Outpatient Management of COVID-19: Rapid Evidence Review

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Common presenting symptoms of coronavirus disease 2019 include fever, dry cough, shortness of breath, and fatigue. However, patients may have a wide range of symptoms representing a spectrum of mild to severe illness. Symptoms in children tend to be milder and may include fever, cough, and feeding difficulty. The incubation period is two to 14 days, although symptoms typically appear within five days of exposure. Multiple testing modalities exist, but infection should be confirmed by polymerase chain reaction testing using a nasopharyngeal swab. There are no evidence-based treatments appropriate for use in the outpatient setting; management is supportive and should include education about isolation. In hospitalized patients, remdesivir should be considered to reduce time to recovery, and low-dose dexamethasone should be considered in patients who require supplemental oxygen. Overall, 85% of patients have mild illness, whereas 14% have severe disease requiring hospitalization, including 5% who require admission to an intensive care unit. Predictors of severe disease include increasing age, comorbidities, lymphopenia, neutrophilia, leukocytosis, low oxygen saturation, and increased levels of C-reactive protein, D-dimer, transaminases, and lactate dehydrogenase. (*Am Fam Physician*. 2020;102(8):478-486. Copyright © 2020 American Academy of Family Physicians.)

The coronavirus disease 2019 (COVID-19) pandemic is caused by an enveloped single-stranded RNA novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were reported in Wuhan City, China, in December 2019; the United States confirmed its first cases one month later. Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome, also caused by coronaviruses, have caused significantly lower global mortality.

Epidemiology

• The basic reproductive number (infections per index case) of COVID-19 is unknown. One systematic review estimated a range of 1.9 to 6.5.[1]

• Studies in the United States and Switzerland based on antibody sampling estimated seroprevalence between 1.1% and 10.9%.[2]

• Pathogenic factors contributing to the virulence of SARS-CoV-2 include transmissibility via respiratory droplets and asymptomatic spread via healthy-appearing individuals.

• The true incidence of COVID-19 in the United States is unknown and varies geographically.[3]

• It is estimated that only one in approximately 80 COVID-19 infections was diagnosed in March 2020, and there is promise in disease modeling that extrapolates from influenza-like illness.[4]

Screening and Prevention

• Physical distancing of at least 6 ft (1.8 m) slows the spread of infection by decreasing the mean number of people infected per case, particularly when combined with other measures such as mask wearing in public, school closures, and travel restrictions.[5,6]

• Contact tracing has reduced the spread of infection early during outbreaks in some countries.[7]

• The Centers for Disease Control and Prevention (CDC) recommends that close contacts of a person with COVID-19 quarantine for 14 days after the last exposure and monitor for fever and other symptoms daily.[8] People suspected of having COVID-19 should isolate within their home to prevent infection spread, stay in a specific "sick room" if they live with others, and use a separate bathroom, if possible.[8]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
Close contacts of patients with COVID-19 should quarantine for 14 days with daily monitoring for fever and other symptoms.[8]	C	Expert opinion based on disease modeling
Telehealth can be used for initial triage of patients with respiratory symptoms of COVID-19; further care should be based on vital signs, physical examination findings, social considerations, and risk factors.[11,17]	C	Expert opinion in the absence of clinical trials
Infection with severe acute respiratory syndrome coronavirus 2 should be confirmed by polymerase chain reaction testing using a nasopharyngeal swab.[38]	C	Expert opinion and cross-sectional studies of diagnostic accuracy
Management of COVID-19 in the outpatient setting is focused on supportive care and reducing the risk of transmission via isolating at home.[41]	C	Expert opinion
Dexamethasone, 6 mg per day for 10 days, reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen (NNT = 29) and mechanical ventilation (NNT = 9), but not in hospitalized patients or outpatients who do not require supplemental oxygen.[46]	B	Well-designed RCT
Remdesivir (Veklury) shortens time to recovery in hospitalized patients with COVID-19 but has not been proven to reduce mortality.[48,49]	B	Two RCTs, one of which was positive and one of which was negative but underpowered

