CLINICAL PRACTICE

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Mild or Moderate Covid-19

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 73-year-old man with hypertension and chronic obstructive pulmonary disease reports that he has had fever, cough, and shortness of breath for 2 days. His medications include losartan and inhaled glucocorticoids. He lives alone. How should he be evaluated? If he has coronavirus disease 2019 (Covid-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), then how should he be treated?

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THE CLINICAL PROBLEM

Coronaviruses typically cause common cold symptoms, but two betacoronaviruses — SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) — can cause pneumonia, respiratory failure, and death. In late 2019, infection with a novel betacoronavirus, subsequently named SARS-CoV-2, was reported in people who had been exposed to a market in Wuhan, China, where live animals were sold. Since then, there has been rapid spread of the virus, leading to a global pandemic of Covid-19. Here, we discuss the presentation and management of Covid-19 in patients with mild or moderate illness, as well as prevention and control of the infection. Discussion of Covid-19 that occurs in children and during pregnancy and of severe disease is beyond the scope of this article.

STRATEGIES AND EVIDENCE

Coronaviruses are RNA viruses that are divided into four genera; alphacoronaviruses and betacoronaviruses are known to infect humans.[1] SARS-CoV-2 is related to bat coronaviruses and to SARS-CoV, the virus that causes SARS.[2] Similar to SARS-CoV, SARS-CoV-2 enters human cells through the angiotensin-converting–enzyme 2 (ACE2) receptor.[3] SARS-CoV-2 has RNA-dependent RNA polymerase and proteases, which are targets of drugs under investigation.

An audio version of this article is available at NEJM.org

TRANSMISSION

SARS-CoV-2 is primarily spread from person to person through respiratory particles, probably of varying sizes, which are released when an infected person coughs, sneezes, or speaks.[4] Because both smaller particles (aerosols) and larger particles (droplets) are concentrated within a few meters, the likelihood of transmission decreases with physical distancing and increased ventilation. Most SARS-

KEY CLINICAL POINTS

MILD OR MODERATE COVID-19

- Covid-19 has a range of clinical manifestations, including cough, fever, myalgias, gastrointestinal symptoms, and anosmia.
- Diagnosis of Covid-19 is commonly made through detection of SARS-CoV-2 RNA by PCR testing of a nasopharyngeal swab or other specimens, including saliva. Antigen tests are generally less sensitive than PCR tests but are less expensive and can be used at the point of care with rapid results.
- Evaluation and management of Covid-19 depend on the severity of the disease. Patients with mild disease usually recover at home, whereas patients with moderate disease should be monitored closely and sometimes hospitalized.
- Remdesivir and dexamethasone have demonstrated benefits in hospitalized patients with severe Covid-19, but in patients with moderate disease, dexamethasone is not efficacious (and may be harmful) and data are insufficient to recommend for or against routine use of remdesivir.
- Infection control efforts center on personal protective equipment for health care workers, social distancing, and testing.

CoV-2 infections are spread by respiratory-particle transmission within a short distance (when a person is <2 m from an infected person).[5,6] Aerosols can be generated during certain procedures (e.g., intubation or the use of nebulizers) but also occur with other activities and under special circumstances, such as talking, singing, or shouting indoors in poorly ventilated environments[7-10]; in these situations, transmission over longer distances may occur.[5,6] Because respiratory transmission is so prominent, masking and physical distancing markedly decrease the chance of transmission.[11] SARS-CoV-2 RNA has been detected in blood and stool, although fecal–oral spread has not been documented. An environmental and epidemiologic study of a small cluster of cases suggested the possibility of fecal aerosol–associated airborne transmission after toilet flushing, but this is likely to be rare.[12] Under laboratory conditions, SARS-CoV-2 may persist on cardboard, plastic, and stainless steel for days.[8,13] Contamination of inanimate surfaces has been proposed to play a role in transmission,[9] but its contribution is uncertain and may be relatively small.

