

# Novel coronavirus (2019-nCoV) infection

## TERMINOLOGY

### CLINICAL CLARIFICATION

- 2019-nCoV infection 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
- Outbreak began in China, where its effects to date are most widespread; it has since spread to many other countries, although quarantines have helped to limit transmission therein to date<sup>1</sup>
- Illness ranges in severity from asymptomatic or mild to severe; a significant proportion of patients with clinically evident infection develop severe disease<sup>1</sup>
  - Overall mortality rate among diagnosed cases is about 2%
- 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,<sup>2</sup> similar to the agents of SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome)

## 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 dyspnea and shock<sup>3</sup>
  - Most common complaints are fever (almost universal) and cough, which may or may not be productive<sup>3,4</sup>
  - Myalgia and fatigue are common<sup>3</sup>
  - Patients with moderate to severe disease complain of dyspnea<sup>3</sup>
  - Hemoptysis has been reported in a small percentage of patients<sup>3</sup>
  - Pleuritic chest pain has been reported<sup>5</sup>
  - Upper respiratory tract symptoms (eg, rhinorrhea, sneezing, sore throat) are unusual<sup>3,4</sup>
  - Headache and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) are uncommon but may occur<sup>3</sup>
  - 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 infection (eg, China) is relevant<sup>6</sup>
- 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 fever<sup>3</sup>
  - Hypotension, tachycardia, and cool/clammy extremities suggest shock
    - In children, hypotension plus 2 or 3 of the following criteria:<sup>7</sup>
      - 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 2019-nCoV (2019 novel coronavirus)
  - Person-to-person transmission has been documented<sup>5</sup> and is presumed to occur by close contact,<sup>6</sup> probably via respiratory droplets<sup>8</sup>
    - It is not known when in the course of infection a person becomes contagious to others. Chinese authorities report the possibility that the virus may be transmitted before symptoms develop, and a case report from Germany has been published but is disputed; if such transmission truly exists, its frequency is not yet known<sup>9,10</sup>
  - Additional means of transmission have not been ruled out (eg, contact with infected environmental surfaces)

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- Risk factors and/or associations
  - Age
    - Most reported cases are adults of middle age and older,<sup>4,3</sup> but several pediatric infections<sup>5</sup> have been reported
  - Sex
    - In published case series, males have been affected more often than females overall<sup>4,2,5,3</sup>
  - Other risk factors/associations
    - Early on, an association was noted between infected persons and a market in Wuhan that sold seafood, livestock, and wild game; infection was presumed to have been acquired by exposure to infected animals<sup>11</sup>
    - 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 unknown<sup>12</sup>

## DIAGNOSTIC PROCEDURES

- Primary diagnostic tools
  - Infection should be suspected in persons with a compatible respiratory illness and exposure history
  - Chest imaging is essential to document presence of pneumonia and to assess severity; both plain radiography and CT have been used<sup>4</sup>
  - Oxygenation should be assessed by peripheral saturation (eg, pulse oximetry) or by arterial blood gas test<sup>7</sup>
  - A polymerase chain reaction test has been developed and test kits are being distributed; currently, testing is coordinated by public health authorities. Attempts to culture the virus are not recommended<sup>6</sup>
  - CDC<sup>6</sup> and WHO<sup>7</sup> have slightly different criteria for whom to test:
    - Recent travel (within 14 days) from Wuhan, Hubei Province, China (WHO, CDC)
      - If prevalence in other areas increases, this criterion may broaden. A map of areas reporting cases<sup>13</sup> is available through CDC, but it must be noted that it includes countries reporting just a single case, in which risk to general population is extremely low
    - Close contact with an ill person suspected or known to have infection due to 2019-nCoV (WHO, CDC)
      - CDC defines close contact as being within 2 m (6 ft) or within a room or care area for a prolonged period without personal protective equipment *or* having direct contact with secretions of a person with 2019-nCoV infection
    - Exposure to a health care facility in a country where hospital-associated 2019-nCoV infections have been reported (WHO)
    - Disease occurs in a health care worker who has been working in an environment where patients with severe acute respiratory tract infections are being cared for, without regard to place of residence or history of travel (WHO)
    - Person develops an unusual or unexpected clinical course, especially sudden deterioration 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)
  - Collection of specimens from upper respiratory tract, lower respiratory tract, and serum is recommended for polymerase chain reaction testing; 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<sup>6</sup>
    - CDC provides specific instructions for collection and handling of specimens:<sup>14</sup>
      - Upper respiratory tract
        - Both a nasopharyngeal and an oropharyngeal swab should be obtained; only synthetic fiber swabs with plastic shafts are acceptable. The 2 specimens should be submitted in separate containers
          - Insert swab into nostril parallel to palate. Leave swab in place for a few seconds to absorb secretions
          - Swab the posterior pharynx, avoiding the tongue and tonsils<sup>7</sup>
        - 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 advises 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 2019-nCoV polymerase chain reaction testing<sup>6</sup>

