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such as temperature and ventilation. Viruses transmitted by this route are SARS-CoV, measles virus, and VZV. Patients with these infections should be managed with personal respiratory protection and special ventilation and air handling. Providers should wear an N95 respirator selected with fit-testing, which must be repeated annually. Powered air-purifying respirators (PAPRs) are used in some cases. The patient should be housed in an airborne-infection isolation room—a negative-pressure room that has a minimum of six air exchanges per hour and exhausts through high-efficiency particulate air (HEPA) filtration or directly to the outside.

**GLOBAL CONSIDERATIONS**

- ■ **HENDRA AND NIPAH VIRUSES** These emerging paramyxoviruses, which are grouped in their own new genus (Henipavirus), may not be respiratory pathogens in a conventional sense, but they probably infect humans by the respiratory route. Nipah virus is a newly recognized zoonotic virus, named after the location in Malaysia where it was first identified in 1999, and has caused significant outbreaks in Bangladesh and India. It has caused disease in humans who have had contact with infectious animals. Hendra virus (formerly called equine morbillivirus) is another closely related zoonotic paramyxovirus and was first isolated in Australia in 1994. The viruses have caused only a few localized outbreaks, but their wide host range and ability to cause high mortality raise concerns for the future. The natural host of these viruses is thought to be a certain species of fruit bat present in Australia and the Pacific. Pigs may be an intermediate host for transmission to humans in Nipah infection and horses in Hendra infection. Although the mode of transmission from animals to humans is not defined, inoculation of infected materials onto the respiratory tract probably plays a role. The clinical presentation usually appears to be an influenza-like syndrome that progresses to encephalitis, includes respiratory illness, and causes death in about half of identified cases.
- ■ **BUNYAVIRIDAE: HANTAVIRUS** Intermittent outbreaks of hantavirus infection occur in South America and cause a severe lung infection: HPS. In addition, >800 cases of HPS have been reported in the United States, caused by the Sin Nombre hantavirus. The disease was first recognized during an outbreak in 1993. About one-third of recognized cases end in death. The Four Corners outbreak (at the intersection of the northwestern corner of New Mexico, the northeastern corner of Arizona, the southeastern corner of Utah, and the southwestern corner of Colorado) is well known; however, cases now have been reported in at least 32 states. Outbreaks of HPS also have occurred in South America, especially in Chile, caused by the related Andes hantavirus. Patients with HPS usually present with an influenza-like illness, including fever. Findings on physical examination are nonspecific, often consisting only of fever and elevated respiratory and heart rates. In addition to respiratory symptoms, abdominal pain is common.

Diagnosis is often delayed until illness becomes severe, at which point intubation and mechanical ventilation may be required for respiratory support. SUMMARY Viruses are the leading causes of acute lower respiratory tract infection in most populations. Influenza virus and RSV are the most common pathogens; hMPV, PIV3, and rhinoviruses account for most other acute viral respiratory infections. Infection in otherwise healthy adults generally leads to partial immunity to these pathogens, with protection against severe lower respiratory disease. However, reinfection, with upper respiratory tract illness, is common throughout life. Special populations such as immunocompromised patients, institutionalized frail elderly patients, and patients with COPD are at highest risk for severe disease. ■ ■ FURTHER READING Beard KR et al: Treatment of influenza with neuraminidase inhibitors. *Curr Opin Infect Dis* 31:51, 2018. Falsey AR et al: Bacterial complications of respiratory tract viral illness: A comprehensive evaluation. *J Infect Dis* 208:432, 2013.

Fry AM et al: Seasonal trends of human parainfluenza viral infections:

United States, 1990–2004. *Clin Infect Dis* 43:1016, 2006. Hammitt LL et al: Nirsevimab for prevention of RSV in healthy latepreterm and term infants. *N Engl J Med* 386:837, 2022. Liu J-W et al: Comparison of antiviral agents for seasonal influenza outcomes in healthy adults and children: A systematic review and network meta-analysis. *JAMA Netw Open* 4:e2119151, 2021. Monto AS, Cavallaro JJ: The Tecumseh study of respiratory illness. II. Patterns of occurrence of infection with respiratory pathogens, 1965–1969. *Am J Epidemiol* 94:280, 1971. Papi A et al: Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med* 388:595, 2023. Walsh EE et al: Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med* 388:1465, 2023. Williams JV et al: Human metapneumovirus infection plays an etiologic role in acute asthma exacerbations requiring hospitalization in adults. *J Infect Dis* 192:1149, 2005. James E. Crowe, Jr.

