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Coronavirus disease 2019 (COVID-19)

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INTRODUCTION

Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019 [1]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV.

Understanding of COVID-19 is evolving. Interim guidance has been issued by the World Health Organization and by the United States Centers for Disease Control and Prevention [2,3]. Links to these and other related society guidelines are found elsewhere. (See 'Society guideline links' below.)

This topic will discuss the epidemiology, clinical features, diagnosis, management, and prevention of COVID-19. Community-acquired coronaviruses, severe acute respiratory syndrome (SARS) coronavirus, and Middle East respiratory syndrome (MERS) coronavirus are discussed separately. (See "Coronaviruses" and "Severe acute respiratory syndrome (SARS)" and "Middle East respiratory syndrome coronavirus: Virology, pathogenesis, and epidemiology".)

VIROLOGY

Full-genome sequencing and phylogenic analysis indicated that the coronavirus that causes COVID-19 is a betacoronavirus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat coronaviruses), but in a different clade. The structure of the receptor-binding gene region is very similar to that of the SARS coronavirus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry [4]. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has proposed that this virus be designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5].

The Middle East respiratory syndrome (MERS) virus, another betacoronavirus, appears more distantly related [6,7]. The closest RNA sequence similarity is to two bat coronaviruses, and it appears likely that bats are the primary source; whether COVID-19 virus is transmitted directly from bats or through some other mechanism (eg, through an intermediate host) is unknown [8]. (See "Coronaviruses", section on 'Viral serotypes'.)

In a phylogenetic analysis of 103 strains of SARS-CoV-2 from China, two different types of SARS-CoV-2 were identified, designated type L (accounting for 70 percent of the strains) and type S (accounting for 30 percent) [9]. The L type predominated during the early days of the epidemic in China, but accounted for a lower proportion of strains outside of Wuhan than in Wuhan. The clinical implications of these findings are uncertain.

EPIDEMIOLOGY

Geographic distribution — Globally, more than 800,000 confirmed cases of COVID-19 have been reported. Updated case counts in English can be found on the World Health Organization and European Centre for Disease Prevention and Control websites. An interactive map highlighting confirmed cases throughout the world can be found here.

Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, more than 80,000 COVID-19 cases have been reported in China, with the majority of those from Hubei and surrounding provinces. A joint World Health Organization (WHO)-China fact-finding mission estimated that the epidemic in China peaked between late January and early February 2020 [10], and the rate of new cases decreased substantially by early March.

However, cases have been reported in all continents, except for Antarctica, and have been steadily rising in many countries. These include the United States, most countries in Western Europe (including the United Kingdom), and Iran.

Route of transmission — Understanding of the transmission risk is incomplete. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals, where most patients had worked or visited and which was subsequently closed for disinfection [11]. However, as the outbreak progressed, person-to-person spread became the main mode of transmission.

Person-to-person spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is thought to occur mainly via respiratory droplets, resembling the spread of influenza. With droplet transmission, virus released in the respiratory secretions when a person with infection coughs, sneezes, or talks can infect another person if it makes direct contact with the mucous membranes; infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Droplets typically do not travel more than six feet (about two meters) and do not linger in the air. Although one letter to the editor described a study in which SARS-CoV-2 remained viable in experimentally generated aerosols for at least three hours, the relevance of this to the epidemiology of COVID-19 and its clinical implications are unclear [12]. Given the current uncertainty regarding transmission mechanisms, airborne precautions are recommended in certain situations. (See 'Infection control for suspected or confirmed cases' below.)

SARS-CoV-2 RNA has been detected in blood and stool specimens [13-15]. Live virus has been cultured from stool in some cases [16], but according to a joint WHO-China report, fecal-oral transmission did not appear to be a significant factor in the spread of infection [17].

Period of infectivity — The interval during which an individual with COVID-19 is infectious is uncertain. Most data informing this issue are from studies evaluating viral RNA detection from respiratory and other specimens. However, detection of viral RNA does not necessarily indicate the presence of infectious virus.

Viral RNA levels appear to be higher soon after symptom onset compared with later in the illness [18]; this raises the possibility that transmission might be more likely in the earlier stage of infection, but additional data are needed to confirm this hypothesis.

The duration of viral shedding is also variable; there appears to be a wide range, which may depend on severity of illness. In one study of 21 patients with mild illness (no hypoxia), 90 percent had repeated negative viral RNA tests on nasopharyngeal swabs by 10 days after the onset of symptoms; tests were positive for longer in patients with more severe illness [19]. In another study of 137 patients who survived COVID-19, the median duration of viral RNA shedding from oropharyngeal specimens was 20 days (range of 8 to 37 days) [20].

The reported rates of transmission from an individual with symptomatic infection vary by location and infection control interventions. According to a joint WHO-China report, the rate of secondary COVID-19 ranged from 1 to 5 percent among tens of thousands of close contacts of confirmed patients in China [17]. Among crew members on a cruise ship, 2 percent developed confirmed infection [21]. In the United States, the symptomatic secondary attack rate was 0.45 percent among 445 close contacts of 10 confirmed patients [22].

Transmission of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period) has also been described [23-28]. However, the extent to which this occurs remains unknown. Large-scale serologic screening may be able to provide a better sense of the scope of asymptomatic infections and inform epidemiologic analysis; several serologic tests for SARS-CoV-2 are under development [29].

Immunity — Antibodies to the virus are induced in those who have become infected. Preliminary evidence suggests that some of these antibodies are protective, but this remains to be definitively established. Moreover, it is unknown whether all infected patients mount a protective immune response and how long any protective effect will last.

Data on protective immunity following COVID-19 are emerging but still in very early stages. A case series evaluating convalescent plasma for treatment of COVID-19 identified neutralizing activity in plasma of recovered patients that appeared to be transferred to recipients following plasma infusion [30]. Similarly, one preliminary study derived monoclonal antibodies from convalescent patients' B-cells that targeted the receptor-binding domain of the spike protein and had neutralizing activity in a pseudovirus model [31]; another reported that rhesus macaques infected with SARS-CoV-2 did not develop reinfection following recovery and rechallenge [32]. However, neither of these studies has been published in a peer reviewed journal, and further confirmation of these findings is needed.

CLINICAL FEATURES

Incubation period — The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately four to five days after exposure [33-35].

In a study of 1099 patients with confirmed symptomatic COVID-19, the median incubation period was four days (interquartile range two to seven days) [34].

Using data from 181 publicly reported, confirmed cases in China with identifiable exposure, one modeling study estimated that symptoms would develop in 2.5 percent of infected individuals within 2.2 days and in 97.5 percent of infected individuals within 11.5 days [36]. The median incubation period in this study was 5.1 days.

Spectrum of illness severity — The spectrum of symptomatic infection ranges from mild to critical; most infections are not severe [35,37-42]. Specifically, in a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed infections with an estimation of disease severity [43]:

- Mild (no or mild pneumonia) was reported in 81 percent.
- Severe disease (eg, with dyspnea, hypoxia, or >50 percent lung involvement on imaging within 24 to 48 hours) was reported in 14 percent.
- Critical disease (eg, with respiratory failure, shock, or multiorgan dysfunction) was reported in 5 percent.
- The overall case fatality rate was 2.3 percent; no deaths were reported among noncritical cases.

According to a joint World Health Organization (WHO)-China fact-finding mission, the case-fatality rate ranged from 5.8 percent in Wuhan to 0.7 percent in the rest of China [17]. Most of the fatal cases occurred in patients with advanced age or underlying medical comorbidities [20,43]. (See 'Risk factors for severe illness' below.)

The proportion of severe or fatal infections may vary by location. As an example, in Italy, 12 percent of all detected COVID-19 cases and 16 percent of all hospitalized patients were admitted to the intensive care unit; the estimated case fatality rate was 7.2 percent in mid-March [44,45]. In contrast, the estimated case fatality rate in mid-March in South Korea was 0.9 percent [46]. This may be related to distinct demographics of infection; in Italy, the median age of patients with infection was 64 years, whereas in Korea the median age was in the 40s. (See 'Impact of age' below.)

Risk factors for severe illness — Severe illness can occur in otherwise healthy individuals of any age, but it predominantly occurs in adults with advanced age or underlying medical comorbidities. The impact of age is discussed elsewhere. (See 'Impact of age' below.)

Comorbidities that have been associated with severe illness and mortality include [20,43,47]:

- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Chronic lung disease
- Cancer
- Chronic kidney disease

In a subset of 355 patients who died with COVID-19 in Italy, the mean number of pre-existing comorbidities was 2.7, and only 3 patients had no underlying condition [45].