COVID-19 = coronavirus disease 2019; NNT = number needed to treat; RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; **B** = inconsistent or limited-quality patient-oriented evidence; **C** = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

TABLE 1

Recommended Personal Protective Equipment for Clinicians Providing Direct Care to Patients with Coronavirus Disease 2019

Scenario	Equipment
Patient without respiratory symptoms	Standard precautions, surgical masks, and eye protection
Patient with respiratory symptoms	Surgical mask, gown, gloves, and eye protection
Collection of nasal swab in patient with suspected or confirmed infection*	N95 or higher-level respirator (or surgical mask if respirator is not available), eye protection, gloves
Non–aerosol-generating procedure	Surgical mask, face shield, gown, and gloves[14]
Aerosol-generating procedure†	N95 or powered air-purifying respirator, eye protection, isolation gown, gloves

*—Institutional guidelines vary. See reference 11 for more information. If respirators are not readily available, they should be prioritized for use during other procedures with higher risk of producing infectious aerosols.
†—Any medical procedure that can convert a physical substance into particles small and light enough to be carried by air, such as nebulizer treatment, cardiopulmonary resuscitation, high-flow nasal oxygen, sputum induction, chest physiotherapy, bilevel or continuous positive airway pressure, endotracheal intubation, airway suction, high-frequency oscillatory ventilation, tracheostomy, or bronchoscopy.
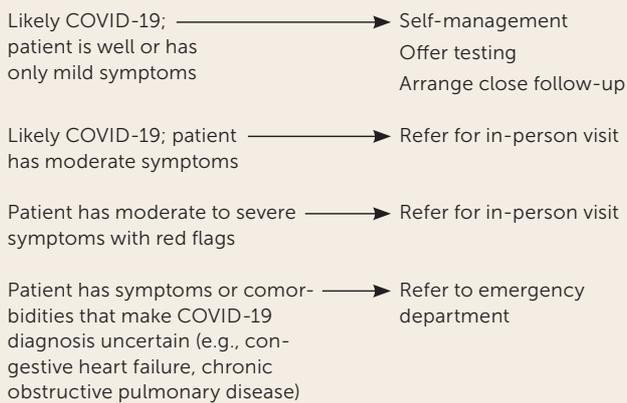
Information from references 11-14.

- The CDC recommends wearing face masks when in a public space where appropriate physical distancing may be difficult.[9] This practice may reduce viral transmission (Howard J, et al., and Kai D, et al., unpublished data, 2020), particularly from asymptomatic or presymptomatic individuals.[10]
- Patients with respiratory symptoms should wear a surgical mask in health care settings. Those without respiratory symptoms should wear a cloth face mask per CDC recommendations.
- *Table 1* lists recommended personal protective equipment for clinicians based on different clinical scenarios.[11-14]
- A vaccine for SARS-CoV-2 has not yet been deployed, but more than 100 are in development and 36 are in clinical evaluation.[15] Although other vaccines do not protect against SARS-CoV-2 infection, routine vaccinations are still recommended.[16]

Diagnosis

- The diagnosis of COVID-19 is made clinically and is supported by laboratory results and radiographic findings. COVID-19 should be suspected in patients with known or suspected exposure within the past 14 days, or in the setting of active SARS-CoV-2 transmission in the community.

Likely COVID-19; patient is well or has only mild symptoms → Self-management / Offer testing / Arrange close follow-up

Likely COVID-19; patient has moderate symptoms → Refer for in-person visit

Patient has moderate to severe symptoms with red flags → Refer for in-person visit

Patient has symptoms or comorbidities that make COVID-19 diagnosis uncertain (e.g., congestive heart failure, chronic obstructive pulmonary disease) → Refer to emergency department

Red flag symptoms of COVID-19:
- Blue lips or face
- Cold, clammy, or pale and mottled skin
- Coughing up blood
- Difficult to arouse
- Heart rate > 110 beats per minute
- Little or no urine output
- New confusion
- Nonblanching rash
- Oxygen saturation < 93%
- Respiratory rate > 22 breaths per minute
- Severe pain or pressure in chest
- Severe shortness of breath at rest
- Systolic blood pressure < 100 mm Hg

COVID-19 = coronavirus disease 2019.