SARS-CoV-2 and

COVID-19 CHAPTER 205 CORONAVIRUS DISEASE 2019 (COVID-19) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; ICTV name Betacoronavirus pandemicum) emerged in 2019 in an outbreak in Wuhan, China, that spread worldwide and caused a severe pandemic. SARS-CoV-2 is the cause of a respiratory disease called COVID-19. The virus is a member of the Betacoronavirus genus that not only includes the highly pathogenic viruses severe acute respiratory syndrome

coronavirus 1 (SARS-CoV-1; ICTV name Betacoronavirus pandemicum) (which caused a smaller epidemic in 2002–2003) and Middle East respiratory syndrome coronavirus (MERS-CoV or HCoV-EMC; ICTV name Betacoronavirus cameli) (which caused small epidemics in 2012, 2015, and 2018 with continuing sporadic cases), but also contains the common cold viruses human coronavirus OC43 (HCoV-OC43 or betacoronavirus 1; ICTV name Betacoronavirus gruedinisi) and human coronavirus HKU1 (HCoV-HKU1; ICTV name Betacoronavirus hongkongense). These are enveloped, positive-sense RNA viruses encoded by a viral RNA genome that is quite large, a single linear RNA segment of nearly 30,000 nucleotides that encodes four structural proteins, designated the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins, and a large polyprotein that is cleaved into 16 nonstructural proteins in infected cells. The trimeric S protein is primed by the transmembrane protease serine 2 (TMPRSS2) to facilitate entry of SARS-CoV-2. SARS-CoV-2 S protein is a type 1 fusion machine that also mediates attachment using a receptor-binding domain

(RBD) that binds to the human angiotensin-converting enzyme 2 (hACE2) protein receptor. SARS-CoV-2 and COVID-19 ■ ■ EPIDEMIOLOGY The origins of the virus and mode of exposure to the first human cases remain unresolved, but the virus likely existed prior to the outbreak in some form in a bat reservoir. Infection was first detected in humans in 2019 in Wuhan, China; it rapidly spread by human-to-human transmission through all provinces of China and then worldwide. The World Health Organization (WHO) designated SARS-CoV-2 a Public Health Emergency of International Concern on January 30, 2020, and declared the outbreak a pandemic on March 11, 2020, leading to several years of global disruption. On May 5, 2023, the WHO declared an end to the global COVID-19 emergency. As of September 2024, the

virus had caused >700 million cases and >7 million deaths worldwide, although most countries have now stopped accurate reporting of cases. The basic reproduction number ( $R_0$ ) (the expected number of cases generated directly by one case in a population in which all individuals are susceptible to infection) of SARS-CoV-2 has been estimated to peak around 6, which is substantially higher than that of seasonal influenza (typically 1–2). Densely populated settings such as prisons, cruise ships, nursing homes, airplanes, and large indoor gatherings facilitate high transmission efficiency. Transmission in outdoor settings is less common. Healthcare workers and those working in dentistry have a high potential for exposure. Certain individuals may have contributed to extraordinarily high transmission events (so-called “superspreaders”). Transmission does occur in school settings, although schools have not been considered a primary driver of population transmission and children have lower rates of severe disease than adults. Spread of SARS-CoV-2 is primarily via respiratory droplets transmitted between persons in proximity when the droplets make direct contact with mucous membranes. Airborne transmission by small particle from person-to-person may occur, but airborne transmission over long distances is unlikely. Fomite transmission by contact with contaminated surfaces occurs; therefore, hand washing in environments of exposure has been advised. Large-scale frequent surface decontamination efforts have been deployed in public spaces, but the effect of these cleanings on reducing transmission is uncertain.

For replication, coronaviruses use RNA-dependent RNA polymerases that are error prone, allowing viral variants to occur frequently. Most variant residues have no effect or are deleterious to the virus. However, some variations affect transmission, disease severity, antigenicity (and thus efficacy and effectiveness of immunity induced by prior vaccination or infection), the effectiveness of therapies, the sensitivity and specificity of diagnostic tools, and the effectiveness of social and public health measures. Rapid evolution of variants has been a distinguishing feature of the COVID-19 pandemic. The WHO has established a Technical Advisory Group on SARS-CoV-2 Virus Evolution to follow and report variant evolution. The group has developed terminology concerning variants under monitoring (VUMs), variants of interest (VOIs), and variants of concern (VOCs) to draw attention to virus evolution. In 2024, the WHO launched a WHO Coronavirus Network (CoViNet) to facilitate early and accurate detection of coronaviruses and variant tracking. The WHO Technical Advisory Group on COVID-19 Vaccine Composition assesses the analyses of the likely effects of emerging VOCs on the performance of COVID-19 vaccines. PART 5 Infectious Diseases Advanced age is the principal risk factor for severe illness from COVID-19 (marked by need for hospitalization, intensive care, and mechanical ventilation). More than 95% of COVID-19 deaths occur in persons older than 45 years, and >80% of deaths occur in those older than 65 years. Preexisting social and health disparities put some groups at increased risk of illness or death from COVID-19, including