Among patients with advanced age and medical comorbidities, COVID-19 is frequently severe. For example, in a SARS-CoV-2 outbreak across several long-term care facilities in Washington State, the median age of the 101 facility residents affected was 83 years, and 94 percent had a chronic underlying condition; the hospitalization and preliminary case fatality rates were 55 and 34 percent, respectively [48].

Males have comprised a disproportionately high number of deaths in cohorts from China and Italy [45,49].

Particular laboratory features have also been associated with worse outcomes. These include [20,50,51]:

- Lymphopenia
- Elevated liver enzymes
- Elevated lactate dehydrogenase (LDH)
- Elevated inflammatory markers (eg, C-reactive protein [CRP], ferritin)
- Elevated D-dimer (>1 mcg/mL)
- Elevated prothrombin time (PT)
- Elevated troponin
- Elevated creatine phosphokinase (CPK)
- Acute kidney injury

As an example, in one study, progressive decline in the lymphocyte count and rise in the D-dimer over time were observed in nonsurvivors compared with more stable levels in survivors [40].

Impact of age — Individuals of any age can acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease.

In several cohorts of hospitalized patients with confirmed COVID-19, the median age ranged from 49 to 56 years [38-40]. In a report from the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed infections, 87 percent of patients were between 30 and 79 years old [43]. Older age was also associated with increased mortality, with case fatality rates of 8 and 15 percent among those aged 70 to 79 years and 80 years or older, respectively. Similar findings were reported from Italy, with case fatality rates of 12 and 20 percent among those aged 70 to 79 years and 80 years or older, respectively [45].

In the United States, 2449 patients diagnosed with COVID-19 between February 12 and March 16, 2020 had age, hospitalization, and intensive care unit (ICU) information available [52]; 67 percent of cases were diagnosed in those aged ≥45 years, and, similar to findings from China, mortality was highest among older individuals, with 80 percent of deaths occurring in those aged ≥65 years.

Symptomatic infection in children appears to be uncommon; when it occurs, it is usually mild, although severe cases have been reported [53-56]. In the large Chinese report described above, only 2 percent of infections were in individuals younger than 20 years old [43]. Similarly, in South Korea, only 6.3 percent of nearly 8000 infections were in those younger than 20 years old [46]. In a small study of 10 children in China, clinical illness was mild; 8 had fever, which resolved within 24 hours, 6 had cough, 4 had sore throat, 4 had evidence of focal pneumonia on CT, and none required supplemental oxygen [54]. In another study of six

children aged 1 to 7 years who were hospitalized in Wuhan with COVID-19, all had fever >102.2°F/39°C and cough, four had imaging evidence of viral pneumonia, and one was admitted to the intensive care unit; all children recovered [55].

Asymptomatic infections — Asymptomatic infections have also been described [35,57-59], but their frequency is unknown.

In a COVID-19 outbreak on a cruise ship where nearly all passengers and staff were screened for SARS-CoV-2, approximately 17 percent of the population on board tested positive as of February 20; about half of the 619 confirmed COVID-19 cases were asymptomatic at the time of diagnosis [60]. A modeling study estimated that 18 percent were true asymptomatic cases (ie, did not go on to develop symptoms), although this was based on a number of assumptions, including the incubation period [61].

Similarly, in a smaller COVID-19 outbreak within a skilled nursing facility, 13 of the of the 23 residents who had a positive screening test were asymptomatic at the time of diagnosis, but 10 of them ultimately developed symptoms over the next seven days [62].

Even patients with asymptomatic infection may have objective clinical abnormalities [27,63]. As an example, in a study of 24 patients with asymptomatic infection who all underwent chest computed tomography (CT), 50 percent had typical ground-glass opacities or patchy shadowing, and another 20 percent had atypical imaging abnormalities [27]. Five patients developed low-grade fever, with or without other typical symptoms, a few days after diagnosis. In another study of 55 patients with asymptomatic infection identified through contact tracing, 67 percent had CT evidence of pneumonia on admission; only two patients developed hypoxia, and all recovered [63].

Clinical manifestations

Initial presentation — Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging [34,38-40]. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections.

In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of illness were [40]:

- Fever in 99 percent
- Fatigue in 70 percent
- Dry cough in 59 percent
- Anorexia in 40 percent
- Myalgias in 35 percent
- Dyspnea in 31 percent
- Sputum production in 27 percent

Other cohort studies of patients from Wuhan with confirmed COVID-19 have reported a similar range of clinical findings [38,40,64,65]. However, fever might not be a universal finding. In one study, fever was reported in almost all patients, but approximately 20 percent had a very low grade fever <100.4°F/38°C [38]. In another study of 1099 patients from Wuhan and other areas in China, fever (defined as an axillary

temperature over 99.5°F/37.5°C) was present in only 44 percent on admission but was ultimately noted in 89 percent during the hospitalization [34].

Although not highlighted in the initial cohort studies from China, smell and taste disorders (eg, anosmia and dysgeusia) have also been reported as common symptoms in patients with COVID-19 [66,67]. In a survey of 59 patients with COVID-19 in Italy, 34 percent self-reported either a smell or taste aberration and 19 percent reported both [67]. Whether this is a distinguishing feature of COVID-19 is uncertain.

Other, less common symptoms have included headache, sore throat, and rhinorrhea. In addition to respiratory symptoms, gastrointestinal symptoms (eg, nausea and diarrhea) have also been reported; and in some patients, they may be the presenting complaint [38,40].

Course and complications — As above, symptomatic infection can range from mild to critical. (See 'Spectrum of illness severity' above.)

Some patients with initially mild symptoms may progress over the course of a week. In one study of 138 patients hospitalized in Wuhan for pneumonia due to SARS-CoV-2, dyspnea developed after a median of five days since the onset of symptoms, and hospital admission occurred after a median of seven days of symptoms [40]. In another study, the median time to dyspnea was eight days [38].

Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease and can manifest shortly after the onset of dyspnea. In the study of 138 patients described above, ARDS developed in 20 percent a median of eight days after the onset of symptoms; mechanical ventilation was implemented in 12.3 percent [40]. In another study of 201 hospitalized patients with COVID-19 in Wuhan, 41 percent developed ARDS; age greater than 65 years, diabetes mellitus, and hypertension were each associated with ARDS [50].

Other complications have included arrhythmias, acute cardiac injury, and shock [40,49,68]. In one study, these were reported in 17, 7, and 9 percent, respectively [40]. In a series of 21 severely ill patients admitted to the ICU in the United States, one-third developed cardiomyopathy [68].

Some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated proinflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses [38,69]. (See 'Risk factors for severe illness' above.)

According to the WHO, recovery time appears to be around two weeks for mild infections and three to six weeks for severe disease [10].

Laboratory findings — In patients with COVID-19, the white blood cell count can vary. Leukopenia, leukocytosis, and lymphopenia have been reported, although lymphopenia appears most common [13,38-40]. Elevated lactate dehydrogenase and ferritin levels are common, and elevated aminotransferase levels have also been described. On admission, many patients with pneumonia have normal serum procalcitonin levels; however, in those requiring ICU care, they are more likely to be elevated [38-40].

High D-dimer levels and more severe lymphopenia have been associated with mortality [39].

Imaging findings — Chest CT in patients with COVID-19 most commonly demonstrates ground-glass opacification with or without consolidative abnormalities, consistent with viral pneumonia [65,70]. Case series

have suggested that chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. Less common findings include pleural thickening, pleural effusion, and lymphadenopathy.

Chest CT may be helpful in making the diagnosis, but no finding can completely rule in or rule out the possibility of COVID-19. In a study of 1014 patients in Wuhan who underwent both reverse-transcription polymerase chain reaction (RT-PCR) testing and chest CT for evaluation of COVID-19, a "positive" chest CT for COVID-19 (as determined by a consensus of two radiologists) had a sensitivity of 97 percent, using the PCR tests as a reference; however, specificity was only 25 percent [71]. The low specificity may be related to other etiologies causing similar CT findings. In another study comparing chest CTs from 219 patients with COVID-19 in China and 205 patients with other causes of viral pneumonia in the United States, COVID-19 cases were more likely to have a peripheral distribution (80 versus 57 percent), ground-glass opacities (91 versus 68 percent), fine reticular opacities (56 versus 22 percent), vascular thickening (59 versus 22 percent), and reverse halo sign (11 versus 1 percent), but less likely to have a central and peripheral distribution (14 versus 35 percent), air bronchogram (14 versus 23 percent), pleural thickening (15 versus 33 percent), pleural effusion (4 versus 39 percent), and lymphadenopathy (2.7 versus 10 percent) [72]. A group of radiologists in that study was able to distinguish COVID-19 with high specificity but moderate sensitivity.

