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 calls to report that he has had a fever (maximal temperature, 38.3°C) and a dry cough for the past 2 days. He notes that his shortness of breath has worsened. 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-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) — can cause severe 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 seafood 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-1, the virus that causes severe acute respiratory syndrome (SARS).[2] Similar to SARS-CoV-1, 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.

TRANSMISSION

SARS-CoV-2 is primarily spread from person to person through respiratory droplets, which are typically released when an infected person coughs or sneezes. Because droplets usually fall within a few meters, the likelihood of transmission is decreased if people remain at least 2 m apart. Transmission is thought not to normally occur through the inhalation of aerosols (virions suspended in air), but there are concerns that the virus may be aerosolized during certain activities (e.g., singing)[4] or pro-

KEY CLINICAL POINTS

MILD OR MODERATE COVID-19

- Covid-19 (the illness caused by SARS-CoV-2) has a range of clinical manifestations, including cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia.
- Diagnosis of Covid-19 is usually based on detection of SARS-CoV-2 by PCR testing of a nasopharyngeal swab or other specimen.
- Evaluation and management of Covid-19 depends on the severity of the disease; patients with mild disease typically recover at home.
- Patients with moderate or severe Covid-19 are usually hospitalized for observation and supportive care.
- There are no proven therapies for Covid-19; thus, referral of patients to clinical trials is critical.
- Infection control and prevention efforts center on personal protective equipment for health care workers, social distancing, and testing.

cedures (e.g., intubation or the use of nebulizers) and that it may linger in aerosols for more than 3 hours.[5] SARS-CoV-2 RNA has been detected in blood and stool, although fecal–oral spread has not been documented. SARS-CoV-2 may persist on cardboard, plastic, and stainless steel for days.[5,6] As a result, contamination of inanimate surfaces may play a role in transmission.[4,7]

A major challenge to containing the spread of SARS-CoV-2 is that presymptomatic people are infectious.[8] Recent reports suggest that patients may be infectious 1 to 3 days before symptom onset and that up to 40 to 50% of cases may be attributable to transmission from asymptomatic or presymptomatic people.[4,9] Just before or soon after symptom onset, patients have high nasopharyngeal viral levels, which then fall over the course of approximately 1 week.[10] Patients with severe disease may shed the virus for longer periods, although the duration of infectious viral shedding is unclear.[11]

CLINICAL MANIFESTATIONS

The median incubation period, from exposure to symptom onset, is approximately 4 to 5 days, and 97.5% of patients who are symptomatic will have symptoms within 11.5 days after infection.[12] Symptoms may include fever, cough, sore throat, malaise, and myalgias. Some patients have gastrointestinal symptoms, including anorexia, nausea, and diarrhea.[13,14] Anosmia and ageusia have also been reported.[15,16] In some series of hospitalized patients, shortness of breath developed a median of 5 to 8 days after initial symptom onset[13,17]; its occurrence is suggestive of worsening disease.

Risk factors for complications of Covid-19 include older age (e.g., >65 years), cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity.[17-21] It is unclear whether certain other conditions (kidney disease, immunosuppression, cancer, and uncontrolled human immunodeficiency virus [HIV] infection) confer an increased risk of complications, but because these conditions may be associated with worse outcomes after infection with other 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 in some series include an increasing white-cell count with lymphopenia, a prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, D-dimer, interleukin-6, C-reactive protein, and procalcitonin.[13,19,22-24] When abnormalities are present on imaging, the typical findings are ground-glass opacifications or consolidation.[25]

DIAGNOSIS

The diagnosis of Covid-19 is usually based on the detection of SARS-CoV-2 by means of polymerase-chain-reaction (PCR) assay.[26] Soon after symptom onset, the sensitivity of PCR testing of nasopharyngeal swabs appears to be high, but false negatives may occur, with uncertain frequency. If a person is suspected to have Covid-19 but has negative testing of a nasopharyngeal swab, repeat testing is prudent, especially if that person lives in an area with active community transmission.[27]