Algorithm for telehealth triage of patients with diagnosed or suspected COVID-19.

Information from reference 17.

TABLE 2

Signs and Symptoms of Coronavirus Disease 2019

Adults
Anosmia or altered taste (64%)
Fever (56% to 99%)
Cough (55% to 82%)
Anorexia (40%)
Fatigue (38% to 70%)
Sputum production (27% to 34%)
Shortness of breath (19% to 57%)
Chills (12% to 15%)
Myalgias (11% to 45%)
Dizziness (8% to 9%)
Sore throat (5% to 14%)
Headache (3% to 14%)
Diarrhea (2% to 24%)
Chest pain (2% to 15%)
Nasal congestion or rhinorrhea (2% to 5%)
Rash or skin discoloration (1% to 20%)
Nausea and vomiting (1% to 19%)
Hemoptysis (1% to 2%)
Conjunctivitis (1%)

Children
Pharyngeal erythema (46%)
Cough (44% to 54%)
Fever (41% to 56%)
Diarrhea (8%)
Fatigue (8%)
Rhinorrhea (8%)
Vomiting

Information from references 20-29.

- When possible, patients should be triaged via telehealth before they receive in-person care *(Figure 1)*.[17]
- Physicians should be aware of anchoring bias when considering a diagnosis of COVID-19. Given the wide variability in presentations, it should be considered as one among several potential etiologies.
- The differential diagnosis includes:
  - Acute pulmonary edema
  - Acute respiratory distress syndrome
  - Chronic obstructive pulmonary disease exacerbation
  - Community-acquired pneumonia (bacterial or viral)
  - Influenza
  - Interstitial lung disease
  - Nonspecific viral upper respiratory tract infection
  - Opportunistic pulmonary infection
  - Pulmonary embolism
  - Streptococcal pharyngitis

SIGNS AND SYMPTOMS

- The incubation period of SARS-CoV-2 is two to 14 days, although symptoms generally appear within five days of exposure.[18]

- Common presenting symptoms include fever, dry cough, shortness of breath, and fatigue[19]; however, patients may have a wide range of symptoms representing a spectrum of mild to severe illness *(Table 2)*.[20-29]
- Moderate to severe anosmia and altered taste are commonly reported.[24]
- Symptoms in children tend to be milder than in adults and may include fever, cough, and feeding difficulty (Arnaout R, et al., unpublished data, 2020).[21]
- Pregnant and recently pregnant women are less likely to present with fever and myalgias compared with nonpregnant patients of reproductive age.[30]
- A high proportion of patients with SARS-CoV-2 infection (about 40%) are asymptomatic, particularly younger patients.[31]
- Multisystem inflammatory syndrome in children is thought to be related to COVID-19. Signs include prolonged fever and clinically severe illness with multiorgan involvement. The diagnosis is supported by laboratory confirmation of inflammation, evidence of recent SARS-CoV-2