In one report of 21 patients with laboratory-confirmed COVID-19 who did not develop severe respiratory distress, lung abnormalities on chest imaging were most severe approximately 10 days after symptom onset [64]. However, chest CT abnormalities have also been identified in patients prior to the development of symptoms and even prior to the detection of viral RNA from upper respiratory specimens [65,73].

EVALUATION AND DIAGNOSIS

Clinical suspicion and criteria for testing — The possibility of COVID-19 should be considered primarily in patients with new onset fever and/or respiratory tract symptoms (eg, cough, dyspnea). It should also be considered in patients with severe lower respiratory tract illness without any clear cause. Although these syndromes can occur with other viral respiratory illnesses, the likelihood of COVID-19 is increased if the patient:

- Resides in or has traveled within the prior 14 days to a location where there is community transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; ie, large numbers of cases that cannot be linked to specific transmission chains) (see 'Geographic distribution' above); or
- Has had close contact with a confirmed or suspected case of COVID-19 in the prior 14 days, including through work in health care settings. Close contact includes being within approximately six feet (about two meters) of a patient for a prolonged period of time while not wearing personal protective equipment (PPE) or having direct contact with infectious secretions while not wearing PPE.

Patients with suspected COVID-19 who do not need emergency care should be encouraged to call prior to presenting to a health care facility for evaluation. Many patients can be evaluated regarding the need for testing over the phone. For patients in a health care facility, infection control measures should be implemented as soon as the possibility of COVID-19 is suspected. (See 'Infection control for suspected or confirmed cases' below.)

The diagnosis cannot be definitively made without microbiologic testing, but limited capacity may preclude testing all patients with suspected COVID-19. Local health departments may have specific criteria for testing. In the United States, the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America have suggested priorities for testing (table 1); high-priority individuals include hospitalized patients (especially critically ill patients with unexplained respiratory illness), symptomatic health care workers, and symptomatic individuals who have risk factors for severe disease [74,75].

Testing criteria suggested by the World Health Organization (WHO) can be found in its technical guidance online. These are the same criteria used by the European Centre for Disease Prevention and Control.

An approach to suspected cases when testing is not available is discussed elsewhere. (See 'COVID-19 testing not readily available' below.)

Laboratory testing — Patients who meet the testing criteria discussed above should undergo testing for SARS-CoV-2 (the virus that causes COVID-19) in addition to testing for other respiratory pathogens (eg, influenza, respiratory syncytial virus). (See "Diagnostic approach to community-acquired pneumonia in adults", section on 'Diagnostic testing for microbial etiology'.)

In the United States, the CDC recommends collection of a nasopharyngeal swab specimen to test for SARS-CoV-2 [76]. An oropharyngeal swab can be collected but is not essential; if collected, it should be placed in the same container as the nasopharyngeal specimen. Oropharyngeal, nasal mid-turbinate, or nasal swabs are acceptable alternatives if nasopharyngeal swabs are unavailable.

Expectorated sputum should be collected from patients with productive cough; induction of sputum is not recommended. A lower respiratory tract aspirate or bronchoalveolar lavage should be collected from patients who are intubated. Additional information on testing and handling of clinical specimens can be found on the CDC website.

In a study of 205 patients with COVID-19 who were sampled at various sites, the highest rates of positive viral RNA tests were reported from bronchoalveolar lavage (95 percent, 14 of 15 specimens) and sputum (72 percent, 72 of 104 specimens), compared with oropharyngeal swab (32 percent, 126 of 398 specimens) [16]. Data from this study suggested that viral RNA levels are higher and more frequently detected in nasal compared with oral specimens, although only eight nasal swabs were tested.

SARS-CoV-2 RNA is detected by reverse-transcription polymerase chain reaction (RT-PCR) [77]. In the United States, testing is performed by the CDC, by local public health departments, by hospitals that have developed and validated their own tests, and by certain commercial reference laboratories.

A positive test for SARS-CoV-2 generally confirms the diagnosis of COVID-19, although false-positive tests are possible.

If initial testing is negative but the suspicion for COVID-19 remains, the WHO recommends resampling and testing from multiple respiratory tract sites [78]. Infection control precautions for COVID-19 should continue while repeat evaluation is being performed.

The accuracy and predictive values of SARS-CoV-2 testing have not been systematically evaluated, and the sensitivity of testing likely depends on the precise test as well as the type of specimen obtained. Negative

RT-PCR tests on oropharyngeal swabs despite CT findings suggestive of viral pneumonia have been reported in some patients who ultimately tested positive for SARS-CoV-2 [73].

Serologic tests, once generally available, should be able to identify patients who have either current or previous infection but a negative PCR test. In one study that included 58 patients with clinical, radiographic, and epidemiologic features suspicious for COVID-19 but with negative SARS-CoV-2 PCR testing, an immunoglobulin (Ig)M ELISA was positive in 93 percent (and was negative when tested on plasma specimens that predated the COVID-19 outbreak) [79].

For safety reasons, specimens from a patient with suspected or documented COVID-19 should **not** be submitted for viral culture.

The importance of testing for other pathogens was highlighted in a report of 210 symptomatic patients with suspected COVID-19; 30 tested positive for another respiratory viral pathogen, and 11 tested positive for SARS-CoV-2 [37]. In addition, coinfection with SARS-CoV-2 and other respiratory viruses, including influenza, has been reported [80,81], and this may impact management decisions.

MANAGEMENT

Site of care

Home care — Home management is appropriate for patients with non-severe infection (eg, fever, cough, and/or myalgias without dyspnea) who can be adequately isolated in the outpatient setting [13,82,83]. Management of such patients should focus on prevention of transmission to others and monitoring for clinical deterioration, which should prompt hospitalization.

There should be a low threshold to clinically evaluate in person patients who have risk factors for more severe illness, even if they have only mild symptoms, to ensure they are stable enough for home care (see 'Risk factors for severe illness' above). If such patients are cared for at home, they should remain in frequent contact with their provider to closely monitor for any symptoms or signs suggestive of clinical worsening.

Outpatient management is mainly supportive with hydration, antipyretics, and analgesics, if necessary. Outpatients with COVID-19 should stay at home and try to separate themselves from other people and animals in the household. They should wear a facemask when in the same room (or vehicle) as other people and when presenting to health care settings. Disinfection of frequently touched surfaces is also important, as discussed elsewhere. (See 'Environmental disinfection' below.)

The optimal duration of home isolation is uncertain. The United States Centers for Disease Control and Prevention (CDC) has issued recommendations on discontinuation of home isolation, which include both test-based and non-test-based strategies [84,85]. The choice of strategy depends upon the patient population (eg, immunocompromised versus nonimmunocompromised), the availability of testing supplies, and access to testing.

- When a **test-based** strategy is used, patients may discontinue home isolation when there is:
  - Resolution of fever without the use of fever-reducing medications **AND**
  - Improvement in respiratory symptoms (eg, cough, shortness of breath) **AND**

- Negative results of a US Food and Drug Administration (FDA) emergency use-authorized molecular assay for COVID-19 from at least two consecutive nasopharyngeal swab specimens collected ≥24 hours apart (total of two negative specimens)

- When a **non-test-based** strategy is used, patients may discontinue home isolation when the following criteria are met:

  - At least seven days have passed since symptoms first appeared **AND**

  - At least three days (72 hours) have passed since recovery of symptoms (defined as resolution of fever without the use of fever-reducing medications **and** improvement in respiratory symptoms [eg, cough, shortness of breath])

In some cases, patients may have had laboratory-confirmed COVID-19, but they did not have any symptoms when they were tested. In such patients, home isolation may be discontinued when at least seven days have passed since the date of their first positive COVID-19 test so long as there was no evidence of subsequent illness.

For health care workers with confirmed or suspected COVID-19, decisions about return to work should be made in the context of the provider's local circumstances (eg, availability of testing, staffing shortages) [86]. More detailed information regarding criteria for return to work, as well as return to work practices and work restrictions, is found on the CDC website.

The use of non-test-based strategies that use time since illness onset and time since recovery as the criteria for discontinuing precautions is based upon findings that transmission is most likely to occur in the early stage of infection. However, data are limited, particularly in immunocompromised patients, and this strategy may not prevent all instances of secondary spread [84,85]. Protocols in other countries and at specific institutions may differ on the duration of home isolation when testing for viral clearance cannot be performed; as an example, the World Health Organization (WHO) suggests that home isolation in patients with documented COVID-19 should continue for at least two weeks after symptom resolution [87]. (See 'Route of transmission' above.)

More detailed interim recommendations on home management of patients with COVID-19 can be found on the WHO and CDC websites [83,88,89].