A major challenge to containing the spread of SARS-CoV-2 is that asymptomatic and presymptomatic people are infectious.[14] Patients may be infectious 1 to 3 days before symptom onset, and up to 40 to 50% of cases may be attributable to transmission from asymptomatic or presymptomatic people.[7,15] Just before and soon after symptom onset, patients have high nasopharyngeal viral levels, which then fall over a period of 1 to 2 weeks.[16] Patients may have detectable SARS-CoV-2 RNA on polymerase-chain-reaction (PCR) tests for weeks to months, but studies that detect viable virus and contact-tracing assessments suggest that the duration of infectivity is much shorter; current expert recommendations support lifting isolation in most patients 10 days after symptom onset if fever has been absent for at least 24 hours (without the use of antipyretic agents) and other symptoms have decreased.[17-19]

CLINICAL MANIFESTATIONS

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness. Among patients who are symptomatic, the median incubation period is approximately 4 to 5 days, and 97.5% have symptoms within 11.5 days after infection.[20] Symptoms may include fever, cough, sore throat, malaise, and myalgias. Some patients have gastrointestinal symptoms, including anorexia, nausea, and diarrhea.[21,22] Anosmia and ageusia have been reported in up to 68% of patients and are more common in women than in men.[23] In some series of hospitalized patients, shortness of breath developed a median of 5 to 8 days after initial symptom onset[21,24]; its occurrence is suggestive of worsening disease.

Risk factors for complications of Covid-19 include older age, cardiovascular disease, chronic lung disease, diabetes, and obesity (Table 1).[24,26-29] It is unclear whether other conditions (e.g., uncontrolled human immunodeficiency virus infection or use of immunosuppressive medications) confer an increased risk of complications, but because these conditions may be associated with worse outcomes after infection with other

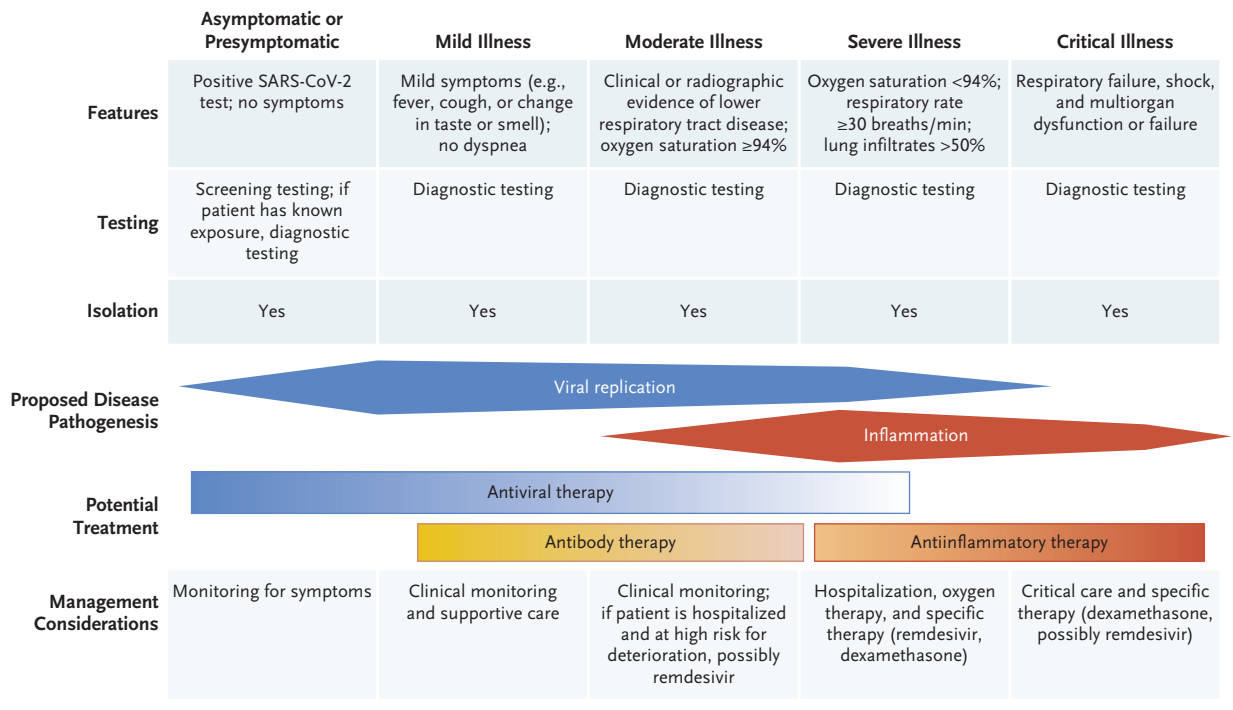

Figure 1. Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity.