TABLE 3

Summary of Testing Modalities for COVID-19

Type of test	Comments
Antibody test	The antibody test is most useful for epidemiologic purposes and in children with multisystem inflammatory syndrome to provide evidence of current or past COVID-19 infection.[34]
	It detects the presence of IgM and IgG antibodies to SARS-CoV-2, which emerge approximately five and 14 days after symptom onset, respectively (Wajnberg A, et al., unpublished data, 2020). A positive result can indicate prior infection or exposure, which is important for detecting infections with few or no symptoms.
	Early evidence suggests that most patients develop a vigorous antibody response to SARS-CoV-2,[35] but it is not known if this correlates with resistance to future infection.
	Results should not be used as the sole basis on which to diagnose or exclude SARS-CoV-2 infection.
	A positive result may be due to current or past infection with non–SARS-CoV-2 coronavirus strains.[36]
	Even tests with good specificity can yield more false-positive than true-positive results when population prevalence is low.[37]
PCR test	The PCR test detects the presence of coronavirus RNA and is used to confirm the diagnosis of COVID-19.
	Positive results do not rule out bacterial infection or coinfection with other viruses.
	Sensitivity varies depending on time from symptom onset,[38] so results should be interpreted based on clinical and epidemiologic factors.[39]
	Nasopharyngeal swabs are somewhat more sensitive than oropharyngeal swabs. If both are collected, they may be combined and tested simultaneously in a single reaction to conserve reagents.[40]
	Reliability is unknown because there is no standard diagnostic test,[2] there are multiple test types, production methods are inconsistent, and implementation varies around the world. Extrapolating from data on PCR tests for influenza, the PCR rapid test for COVID-19 may be highly specific (90% to 95%), meaning a positive result is good at ruling in infection, but only moderately sensitive (50% to 70%), meaning a negative result does not reliably rule out infection (Arnaout R, et al., unpublished data, 2020).[41]
	A negative result should be taken in the context of other symptoms, exposures, and the clinical presentation to guide recommendations.
Point-of-care tests	Results are available within minutes.
	Nucleic acid amplification testing targets part of the *RdRp* gene that is specific to SARS-CoV-2.
	Antigen testing uses antibodies and immunofluorescence to detect the presence of SARS-CoV-2.
	The reliability, sensitivity, and specificity of these tests are variable.[37]

COVID-19 = coronavirus disease 2019; Ig = immunoglobulin; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Information from references 2 and 34-42.

swab.[38] Antibody testing is most useful for epidemiologic purposes.[21] Point-of-care testing provides rapid results, but the reliability of these tests is not clear.[37]

• The decision to test depends on variables such as availability of test kits and reagents, and implications for treatment, infection control, and public health.

• In addition to patients with signs or symptoms of COVID-19, testing should be considered for patients who:
  ◦ Have a known or suspected exposure (including neonates born to a mother diagnosed with COVID-19)
  ◦ Will undergo a planned surgery or aerosol-generating procedure
  ◦ Are undergoing chemotherapy
  ◦ Are part of a group disproportionately affected by COVID-19, such as Black, Latino, Pacific Islander, or American Indian/Alaska Native communities.[11,43]