Hospital care — Some patients with suspected or documented COVID-19 have severe disease that warrants hospital care. Management of such patients consists of ensuring appropriate infection control, as below (see 'Infection control for suspected or confirmed cases' below), and supportive care. Investigational approaches are also being evaluated (see 'Investigational approaches' below). Clinical guidance can be found on the WHO and CDC websites [13,82].

Patients with severe disease often need oxygenation support. High-flow oxygen and noninvasive positive pressure ventilation have been used, but the safety of these measures is uncertain, and they should be considered aerosol-generating procedures that warrant specific isolation precautions. (See "Coronavirus disease 2019 (COVID-19): Critical care issues", section on 'Respiratory care of the nonintubated patient'.)

Some patients may develop acute respiratory distress syndrome (ARDS) and warrant intubation with mechanical ventilation. Management of ARDS in patients with COVID-19 and other critical care issues are

discussed in detail elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care issues".)

Limited role of glucocorticoids — The WHO and CDC recommend glucocorticoids **not** be used in patients with COVID-19 pneumonia unless there are other indications (eg, exacerbation of chronic obstructive pulmonary disease) [13,82]. Glucocorticoids have been associated with an increased risk for mortality in patients with influenza and delayed viral clearance in patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Although they were widely used in management of severe acute respiratory syndrome (SARS), there was no good evidence for benefit, and there was persuasive evidence of adverse short- and long-term harm [90]. (See "Treatment of seasonal influenza in adults", section on 'Adjunctive therapies' and "Middle East respiratory syndrome coronavirus: Treatment and prevention", section on 'Treatment'.)

The use of glucocorticoids among critically ill patients with COVID-19 is discussed elsewhere. (See "Coronavirus disease 2019 (COVID-19): Critical care issues", section on 'Glucocorticoids'.)

Uncertainty about NSAID use — Some clinicians have suggested the use of non-steroidal anti-inflammatory drugs (NSAIDs) early in the course of disease may have a negative impact on disease outcome [91,92]. These concerns are based on anecdotal reports of a few young patients who received NSAIDs early in the course of infection and experienced severe disease. However, there have been no clinical or population-based data that directly address the risk of NSAIDs. The European Medicines Agency (EMA) and the WHO do not recommend that NSAIDs be avoided when clinically indicated [93,94]. Given the uncertainty, we suggest acetaminophen as the preferred antipyretic agent, if possible, and if NSAIDs are needed, the lowest effective dose should be used. However, we do not suggest that NSAIDs be stopped in patients who are on them chronically for other conditions, unless there are other reasons to stop them (eg, renal injury, gastrointestinal bleeding).

Investigational approaches — A number of investigational approaches are being explored for antiviral treatment of COVID-19, and enrollment in clinical trials should be discussed with patients or their proxies. A registry of international clinical trials can be found on the WHO website and at clinicaltrials.gov.

Certain investigational agents have been described in observational series or are being used anecdotally based on in vitro or extrapolated evidence. It is important to acknowledge that there are no controlled data supporting the use of any of these agents, and their efficacy for COVID-19 is unknown.

- Remdesivir – Several randomized trials are underway to evaluate the efficacy of remdesivir for moderate or severe COVID-19 [95]. Remdesivir is a novel nucleotide analogue that has activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro and related coronaviruses (including SARS and MERS-CoV) both in vitro and in animal studies [96,97]. Remdesivir is an intravenous agent; reported side effects include nausea, vomiting, and transaminase elevations. It is also prepared in a cyclodextrin vehicle, so there is concern for potentially toxic accumulation of the vehicle in renal impairment. Exclusion criteria vary by trials but include alanine aminotransferase level >5 times the upper limit of normal and chronic kidney disease (creatinine clearance <30 or <50 mL/min, depending on the trial); some trials also exclude use of a different COVID-19-targeted therapy within 24 hours prior to remdesivir initiation. The compassionate use of remdesivir through an investigational new drug application was described in a case report of one of the first patients with COVID-19 in the United States [98]. Any clinical impact of remdesivir on COVID-19 remains unknown.

- Chloroquine/hydroxychloroquine – Both chloroquine and hydroxychloroquine have been reported to inhibit SARS-CoV-2 in vitro, although hydroxychloroquine appears to have more potent antiviral activity [99].

  Clinical data evaluating hydroxychloroquine or chloroquine are limited, and their efficacy against SARS-CoV-2 is unknown. Nevertheless, given the lack of clearly effective interventions and the in vitro antiviral activity, some clinicians think it is reasonable to use hydroxychloroquine in hospitalized patients with severe disease or risk for severe disease who are not eligible for clinical trials. In the United States, the FDA issued an emergency use authorization to allow the use of these agents in adolescents or adults hospitalized for COVID-19 when participation in clinical trials is not feasible [100]. However, if these agents are used outside of a clinical trial, the possibility of drug toxicity (including QTc prolongation, in particular, as well as cardiomyopathy and retinal toxicity) and drug interactions should be considered prior to use, especially in individuals who may be more susceptible to these effects, and the patients should be monitored closely for adverse effects during use. The American College of Cardiology has suggested QTc monitoring parameters in this setting [101]. Optimal dosing is uncertain; the FDA suggests hydroxychloroquine 800 mg on day 1 then 400 mg daily and chloroquine 1 g on day 1 then 500 mg daily, each for four to seven days total depending on clinical response [100]. Other hydroxychloroquine regimens used include 400 mg twice daily on day 1 then daily for five days, 400 mg twice daily on day 1 then 200 mg twice daily for four days, and 600 mg twice daily on day 1 then 400 mg daily for four days [102].

  Use of chloroquine is included in treatment guidelines from China's National Health Commission and was reportedly associated with reduced progression of disease and decreased duration of symptoms [103,104]. However, primary data supporting these claims have not been published [105].

  Other published clinical data on either of these agents are limited. In an open-label study of 36 patients with COVID-19, use of hydroxychloroquine (200 mg three times per day for 10 days) was associated with a higher rate of undetectable SARS-CoV-2 RNA on nasopharyngeal specimens at day 6 compared with no specific treatment (70 versus 12.5 percent) [106]. In this study, the use of azithromycin in combination with hydroxychloroquine appeared to have additional benefit, but there are methodologic concerns about the control groups for the study, and the biologic basis for using azithromycin in this setting is unclear. In a randomized trial of 30 adults with COVID-19 in Shanghai, the proportion of patients with nasopharyngeal viral clearance at day 7 was not different with hydroxychloroquine (400 mg daily for five days) compared with standard of care, and one patient in the hydroxychloroquine group progressed to severe disease; interferon and other antiviral agents were used in both arms, which could be confounding factors [107].

- **IL-6 pathway inhibitors** – Treatment guidelines from China's National Health Commission include the interleukin (IL)-6 receptor inhibitor tocilizumab for patients with severe COVID-19 and elevated IL-6 levels. This agent, as well as sarilumab and siltuximab, which also target the IL-6 pathway, are being evaluated in clinical trials [108].

- **Convalescent plasma** – In the United States, the Food and Drug Administration is accepting emergency investigational new drug applications for use of convalescent plasma for patients with severe or life-threatening COVID-19 [109]. A case series described administration of plasma from donors who had completely recovered from COVID-19 to five patients with severe COVID-19 on mechanical

ventilation and persistently high viral titers despite investigational antiviral treatment [30]. The patients had decreased nasopharyngeal viral load, decreased disease severity score, and improved oxygenation by 12 days after transfusion, but these findings do not establish a causal effect. Finding appropriate donors and establishing testing to confirm neutralizing activity of plasma may be logistical challenges. (See "Clinical use of plasma components", section on 'Convalescent plasma'.)

- Favipiravir – Favipiravir is an RNA polymerase inhibitor that is available in some Asian countries for treatment of influenza and is being evaluated in clinical trials for treatment of COVID-19. In a study of patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days) and more frequent radiographic improvement (in 91 versus 62 percent by day 14) compared with lopinavir-ritonavir [110]. However, other therapies were administered in this non-randomized, open-label study, so the results should be interpreted with caution given potential confounders.

- Lopinavir-ritonavir – Lopinavir-ritonavir appears to have little to no role in the treatment of SARS-CoV-2 infection. This combined protease inhibitor, which has primarily been used for HIV infection, has in vitro activity against the SARS-CoV [111] and appears to have some activity against MERS-CoV in animal studies [112]. However, there was no difference in time to clinical improvement or mortality at 28 days in a randomized trial of 199 patients with severe COVID-19 given lopinavir-ritonavir (400/100 mg) twice daily for 14 days in addition to standard care versus those who received standard of care alone [113].