persons with disabilities and many racial/ethnic minority groups. Male sex is associated with higher risk of severe disease (odds ratio, ~1.8). Most individuals who die have preexisting comorbidities. The risk of severe COVID-19 illness increases markedly with elevated body mass index (BMI). Overweight condition (BMI >25 but <30), obesity (BMI ≥30 but <40), and severe obesity (BMI ≥40) are risk factors for progressively increased severe COVID-19. Substance use, such as alcohol, opioid, or cocaine use disorder, and current or former smoking both increase risk. Pregnant women are more likely to suffer more severe illness. Most other medical conditions increase the risk of severe illness, but conditions that especially increase risk are as follows: (1) chronic lung diseases, including COPD, moderate to severe asthma, cystic fibrosis, and pulmonary hypertension interstitial lung disease; (2) cancer or cancer treatments, including hematologic malignancies, solid organ transplant, and stem cell transplant; (3) immunodeficiency, including primary immunodeficiency caused by inherited genetic defects or secondary or acquired immunodeficiency caused by prolonged use of corticosteroids, other immunosuppressive drugs, or HIV type 1 (HIV-1) infection; (4) hemoglobin blood disorders, including thalassemia or sickle cell disease; (5) cerebrovascular disease, such as stroke; (6) cognitive impairment or other neurologic conditions; (7) heart conditions,

including arterial hypertension, heart failure, coronary artery disease, and cardiomyopathies; (8) obstructive sleep apnea; (9) chronic inflammatory, autoimmune, and rheumatic diseases; (10) type 1 or type 2 diabetes mellitus; (11) chronic liver disease, especially cirrhosis; and (12) genetic conditions, especially Down syndrome. A multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome (PMIS) has been associated with COVID-19, comprising a persistent fever, involvement of multiple organ systems (including gastrointestinal, dermatologic, cardiac, renal, hematologic, and neurologic), and elevated circulating inflammatory markers. The highest-risk individuals for MIS-C in the United States are Black and Latino children age 3–12 years. A similar syndrome in adults (MIS-A) may occur rarely. ■ ■PREVENTATIVE MEASURES Early in the epidemic, public health methods for prevention were limited mostly to nonpharmaceutical interventions (NPIs), including social distancing (staying at least 6 ft from other persons in public to avoid infection), social isolation (staying away from other persons when infected), quarantine (staying at home for 14 days after potential exposure), limiting travel, and working from home. When a local epidemic persists, prior to entering health care settings, patients often are screened for clinical signs or symptoms common in COVID-19, especially fever, respiratory symptoms (cough, dyspnea, sore throat), myalgias, and anosmia/hyposmia. Universal masking has been required in many health care settings during epidemic conditions, although effectiveness of masking in community or health settings has been difficult to assess. Most mask studies have been observational and confounded by lack of consistency in concurrent interventions, study of exposure to variants with differing R0 values, differences in mask type (N95, KN95, FFP2, paper medical or surgical, or cloth masks), poor compliance, and other factors. Most experts conclude that masking, use of personal protective equipment, and hand washing are highly appropriate in health care settings with infected patients and may have some benefit in community settings. Most organizations and governments responsible for public health decisions have discontinued mandatory policies in favor of softer recommendations. ■ ■CLINICAL MANIFESTATIONS The disease course varies widely, including asymptomatic infection, mild disease, moderate disease, or severe disease requiring hospitalization, oxygen therapy, intensive care, and mechanical ventilation. A substantial proportion of patients (possibly a third of those infected) are

