COVID-19: An Overview

1

Harish Moorjani and S. K. Gupta

The coronavirus disease 2019 (COVID-19) is a viral infection caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has emerged as a global pandemic leading to a massive loss of human life worldwide due to its high transmissibility.

1.1 Epidemiology

Epidemiology assumes a vital role during a pandemic. A quick analysis of data regarding infection, hospitalizations, recoveries, and deaths helps frame policy and guidelines. Model-based projections are useful guiding tools in the initial days or weeks of a pandemic; however, real-world data assumes greater significance as the pandemic evolves.

1.2 The Virus and Its Variants

At the beginning of the pandemic, a novel coronavirus was identified as the causative organism for a few cases of a particular type of pneumonia noticed in Wuhan, China, in 2019. The disease soon spread in China, and later the contagion engulfed the whole world to be declared a pandemic by WHO on March 11, 2020. In February 2020, the World Health Organization labeled the disease COVID-19, and the virus causing the disease was named SARS-CoV-2 by the experts. The enveloped

H. Moorjani (✉)
Clinical Assistant Professor of Medicine, New York Medical College, Valhalla, NY, USA

S. K. Gupta
GS Medical College, Pilkhuwa, UP, India

Max Super Speciality Hospital, Delhi, India

A. Mohan, S. Mittal (eds.), *Post COVID-19 Complications and Management*,
https://doi.org/10.1007/978-981-19-4407-9_1

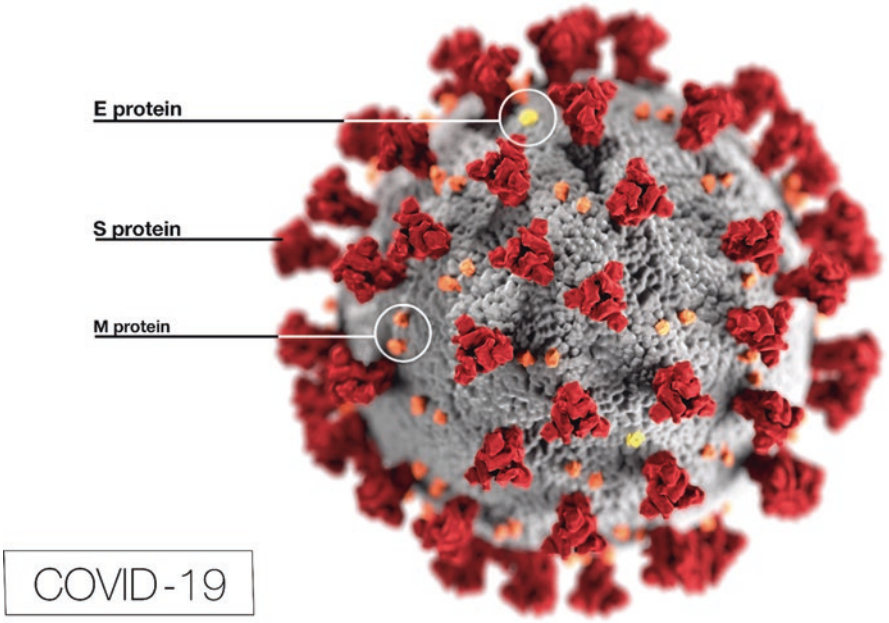

Fig. 1.1 Protein structure of SARS-CoV-2 (Image courtesy: Centers for Disease Control and Prevention)

positive-stranded RNA virus enters the host cell through ACE-2 receptors by latching its spike proteins (Fig. 1.1).