Institutional protocols — Several academic medical institutions in the United States have developed COVID-19 management protocols and made them publicly available. Given the paucity of high-quality clinical evidence on the management of COVID-19, the safety and efficacy of these strategies are uncertain:

- Brigham and Women's Hospital
- Massachusetts General Hospital
- Michigan Medicine
- Nebraska Medicine
- Penn Medicine
- University of Washington Medicine

PREVENTION

In the health care setting

Screening and precautions for fever or respiratory symptoms — Screening patients for clinical manifestations consistent with COVID-19 (eg, fever, cough, dyspnea) prior to entry into a health care facility can help identify those who may warrant additional infection control precautions. This can be done over the phone before the patient actually presents to a facility. Routine visits should be postponed for patients with these manifestations; if they need to present for medical care, they should be advised to wear a facemask. Separate waiting areas for patients with respiratory symptoms should be designated, if possible, at least six feet away from the regular waiting areas.

In locations where community transmission is ongoing, postponing all elective procedures or non-urgent visits and using virtual (eg, through video communication) visits may be useful strategies to reduce the risk of

exposure in the health care setting [114].

In some settings, such as long-term care facilities, the United States Centers for Disease Control and Prevention (CDC) recommends that standard, contact, and droplet precautions in addition to eye protection be used for any patient with an undiagnosed respiratory infection who is not under consideration for COVID-19 [115]. Some institutions have instituted policies requiring health care workers to wear masks in all clinical settings. These strategies may help reduce the risk of spread from unsuspected virus carriers.

Infection control precautions for suspect COVID-19 cases are discussed below.

Infection control for suspected or confirmed cases — Infection control to limit transmission is an essential component of care in patients with suspected or documented COVID-19.

Individuals with suspected infection in the community should be advised to wear a medical mask to contain their respiratory secretions prior to seeking medical attention. (See 'Evaluation and diagnosis' above.)

In the health care setting, the World Health Organization (WHO) and CDC recommendations for infection control for suspected or confirmed infections differ slightly:

- The WHO recommends standard, contact, and droplet precautions (ie, gown, gloves, and mask), with eye or face protection [116]. The addition of airborne precautions (ie, respirator) is warranted during aerosol-generating procedures (as detailed below).

  The CDC recommends that patients with suspected or confirmed COVID-19 be placed in a single-occupancy room with a closed door and dedicated bathroom [114]. The patient should wear a facemask if being transported out of the room (eg, for studies that cannot be performed in the room). An airborne infection isolation room (ie, a single-patient negative pressure room) should be reserved for patients undergoing aerosol-generating procedures (as detailed below).

  Any personnel entering the room of a patient with suspected or confirmed COVID-19 should wear the appropriate personal protective equipment (PPE): gown, gloves, eye protection, and a respirator (eg, an N95 respirator). If supply of respirators is limited, the CDC acknowledges that facemasks are an acceptable alternative (in addition to contact precautions and eye protection), but respirators should be worn during aerosol-generating procedures [114].

Aerosol-generating procedures include tracheal intubation, noninvasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, upper endoscopy, and bronchoscopy. The CDC does not consider nasopharyngeal or oropharyngeal specimen collection an aerosol-generating procedure that warrants an airborne isolation room, but it should be performed in a single-occupancy room with the door closed, and any personnel in the room should wear a respirator (or if unavailable, a facemask) [114].

Health care workers should pay special attention to the appropriate sequence of putting on (figure 1) and taking off (figure 2) PPE to avoid contamination.

For health care workers who have had a potential exposure to COVID-19, the CDC has provided guidelines for work restriction and monitoring. The approach depends upon the duration of exposure, the patient's symptoms, whether the patient was wearing a facemask, the type of PPE used by the provider, and whether an aerosol-generating procedure was performed. Some local health departments allow health care workers

to return to work following an exposure if they adhere to cough and hand hygiene, wear a facemask while at the health care facility until 14 days after the exposure, and monitor daily for fever or respiratory symptoms, the presence of which would prompt immediate self-isolation [117].

The importance of infection control in preventing the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in health care settings has been demonstrated in several studies. In one report of 138 patients with COVID-19 in China, it was estimated that 43 percent acquired infection in the hospital setting [40]. In Washington State, suboptimal use of infection control procedures contributed to the spread of infection to 81 residents, 34 staff members, and 14 visitors [118].

Strategies for PPE shortages — Limited availability of personal protective equipment (PPE) has complicated medical care of patients with suspected or documented COVID-19 (and other transmissible conditions) worldwide.

In the United States, the CDC offers guidance on optimizing the supply of PPE when sudden increases in patient volume threaten a facility's PPE capacity [119]. Strategies include canceling non-urgent procedures or visits that would warrant use of PPE, prioritizing the use of certain PPE for the highest risk situations, and cautious extended or limited reuse of PPE.

There has also been interest in decontamination of PPE for reuse, in particular for N95 respirators. Decontamination with ultraviolet (UV) light was evaluated in the context of the H1N1 influenza pandemic; in experimental models, UV irradiation was observed to reduce H1N1 influenza viability on N95 respirator surfaces at doses below the threshold observed to impair the integrity of the respirator [120-122]. Coronaviruses can also be inactivated by UV irradiation, but comparable studies have not been performed with SARS-CoV-2, and the dose needed to inactivate the virus on a respirator surface is unknown. Nebraska Medicine has implemented a protocol for UV irradiation of N95 respirators in the context of the COVID-19 pandemic based on the dose generally needed to inactivate other single-stranded RNA viruses on surfaces [123].

Duke University Health System is using hydrogen peroxide vapor for N95 decontamination [124]. Hydrogen peroxide vapor has been observed to inactivate other non-coronavirus single-stranded RNA viruses on environmental surfaces [125,126].

Equipment used for protection in other industries is also being explored as an alternative to standard health care PPE, such as elastometric half-mask respirators in place of N95 respirators [127].

Discontinuation of precautions — The decision to discontinue infection control precautions for hospitalized patients with COVID-19 should be made on a case-by-case basis in consultation with experts in infection prevention and control and public health officials. In the United States, the CDC recommends that hospitalized patients meet all of the following criteria before discontinuation of precautions: resolution of fever (without antipyretics), improvement in respiratory symptoms, and two negative reverse-transcription polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 on sequential nasopharyngeal specimens collected ≥24 hours apart [128]. Although a non-test-based strategy (ie, that allows discontinuation of precautions after specific time intervals since symptom onset and symptom resolution) may be appropriate for patients managed at home, this test-based strategy is preferred for hospitalized patients and those being transferred to a long-term care facility. If patients are ready to be discharged home prior to meeting criteria for

discontinuation of precautions, they can be sent home with instructions to self-isolate until they meet either test-based or non-test-based criteria. (See 'Home care' above.)

Whether a test-based strategy reliably identifies patients who are no longer infectious is unknown. Positive RT-PCR tests for SARS-CoV-2 RNA were reported in laboratory-confirmed COVID-19 patients after they had clinically improved and tested negative on two consecutive tests [129]. Another report described 22 patients with COVID-19 who had detectable viral RNA in fecal and/or sputum specimens for up to 13 and 39 days, respectively, even though the viral RNA was no longer detectable in pharyngeal specimens [130]. The clinical significance of these findings is uncertain; it is unknown whether these individuals continued to shed infectious virus.

Environmental disinfection — To help reduce the spread of COVID-19 virus, environmental infection control procedures should also be implemented [83,89,114,116,131]. In United States health care settings, the CDC states routine cleaning and disinfection procedures are appropriate for COVID-19 virus [114].

Products approved by the Environmental Protection Agency (EPA) for emerging viral pathogens should be used; a list of EPA-registered products can be found here. Specific guidance on environmental measures, including those used in the home setting, is available on the CDC and WHO websites. Additional information is also found in a separate topic review. (See "Coronaviruses", section on 'Treatment and prevention'.)

The importance of environmental disinfection was illustrated in a study from Singapore, in which viral RNA was detected on nearly all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of a patient with symptomatic mild COVID-19 prior to routine cleaning [132]. Viral RNA was not detected on similar surfaces in the rooms of two other symptomatic patients following routine cleaning (with sodium dichloroisocyanurate). Of note, viral RNA detection does not necessarily indicate the presence of infectious virus.

It is unknown how long SARS-CoV-2 can persist on surfaces [12,131,133]; other coronaviruses have been tested and may survive on inanimate surfaces for up to six to nine days without disinfection. In a study evaluating the survival of viruses dried on a plastic surface at room temperature, a specimen containing SARS-CoV (a virus closely related to SARS-CoV-2) had detectable infectivity at six but not nine days [133]. However, in a systematic review of similar studies, various disinfectants (including ethanol at concentrations between 62 and 71 percent) inactivated a number of coronaviruses related to SARS-CoV-2 within one minute [131].