Adapted from Gandhi.[41] According to the Centers for Disease Control and Prevention, "Diagnostic testing for SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] is intended to identify current infection in individuals and is performed when a person has signs or symptoms consistent with Covid-19, or when a person is asymptomatic but has recent known or suspected exposure to SARS-CoV-2. Screening testing for SARS-CoV-2 is intended to identify infected persons who are asymptomatic and without known or suspected exposure to SARS-CoV-2. Screening testing is performed to identify persons who may be contagious so that measures can be taken to prevent further transmission."[39]

respiratory pathogens, close monitoring of patients with Covid-19 who have these conditions is warranted.

Laboratory findings in hospitalized patients may include lymphopenia and elevated levels of D-dimer, lactate dehydrogenase, C-reactive protein, and ferritin. At presentation, the procalcitonin level is typically normal. Findings associated with poor outcomes include an increasing white-cell count with lymphopenia, prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, D-dimer, interleukin-6, C-reactive protein, and procalcitonin.[21,27,30-32] When abnormalities are present on imaging, typical findings are ground-glass opacifications or consolidation.[33]

DIAGNOSIS

Diagnostic testing to identify persons currently infected with SARS-CoV-2 usually involves the detection of SARS-CoV-2 nucleic acid by means of PCR assay. Just before and soon after symptom onset, the sensitivity of PCR testing of nasopharyngeal swabs is high.[34] If testing is negative in a person who is suspected to have Covid-19, then repeat testing is recommended.[35] The specificity of most SARS-CoV-2 PCR assays is nearly 100% as long as no cross-contamination occurs during specimen processing.

The Food and Drug Administration (FDA) has issued emergency use authorizations (EUAs) for commercial PCR assays validated for use with multiple specimen types, including nasopharyngeal, oropharyngeal, and mid-turbinate and anterior nares (nasal) swabs, as well as the most recently validated specimen type, saliva.[36] (A video demonstrating how to obtain a nasopharyngeal swab specimen is available at NEJM.org.) The FDA EUA allows patient collection of an anterior nares specimen with observation by a health

Table 1. Risk Factors for Severe Covid-19.*

Older age
Chronic obstructive pulmonary disease
Cardiovascular disease (e.g., heart failure, coronary artery disease, or cardiomyopathy)
Type 2 diabetes mellitus
Obesity (body-mass index, ≥30)
Sickle cell disease
Chronic kidney disease
Immunocompromised state from solid-organ transplantation
Cancer

* Data are adapted from the Centers for Disease Control and Prevention (CDC).[25] Of note, there has been a disproportionate burden of Covid-19 on racial and ethnic minorities and the poor. Studies indicate that the risk of severe disease increases with age. Male sex is not currently included on the CDC list of risk factors but has been noted in some reports to be associated with severe disease. Additional conditions that may confer an increased risk but for which the data are unclear include asthma (moderate to severe), cerebrovascular diseases, cystic fibrosis, hypertension, other immunocompromised states or use of immunosuppressive therapy, neurologic conditions such as dementia, liver disease, pregnancy, pulmonary fibrosis, smoking, thalassemia, and type 1 diabetes mellitus. The body-mass index is the weight in kilograms divided by the square of the height in meters.

care worker,[37] which can reduce exposures for health care workers. Patient collection at home with shipment to a laboratory has been shown to be safe and effective, but access is limited in the United States.[38] Testing of lower respiratory tract specimens may have higher sensitivity than testing of nasopharyngeal swabs.[16]

The FDA has also granted EUAs for rapid antigen testing to identify SARS-CoV-2 in a nasopharyngeal or nasal swab. Antigen tests are generally less sensitive than reverse-transcriptase–PCR tests but are less expensive and can be used at the point of care with results in 15 minutes. They may be particularly useful when rapid turnaround is critical, such as in high-risk congregate settings.[39]

In addition, EUAs have been issued for several serologic tests for SARS-CoV-2. The tests measure different immunoglobulins and detect antibodies against various viral antigens with the use of different analytic methods, so direct comparison of the tests is challenging. Anti–SARS-CoV-2 antibodies are detectable in the majority of patients 14 days or more after the development of symptoms.[40] Their use in diagnosis is generally reserved for people who are suspected to have Covid-19 but have negative PCR testing and in whom symptoms began at least 14 days earlier. Antibody testing after 2 weeks also may be considered when there is a clinical or epidemiologic reason for detecting past infection, such as serosurveillance. Because antibody levels may decrease over time and the correlates of immunity are not yet known, serologic test results cannot currently inform whether a person is protected against reinfection.[40]

EVALUATION

Evaluation of Covid-19 is guided by the severity of illness (Fig. 1). According to data from China, 81% of people with Covid-19 had mild or moderate disease (including people without pneumonia and people with mild pneumonia), 14% had severe disease, and 5% had critical illness.[42]

Patients who have mild signs and symptoms generally do not need additional evaluation. However, some patients who have mild symptoms initially will subsequently have precipitous clinical deterioration that occurs approximately 1 week after symptom onset.[24,26] In patients who have risk factors for severe disease (Table 1), close monitoring for clinical progression is warranted, with a low threshold for additional evaluation.