SARS-CoV-2, like other RNA viruses including influenza, is prone to making errors in its genetic code during replication, resulting in mutations. New mutations can produce variants which have properties different from the original strain. When any variant becomes more virulent, showing faster transmission or causing severe disease overriding the existing immunity, it is called a variant of concern. The SARS-CoV-2, within 2 months of its origin, mutated to a variant carrying the D614G spike protein mutation, and the mutant was called G614. The G614 variant had a fitness advantage and soon became the globally dominant form of SARS-CoV-2. In the absence of any effective antiviral drug, the virus evolves to more virulent forms. Notable changes in the virus have been named Alpha, Beta, Gamma, and Delta variants by WHO in May 2021. Variants should not be confused with Alpha, Beta, Gamma, and Delta families of coronavirus. All variants of SARS-CoV-2 belong to the Beta coronavirus family. The Alpha variant was detected in England (Kent) as early as September 2020. It was 43–90% more transmissible than pre-existing variants of SARS-CoV-2 [1]. The virus further mutated with significant double mutation evolving into Delta variant. The P681R mutation in the Delta variant speeds up the spread of SARS-CoV-2 from cell to cell. It was first detected in India in October 2020 and rapidly spread across the globe within the next few months. Beta is the South African variant, and Gamma is the Brazilian variant. On

November 24, 2021, a new variant of SARS-CoV-2, B.1.1.529, was reported to the WHO. This new variant was first detected in specimens collected on November 11, 2021, in Botswana and on November 14, 2021, in South Africa. On November 26, 2021, the WHO named the B.1.1.529 Omicron.

As per WHO, more than 438 million cases and 5.96 million deaths have been reported worldwide; however, the true incidence based on serosurveys is up to ten times higher as a large number of cases remain underreported due to subclinical infections, poor testing, and lack of reporting [2].

1.3 Infection

Having established a reservoir in humans, the disease spreads from person to person. Respiratory droplets, expelled by the infected person on coughing, talking, or sneezing and inhaled by subjects within close range of 2 m, remain the primary source of spread. Direct contact of infected hands with mucus membranes in eyes, nose, and mouth can also lead to infection. However, surface contact through fomites is no longer considered an important source of transmission. On the other hand, airborne transmission is now considered an important mode of transmission. Although viral particles can be detected in body specimens such as semen, stool, tears, and blood, transmission via these non-respiratory means remains uncertain [3].

The incubation period, defined as the time of exposure until the onset of symptoms, averages 4 to 5 days but could range between 2 and 14 days.

Individuals remain most infectious between 2 days before and 1 day after the onset of symptoms; contagiousness declines within 7 days of onset of symptoms irrespective of virus levels in the nose. Close contact for long durations increases the risk of transmission, especially in immunity naïve subjects. It can take a couple of days after exposure to COVID-19 to become infected with the virus and for the polymerase chain reaction (PCR) test to become positive. Hence, if the test is negative 24 h after exposure, the Centers for Disease Control and Prevention (CDC) recommends a retesting 5 to 7 days later even if the individual is asymptomatic. However, testing strategies continue to get updated depending on the disease burden.

1.4 Prevention

Preventive measures include: maintaining a physical distance of more than 2 m, wearing an appropriate mask, frequent hand-washing, and using alcohol-based sanitizers with at least 60% or 70% alcohol. Mass vaccination remains the key to pandemic control and disease eradication. Postexposure precautions include monitoring for symptoms in quarantine for 10–14 days, especially for unvaccinated individuals. Fully vaccinated/immunized individuals should be exempted from quarantine but advised to get tested 3–5 days after exposure and wear a mask in public until the test is negative, or for 14 days [4].

1.5 Clinical Features

The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical and fatal illness. Patients should be suspected of having COVID-19 when they present with compatible symptoms, or have had recent close contact with a confirmed patient with COVID-19. The proportion of infections that remain asymptomatic is unclear. In longitudinal studies, the follow-up to identify patients testing positive who develop symptoms is sometimes not performed. Nevertheless, seroprevalence studies suggest that up to 40% of infections are asymptomatic [5]. Most symptomatic infections are mild. However, severe disease (hypoxia and pneumonia) has been reported in 15 to 20% of symptomatic infections; these can occur in patients of any age but usually occurs in adults with advanced age or in persons with underlying medical comorbidities like diabetes, hypertension, chronic obstructive pulmonary disease (COPD), obesity, cardiac diseases, chronic kidney disease (CKD), etc. In addition, some patients with initially mild symptoms may progress to severe illness over the course of days.