asymptomatic, but those individuals can transmit the virus to others. Most individuals with symptomatic infection have mild disease (no pneumonia). Severe disease, typically requiring hospitalization and involving pneumonia and associated manifestations (dyspnea, radiographic involvement of more than half of the lung, and/or hypoxia with oxygen saturation  $\leq 94\%$ ), is common. Critical disease with manifestations of respiratory failure requiring mechanical ventilation, multiorgan failure, or shock occurs and requires intensive care. ■ ■ **DIAGNOSIS OF COVID-19** Testing for COVID-19 is recommended during periods of respiratory symptoms, or 5 days or later after exposure without active symptoms. COVID-19 tests usually use a sample taken from the nasopharynx or sometimes a saliva sample. There are two major types of approved diagnostic tests: antigen tests (for proteins of SARS-CoV-2) and molecular tests (for genetic material of SARS-CoV-2). Antigen tests are often used as screening tests and sometimes called rapid or at-home tests. Approved protein-detection antigen test devices are reliable and accurate, but they are less accurate than molecular tests, especially when testing exposed persons without symptoms. COVID-19 diagnostic tests are widely available from health care professionals, hospitals and clinics, and some pharmacies or other testing sites in the community. In the United States, at-home COVID-19 tests approved by the U.S. Food and Drug Administration (FDA) are available for free or for purchase. Molecular tests are nucleic acid amplification tests (NAATs), most often performed using reverse transcription polymerase chain

reaction (RT-PCR) to convert the viral RNA genome to DNA copies (cDNA) and amplify the copy number for enhanced sensitivity. PCR tests are not rapid and cannot be performed at home, so they are typically performed in professional health care settings and processed in a reference laboratory using specialized equipment. Nasopharyngeal swabs are used mostly commonly, while saliva testing also has been implemented, especially in large-scale population screening efforts. Other more general laboratory tests have been used during medical management of severe or critical illness. Most immune profiling tests reveal widespread abnormalities consistent with systemic disease including lymphopenia and thrombocytopenia; elevated inflammatory markers, such as interleukin 6 (IL-6), tumor necrosis factor  $\alpha$ , ferritin, and C-reactive protein; elevated liver enzymes and lactate dehydrogenase; elevated markers of acute kidney injury; elevated D-dimer and prothrombin time; and elevated troponin and creatine phosphokinase. Research-grade tests show that beneficial components of the adaptive immune response, including antibodies and T cells, also arise during the first 1–2 weeks after exposure. Chest radiographs may exhibit abnormal findings such as consolidation and ground-glass opacities that are distributed bilaterally, especially in the lower lung regions, but may also be normal despite respiratory compromise. Chest computed tomography (CT) has features (ground-glass opacifications with or without mixed consolidation, pleural thickening, interlobular septal thickening, and air bronchograms) that can be systematically interpreted as typical, indeterminate, or atypical for COVID-19. Chest CT may be more sensitive than radiographs, but CT should be used principally for medical management of respiratory disease, not as a primary diagnostic tool for COVID-19. Lung ultrasound also has been used to image the lungs to detect some COVID-19 abnormalities. ■ ■ **CLINICAL COURSE** The onset of disease manifests typically within 4–5 days after exposure and nearly always within 14 days. Symptoms include cough, fever, myalgia, headache, dyspnea, sore throat, and gastrointestinal symptoms of nausea, vomiting, or diarrhea. Sudden onset of dysgeusia and anosmia (loss of taste and smell) occurs in a substantial number of cases, which often resolves in weeks to months. Diverse dermatologic findings occur in patients with COVID-19. General decline of health status, including onset or worsening of dementia, can occur in older individuals, especially those with

cognitive impairment. Mental health consequences of the acute disease, isolation measures, and medical management regimens are common, including fatigue, depression, general and social anxiety, sleep disturbances, cognitive deficits, post-traumatic symptoms, and substance abuse disorder. Long COVID is a chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months with a wide range of symptoms or conditions that may improve, worsen, or be ongoing. The symptoms are varied and can include neuropsychiatric disorders and pain syndromes in addition to respiratory and metabolic changes. People with long COVID may experience many symptoms related to alterations in mental health and decreased brain function and experience increased suicidal ideation, which may increase suicide risk. ■ ■ **COMPLICATIONS** Severe complications of infection can occur. The major complication in patients with severe disease is acute respiratory distress syndrome requiring oxygen therapy and mechanical ventilation. Disseminated intravascular coagulation is a complication in severe disease. Thromboembolic complications are common in severe disease, mostly occurring as venous thromboembolism, including pulmonary embolism or deep vein thrombosis. Events stemming from arterial thrombosis, including acute stroke or ischemia of the limbs, are reported. Cardiac complications manifest as heart failure, myocardial injury, or arrhythmias and cardiovascular syndromes, especially shock. Acute kidney injury requiring dialysis can occur. Encephalopathy occurs in critically ill patients, and delirium in the intensive care unit setting reduces overall survival. Other neurologic complications including seizures, ataxia, or motor or sensory deficits have been reported. Those with COVID-19 disease and laboratory markers of excessive inflammatory

response can exhibit a pattern of persistent fever and multiorgan disease with high risk of fatal outcome. An excessive proinflammatory host response to SARS-CoV-2 infection likely contributes directly to pulmonary pathology and severity of COVID-19. Manifestations typically mediated by autoantibodies have been reported. Disease is usually caused by direct viral pathogenesis in tissues or the associated immune response, but secondary bacterial or fungal infections do occur, usually as bacteremia or respiratory infections.