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- 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)
- Laboratory
  - Positive identification of 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<sup>3,4,5</sup>
    - Anemia was noted in about half of patients in one series<sup>4</sup>
    - Both elevated and low platelet counts have been seen<sup>4,5,3</sup>
    - Levels of D-dimer and fibrinogen may be elevated<sup>5,3</sup>
    - Elevated levels of lactate dehydrogenase and liver enzymes (ALT and AST) are common<sup>3,4</sup>
    - Serum procalcitonin levels are usually within reference range; elevated levels have been seen in patients with secondary infection<sup>3</sup>
    - Serum levels of some other acute phase reactants (eg, C-reactive protein, ferritin) are elevated in most patients, as is the erythrocyte sedimentation rate<sup>4</sup>
  - Lactate level of 2 mmol/L or higher suggests presence of septic shock<sup>7</sup>
- Imaging
  - Chest imaging (eg, plain radiography, CT) has shown abnormalities in all 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<sup>2,5,4,3</sup>

## DIFFERENTIAL DIAGNOSIS

- Most common
  - *Because infection due to 2019-nCoV cannot be distinguished clinically from other causes of pneumonia, an important differentiator is a history of close contact with a diagnosed case or history of recent travel (within 14 days) to an affected area (eg, China)*
  - Influenza
    - Presentation includes fever, dry cough, and myalgias; unlike with 2019-nCoV infection, 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

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## DISPOSITION

- Admission criteria
  - Nonsevere pneumonia
    - Radiographic evidence of pneumonia; progressive clinical illness with indications for supplemental oxygen and hydration; inadequate care at home<sup>15,7</sup>
    - 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 measures<sup>15</sup>
  - Criteria for ICU admission
    - WHO provides criteria for severe pneumonia<sup>7</sup>
      - Severe pneumonia characterized by tachypnea (respiratory rate greater than 30 breaths per minute), severe respiratory distress, inadequate oxygenation (eg, SpO<sub>2</sub> less than 90%)
      - Pediatric criteria include central cyanosis or SpO<sub>2</sub> 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

## TREATMENT OPTIONS

- Standard, contact, and airborne precautions should be implemented as soon as the diagnosis is suspected<sup>16</sup>
  - 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
  - Lopinavir-ritonavir is FDA-approved for treatment of HIV infection. It has been used for other coronavirus infections; it was used empirically for SARS<sup>17</sup> and is being studied in the treatment of MERS<sup>18</sup>
    - Chinese health authorities plan to begin use of this combination in conjunction with interferon alfa for treatment of patients with infection due to 2019-nCoV<sup>19</sup>
  - Remdesivir is an experimental antiviral agent with significant in vitro activity against coronaviruses<sup>20,21</sup> and some evidence of efficacy in an animal model of MERS<sup>21</sup>
- Corticosteroid therapy is not recommended for either viral pneumonia or acute respiratory distress syndrome<sup>7</sup>
- Until a diagnosis of 2019-nCoV 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<sup>7</sup>
- Otherwise, treatment is largely supportive and includes oxygen supplementation and conservative fluid support<sup>7</sup>
- Management of septic shock includes cautious fluid resuscitation and use of vasopressors if fluid administration does not restore adequate perfusion. WHO provides guidance specific to the treatment of shock in patients with infection due to 2019-nCoV<sup>7</sup>
- Nondrug and supportive care
  - WHO provides specific guidance for oxygenation, ventilation, and fluid management<sup>7</sup>
    - Oxygenation and ventilation
      - Nasal cannula at 5 L/minute, titrated to target peripheral oxygen saturation: SpO<sub>2</sub> of 90% or higher in nonpregnant adults; 92% or higher in pregnant patients
      - In most children the target SpO<sub>2</sub> 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 SpO<sub>2</sub> of 94% or higher is recommended
      - High-flow nasal oxygen or noninvasive ventilation may be necessary to achieve adequate oxygenation in some patients
      - Mechanical ventilation may be 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 and inspiratory pressures less than 30 cm H<sub>2</sub>O