Fever, cough, myalgia, and headache remain the most common symptoms. Diarrhea, sore throat, and loss of smell and taste may be other common presenting complaints [6, 7]. Seasonal viral infections, including flu and common cold, may have a similar presentation. However, there are no pathognomic features that distinguish COVID-19 from other respiratory infections.

Asymptomatic individuals, who get tested following close contact with a patient of COVID-19 or for some other reason, should be advised careful monitoring and isolation. Patients with any signs and symptoms of COVID-19 (e.g., cough, fever, sore throat, malaise, headache, body ache, diarrhea, loss of taste and smell) but who maintain oxygen saturation > 94% on room air and do not have any evidence of pneumonitis on chest imaging are classified as mild disease. These patients can be monitored at home. On the other hand, individuals with mild disease but with comorbidities such as diabetes, hypertension, coronary artery disease, chronic kidney disease, or COPD and who are solid organ transplant recipients, are more than 65 years, or are on immunosuppressive therapy may require close in-hospital monitoring due to higher risk of progression to severe disease.

Patients showing any symptom of disease along with bilateral ground-glass opacities/consolidation on X-ray chest or lung ultrasound, or hypoxia manifested by SpO2 less than or equal to 94%, are labeled as having moderate disease and need hospitalization. Individuals with SpO2 < 90%, requiring mechanical ventilation with PaO2/FiO2 of 151–300 mm Hg, or respiratory rate > 30 breaths/min are classified as having severe disease and require ICU care.

1.6 Happy Hypoxia in COVID-19

Blood oxygen saturation (SpO2) for a healthy person remains in the range of 97 to 100% irrespective of age. Decline in SpO2 below 94% (or even earlier) leads to symptoms such as fatigue, air hunger, respiratory discomfort, and breathlessness.

Surprisingly, however, some patients with COVID-19 pneumonia do not demonstrate these manifestations even at very low SpO2 and may appear very comfortable. This situation is termed as happy hypoxia. The SARS-CoV-2, on one hand, causes hypoxic damage, while on the other, it blunts the body's defense mechanism to detect and repair the damage. Persistent hypoxia in COVID-19 may impair tissue oxygenation and lead to multi-organ failure. Pulse oximetry is the only noninvasive way to detect hypoxia both in home and hospital settings. Therefore, no patient should be treated at home without a suitable pulse oximeter, even in remote areas.

Apart from the above clinical symptoms and signs, some laboratory parameters such as lymphopenia, deranged NLR (neutrophil/lymphocyte ratio), elevated D-dimer, and elevated inflammatory markers as C-reactive protein (CRP) and LDH have been associated with severe COVID-19 and worse outcomes [8].

1.7 Complications

In patients with severe disease, development of hypoxemic respiratory failure leading to acute respiratory distress syndrome (ARDS) is the major complication. Other complications include pulmonary thromboembolism, myocarditis, acute renal failure, and inflammatory complications. In addition, the multisystem inflammatory syndrome can occur in children. About 40% of patients may have persistent symptoms following acute COVID-19 called "long COVID," which remains the primary focus of the subsequent chapters in this book.

1.8 Diagnosis of COVID-19

The possibility of COVID-19 should be considered in all patients with acute respiratory symptoms with or without fever, especially in cases where no other etiology can be identified. All symptomatic patients with suspected COVID-19 should undergo testing for SARS-CoV-2.

1.8.1 Nucleic Acid Amplification Test (NAAT)

Nucleic acid amplification test (NAAT) with a reverse transcription-polymerase chain reaction (RT-PCR) assay is the preferred diagnostic test to detect SARS-CoV-2 RNA from the upper respiratory tract in patients with suspected COVID-19.

NAATs detect SARS-CoV-2 RNA in patient specimens and are highly specific. Although these tests can detect very low levels of viral RNA, their sensitivity depends on the type and quality of the specimen obtained, the duration of illness at the time of testing, and the specific assay. However, a positive NAAT for SARS-CoV-2 is confirmatory for the diagnosis of COVID-19. Conversely, false-negative results may occur in 2 to 40% of patients. Therefore, in symptomatic individuals with high suspicion for COVID-19, an initial negative NAAT result should be

confirmed with a repeat test. In hospitalized patients with lower respiratory tract disease, performing NAAT on lower respiratory tract specimens like BAL (bronchoalveolar lavage) may yield better results.

