dirty laundry and use highest possible temperatures for washing and drying, based on washing instructions on the items
 - Clean surfaces with diluted bleach solution or an EPA-approved disinfectant
 - Restrict contact to minimum number of caregivers and, in particular, ensure that persons with underlying medical conditions are not exposed to the patient
- In health care settings^{58, 31}
 - CDC provides preparedness checklists⁵⁹ for outpatient and inpatient health care settings
 - Provide the patient with a face mask and place the patient in a closed room (preferably with structural and engineering safeguards against airborne transmission, such as negative pressure and frequent air exchange)
 - Persons entering the room should follow standard, contact, and airborne precautions
 - Gloves, gowns, eye protection, and respirator (N95 or better) with adherence to hospital donning and doffing protocols
 - In circumstances in which supplies of N95 respirators and other protective equipment are short, their use should be prioritized for aerosol-generating procedures; standard surgical face masks should be used for other situations
 - Equipment used for patient care should be single-use (disposable) or should be disinfected between patients; WHO⁵⁸ suggests using 70% ethyl alcohol
 - Criteria for discontinuation of isolation precautions may vary depending on resources. Currently, CDC offers 2 strategies based on test-based or non-test-based criteria. A test-based approach is recommended for patients who are hospitalized, are severely immunocompromised, or are being transferred to a long-term care or assisted living facility⁶⁰
 - Test-based
 - Demonstration of negative results of molecular assays for SARS-CoV-2 RNA on nasopharyngeal swabs obtained at least 24 hours apart (a single specimen suffices for each test), *and*
 - Subjective and objective evidence of clinical improvement, including absence of fever without use of antipyretic medication
 - Non-test-based
 - Subjective and objective evidence of improvement in respiratory symptoms and absence of fever without use of antipyretic medication for 72 hours, *and*
 - At least 7 days since onset of symptoms

SYNOPSIS

KEY POINTS

- COVID-19 (coronavirus disease 2019) is respiratory tract infection due to a novel coronavirus, SARS-CoV-2 (initially called 2019-nCoV); as of March 11, 2020, extent of infection was declared pandemic by the WHO¹
- Virus is thought to be zoonotic in origin, but the animal reservoir is not yet known, and human-to-human transmission is widespread

Coronavirus: novel coronavirus (COVID-19) infection

- Infection ranges from asymptomatic to severe; symptoms 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. Upper respiratory tract symptoms (eg, rhinorrhea, sore throat) are uncommon⁶
- A significant proportion of clinically evident cases are severe; the mortality rate among diagnosed cases is generally about 2% to 3% but varies by country²
- Infection should be suspected based on presentation with a clinically compatible history and known or likely exposure (eg, residence in or travel to an affected area within the past 14 days, exposure to a known or suspected case, exposure to a health care setting in which patients with severe respiratory tract infections are managed)
- 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 or serum specimens
- There is no specific antiviral therapy, although compassionate use and trial protocols for several agents are underway; 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
- There is no vaccine available to prevent this infection; infection control measures are the mainstay of prevention (ie, hand and cough hygiene; physical distancing; standard, contact, and airborne precautions in health care)

URGENT ACTION

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

PITFALLS

- It is possible (but not yet well established) that 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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