■ ■ **GENERAL MEDICAL MANAGEMENT** Medical management of COVID-19 is focused on severe respiratory illness and systemic disease manifestations. As bacterial infection is an uncommon complication of COVID-19, antibiotics are not generally indicated, but when the diagnosis is uncertain, empiric antibiotic regimens for community-acquired or health care-associated pneumonia should be considered. Since there is such a substantial risk of thromboembolic complications, many experts recommend pharmacologic prophylaxis of venous thromboembolism for all hospitalized patients with COVID-19. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used as antipyretic agents, but questions have been raised about a possible association between NSAID use and worse outcomes with COVID-19; when possible, the preferred antipyretic agent is acetaminophen. Immunosuppressed individuals are at higher risk of severe illness or death; therefore, on a case-by-case basis, providers should decide whether to continue immunomodulatory agents such as steroids or other immunosuppressive drugs that were indicated for preexisting conditions prior to onset of COVID-19. Generally, experts agree that the best course usually is to continue common preexisting medications of aspirin, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. CHAPTER 205 The time to recovery from COVID-19 is affected by the severity of disease, the individual's preexisting comorbidities, and age. Generally, symptomatic infection is an acute syndrome that resolves in 2 weeks in ~80% of persons, especially following mild or moderate disease. Individuals with severe disease often

require longer for recovery, on the order of several months. However, a subset of individuals with infection progress to a recurring or persisting pattern of symptoms, most commonly including fatigue, cognitive deficits, cough, dyspnea, or chest pain. Those with severe acute pulmonary or cardiac injury may have persisting respiratory or cardiac impairment. Diverse long-term adverse mental health consequences of infection are common, and the public health measures used to manage the pandemic also have led to social isolation with adverse mental health consequences.

**SARS-CoV-2 and COVID-19 ■ ■SPECIFIC TREATMENTS** The approach to specific treatment of COVID-19 of varying levels of severity continues to evolve, especially because emerging SARS-CoV-2 variants exhibit differing properties of transmission efficiency and capacity to cause disease. Most options fall into the categories of small-molecule viral inhibitors, polyclonal or monoclonal antibodies, and immunomodulators. The recommended use of these medical countermeasures can be grouped under categories of outpatient management of mild disease or hospital management of severe disease. We recommend consulting up-to-date recommendations from groups authorized to provide expert or governmental guidelines, including the National Institutes of Health (NIH) COVID-19 Treatment Guidelines Panel in the United States or the WHO for international settings (see “Further Reading,” below). Many but not all of the guidelines from such groups are harmonized. During the early years of the pandemic, numerous countermeasures were authorized (i.e., not necessarily fully approved) under the Emergency Use Authorization (EUA) authority that allows the FDA to facilitate the availability and use of medical countermeasures prior to full licensure when the secretary of the Department of Health and Human Services declares that an EUA is appropriate for a public health emergency. However, the WHO ended Public Health Emergency of International Concern status for COVID on May 5, 2023, and now proper drug use once again typically requires FDA approval. Antiviral drugs (including small-molecule inhibitors and polyclonal or monoclonal antibodies) have the most potential to alter the clinical

course early in infection, since they may reduce the peak titer of virus, a parameter that is likely correlated with severity of disease. Later in the clinical course, anti-inflammatory medications may be of more benefit since the pathogenesis of disease is driven increasingly more over time by tissue inflammation and systemic inflammatory responses than by direct viral cytopathic effect.

**■ ■OUTPATIENT MANAGEMENT** Most patients with COVID-19 can be managed as outpatients. Individuals who are infected but have mild disease can be treated with supportive care only. The decision to use antiviral drugs is driven principally by medical risk factors, but it should also consider available resources, the clinical situation, and the patient’s social circumstances. Shared clinical decision-making should be used regarding COVID-19-specific therapy to accommodate the individual’s values and preferences in addition to medical risk factors. Risk-benefit ratios are difficult to assess. Reducing viral load has the potential to reduce acute disease and complications, but COVID medications also have the potential to cause adverse effects or drug-drug interactions, and they carry the risk of causing a rebound COVID-19 phenomenon that then may require prolongation of isolation. COVID-19-specific therapy is not recommended for individuals who have asymptomatic SARS-CoV-2 infection. Symptomatic patients who are most likely to benefit from specific antiviral treatment are individuals who are older, unvaccinated, with multiple medical comorbidities, and/or with immunocompromised conditions. Others who lack these risks might benefit to some degree, but since their risk of hospitalization or death is low the impetus to risk side effects is much less compelling. For symptomatic adults who are at increased risk, many experts recommend treating immunocompetent unvaccinated adults