• Testing asymptomatic people after an exposure is recommended five to seven days after the exposure based on the median viral incubation period. Testing should not occur for at least 48 hours after exposure. Asymptomatic contacts with negative test results still must quarantine for 14 days.[11]
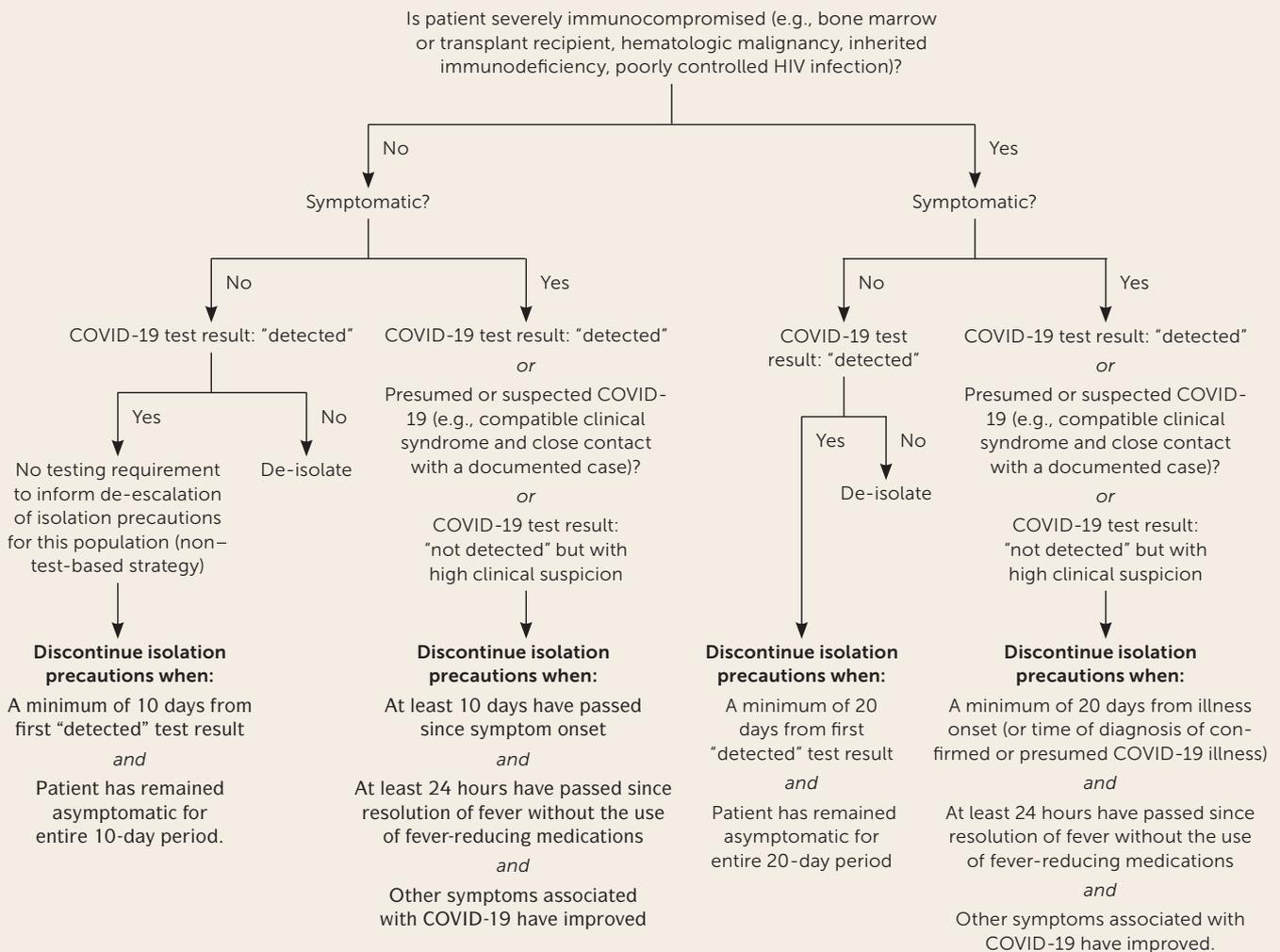
• Retesting can be considered to confirm disease resolution in immunocompromised patients if enough testing capacity exists.[11]

• Radiographic findings in patients with COVID-19 may include[41]:
  ◦ "Crazy paving" (i.e., ground-glass opacity with superimposed interlobular and intralobular septal thickening)
  ◦ Dense consolidation

infection, or exposure and no other obvious microbial cause of inflammation.[32,33]

TESTING

• There are multiple testing modalities for COVID-19 *(Table 3).*[2,34-42] Acute infection should be confirmed with polymerase chain reaction testing using a nasopharyngeal

  ◦ Ground-glass opacity
  ◦ Multifocal ground-glass opacity

• In hospitalized patients, the following laboratory tests can help assess prognosis and identify patients at risk of vascular and thrombotic complications[41]:
  ◦ Complete blood count with differential
  ◦ C-reactive protein level

FIGURE 2

Is patient severely immunocompromised (e.g., bone marrow or transplant recipient, hematologic malignancy, inherited immunodeficiency, poorly controlled HIV infection)?

No

Symptomatic?