Preventing exposure in the community — The following general measures are recommended to reduce transmission of infection:

- Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60 percent alcohol is a reasonable alternative if the hands are not visibly dirty.
- Respiratory hygiene (eg, covering the cough or sneeze).
- Avoiding touching the face (in particular eyes, nose, and mouth).
- Avoiding crowds (particularly in poorly ventilated spaces) if possible and avoiding close contact with ill individuals.

- Cleaning and disinfecting objects and surfaces that are frequently touched. The CDC has issued guidance on disinfection in the home setting; a list of EPA-registered products can be found here.

In particular, older adults and individuals with chronic medical conditions should be encouraged to follow these measures.

If SARS-CoV-2 is prevalent in the community, residents should be encouraged to practice social distancing by staying home as much as possible. In the United States, the CDC has provided guidance for cancelling and postponing gatherings [134].

For people without respiratory symptoms, the CDC, the European Centre for Disease Prevention and Control, and the WHO do not recommend wearing a medical mask in the community, even if COVID-19 is prevalent in the area [2,135,136]. Wearing a mask does not decrease the importance of other general measures to prevent infection, and it may result in unnecessary cost and supply problems.

Individuals who are caring for patients with suspected or documented COVID-19 at home, however, should wear a tightly fitting medical mask when in the same room as that patient.

Individuals who develop an acute respiratory illness (eg, with fever and/or respiratory symptoms) should be encouraged to stay home from school or work for the duration of the illness. Some may warrant evaluation for COVID-19. (See 'Clinical suspicion and criteria for testing' above.)

The CDC has included recommended measures to prevent spread in the community on its website.

Managing asymptomatic individuals with potential exposure — Individuals who have had travel to high-risk areas or are contacts of patients with suspected or confirmed COVID-19 should practice social distancing and be monitored for development of consistent symptoms and signs (fever, cough, or dyspnea); in some cases, quarantine may be warranted. Clinical manifestations should prompt at least self-isolation at home and clinician assessment for the need for medical evaluation. (See 'Clinical suspicion and criteria for testing' above.)

In the United States, the level of risk (based on the travel location or the type of contact) informs whether monitoring and isolation are done by the individual or with the involvement of public health personnel. Categories of risk and the suggested monitoring and isolation strategies can be found on the CDC website.

Global public health measures — On January 30, 2020, the WHO declared the COVID-19 outbreak a public health emergency of international concern and, in March 2020, began to characterize it as a pandemic in order to emphasize the gravity of the situation and urge all countries to take action in detecting infection and preventing spread. The WHO has indicated three priorities for countries: protecting health workers, engaging communities to protect those at highest risk of severe disease (eg, older adults and those with medical comorbidities), and supporting vulnerable countries in containing infection [10].

The WHO does not recommend international travel restrictions but does acknowledge that movement restriction may be temporarily useful in some settings. The WHO advises exit screening for international travelers from areas with ongoing transmission of COVID-19 virus to identify individuals with fever, cough, or potential high-risk exposure [137,138]. Many countries also perform entry screening (eg, temperature, assessment for signs and symptoms). More detailed travel information is available on the WHO website.

In the United States, the CDC currently recommends that individuals avoid all nonessential international travel and nonessential travel from some domestic locations [139]. Because risk of travel changes rapidly, travelers should check United States government websites for possible restrictions.

Investigational approaches — Numerous vaccine candidates are being evaluated for prevention of COVID-19. The first vaccine to undergo preliminary study in humans in the United States uses a messenger RNA platform to result in expression of the viral spike protein in order to induce an immune response [140].

Clinical trials are also being conducted in the United States and elsewhere to evaluate the safety and efficacy of post-exposure drug prophylaxis against COVID-19 [141,142]. No agent is known to be effective in preventing infection; we suggest post-exposure prophylaxis not be attempted outside a clinical trial.

SPECIAL SITUATIONS

Pregnant and breastfeeding women — The approach to prevention, evaluation, diagnosis, and treatment of pregnant women with suspected COVID-19 is similar to that in nonpregnant individuals (as described above). The American College of Obstetricians and Gynecologists/Society of Maternal-Fetal Medicine has published online guidance for evaluation and care of pregnant women with suspected COVID-19 (available at acog.org and smfm.org). Other experts have published similar guidance.

Although severe sequelae of maternal infection have been reported, including one woman who was placed on extracorporeal membrane oxygenation (ECMO), there have been no maternal deaths [143], and there is an anecdotal report from Italy suggesting that few, if any, pregnant women have required mechanical ventilation. The risk of vertical transmission is unclear. In a review of 38 pregnant women with COVID-19, no cases of intrauterine transmission were documented [144]. Subsequently, at least four possible cases have been reported. One infant delivered by cesarean in a negative-pressure isolation room had elevated IgM and cytokine levels and an elevated white blood cell count but remained asymptomatic; five reverse-transcription polymerase chain reaction (RT-PCR) tests on nasopharyngeal swabs over time were negative [145]. Three other infants born by cesarean under strict infection control and prevention procedures had pneumonia within two days of birth, and nasopharyngeal and anal cultures were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [146]. Additional suspicious cases (elevated IgM in the newborn) continue to be reported [147]; however, positive IgM results alone are not definitive evidence of in utero infection [148].

Infected women appear to have an increased frequency of preterm labor and cesarean delivery for abnormal fetal heart rate tracings. This is likely related to severe maternal illness, but detailed reports are not available. Pregnancy and childbirth do not appear to aggravate the clinical course, and some mothers have recovered without undergoing delivery [149].

Cesarean delivery is performed for standard obstetric indications. Additional information on labor and delivery is available separately. (See "Management of normal labor and delivery", section on 'COVID-19'.)

The United States Centers for Disease Control and Prevention (CDC) has advised hospitals to consider temporarily separating (eg, in separate rooms) the mother with confirmed or suspected COVID-19 from her baby until the mother's transmission-based precautions are discontinued [150]. This is a shared decision between parents and health care providers. Additionally, infants born to mothers with confirmed COVID-19

should be considered a patient under investigation and appropriately isolated and evaluated [150,151]. (See 'Evaluation and diagnosis' above.)

For women with suspected or confirmed COVID-19 in the third trimester who recover and have no medical/obstetric indications for prompt delivery, it is reasonable to postpone planned cesarean delivery or induction of labor until a negative testing result is obtained or isolation status is lifted to minimize postnatal transmission to the neonate [152].

It is unknown whether the virus can be transmitted through breast milk. The only report of testing found no virus in the maternal milk of six patients [153]. However, droplet transmission could occur through close contact during breastfeeding. Thus, mothers with confirmed COVID-19 or symptomatic mothers with suspected COVID-19 should take precautions to prevent transmission to the infant during breastfeeding (including assiduous hand hygiene and use of a facemask) [83,151,154]. Alternatively, to minimize direct contact, the infant can be fed expressed breastmilk by another caregiver until the mother has recovered, provided that the other caregiver is healthy and follows hygiene precautions. In such cases, the mother should use strict hand washing before pumping and wear a mask during pumping. If possible, the pumping equipment should be thoroughly cleaned by a healthy person.

Women who choose not to breastfeed must take similar precautions to prevent transmission through close contact when formula is used.

COVID-19 testing not readily available — In some cases, testing for COVID-19 may not be accessible, particularly for individuals who have a compatible but mild illness that does not warrant hospitalization and do not have a known COVID-19 exposure or high-risk travel history.

In the United States, there is limited official guidance for this situation, and the approach may depend on the prevalence of COVID-19 in the area. If the clinician has sufficient concern for possible COVID-19 (eg, there is community transmission), it is reasonable to advise the patient to self-isolate at home (if hospitalization is not warranted) and alert the clinician about worsening symptoms. The optimal duration of home isolation in such cases is uncertain. A discussion of when home isolation can be discontinued in patients with confirmed COVID-19 can be found above. (See 'Home care' above.)

Managing chronic medications

Patients receiving ACE inhibitors/ARBs — Patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents. This approach is supported by multiple guideline panels [155-159].

There has been speculation that patients with COVID-19 who are receiving these agents may be at increased risk for adverse outcomes [160,161]. Angiotensin-converting enzyme 2 (ACE2) is a receptor for SARS-CoV-2 [162,163], and renin-angiotensin-aldosterone system inhibitors can increase ACE2 levels. Although patients with cardiovascular disease, hypertension, and diabetes may have a more severe clinical course in the setting of infection with SARS-CoV-2, there is no evidence to support an association with these agents. In addition, stopping these agents in some patients may exacerbate comorbid cardiovascular or kidney disease and lead to increased mortality [164].