The type of specimen that is collected depends on which specimens have been validated for use with the specific PCR test. Most PCR assays used in the United States can test nasopharyngeal

Table 1. Established and Potential Risk Factors for Severe Covid-19.*

Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease

* Data are adapted from the Centers for Disease Control and Prevention (CDC). Some of these risk factors are established. Others (e.g., immunocompromise or human immunodeficiency virus infection with a CD4 cell count of <200 per microliter or uncontrolled viremia) are conditions that confer an increased risk of complications from infection with other respiratory pathogens, but their effect on coronavirus disease 2019 (Covid-19) is not yet known. 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.

† Immunocompromise includes human immunodeficiency virus infection with a CD4 cell count of less than 200 per microliter or uncontrolled viremia, prolonged use of glucocorticoids or other immunomodulating medications, a history of bone marrow or organ transplantation, and a history of smoking.

swabs. (A video demonstrating how to obtain a nasopharyngeal swab specimen is available at NEJM.org.) However, laboratories are increasingly able to test sputum and lower respiratory tract specimens. Sputum samples (or endotracheal aspirates from intubated patients) may be easier to obtain in some settings, and testing of sputum may be more sensitive than testing of a nasopharyngeal swab.[28] Sputum induction is contraindicated because of concerns about aerosolization. There are limited data regarding the use of oropharyngeal swabs; in one study, testing of these swabs was less sensitive than testing of nasopharyngeal swabs, particularly later in the disease course.[29] If a nasopharyngeal swab cannot be obtained (e.g., because of supply shortages), the Centers for Disease Control and Prevention (CDC) recommends the use of an oropharyngeal swab.[30] The Food and Drug Administration (FDA) recently recognized on-site self-collection of an anterior nares specimen as an acceptable method of collection[31]; this option may facilitate home-based testing and reduce exposures for health care workers.

EVALUATION

Evaluation and management of Covid-19 is guided by the severity of the illness. According to initial 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.[32]

Patients who have mild signs and symptoms generally do not need additional evaluation, and depending on the risk profile, they may not even need to undergo Covid-19 testing, since the infection will usually resolve. However, some patients who have mild symptoms initially will subsequently have precipitous clinical deterioration that occurs approximately 1 week after symptom onset.[17,18] 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. A 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 considered.

If findings on the initial assessment are suggestive of moderate or severe illness, hospitalization is generally warranted. Patients with moderate disease may have dyspnea, but the blood oxygen saturation is usually at least 94% 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).[32]

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 affects 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 (CT) 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.[33]

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. The prognostic value and clinical utility of the results of these and other tests remain uncertain.

MANAGEMENT OF MILD OR MODERATE COVID-19

Patients who have mild illness usually recover at home, with supportive care and isolation in accordance with guidelines.[34] 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 or severe disease are usually monitored in the hospital. If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is a reasonable option but should be stopped as soon as possible. Empirical treatment for influenza may be considered during the period when seasonal influenza transmission is occurring, until results of specific testing are known.

There are no approved treatments for Covid-19; thus, people with Covid-19 should be referred to clinical trials. Several agents have been touted as treatments for Covid-19, but at this point, the data are insufficient to inform a recommendation for or against the use of these agents outside of clinical trials; well-conducted randomized trials will be critical in determining how Covid-19 should be treated.

Hydroxychloroquine and Chloroquine with or without Azithromycin

Chloroquine and hydroxychloroquine have in vitro activity against SARS-CoV-2, perhaps by blocking endosomal transport.[35] Hydroxychloroquine also has antiinflammatory effects. Chloroquine is recommended in China for the treatment of Covid-19, but high-quality data are lacking to show whether it or hydroxychloroquine is safe and effective for this indication. A small open-label, nonrandomized study from France showed a higher rate of SARS-CoV-2 clearance by day 6 in 14 patients who were treated with hydroxychloroquine than in patients who declined to participate in the study or were at a different clinic. The effects appeared to be greater in the 6 patients who were receiving hydroxychloroquine combined with azithromycin; 6 patients in the hydroxychloroquine group were excluded from the analysis, a factor that potentially biases the results.[36] A case series showed high rates of viral clearance and clinical improvement in patients treated with hydroxychloroquine plus azithromycin.[37] However, both studies had substantial methodologic limitations, including a lack of adequate comparison groups.