50 years of age, all adults  $\geq 65$  years of age regardless of vaccination status, immunocompetent adults of any age who have multiple medical risk factors for progression to severe disease, and immunocompromised adults of any age. As of late 2024, the principal antiviral drug for use in outpatients is nirmatrelvir-ritonavir, which should be administered as soon as possible and within 5 days after symptom onset. The typical dose is nirmatrelvir 300 mg and ritonavir 100 mg orally twice daily for 5 days, but the dose should be adjusted for reduced renal function and should be avoided in patients with severe renal dysfunction. Drug interactions are possible, so prior to prescribing, providers should review all medications and consider potential drug interactions in consultation with a pharmacist or using online tools. In a minority of cases, viral shedding occurs again after an initial improvement, with or without mild symptoms, requiring an extension of the period of isolation. Patients on treatment should be counseled to return for reevaluation if the patients experience worsening or new-onset mental status changes such as confusion or worsening respiratory symptoms such as dyspnea. Patients should be counseled on an appropriate period of self-isolation to achieve infection control, per current recommendations of the U.S. Centers for Disease Control and Prevention (CDC). PART 5 Infectious Diseases If nirmatrelvir-ritonavir is not available or suitable, alternatives that are more difficult to administer are available. Remdesivir is approved, but administration requires three IV doses over 3 days. The processing in vivo of this broad-spectrum antiviral prodrug causes intracellular delivery of an active chemical that serves as a ribonucleotide analogue inhibitor of SARS-CoV-2 RNA polymerase. Molnupiravir is an anti viral small-molecule drug that is metabolized into a ribonucleoside analogue that inhibits viral reproduction by promoting widespread mutations in the replication of viral RNA by RNA-directed RNA polymerase. In December 2021, the FDA granted an EUA to molnupiravir for use in certain populations where other treatments are not feasible, but with a black box warning about its mutagenic properties that limit its use in patients with pregnancy potential. Virus-neutralizing antibodies delivered as monoclonal human antibodies or antibody combinations or as constituents of high-titer convalescent plasma also have been authorized for postexposure prophylaxis or treatment of outpatient COVID-19, but new variants arise and reduce their effectiveness and often lead to withdrawal of authorization. Many other therapies have been used without specific authorization or approval and are of uncertain benefit. Antibiotics are

not recommended for routine treatment of COVID-19, as bacterial complications are unusual. Dexamethasone, prednisone, and other corticosteroids have been used in the setting of COVID-19 infection accompanied by acute exacerbation of chronic obstructive pulmonary disease or asthma.

■ ■ INPATIENT MANAGEMENT Indications for Hospitalization COVID-19 patients with symptoms suggestive of more severe disease—especially moderate to severe dyspnea, cyanosis, change in mental status or chest pain, reduced urine output or anuria, with or without oxygen saturation  $\leq 94\%$ —should be evaluated in an emergency department. The NIH COVID-19 Treatment

