COVID-19 - Ambulatory (2.1)

Clinical Overview Synopsis

ClinicalKey Clinical Overviews provide additional specific guidance for:
Coronavirus: novel coronavirus (COVID-19) infection

Guidance

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 WHO
- Virus is thought to be zoonotic in origin, but the animal reservoir is not yet known, and human-to-human transmission is widespread
- 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 (e.g., rhinorrhea, sore throat) are uncommon
- A significant proportion of clinically evident cases are severe; the mortality rate among diagnosed cases is generally about 2% to 3% but varies by country
- Infection should be suspected based on presentation with a clinically compatible history and known or likely exposure (e.g., 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 healthcare).

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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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


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Assessments

Guidance

Screening, COVID-19 ~

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

Screening tests

- Screening and triage to isolation and testing with polymerase chain reaction are based on clinical presentation and exposure history:
- 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)


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Temperature Once
Assess: Travel and at risk contact history

Point of Care Testing
Fingerstick Glucose, Once

Patient Education
Patient education: Infection Education

Guidance

Household Members and Caregivers, COVID-19 ~

Household members/caregivers should:

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  - 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


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Patient education: Monitoring body temperature; Check temperature at least once per day

Guidance

At Home Monitoring, COVID-19 ~

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 more into the course of illness.

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Precautions

Guidance

Transmission-Based Precautions, COVID-19 ~

Standard, contact, and airborne precautions should be implemented as soon as the diagnosis is suspected.

- 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.

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Precaution: Airborne

Guidance

Airborne Precautions, COVID-19 ~
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

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Precaution: Contact
Precaution: Droplet
Precaution: Standard

Medications

Guidance

COVID-19 Medication Guidance, COVID-19 ~

- 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 arrhythmias
    - 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 considered
    - 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 feasible
    - 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 agents
  - Remdesivir is an experimental antiviral agent with significant in vitro activity against coronaviruses and some evidence of efficacy in an animal model of MERS
    - Several clinical trials are in progress, and the drug may be available through expanded access and compassionate use programs
  - Lopinavir-ritonavir is FDA-approved for treatment of HIV infection. It has been used for other coronavirus infections; it was used empirically for SARS and is being studied in the treatment of MERS
    - In China this combination is used in conjunction with interferon alfa for treatment of some patients with COVID-19
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 specimens.

- Surviving Sepsis Campaign guideline on managing critically ill adults with COVID-19 recommends against use of lopinavir-ritonavir.
- 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 efficacy.

- 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, tocilizumab and sarilumab 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 antibodies.
- Studies on the therapeutic efficacy of convalescent plasma are underway in various countries. In the United States, authorization must be obtained through FDA.
- 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 safety.
- Information on therapeutic trials and expanded access 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 syndrome.
- 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 preferred.
- 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 control.
- 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 factors.
  - 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-escalation.

- Otherwise, treatment is largely supportive and includes oxygen supplementation and conservative fluid support.
  - 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).
    - 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 Hg.
    - 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 norepinephrine.
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 norepinephrine.

In children, epinephrine is considered the first line agent, and norepinephrine may be added if necessary.

**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.
    - 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.


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**Antipyretics**

Acetaminophen Oral Tablet; 650 mg Every 4 hours (PRN: Temperature greater than 38 degree celsius); Do not exceed 4000 mg acetaminophen in 24 hours from all sources

Acetaminophen Rectal Suppository; 650 mg Every 4 hours (PRN: Temperature greater than 38 degree celsius); Do not exceed 4000 mg acetaminophen in 24 hours from all sources

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**Laboratory**

**Guidance**

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**Laboratory Testing, COVID-19**

Laboratory testing recommendations:

- Positive identification of SARS-CoV-2 (2019-nCoV) 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
  - Anemia was noted in about half of patients in one series
Both elevated and low platelet counts have been seen
- A prolonged prothrombin time has been reported
- Levels of D-dimer and fibrinogen may be elevated
- Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common
- Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection
- Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate
- Lactate level of 2 mmol/L or higher suggests presence of septic shock

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Chemistry
Lab: Basic Metabolic Profile, Once
Lab: Comprehensive Metabolic Panel, Once
Lab: C-Reactive Protein, Once
Lab: D-Dimer, Quantitative, Once
Lab: Ferritin, Once
Lab: Fibrinogen, Once
Lab: Lactic Acid, Venous, Once

Guidance
Lactate, COVID-19 ~
Lactate level of 2 mmol/L or higher suggests presence of septic shock

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Hematology
Lab: Complete Blood Count (CBC), Once
Lab: Erythrocyte sedimentation rate (ESR), Once
Lab: Prothrombin time (PT) with INR, Once
Lab: Partial Thromboplastin Time, Once

Microbiology
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07 April 2020
Influenza A/B Antigen, Respiratory Illness ~

Nasal Influenza A and B virus antigen

- Obtain nasal swab samples to test for influenza in patients with suspected viral pneumonia
- Use a rapid influenza diagnostic test if it will change the care of the patient or of other patients. The following factors warrant such testing:
  - Hospitalized patients
  - Patients with high-risk conditions
  - Documentation of institutional outbreaks
  - Atypical timing (e.g., summer months in temperate climates)
  - Under these circumstances, viral culture is recommended to confirm positive results from rapid tests and to identify strain
- Antigen detection tests: rapid influenza diagnostic tests are usually available at the point of care
  - Performed on nasal or nasopharyngeal swab or aspirate
  - Some can distinguish influenza A from influenza B but cannot identify specific strain
  - Sensitivity is 50% to 70%
  - Specificity is 90% to 95%

ClinicalKey. Influenza Clinical Overview.

Community-Acquired Pneumonia in Adults Clinical Overview. ClinicalKey.

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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.


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Real-Time Polymerase chain reaction for SARS-CoV-2; Oropharyngeal swab, Once

**Guidance**

**Pharyngeal Swab, COVID-19**

CDC provides specific instructions for collection and handling of specimens.

**Upper Respiratory Tract Swab**

- 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.


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Real-time polymerase chain reaction (RT-PCR), sputum, Once; For SARS-CoV-2 Respiratory Syncytial Virus (RSV) Antigen, Nose, Once

**Urine**

Lab: Urinalysis, Once

**Radiology**

**Guidance**

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07 April 2020
**Imaging, COVID-19 ~**

Chest imaging (eg, plain radiography, CT) 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.


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**Plain Films**

X-ray, Chest PA/lateral ; History: [add diagnosis, symptom(s)] ; Question: [add reason for exam]

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**CT Scan**

**Guidance**

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**CT Scan, COVID-19 ~**

CT appears to be more sensitive than plain radiographs, but normal CT appearance does not exclude COVID-19


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**CT, Chest without IV contrast ; History: [add diagnosis, symptom(s)] ; Question: [add reason for study]**

**CT, Chest with IV contrast ; History: [add diagnosis, symptom(s)] ; Question: [add reason for study]**

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**Referrals**

Consult: Public Health ; History: [add diagnosis, symptom(s)] ; Question: [add reason for consult] ; further evaluation and management

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**Modules**

Smoking Cessation/Tobacco Withdrawal - Ambulatory Module
Ambulatory Core Orders/Routine Screening - Adult - Module