If new or worsening symptoms (e.g., dyspnea) develop in patients with initially mild illness, additional evaluation is warranted. Physical examination should be performed to assess for tachypnea, hypoxemia, and abnormal lung findings. In addition, testing for other pathogens (e.g., influenza virus, depending on the season, and other respiratory viruses) should be performed, if available, and chest imaging should be done.

Hallmarks of moderate disease are the presence of clinical or radiographic evidence of lower respiratory tract disease but with a blood oxygen saturation of 94% or higher while the patient is breathing ambient air. Indicators of severe disease are marked tachypnea (respiratory rate, ≥30 breaths per minute), hypoxemia (oxygen saturation, ≤93%; ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, <300), and lung infiltrates (>50% of the lung field involved within 24 to 48 hours).[42]

Laboratory testing in hospitalized patients should include a complete blood count and a comprehensive metabolic panel. In most instances, and especially if a medication that af-

fects the corrected QT (QTc) interval is considered, a baseline electrocardiogram should be obtained.

Chest radiography is usually the initial imaging method. Some centers also use lung ultrasonography. The American College of Radiology recommends against the use of computed tomography as a screening or initial imaging study to diagnose Covid-19, urging that it should be used "sparingly" and only in hospitalized patients when there are specific indications.[43]

Additional tests that are sometimes performed include coagulation studies (e.g., D-dimer measurement) and tests for inflammatory markers (e.g., C-reactive protein and ferritin), lactate dehydrogenase, creatine kinase, and procalcitonin.

MANAGEMENT OF COVID-19

Patients who have mild illness usually recover at home, with supportive care and isolation. It may be useful for people who are at high risk for complications to have a pulse oximeter to self-monitor the oxygen saturation.

Patients who have moderate disease should be monitored closely and sometimes hospitalized; those with severe disease should be hospitalized. If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is reasonable but should be stopped as soon as possible. Empirical treatment for influenza may be considered when seasonal influenza transmission is occurring until results of specific testing are known.

Treatment of Covid-19 depends on the stage and severity of disease (Fig. 1).[41] Because SARS-CoV-2 replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state and coagulopathy are thought to lead to clinical complications; in this stage, antiinflammatory medications, immunomodulators, anticoagulants, or a combination of these treatments may be more effective than antiviral agents. There are no approved treatments for Covid-19 but some medications have been shown to be beneficial.

Hydroxychloroquine and Chloroquine with or without Azithromycin

Chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV-2, perhaps by blocking endosomal transport.[44] Results from single-group observational studies and small randomized trials led to initial interest in hydroxychloroquine for the treatment of Covid-19, but subsequent randomized trials did not show a benefit. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial showed that, as compared with standard care, hydroxychloroquine did not decrease mortality among hospitalized patients.[45] In another randomized trial involving hospitalized patients with mild-to-moderate Covid-19, hydroxychloroquine with or without azithromycin did not improve clinical outcomes.[46] Moreover, no benefit was observed with hydroxychloroquine in randomized trials involving outpatients with Covid-19[47,48] or patients who had recent exposure to SARS-CoV-2 (with hydroxychloroquine used as postexposure prophylaxis).[49,50] Current guidelines recommend that hydroxychloroquine not be used outside clinical trials for the treatment of patients with Covid-19.[51,52]