A small randomized trial showed no significant difference in SARS-CoV-2 clearance or the disease course between the hydroxychloroquine group and the control group.[38] Results from additional studies are currently available as non–peer-reviewed preprints. One small trial,[39] for which important details are not yet available, showed a modest improvement in the group that received hydroxychloroquine, as compared with a control group, whereas other studies did not show increased viral clearance or clinical benefit with hydroxychloroquine.[40,41] Study limitations preclude definitive conclusions. Safety concerns with hydroxychloroquine and azithromycin include the potential for QTc prolongation, which is greater when both agents are used together. A study in which patients received high-dose chloroquine was stopped because of a trend toward excessively high mortality.[42]

Determination of the role of hydroxychloroquine with or without azithromycin for the treatment of Covid-19 hinges on the results of well-conducted clinical trials. The FDA has issued an Emergency Use Authorization (EUA) for the use of chloroquine and hydroxychloroquine from the strategic national stockpile for the treatment of hospitalized adults with Covid-19, but this action does not constitute FDA approval of these agents for this indication. The EUA encourages the conduct of and participation in randomized, controlled trials to provide evidence for the effectiveness of these drugs for the treatment of Covid-19.

Lopinavir–Ritonavir

Lopinavir–ritonavir, an HIV-1 protease inhibitor, has been proposed as a treatment, but it is not known whether drug levels adequate to inhibit the SARS-CoV-2 protease can be reliably achieved

in people with Covid-19 who receive this medication. In an open-label, randomized trial involving 199 hospitalized patients, the addition of lopinavir–ritonavir to standard care did not result in faster clinical improvement or brisker drops in SARS-CoV-2 RNA levels.[43] At this time, most experts advise against the use of lopinavir–ritonavir or any other HIV-1 protease inhibitor for the treatment of Covid-19 outside of clinical trials. In addition, people with HIV-1 should be discouraged from changing their antiretroviral regimen to one that includes an HIV-1 protease inhibitor, given the lack of data supporting the use of such drugs for the treatment or prevention of Covid-19.

Remdesivir

Remdesivir, an inhibitor of RNA-dependent RNA polymerase, has had activity against SARS-CoV-2 in vitro[44] and against other coronaviruses in several animal models.[45-47] In a case series involving patients with severe Covid-19 who received remdesivir through a compassionate-use program, the majority of patients had a decrease in the need for oxygen support, but there was no comparison group.[48] Results of ongoing phase 3, randomized, controlled trials are anticipated.

Immunomodulation

Because of concerns that a hyperinflammatory state may drive many of the severe manifestations of Covid-19, several immunomodulating therapies — including glucocorticoids, convalescent plasma, and anticytokine therapy — are under investigation, largely in patients with severe disease. Discussion of these agents is beyond the scope of this article.

USE OF CONCOMITANT MEDICATIONS IN PEOPLE WITH COVID-19

Because SARS-CoV-2 enters human cells through the ACE2 receptor,[3] questions have been raised regarding whether the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) — which may increase ACE2 levels — might increase the acquisition of SARS-CoV-2 or the severity of Covid-19.[49] However, given the absence of definitive clinical data, the current recommendation is that patients who are receiving ACE inhibitors or ARBs for another indication (e.g., hypertension or heart failure) should not stop taking these agents routinely, even if they have Covid-19.[49,50] Some reports have suggested a possible deleterious effect of nonsteroidal antiinflammatory drugs on the course of Covid-19, but several authoritative organizations have noted the absence of clinical data to support this concern.[51-53] Concerns have also been raised about the use of glucocorticoids, and some guidelines suggest that they should not be used in patients with Covid-19 pneumonia.[54] The use of systemic or inhaled glucocorticoids should not be stopped in patients who are taking them for other indications.[54]