No

COVID-19 test result: "detected"

Yes

No testing requirement to inform de-escalation of isolation precautions for this population (non–test-based strategy)

No

De-isolate

Discontinue isolation precautions when:

A minimum of 10 days from first "detected" test result

and

Patient has remained asymptomatic for entire 10-day period.

Yes

COVID-19 test result: "detected"

or

Presumed or suspected COVID-19 (e.g., compatible clinical syndrome and close contact with a documented case)?

or

COVID-19 test result: "not detected" but with high clinical suspicion

Discontinue isolation precautions when:

At least 10 days have passed since symptom onset

and

At least 24 hours have passed since resolution of fever without the use of fever-reducing medications

and

Other symptoms associated with COVID-19 have improved

Yes

Symptomatic?

No

COVID-19 test result: "detected"

Yes

No

De-isolate

Discontinue isolation precautions when:

A minimum of 20 days from first "detected" test result

and

Patient has remained asymptomatic for entire 20-day period

Yes

COVID-19 test result: "detected"

or

Presumed or suspected COVID-19 (e.g., compatible clinical syndrome and close contact with a documented case)?

or

COVID-19 test result: "not detected" but with high clinical suspicion

Discontinue isolation precautions when:

A minimum of 20 days from illness onset (or time of diagnosis of confirmed or presumed COVID-19 illness)

and

At least 24 hours have passed since resolution of fever without the use of fever-reducing medications

and

Other symptoms associated with COVID-19 have improved.

COVID-19 = coronavirus disease 2019.

Algorithm for discontinuation of home isolation after diagnosis of COVID-19.

Information from references 11 and 45.

○ D-dimer assay
○ Lactate dehydrogenase level
○ Troponin level

Treatment

• There are no evidence-based treatments for COVID-19 that are appropriate for use in the outpatient setting; management is supportive.[41]

• The World Health Organization recommends that infants born to women with COVID-19 not be separated from their mothers, and that these mothers initiate and continue breastfeeding.[44]

• Remote patient monitoring via telehealth can be used to detect red flag symptoms that warrant urgent assessment, such as[17]:

○ Fever above 100.4°F (38°C)

○ Heart rate greater than 100 beats per minute with new confusion
○ Oxygen saturation less than 95%
○ Respiratory rate greater than 20 breaths per minute

• *Figure 2* shows a protocol for discontinuing home isolation after COVID-19 diagnosis.[11,45]

DRUG THERAPY

• In addition to supportive care, there are several investigational drugs being explored for the treatment of COVID-19 in hospitalized patients.

• Dexamethasone, 6 mg per day for 10 days, significantly reduced mortality in hospitalized patients with COVID-19 who required supplemental oxygen (number needed to treat [NNT] = 29) or mechanical ventilation (NNT = 9), but not in hospitalized patients who did not require