Remdesivir

Remdesivir, an inhibitor of RNA-dependent RNA polymerase, has activity against SARS-CoV-2 in vitro[53] and in animals.[54] In the final report of the Adaptive Covid-19 Treatment Trial 1 (ACTT-1),[55] which involved hospitalized patients with evidence of lower respiratory tract infection, those randomly assigned to receive 10 days of intravenous remdesivir recovered more rapidly than those assigned to receive placebo (median recovery time, 10 vs. 15 days); mortality estimates by day 29 were 11.4% and 15.2%, respectively (hazard ratio, 0.73; 95% confidence interval, 0.52 to 1.03). In another trial, clinical outcomes with 5 days of remdesivir were similar to those with 10 days of remdesivir.[56] In an open-label, randomized trial involving hospitalized patients with moderate Covid-19 (with pulmonary infiltrates and an oxygen saturation of ≥94%), clinical status was better with 5 days of remdesivir (but not with 10 days of remdesivir) than with standard care, but the benefit was small and of uncertain clinical importance.[57] The FDA has issued an EUA for remdesivir for hospitalized patients with Covid-19.[58] Guidelines recommend remdesivir for the treatment of hospitalized patients with severe Covid-19 but consider data to be insufficient to recommend for or against the routine use of this drug for moderate disease.[51,52] Decisions about the use of remdesivir in hospitalized patients with moderate disease should be individualized

and based on judgment regarding the risk of clinical deterioration.

Convalescent Plasma and Monoclonal Antibodies

Small randomized trials of convalescent plasma obtained from people who have recovered from Covid-19 have not shown a clear benefit.[59] Data from patients with Covid-19 who were enrolled in a large expanded-access program for convalescent plasma in the United States suggested that mortality might be lower with receipt of plasma with a high titer of antibody than with receipt of plasma with a low titer of antibody; the data also suggested that mortality might be lower when plasma is given within 3 days after diagnosis than when plasma is given more than 3 days after diagnosis.[60,61] Interpretation of these data is complicated by the lack of an untreated control group and the possibility of confounding or a deleterious effect of receiving plasma with a low titer of antibody. The National Institutes of Health Covid-19 Treatment Guidelines Panel[51] and the FDA, which issued an EUA for convalescent plasma in August 2020,[60] emphasize that convalescent plasma is not the standard of care for the treatment of Covid-19. Ongoing randomized trials must be completed to determine the role of convalescent plasma.

Monoclonal antibodies directed against the SARS-CoV-2 spike protein are being evaluated in randomized trials as treatment for people with mild or moderate Covid-19 and as prophylaxis for household contacts of persons with Covid-19. Published data are not yet available to inform clinical practice.

Glucocorticoids

Because of concerns that a hyperinflammatory state may drive severe manifestations of Covid-19, immunomodulating therapies have been or are being investigated. In the RECOVERY trial, dexamethasone reduced mortality among hospitalized patients with Covid-19, but the benefit was limited to patients who received supplemental oxygen and was greatest among patients who underwent mechanical ventilation.[62] Dexamethasone did not improve outcomes, and may have caused harm, among patients who did not receive supplemental oxygen, and thus it is not recommended for the treatment of mild or moderate Covid-19.

USE OF CONCOMITANT MEDICATIONS IN PEOPLE WITH COVID-19

Because SARS-CoV-2 enters human cells through the ACE2 receptor,[3] questions were raised regarding whether the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) — which may increase ACE2 levels — might affect the course of Covid-19.[63] However, large observational studies have not shown an association with increased risk,[64] and patients who are receiving ACE inhibitors or ARBs for another indication should not stop taking these agents, even if they have Covid-19.[63,65] In addition, several authoritative organizations have noted the absence of clinical data to support a potential concern about the use of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with Covid-19,[66] and results from a cohort study were reassuring.[67]

INFECTION CONTROL AND PREVENTION

Health care workers must be protected from acquiring SARS-CoV-2 when they are providing clinical care (Table 2). Using telehealth when possible, reducing the number of health care workers who interact with infected patients, ensuring appropriate ventilation, and performing assiduous environmental cleaning are critical. Personal protective equipment (PPE) used while caring for patients with known or suspected Covid-19 should include, at a minimum, an isolation gown, gloves, a face mask, and eye protection (goggles or a face shield). The use of these droplet and contact precautions for the routine care of patients with Covid-19 appears to be effective[5,68] and is consistent with guidelines from the World Health Organization (WHO)[69]; however, the Centers for Disease Control and Prevention (CDC) prefers the use of a respirator (usually an N95 filtering facepiece respirator, a powered air-purifying respirator [PAPR] unit, or a contained air-purifying respirator [CAPR] unit) instead of a face mask[70] but considers face masks to be acceptable where there are supply shortages. The CDC and WHO recommend the use of enhanced protection for aerosol-generating procedures, including the use of a respirator and an airborne infection isolation room. At sites where enhanced protection is not available, the use of nebulizers and other aerosol-generating procedures should be avoided, when possible. In the context of the ongoing pandemic, the possibility of transmission in the absence of symp-

Table 2. SARS-CoV-2 Transmission According to Stage of Infection.