Guidelines Panel recommends hospitalization for patients with oxygen saturation of <94% on room air, respiratory rate of >30 breaths/ min, PaO<sub>2</sub>/FiO<sub>2</sub> <300 mmHg, or lung infiltrates on chest radiograph occupying >50% of lung fields. The decision to hospitalize varies regionally and due to differences in available resources and social risk factors. Management in Hospital Upon hospitalization, the initial assessment should seek to define medical comorbidities or immunocompromising factors and to identify dysfunction in critical organ systems. Fever should be controlled, preferably with acetaminophen. The use of NSAIDs has not been aligned with poor COVID-19 outcomes, but most experts suggest avoiding their use or limiting them to lower effective doses. If the patient uses common chronic medications, those generally should be continued, including aspirin (unless there is a clear bleeding risk), statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Hospitalized patients should receive therapeutic-dose anticoagulation to prevent venous thromboembolism. For patients without any risk factors, additional care is primarily supportive. Patients with risk factors for severe disease typically are treated with remdesivir. Oxygen should be used to support oxygen saturation. Patients receiving low-flow supplemental oxygen are usually treated with remdesivir (for antiviral effect) and low-dose dexamethasone (for anti-inflammatory treatment). Patients treated with high-dose glucocorticoids should be monitored for common adverse effects, especially hyperglycemia and increased risk of co-infection. If the oxygen requirement escalates during the first 4 days of hospitalization despite those treatments, with severe disease and elevated inflammatory markers on laboratory testing, the Janus kinase inhibitor baricitinib or the monoclonal IL-6-blocking antibody tocilizumab can be used. Janus kinase inhibitors typically are used for treatment of rheumatoid arthritis because of their known immunomodulatory effects, which probably also improve inflammation during COVID-19, but baricitinib may also mediate some direct antiviral effects by interfering with viral entry into cells. Alternatively, tocilizumab can be used for immunomodulatory effect. This biologic drug is a humanized monoclonal antibody against the IL-6 receptor that blocks the effect of the cytokine IL-6, which plays an important role in pathogenesis. These immunomodulatory therapies are also usually used for patients admitted to an intensive care unit to receive high-flow supplemental oxygen or noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation. Abatacept or infliximab are alternate immunomodulatory agents that can be used if the first-line immunomodulators are not available. ■ ■ANTIBODY-BASED THERAPIES Passive immunization with SARS-CoV-2 antibodies to achieve antiviral immunity or therapeutic effect has been tested using convalescent plasma (blood plasma taken from persons who have recovered from COVID-19) or human monoclonal antibodies (mAbs). The typical overall composite titer of SARS-CoV-2-neutralizing antibodies in convalescent plasma following a single primary infection is moderately low, limiting its effectiveness and reproducibility. Human mAbs are recombinant proteins made in the laboratory based on the genes encoding an antibody obtained typically from a single SARS-CoV-2-specific B cell isolated from the peripheral blood of a convalescent individual. Numerous mAb products obtained EUA for use in outpatients

with laboratory-confirmed mild to moderate SARS-CoV-2 infection who were at high risk for progressing to severe disease and/or hospitalization, although these EUAs for therapy are now revoked because new variants have escaped their activity. ■ ■TREATMENT OF COMPLICATIONS Severe and complicated COVID-19 is a complex disease that can affect the respiratory and cardiovascular systems and may involve all other major organs. Disease severity and mortality are often determined by complications due to the systemic effects of a hyperinflammatory and hypercoagulable state. Acute respiratory distress syndrome with severe hypoxia and viral sepsis

are common, with acute cardiac injury, arrhythmias, thromboembolic events, acute kidney injury, cytokine storm, oxidative stress, and thrombosis and shock. Each of these organ system diseases must be managed in the context of ongoing viral infection. Bacterial superinfection of COVID-19 probably occurs, but the incidence is uncertain. There are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication, although some experts routinely administer broad-spectrum antibiotics as empiric therapy for bacterial pneumonia to all patients with COVID-19 and moderate or severe hypoxemia. Ideally, providers initiating empiric therapy should attempt to deescalate or stop antibiotics if there is no ongoing evidence of bacterial infection. Several EUAs have been issued for medical management of complications during COVID-19, including replacement solutions for continuous renal replacement therapy and drugs for sedation via continuous infusion in intensive care. Anticoagulation in the face of COVID-19-associated thromboembolic events is an especially complex situation and requires expert consultation.

■ ■ **ANTIBODY-BASED PREVENTION** Antibodies of the IgG isotype typically have an average serum half-life of about 21 days, and thus passive transfer of immune serum or antibodies confers protection of modest duration. During COVID-19, however, proof of principle for the use of a long-acting antibody (LAAB) combination for longer-term prevention of disease was established with the emergency use authorization of the two-antibody combination drug tixagevimab co-packaged with cilgavimab. These antibodies were engineered with variant residues in the Fc portion of the antibody that altered the kinetics of binding and retention to the Fc receptor neonatal (FcRn) that regulates antibody half-life in vivo. This first-in-human authorization of an LAAB enabled protection of individuals who could not be effectively vaccinated, such as the immunocompromised. The FDA terminated the EUA in January 2023 due to the widespread emergence of escape variants in circulation. However, this program established a paradigm for vaccine surrogate use of LAABs in high-risk individuals. In 2024, the FDA granted an EUA for a second LAAB, pemivibart, which is currently limited to use when the combined national frequency of variants with substantially reduced susceptibility to pemivibart is  $\leq 90\%$ . Pemivibart requires IV administration because of the large (4.5 g) dose for pre-exposure prophylaxis of COVID-19 in adults and adolescents ( $\geq 12$  years of age weighing  $\geq 40$  kg) who have moderate to severe immune compromise due to certain medical conditions or receipt of certain immunosuppressive medications or treatments and are unlikely to mount an adequate immune response to COVID-19 vaccination.