Patients receiving immunomodulatory agents — Immunocompromised patients with COVID-19 are at increased risk for severe disease, and the decision to discontinue prednisone, biologics, or other

immunosuppressive drugs in the setting of infection must be determined on a case-by-case basis. (See 'Management' above.)

For individuals with underlying conditions who require treatment with these agents and are **without** evidence of COVID-19, there is no evidence that routinely discontinuing treatment is of any benefit. In addition, discontinuing these medications may result in loss of response when the agent is reintroduced. This approach is supported by statements from American and other dermatology, rheumatology, and gastroenterology societies [165-168].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Coronavirus disease 2019 (COVID-19)".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Coronavirus disease 2019 (COVID-19) (The Basics)")

SUMMARY AND RECOMMENDATIONS

- In late 2019, a novel coronavirus, now designated SARS-CoV-2, was identified as the cause of an outbreak of acute respiratory illness in Wuhan, a city in China. In February 2020, the World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019. (See 'Introduction' above.)
- Since the first reports of COVID-19, infection has spread to include more than 800,000 confirmed cases worldwide, prompting the WHO to declare a public health emergency in late January 2020 and characterize it as a pandemic in March 2020. (See 'Epidemiology' above.)
- The possibility of COVID-19 should be considered primarily in patients with fever and/or respiratory tract symptoms who reside in or have traveled to areas with community transmission or who have had recent close contact with a confirmed or suspected case of COVID-19. Clinicians should also be aware of the possibility of COVID-19 in patients with severe respiratory illness when no other etiology can be

identified. Limitations in testing capacity may preclude testing all patients with suspected infection; suggested priorities include hospitalized patients, symptomatic health care workers, and symptomatic individuals who have risk factors for severe disease (table 1). (See 'Clinical features' above and 'Evaluation and diagnosis' above.)

- In addition to testing for other respiratory pathogens, a nasopharyngeal swab specimen should be collected for reverse-transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. (See 'Evaluation and diagnosis' above.)
- Upon suspicion of COVID-19, infection control measures should be implemented and public health officials notified. In health care settings in the United States, the Centers for Disease Control and Prevention (CDC) recommends a single-occupancy room for patients and gown, gloves, eye protection, and a respirator (or facemask as an alternative) for health care personnel (figure 1 and figure 2). (See 'Infection control for suspected or confirmed cases' above.)
- Management consists of supportive care, although investigational approaches are being evaluated. Home management may be possible for patients with mild illness who can be adequately isolated in the outpatient setting. (See 'Management' above.)
- To reduce the risk of transmission in the community, individuals should be advised to wash hands diligently, practice respiratory hygiene (eg, cover their cough), and avoid crowds and close contact with ill individuals, if possible. Facemasks are not routinely recommended for asymptomatic individuals to prevent exposure in the community. Social distancing is advised, particularly in locations that have community transmission. (See 'Preventing exposure in the community' above.)
- Interim guidance has been issued by the WHO and by the CDC. These are updated on an ongoing basis. (See 'Society guideline links' above.)

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GRAPHICS

Suggested priorities for SARS-CoV-2 (COVID-19) testing

Priority	CDC guidance[1]	IDSA guidance[2]
First	▪ Hospitalized patients ▪ Symptomatic health care workers	▪ Critically ill patients receiving ICU-level care with unexplained viral pneumonia or respiratory failure (regardless of travel or exposure history) ▪ Any individual (including health care workers) with fever or features of a lower respiratory tract illness **and** close contact with patients with laboratory-confirmed COVID-19 within 14 days of symptom onset (including all residents of long-term care facilities with a confirmed case) ▪ Individuals with fever or features of a lower respiratory tract illness who are also immunosuppressed (including patients with HIV), older, or have underlying chronic health conditions ▪ Individuals with fever or features of a lower respiratory tract illness who are critical to the pandemic response, including health care workers, public health officials, and other essential leaders
Second	▪ Patients in long-term care facilities with symptoms ▪ Patients 65 years of age and older with symptoms ▪ Patients with underlying conditions with symptoms ▪ First responders with symptoms	▪ Non-ICU hospitalized patients and long-term care residents with unexplained fever and features of a lower respiratory tract illness*¶
Third	▪ Critical infrastructure workers with symptoms ▪ Individuals who do not meet any of the above categories with symptoms ▪ Health care workers and first responders without symptoms ▪ Individuals with mild symptoms in communities experiencing high COVID-19 hospitalizations	▪ Outpatients who meet criteria for influenza testing (eg, symptoms such as fever, cough, and other suggestive respiratory symptoms plus comorbid conditions, such as diabetes mellitus, chronic obstructive pulmonary disease, congestive heart failure, age >50 years, immunocompromising conditions); testing of outpatient pregnant women and symptomatic children with similar risk factors is also included in this priority level*
Fourth	▪ Individuals without symptoms (non-priority)	▪ Community surveillance as directed by public health and/or infectious diseases authorities

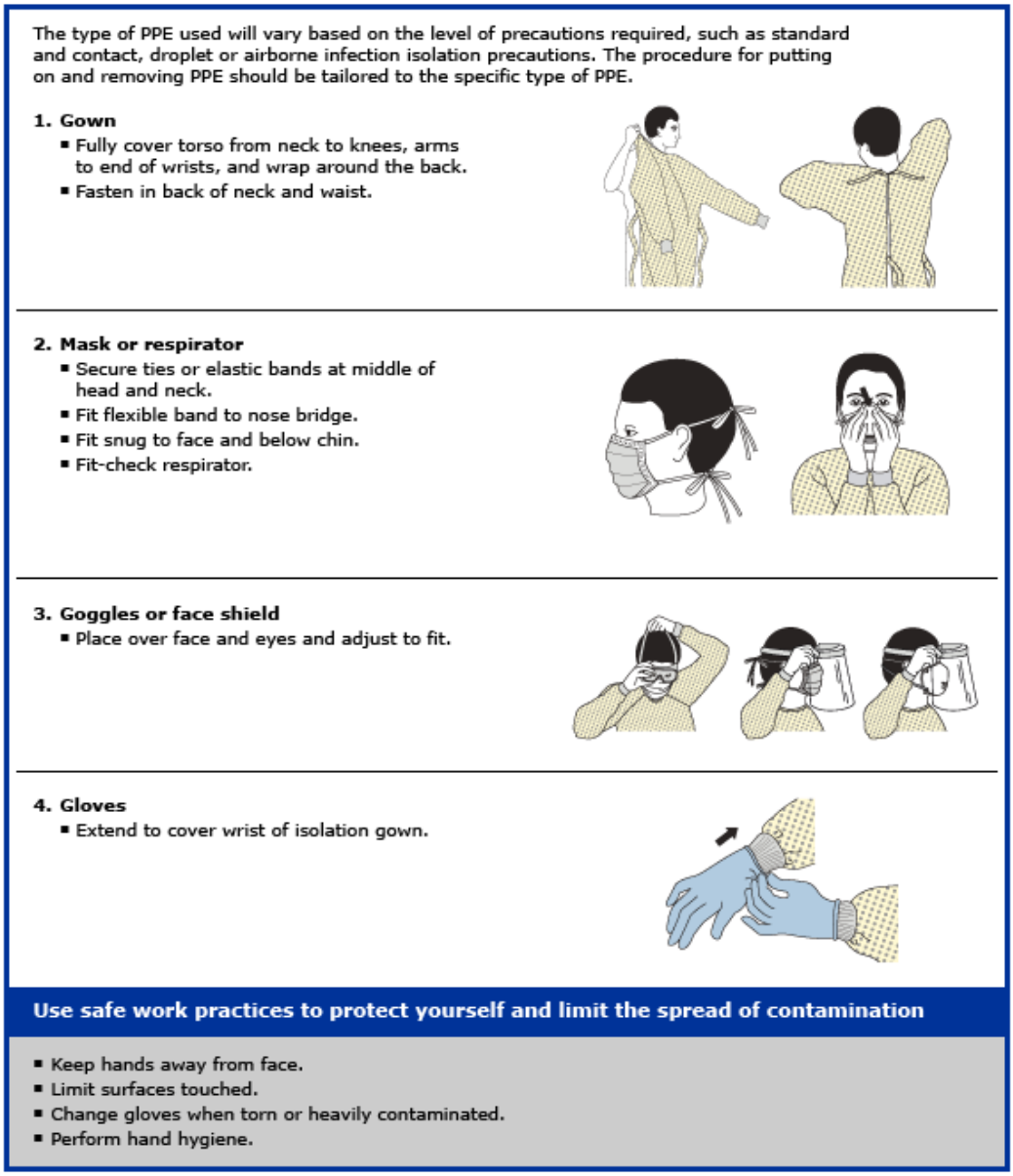
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; COVID-19: coronavirus disease 2019; CDC: United States Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; ICU: intensive care unit.
* The number of confirmed COVID-19 cases in the community should be considered.
¶ As testing becomes more widely available, routine testing of hospitalized patients may be important for infection prevention and management at discharge.