Testing asymptomatic persons should include close contacts of a COVID-19 case, screening in long-term care facilities, shelters for the homeless, and in hospitalized patients in high-prevalence regions. Postexposure testing should be done 5 days after exposure, although the optimal timing is not established.

1.8.2 Rapid Antigen Test

Tests that detect SARS-CoV-2 antigen can be performed rapidly and at the point of care. Rapid antigen tests (RAT) have around 56% sensitivity compared to 72% sensitivity of RT-PCR-based tests [9].

However, antigen testing may be the initial test used in resource-poor settings. They can be helpful in the rapid diagnosis of patients soon after the onset of symptoms. Antigen tests also find a place in serial screening for infection in congregate settings. Rapid antigen test detects S gene, and since many mutants have a deletion of S gene, these are not picked up by the rapid antigen test. On the other hand, RT-PCR detects the ORF and N gene in addition to the S gene. Since antigen tests have lower sensitivity than RT-PCR, a negative RAT should usually be confirmed with RT-PCR.

1.8.3 Serologic Tests

Serologic tests are used to detect antibodies to SARS-CoV-2 in the blood in order to help identify patients who previously had exposure to this virus. However, detectable antibodies generally take at least 2 weeks to develop; thus, serologic tests have little utility for diagnosis in the acute care setting. In addition, serologic assays have variable performance among various company kits. They also have poor positive predictive value in low seroprevalence settings. In addition, serologic assay values may not always correlate with immunity. Sometimes, serologic testing like anti-S antibodies or anti-nucleocapsid antigen antibodies may be the only option left for the diagnosis, especially in patients presenting with symptoms for at least 2 weeks. However, serologic tests may not differentiate acute infection from past infection. Results of serologic testing may also be affected by prior vaccination, while previous COVID-19 vaccination does not influence NAAT or antigen test results. Most serologic tests target the nucleocapsid protein; only serologic tests for spike protein can detect antibody response to currently available mRNA and vector-based vaccines, but they cannot distinguish a vaccine response from a prior infection.

1.9 Management of COVID-19

The spectrum of COVID-19 disease ranges from asymptomatic infection to mild flu-like symptoms to severe pneumonia with ARDS and multi-organ failure. So, our understanding of COVID-19 disease as well as optimizing its management continues to evolve.

The management of adult patients with acute COVID-19 in the outpatient setting (<12 weeks after onset of illness) includes early and appropriate risk stratification, self-care advice, telehealth and clinic management, timely referral to the emergency department (ED), and posthospital discharge care. The approach is guided by increasing clinical experience in the rapidly evolving scenario of evidence-based medicine. Therefore, clinicians should consider the individual patient's clinical and social circumstances to formulate a personal COVID-19 care plan.

The initial clinical evaluation includes assessment of risk factors for progressive disease (see below), oxygenation status, severity of dyspnea, and the patient's general medical condition to determine whether intensive care is required or outpatient care is sufficient.

The patients with the following symptoms/signs should be referred to the ED for further management:

- Shortness of breath (at rest, and inability to speak complete sentences)
- Saturation on room air of ≤90%, regardless of the severity of dyspnea
- Mental status (confusion, change in behavior, drowsiness) or signs and symptoms of inadequate perfusion (hypotension, cyanosis, cardiac chest pain)

Patients can be managed at home without in-person evaluation if they are able to maintain daily clinical contact, promptly report worsening symptoms, and self-isolate for the duration of illness. Telemedicine follow-up depends upon their risk for severe disease and the severity of symptoms.

During home isolation, patients should be provided clear instructions for self-care. The use of paracetamol for fever control, antitussive remedies for relief of cough, and adequate bed rest should be emphasized. For patients with early, symptomatic COVID-19 and risk factors for progression to severe illness (Table 1.1), treatment with monoclonal antibody infusion has been suggested, preferably within 7 to 10 days of symptom onset. Options available through emergency use authorization include casirivimab-imdevimab, sotrovimab, and bamlanivimab-etesevimab and may reduce the risk of progression to severe disease [10].