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, and performing health care environmental cleaning are critical. Personal protective equipment (PPE) should include, at a minimum, an isolation gown, gloves, a face mask, and eye protection (goggles or a face shield). Although the use of droplet-contact precautions (a gown, gloves, a face mask, and eye protection) for the routine care of patients with Covid-19 is consistent with guidelines from other countries and the World Health Organization (WHO),[55-58] the 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.[59] However, in the context of supply shortages, the CDC regards the use of face masks as an acceptable alternative. The CDC and the WHO both 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. Recent studies indicating that transmission occurs before symptom onset may support universal droplet-contact precautions for all initial patient encounters.[4,60-63]

Strategies to facilitate infection prevention and control are needed for people with unstable housing and people who live in congregate settings, where physical distancing is inconsistent or impossible (e.g., dormitories, jails, prisons,

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‡	Yes	Yes	Yes§	Yes	Suspected	Suspected	Suspected	Suspected	Unknown	Eye protection (goggles or face shield) Protection from droplet and contact transmission during routine care Protection from airborne and contact transmission during aerosol-generating procedure
Symptomatic	Yes	Yes	Yes	Yes	Suspected	Yes	Strongly suspected	Strongly suspected	Unknown	Eye protection (goggles or face shield) Protection from droplet and contact transmission during routine care Protection from airborne and contact transmission during aerosol-generating procedure
Postsymptomatic	Yes for limited time, occasionally prolonged	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	None

* 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 possibility that people who remain asymptomatic throughout infection can transmit the virus remains a topic of debate. The presymptomatic stage occurs 1 to 3 days (or possibly longer) before symptom onset. The postsymptomatic stage occurs a minimum of 7 days after symptom onset and at least 3 days after the resolution of fever and improvement 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 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.

detention centers, long-term care facilities, and behavioral health facilities).

AREAS OF UNCERTAINTY

Numerous uncertainties remain in our understanding of the spread of Covid-19 and its management. The contribution of transmission from asymptomatic and presymptomatic people to the community and nosocomial spread of SARS-CoV-2, and the extent to which fomites and aerosols (those not generated by medical procedures) contribute to transmission, are unclear. Data to inform treatment remain limited. Trials are in progress to assess the effects of various medications — such as hydroxychloroquine with or without azithromycin, remdesivir, and favipiravir (which has anti-influenza activity)[64] — on the disease course in patients with different severities of illness, as well as to evaluate hydroxychloroquine as prophylaxis in high-risk or exposed people. Studies are under way to develop an effective vaccine. It is unknown whether infection confers partial or complete 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 interim guidelines for the management and prevention of Covid-19 (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Guidelines from the Infectious Diseases Society of America[54] and the National Institutes of Health[65] highlight the fact that there are no proven therapies for Covid-19 and that randomized trials are critical.

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 PCR testing of a nasopharyngeal swab for SARS-CoV-2, along with an examination and chest radiography. He should be advised to wear a mask en route; after arrival at a health care facility, he would be given a surgical mask and promptly escorted to an examination room. Admission would be warranted for close monitoring given his dyspnea and increased risk. On the basis of the limited available data, we would continue his ARB and inhaled glucocorticoids. In the absence of high-quality data to support any Covid-19–specific therapy, we would recommend enrollment in a randomized clinical trial, if possible. When the patient's condition improves sufficiently for discharge, he should be advised to remain isolated for a minimum of 7 days after symptom onset and for at least 3 days after resolution of fever and improvement in respiratory symptoms. There may be additional local guidance regarding the duration of isolation.

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