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- Use of PEEP may be necessary in patients with acute respiratory distress syndrome. Optimal regimen is not clearly defined, although WHO suggests higher rather than lower pressures
- For patients with severe acute respiratory distress syndrome, prone positioning is recommended
- Extracorporeal membrane oxygenation has been used<sup>3</sup> in severely ill patients, and it can be considered if resources and expertise are available
- Fluid management
  - Overhydration should be avoided, because it may precipitate or exacerbate acute respiratory distress syndrome
  - In patients with shock:
    - Administration of crystalloids (ie, saline or lactated Ringer solution) is recommended
      - Adults: total of 30 mL/kg over the first 3 hours; goal is mean arterial pressure of at least 65 mm Hg (if invasive pressure monitoring is available)
      - Children: 20 mL/kg bolus and up to 40 or even 60 mL/kg over the first hour
- Comorbidities
  - Severe disease due to 2019-nCoV has been associated with chronic conditions such as diabetes, hypertension, and other cardiovascular conditions; existing published guidance does not address management issues specific to these comorbidities<sup>5,3</sup>
- Special populations
  - Pregnant patients
    - WHO guidelines<sup>7</sup> 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)

## 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 more<sup>22</sup> into the course of illness<sup>7</sup>
- In hospitalized patients with proven infection due to 2019-nCoV, repeated testing is recommended to document clearance of virus, defined as 2 consecutive negative results on polymerase chain reaction tests at least 24 hours apart<sup>7</sup>

## COMPLICATIONS AND PROGNOSIS

### COMPLICATIONS

- Most common complication is acute respiratory distress syndrome; other reported complications include:<sup>3,4</sup>
  - Septic shock
  - 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<sup>3,4</sup>
- Otherwise, short and long-term prognosis (eg, recovery of pulmonary function) remains to be seen with time
- Mortality rate of diagnosed cases is about 2%<sup>1</sup>

## 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 2019-nCoV, so that prompt isolation measures can be instituted<sup>16,7</sup>
- Screening tests
  - Screening and triage to isolation are based on clinical presentation and exposure history:<sup>16,7</sup>
    - Presence of respiratory symptoms (cough, dyspnea) and fever (CDC, WHO)
    - Recent (within 14 days) travel to Wuhan City, China (or other areas with widespread infection due to 2019-nCoV) (WHO, CDC)
    - Close contact with a person with known or suspected 2019-nCoV infection while that person was ill (WHO, CDC)

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- Exposure to a health care facility in a country where health care–associated 2019-nCoV infections have been reported (WHO)
- 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 2019-nCoV. Prevention depends on standard infection control measures
- For the general public, avoidance of ill persons and diligent hand hygiene are recommended
- Patients managed at home<sup>23</sup>
  - 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 members
    - 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 healthcare setting
    - Duration of infectious potential and need for precautions has not been established
  - 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<sup>24, 16</sup>
  - CDC provides preparedness checklists<sup>25</sup> 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
    - Equipment used for patient care should be single-use (disposable) or should be disinfected between patients; WHO<sup>24</sup> suggests using 70% ethyl alcohol
  - Criteria for discontinuation of isolation precautions have not been determined. CDC recommends individualized assessment in consultation with public health officials

## SYNOPSIS

### KEY POINTS

- An outbreak of respiratory tract infection due to a novel coronavirus, 2019-nCoV, has recently been recognized; the virus is thought to be zoonotic in origin, but the animal reservoir is not yet known, and it is clear that human-to-human transmission is occurring
- 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 uncommon<sup>3</sup>
- A significant proportion of clinically evident cases are severe; the mortality rate among diagnosed cases is about 2%<sup>1</sup>
- Infection should be suspected based on presentation with a clinically compatible history and known or likely exposure (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



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- 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; standard, contact, and airborne precautions)

## URGENT ACTION

- Triage screening is recommended at registration for medical care to identify patients with symptoms and exposure history that suggest the possibility of 2019-nCoV infection, 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

## PITFALLS

- It is possible (but not yet well established) that persons with prodromal or asymptomatic infection may spread infection, making effective prevention more challenging
- 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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