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Putting on personal protective equipment



Sequence for putting on personal protective equipment.

Reproduced from: Centers for Disease Control and Prevention. Protecting Healthcare Personnel: Sequence for Donning and Removing Personal Protective Equipment. Available at: https://www.cdc.gov/hai/prevent/ppe.html (Accessed on March 20, 2020).

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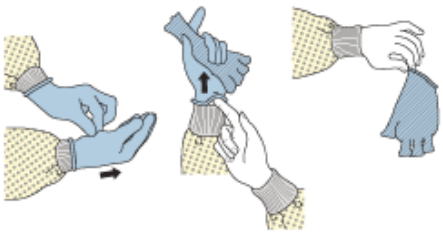
Taking off personal protective equipment

Example 1

There are a variety of ways to safely remove PPE without contaminating your clothing, skin, or mucous membranes with potentially infectious materials. Here is one example. **Remove all PPE before exiting the patient room** except a respirator, if worn. Remove the respirator **after** leaving the patient room and closing the door. Remove PPE in the following sequence:

1. Gloves

- Outside of gloves are contaminated!
- If your hands get contaminated during glove removal, immediately wash your hands or use an alcohol-based hand sanitizer.
- Using a gloved hand, grasp the palm area of the other gloved hand and peel off first glove.
- Hold removed glove in gloved hand.
- Slide fingers of ungloved hand under remaining glove at wrist and peel off second glove over first glove.
- Discard gloves in a waste container.



2. Goggles or face shield

- Outside of goggles or face shield are contaminated!
- If your hands get contaminated during goggle or face shield removal, immediately wash your hands or use an alcohol-based hand sanitizer.
- Remove goggles or face shield from the back by lifting head band or ear pieces.
- If the item is reusable, place in designated receptacle for reprocessing. Otherwise, discard in a waste container.



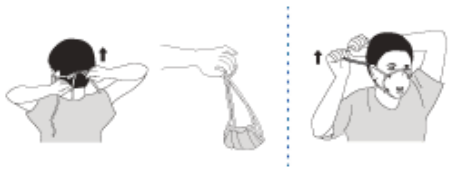
3. Gown

- Gown front and sleeves are contaminated!
- If your hands get contaminated during gown removal, immediately wash your hands or use an alcohol-based hand sanitizer.
- Unfasten gown ties, taking care that sleeves don't contact your body when reaching for ties.
- Pull gown away from neck and shoulders, touching inside of gown only.
- Turn gown inside out.
- Fold or roll into a bundle and discard in a waste container.

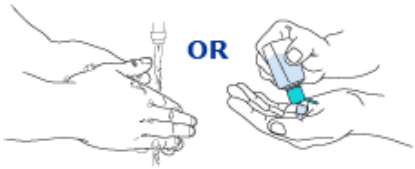


4. Mask or respirator

- Front of mask/respirator is contaminated. **DO NOT TOUCH!**
- If your hands get contaminated during mask/respirator removal, immediately wash your hands or use an alcohol-based hand sanitizer.
- Grasp bottom ties or elastics of the mask/respirator, then the ones at the top, and remove without touching the front.
- Discard in a waste container.



5. Wash hands or use an alcohol-based hand sanitizer immediately after removing all PPE



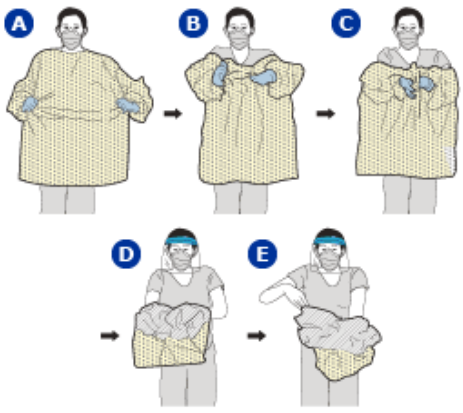
Perform hand hygiene between steps if hands become contaminated and immediately after removing all PPE

Example 2

Here is another way to safely remove PPE without contaminating your clothing, skin, or mucous membranes with potentially infectious materials. **Remove all PPE before exiting the patient room** except a respirator, if worn. Remove the respirator **after** leaving the patient room and closing the door. Remove PPE in the following sequence:

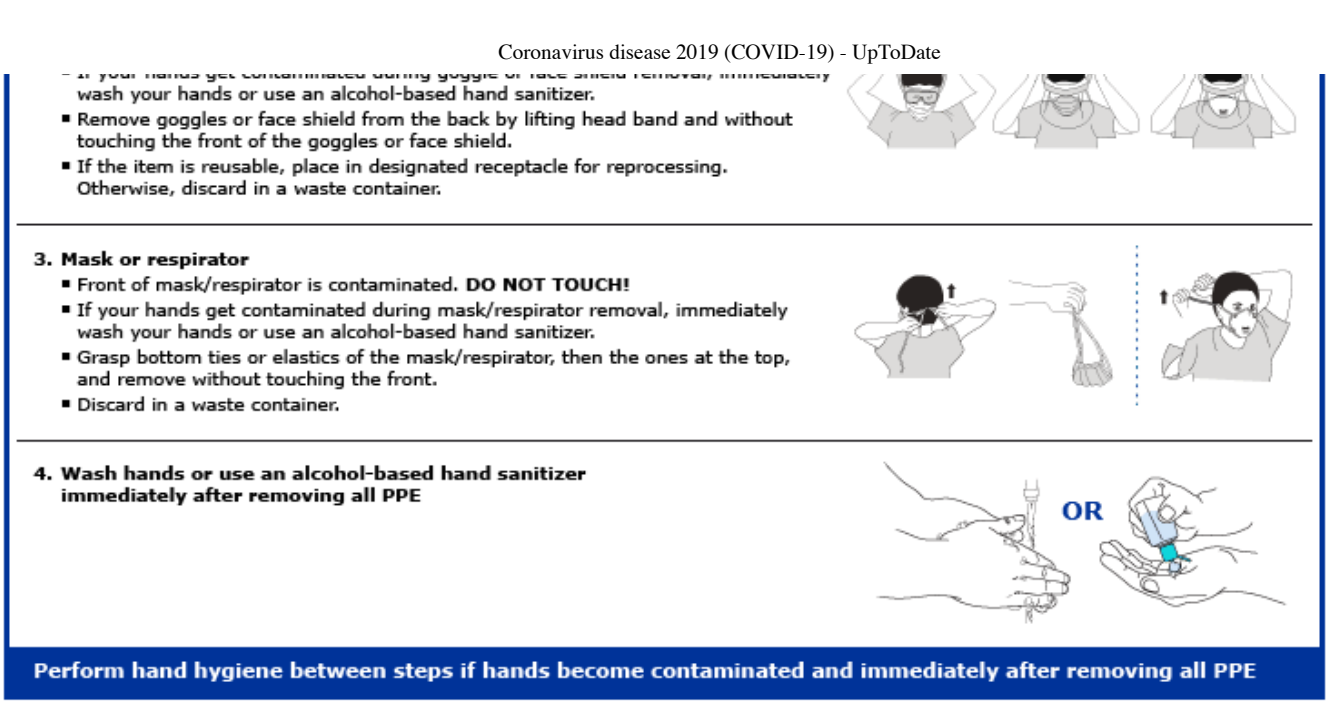
1. Gown and gloves

- Gown front and sleeves and the outside of gloves are contaminated!
- If your hands get contaminated during gown or glove removal, immediately wash your hands or use an alcohol-based hand sanitizer.
- Grasp the gown in the front and pull away from your body so that the ties break, touching outside of gown only with gloved hands.
- While removing the gown, fold or roll the gown inside-out into a bundle.
- As you are removing the gown, peel off your gloves at the same time, only touching the inside of the gloves and gown with your bare hands. Place the gown and gloves into a waste container.



2. Goggles or face shield

- Outside of goggles or face shield are contaminated!
- If your hands get contaminated during goggle or face shield removal, immediately



Reproduced from: Centers for Disease Control and Prevention. Protecting Healthcare Personnel: Sequence for Donning and Removing Personal Protective Equipment. Available at: https://www.cdc.gov/hai/prevent/ppe.html (Accessed on March 20, 2020).

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Kenneth McIntosh, MD Nothing to disclose **Martin S Hirsch, MD** Nothing to disclose **Allyson Bloom, MD** Nothing to disclose

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