■ ■ **PREVENTION BY IMMUNOPROPHYLAXIS** Four COVID vaccines—two based on mRNA (Pfizer-BioNTech and Moderna), one on a subunit protein approach (Novavax), and one on viral vectored technology (Janssen)—have been authorized or approved in the United States. The EUA for the viral vector vaccine based on a human adenovirus that was modified to contain the gene for making the SARS-CoV-2 spike protein was withdrawn in June 2023 due to association with thrombosis with thrombocytopenia syndrome (TTS). Currently, the mRNA vaccines are available to everyone 6 months and older, and the subunit protein vaccine is for anyone 12 years and older. The principal goal of vaccination is preventing severe COVID-19 by

reducing critical illness or death, hospitalization, or medically attended illness in emergency departments and urgent care visits for COVID-19. Prevention of all symptomatic SARS-CoV-2 infections is beneficial and often measured as a secondary endpoint in clinical trials. Preliminary data also suggest that vaccinated persons with COVID are less likely than unvaccinated persons to suffer long COVID syndrome.

COVID vaccine designs were developed in record time in 2020 because of years of prior research on candidate vaccines for related coronaviruses, including SARS-CoV-1 and MERS-CoV. The viral surface spike (S) protein that is the target of protective neutralizing antibodies was engineered from the native “metastable” membrane-bound form to a stabilized “prefusion” conformation of soluble protein. This protein then was encoded by recombinant mRNA formulated in lipid nanoparticle delivery components. Phase 3 clinical data for the original mRNA vaccines delivered in a two-dose primary series showed 95% efficacy for preventing symptomatic COVID, a stunning outcome for this rapid development program. The durability of immunity proved relatively short in subsequent real-world effectiveness studies in adults, which showed that the protection from the mRNA waned over time. In addition, antigenic variant viruses continue to emerge on a regular basis, further eroding the level of vaccine-induced immunity. In response, manufacturers and regulators have supported a program of progressively updating mRNA vaccines to boost levels of immunity and broaden coverage to recognize newer variants. The original mRNA vaccines from both Pfizer and Moderna protected against the original SARS-CoV-2 virus. The mRNAs encoding spike protein antigens have been replaced three times since, with vaccines targeting different variants of the Omicron virus strain. In 2022, vaccines encoding the S protein from both the original strain and the Omicron variants designated BA.4 and BA.5 (“bivalent” vaccines) were deployed. In 2022, the XBB subvariant of Omicron emerged by recombination of two BA.2 sub lineage viruses, leading to the replacement of vaccines in 2023 with a monovalent vaccine based on XBB. In 2024, the mRNA vaccines were updated to protect against KP.2, a further 2024 sublineage known as a FLiRT variant because it contains a phenylalanine (F) to leucine (L) mutation and an arginine (R) to threonine (T) mutation in the S protein. Even as these updated vaccines were rapidly released, new variants continued to emerge.

CHAPTER 205 SARS-CoV-2 and COVID-19 The protein vaccine contains a recombinant form of S protein instead of mRNA encoding S. The gene encoding the S protein is introduced into an insect virus vector (baculovirus) and expressed in insect cells, and then purified and formulated as a nonreplicating nanoparticle that displays multiple copies of S. The protein nanoparticle construct is then formulated with a saponin-based adjuvant named Matrix-M to increase immunogenicity. The protein vaccine demonstrated 100% effectiveness against moderate and severe disease in phase 3 trial results published in 2021. The vaccine was updated for 2024–2025 with antigen based on a JN.1 variant (that emerged prior to the KP.2 variants on which 2024 mRNA vaccines are based), although the manufacturer reported preclinical studies in which the JN.1 nanoparticle vaccine induced cross-reactive antibodies to the later KP.2 and KP.3 variants.

■ ■ FURTHER READING Centers for Disease Control and Prevention: COVID-19. Available at <https://www.cdc.gov/covid/>. Accessed September 10, 2024. Centers for Disease Control and Prevention: Infection control guidance: SARS-CoV-2. Available at <https://www.cdc.gov/covid/hcp/infection-control/>. Accessed September 10, 2024. Infectious Diseases Society of America: IDSA guidelines on the treatment and management of patients with COVID-19. Available at <https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/>. Accessed September 10, 2024. National Institutes of Health: Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at <https://www.ncbi.nlm.nih.gov/books/NBK570371/>. Accessed September 10, 2024. World Health Organization: Therapeutics and COVID-19: Living guideline. Available at <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.2>. Accessed December 21, 2024.

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