Several other therapies are being studied for the treatment of COVID-19, but none have been proven in asymptomatic or mild disease and should be prescribed only in a clinical trial setting. In nonhospitalized patients, the routine use of systemic corticosteroids is not recommended. Patients with underlying respiratory conditions, such as acute exacerbation of asthma or chronic obstructive pulmonary disease (COPD), should receive steroids as indicated. Routine treatment with antibiotics is not indicated unless a bacterial superinfection is suspected or confirmed.

Table 1.1 Risk factors for severe disease [11]

Cancer
Cerebrovascular disease
Children with certain underlying conditions (such as asthma, developmental delay, congenital heart disease, and sickle cell disease)
Chronic kidney disease
COPD and other lung diseases (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis)
Diabetes mellitus
Down syndrome
Cardiac conditions (e.g., heart failure, coronary artery disease, cardiomyopathies)
HIV infection
Neurologic conditions, including dementia
Obesity (BMI ≥30 kg/m2) and overweight (BMI 25 to 29 kg/m2)
Pregnancy
Smoking (current and former)
Sickle cell disease or thalassemia
Solid organ or blood stem cell transplantation
Substance use disorders
Use of corticosteroids or other immunosuppressive medications

It is advised against initiating anticoagulation or antiplatelet therapy in the outpatient setting.

Symptoms of COVID-19 can mimic many other common conditions; hence a broad differential diagnosis is important and should be investigated accordingly. The patient's existing medication regimen does not need to be adjusted. However, use of nebulized medications is preferably avoided to avoid transmission to other healthcare workers and patients. All patients are counseled on the warning symptoms that a clinician should promptly evaluate. All patients should be encouraged to provide a current healthcare proxy and advance directives.

On follow-up, the patient's respiratory status should be evaluated with the same criteria as that used for initial triage. Most patients discharged from the inpatient setting should have a follow-up visit within 2 days either by a teleconference or in-person clinic visit. Temporary housing in structured residential care facilities may be appropriate for some patients following their discharge from hospital.

1.10 Management of Hospitalized Adult Patients with Acute COVID-19

Indications for hospitalization and identification of patients who can be managed in the outpatient setting have been outlined in the beginning of this section.

Evaluation—The evaluation of hospitalized patients with documented COVID-19 should include assessing for risk factors associated with severe illness and identifying organ dysfunction or other comorbidities that could complicate therapy.

- Thromboprophylaxis—COVID-19 has a known association with thromboembolic complications; hence all patients hospitalized with moderate-severe disease should receive pharmacologic prophylaxis for venous thromboembolism as per local guidelines. It is yet unclear whether patients should receive thromboprophylaxis after discharge, and if so, for what duration? Decisions in this regard should be made on a case-by-case basis, primarily depending on risk of subsequent thrombosis.
- Antipyretics—Acetaminophen is widely used for fever management in patients with COVID-19. Guidelines do not recommend the use of nonsteroidal anti-inflammatory drugs (NSAIDs). If NSAIDs are required, then the lowest effective dose should be used. However, NSAIDs should not be discontinued in patients who were already using them for other conditions [12].
- Continuing chronic medications—Patients who are on an ACE inhibitor or ARB, should not stop their medication. Statins as well as aspirin may be continued in hospitalized patients with COVID-19 who are already taking them unless there is a specific concern of bleeding.

In patients with moderate disease, the care is primarily supportive, with close monitoring for disease progression. Additionally, patients with mild to moderate COVID-19 who are hospitalized for reasons other than COVID-19 may be evaluated and considered for monoclonal antibody therapy based on appropriate eligibility criteria.