FIGURE 3
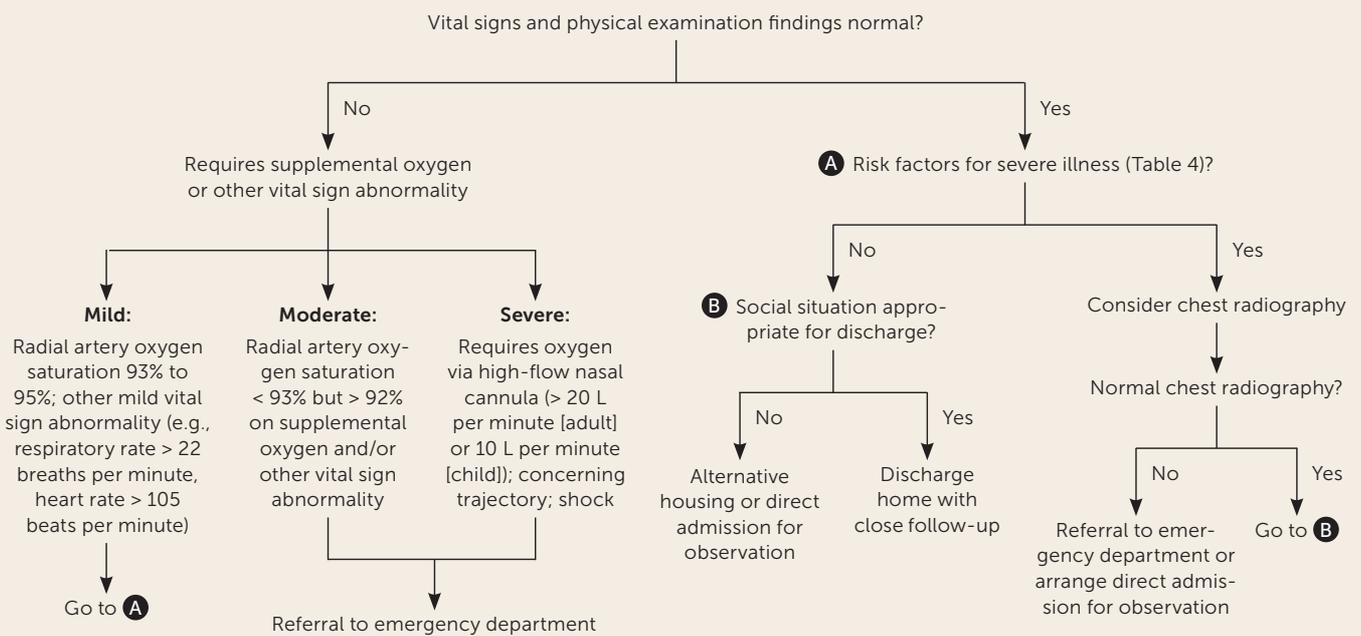
Algorithm for in-person evaluation of patients with diagnosed or suspected symptomatic coronavirus disease 2019.

Information from references 11, 17, 44, 54, and 55.

supplemental oxygen.[46] Systemic corticosteroids are not recommended for outpatients or for hospitalized patients who do not require supplemental oxygen.[47]

• Remdesivir (Veklury) was shown in a U.S. randomized trial to significantly reduce time to recovery (11 vs. 15 days) and to nonsignificantly reduce mortality (7.1% vs. 11.9%; P = .059) in hospitalized patients with COVID-19.[48] A Chinese study found no significant benefit, but the study was underpowered.[49] Remdesivir has not been studied in outpatients with nonsevere illness and is not recommended for this population.

• Hydroxychloroquine (Plaquenil) has not been shown to have clear benefit in patients with mild to severe COVID-19 symptoms, or for postexposure prophylaxis (Horby P, et al., unpublished data, 2020).[50-53]

• There is insufficient evidence to recommend the use of the following treatments for COVID-19[41]:
  ◦ Azithromycin (Zithromax)
  ◦ Convalescent plasma
  ◦ Interferon
  ◦ Ivermectin (Soolantra)
  ◦ Lopinavir/ritonavir (Kaletra)
  ◦ Ribavirin (Virazole)
  ◦ Tocilizumab (Actemra)

REFERRAL, CONSULTATION, AND HOSPITALIZATION

• In the course of an in-person assessment, the appropriate disposition of patients with symptomatic COVID-19 can be guided by vital signs, physical examination findings, respiratory rate, oxygen saturation, social considerations, and risk factors as outlined in *Figure 3*.[11,17,44,54,55]

Prognosis

• International data suggest that 85% of people with COVID-19 have only mild illness, whereas 14% have severe disease requiring hospitalization, including 5% of adults and 2% of children who require admission to an intensive care unit.[56-58] Children tend to have a better prognosis than adults (Arnaout R, et al., unpublished data, 2020).[58]