Stage of Infection*	RNA Detectable in Respiratory Samples, Blood, and Feces	Viable Virus Detectable in Respiratory Samples	Transmission Can Occur	Mechanism of Transmission†						Minimum Recommended Level of Precautions
				Droplet	Natural Aerosol	Aerosol-Generating Procedure	Direct Contact	Indirect Contact	Enteric Route	
Presymptomatic or asymptomatic‡	Yes	Yes	Yes§	Yes	Strongly suspected	Strongly suspected	Suspected	Suspected	Unknown	Protection from droplet and contact transmission during routine care Protection from airborne and contact transmission during aerosol-generating procedure
Symptomatic	Yes	Yes	Yes	Yes	Yes	Yes	Strongly suspected	Suspected	Unknown	Protection from droplet and contact transmission during routine care Protection from airborne and contact transmission during aerosol-generating procedure
Post–acute symptomatic	Yes, often prolonged	No	No	No	No	No	No	No	No	Accordance with updated standard precautions, including use of eye protection (goggles or face shield) and medical mask

* The incubation period of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), from exposure to symptom onset, ranges from 2 to 14 days. The infectious dose is unknown. The presymptomatic stage occurs 1 to 3 days (or possibly longer) before symptom onset. In immunocompetent people with mild-to-moderate Covid-19, the post–acute symptomatic stage occurs 10 days after symptom onset and at least 1 day after the resolution of fever and a decrease in respiratory symptoms.

† In transmission by droplet, large (≥5 μm) respiratory particles that are released by coughing, sneezing, or speaking land on surfaces or mucosal membranes. In transmission by natural aerosol, small (<5 μm) respiratory particles that are generated by human activities (e.g., singing) are inhaled; this does not necessarily indicate long-distance airborne transmission. In transmission by an aerosol-generating procedure, small respiratory particles that are generated by clinical procedures (e.g., intubation, extubation, use of nebulizers, or bronchoalveolar lavage) are inhaled; this does not necessarily indicate long-distance airborne transmission. In transmission by direct contact, the virus is transferred by body-surface contact. In transmission by indirect contact, the virus is transferred from a contaminated surface to a mucosal surface (e.g., eyes, nose, or mouth). In enteric transmission, the virus is transferred by the fecal–oral route; SARS-CoV-2 RNA has been detected in stool but fecal–oral spread has not been documented.

‡ Testing of patients without symptoms may be performed for close contacts of a person with documented SARS-CoV-2 infection, for preoperative screening, during pregnancy at the time of delivery, when they are unable to provide a medical or exposure history, when they live in a high-risk setting (e.g., congregate settings, including long-term care facilities), or during community surveillance activities.

§ This information is based on case reports or case series.

toms supports the universal use of masks and eye protection for all patient encounters.[7,71]

Strategies to facilitate infection prevention and control are needed for people with unstable housing or people who live in crowded facilities or congregate settings, where physical distancing is inconsistent or impossible (e.g., dormitories, jails, prisons, detention centers, long-term care facilities, and behavioral health facilities).

AREAS OF UNCERTAINTY

Many uncertainties remain in our understanding of the spread of Covid-19 and its management. More data are needed to establish the standard of care for patients with mild or moderate disease and to evaluate potential strategies to reduce the risk of infection in exposed persons; numerous clinical trials are registered and ongoing. Studies are under way to develop an effective vaccine; several candidates have been shown to boost immune responses, and large trials are under way to assess their safety and efficacy in preventing Covid-19. It is unknown whether infection confers immunity (and, if so, for how long) and whether results of serologic testing can be used to inform when health care workers and others can safely return to work.

GUIDELINES IN A RAPIDLY CHANGING PANDEMIC

Many professional organizations have developed guidelines for the management and prevention of Covid-19 (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette is at high risk for having Covid-19 with potential complications. Given his dyspnea and risk factors for severe illness, we would refer him for SARS-CoV-2 PCR testing of a nasopharyngeal swab, along with an examination and chest radiography. At a health care facility, he should wear a surgical mask and be promptly escorted to an examination room. He should be assessed for hypoxemia, which, if present, would prompt admission and specific therapies. We would continue his treatment with an ARB and inhaled glucocorticoids. In accordance with current guidelines, we would advise that he remain isolated for 10 days after symptom onset and until he has had resolution of fever for at least 24 hours (without the use of antipyretics) and alleviation of other symptoms.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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