- Approach to severe disease—For patients with severe disease (O_2 saturation $\leq$ 94% on room air or need for oxygenation or ventilatory support), COVID-19 therapy depends on the level of oxygen requirements and ordinal scale [13].
- For hospitalized patients with hypoxemia who are not yet on oxygen, intravenous remdesivir may be used. However, steroid use in these patients is discouraged.
- For hospitalized patients who are on low-flow supplemental oxygen, it is recommended to use low-dose steroids (dexamethasone/methylprednisolone) and IV remdesivir for 5 days. In patients with significantly elevated inflammatory markers and increasing oxygen requirements despite steroids, either baricitinib or tocilizumab may be added on a case-by-case basis.
- For hospitalized patients on high-flow supplemental oxygen or noninvasive ventilation, low-dose dexamethasone should be used. For those who are admitted to an intensive care unit (ICU), either baricitinib or tocilizumab may be used in addition to steroids. The use of IV remdesivir may be extended to 10 days in such cases.

In hospitalized patients with severe disease who require mechanical ventilation or extracorporeal membrane oxygenation, low-dose steroids are recommended. Tocilizumab may be added especially in situations progressing to “cytokine storm.”

The use of other off-label drugs/therapies for the treatment of COVID-19 for hospitalized patients such as hydroxychloroquine, chloroquine, lopinavir-ritonavir, ivermectin, or convalescent plasma is not currently recommended.

1.11 Prognosis of Severe Disease

The mortality from COVID-19 appears driven primarily by the presence of severe ARDS. Several retrospective studies have reported variable mortality from COVID-19-related acute respiratory distress syndrome (ARDS), from 12 to 78%, with an average of 25 to 50%.

Mortality may be on the higher end of this range in resource-limited settings. Reducing mortality may reflect a younger patient population with a lower comorbidity burden during the subsequent surge, reduced burden on institutions, and/or growing expertise with COVID-19 care.

Prolonged symptoms are common during recovery from critical illness due to COVID-19, and many patients suffer from post-acute COVID-19 syndrome (PACS) [14]. In our experience, the rate of long-term complications in critically ill patients with COVID-19 may be higher than usual due to the prolonged nature of intubation and higher use of neuromuscular blockade and sedatives, with or without concurrent glucocorticoid administration. Long-term sequelae that can be seen in patients with COVID-19 and evaluation for and management of PACS are discussed separately.

References

1. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 31. December 10, 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040076/Technical_Briefing_31.pdf. Accessed on December 13, 2021.
2. SARS-CoV-2 variants of concern and variants under investigation. 33.
3. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical characteristics and results of semen tests among men with coronavirus disease 2019. JAMA Netw Open. 2020;3:e208292.
4. CDC. Quarantine & isolation [Internet]. Centers for disease control and prevention 2022 [cited 2022 Apr 15]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html
5. Ma Q, Liu J, Liu Q, Kang L, Liu R, Jing W, et al. Global percentage of asymptomatic SARS-CoV-2 infections among the tested population and individuals with confirmed COVID-19 diagnosis: a systematic review and meta-analysis. JAMA Netw Open. 2021;4:e2137257.
6. CDC. Healthcare Workers [Internet]. Centers for disease control and prevention 2020 [cited 2022 Apr 15]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
7. Clinical features of covid-19 | The BMJ [Internet]. [cited 2022 Apr 15]; Available from: https://www.bmj.com/content/369/bmj.m1470/rapid-responses
8. Serum troponin, D-dimer, and CRP level in severe coronavirus (COVID-19) patients–PubMed [Internet]. [cited 2022 Apr 15]; Available from: https://pubmed.ncbi.nlm.nih.gov/34939346/

9. Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2020;8:CD013705.
10. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab | NEJM [Internet]. [cited 2022 Apr 15]; Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2107934
11. CDC. Cases, Data, and Surveillance [Internet]. Centers for Disease Control and Prevention 2020 [cited 2022 May 25]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/assessing-risk-factors.html
12. Concomitant Medications [Internet]. COVID-19 Treatment Guidelines [cited 2022 Apr 20]; Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/concomitant-medications/
13. Marshall JC, Murthy S, Diaz J, Adhikari NK, Angus DC, Arabi YM, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20:e192–7.
14. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601–15.