• The overall mortality rate from COVID-19 has been estimated to be 0.66% to 0.9%, although estimates are difficult because of the number of undiagnosed cases.[59,60] Observed rates vary considerably (2.3% to 7.2%) depending on location and test availability. As of July 21, 2020, the Johns Hopkins Center for Health Security reported a U.S. case fatality rate of 3.7%.[2] Case fatality rates increase with age.[6,56,59,60]

• Predictors of more severe disease or death include clinical factors, comorbidities, and laboratory findings *(Table 4)*.[37,61-64] Common risk factors in hospitalized patients include[62,63]:
  ◦ Cardiovascular disease
  ◦ Chronic kidney disease
  ◦ Chronic liver disease
  ◦ Chronic obstructive pulmonary disease
  ◦ Diabetes mellitus
  ◦ Hypercholesterolemia
  ◦ Hypertension
  ◦ Malignancy

TABLE 4

Risk Factors for Severe Illness in Adults with COVID-19

Clinical factors

Body mass index ≥ 30 kg per m²

Dyspnea, increased respiratory rate, decreased oxygen saturation

Male sex

Older age*

Comorbidities

Blood disorders (e.g., sickle cell disease, patient taking blood thinners)

Chronic kidney disease

Chronic liver disease

Chronic lung disease (e.g., chronic obstructive pulmonary disease, asthma)

Current or recent (within two weeks) pregnancy

Endocrine disorders (e.g., diabetes mellitus)

Heart disease (e.g., congestive heart failure, coronary artery disease, hypertension)

Immunosuppression (e.g., autoimmune disease, malignancy, HIV infection)

Neurologic or neurodevelopmental conditions

Laboratory findings

Elevated C-reactive protein, lactate dehydrogenase, alanine transaminase, aspartate transaminase, or D-dimer level

Leukocytosis

Low albumin level

Lymphopenia

Neutrophilia

COVID-19 = coronavirus disease 2019; ICU = intensive care unit.

*—Among adults 65 to 84 years of age who are diagnosed with COVID-19, 31% to 59% are hospitalized, 11% to 31% are admitted to the ICU, and 4% to 11% die. Among adults 85 years and older who are diagnosed with COVID-19, 31% to 70% are hospitalized, 10% to 27% are admitted to the ICU, and 10% to 27% die.[37]

Information from references 37 and 61-64.

- ○ Obesity
- ○ Obstructive sleep apnea
- In pregnant women, COVID-19 may increase the risk of complications such as preterm birth and preterm premature rupture of membranes. The risk of vertical transmission and risks to newborns are not well understood.[30]
- A 10-item clinical prediction rule has been developed and externally validated to determine the prognosis of patients with COVID-19 (http://118.126.104.170).[65] However, it requires imaging and extensive laboratory testing.
- Acute complications of COVID-19 include pneumonia, acute respiratory distress syndrome, stroke, and arterial and venous thrombosis. Hospitalized patients may have debility[66] and mental health effects.[67] Factors that may increase the risk of these complications include:

TABLE 5

Additional COVID-19 Resources

BMJ's COVID-19 hub

https://www.bmj.com/coronavirus

European Centre for Disease Prevention and Control: contact tracing for COVID-19

https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-Contract-tracing-scale-up.pdf

Infectious Diseases Society of America: COVID-19 treatment guidelines

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

National Institutes of Health: COVID-19 treatment guidelines

https://www.covid19treatmentguidelines.nih.gov

World Health Organization: interim guidance on clinical management of COVID-19

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

COVID-19 = coronavirus disease 2019.

- ○ A diet with inadequate fruits and vegetables (Adams ML, et al., unpublished data, 2020)
- ○ Body mass index greater than 40 kg per m²[61]
- ○ Sedentary lifestyle
- ○ Smoking
- The long-term health effects of COVID-19 are under investigation.
- Approximately 35% of people with COVID-19 have not returned to their previous level of health 14 to 21 days after diagnosis. These "long haulers" have a syndrome referred to as long COVID.[68]
- *Table 5* lists additional COVID-19 resources for clinicians.

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