ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

Chapter e132: Coronavirus Disease (COVID-19)

Jason M. Pogue; Erin K. McCreary; Julie Ann Justo

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 37, Coronavirus Disease (COVID-19).

KEY CONCEPTS

All information in this chapter is current as of August 1, 2022. The COVID-19 pandemic is a rapidly evolving situation with frequently changing information. While this text should serve as a foundational reference, the National Institutes of Health (NIH) and Infectious Diseases Society of America (IDSA) COVID-19 Treatment Guidelines and the Centers for Disease Control and Prevention (CDC) COVID-19 Vaccination site should be referenced electronically for the most current treatment and prevention recommendations.

KEY CONCEPTS

1. Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, is associated with significant morbidity and mortality particularly among patients 65 years of age and older, those with multiple chronic comorbidities, and/or patients of select racial and ethnic backgrounds.
2. The primary route of transmission of SARS-CoV-2 is direct person-to-person respiratory transmission via infected particles (ie, droplets, aerosols). Risk of transmission is greatest for individuals in close contact for a significant period of time, especially while indoors. Transmission can occur from symptomatic, presymptomatic, or asymptomatic individuals.
3. COVID-19 disease progression occurs in three phases of increasing severity: (i) early infection, (ii) pulmonary phase, and (iii) hyperinflammation. The majority of patients recover in the early infection phase; yet a small proportion may progress to the pulmonary and hyperinflammation phases.
4. Signs and symptoms typically emerge 3 to 5 days from onset of infection but may occur sooner or take up to 14 days to manifest. Common symptoms include rhinorrhea, headache, sore throat, sneezing, cough, and fever/chills. Evolving variants manifest differently both with regards to timing and type of symptom onset. Oxygenation status and patient location (hospitalized vs nonhospitalized) are defining characteristics that determine eligibility for specific pharmacotherapy.
5. Symptomatic COVID-19 is diagnosed by a positive nucleic acid amplification test (NAAT) or antigen test for SARS-CoV-2. Asymptomatic infection is a positive test in the absence of symptoms. Probable COVID-19 can be diagnosed by a compatible syndrome in either the absence of viral testing or a negative test. False negative tests are most common early in infection and with use of antigen tests.
6. Four vaccines are available in the United States: two using an mRNA technology platform (Pfizer, Moderna), one using an adenovirus vector platform (Johnson & Johnson), and one using an adjuvanted recombinant spike protein platform (Novovax). All eligible patients should receive a vaccination series as soon as possible to prevent COVID-19.
7. One combination monoclonal antibody product, tixagevimab and cilgavimab, is available for pre-exposure prophylaxis against SARS-CoV-2 for immunocompromised patients who may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available vaccine is not recommended due to history of severe allergy to any vaccine component.
8. Therapeutic management of mild-to-moderate COVID-19 in high-risk, nonhospitalized adult patients should include symptomatic management and either ritonavir-boosted nirmatrelvir, 3 days of remdesivir, or monoclonal antibody therapy. If none of these therapies are available, molnupiravir may be considered.
9. Therapeutic management of severe COVID-19 in hospitalized patients requiring supplemental oxygen should include dexamethasone, remdesivir, and therapeutic anticoagulation unless contraindicated.
10. Therapeutic management of severe to critical illness from COVID-19 in hospitalized patients with rapidly increasing oxygen needs and systemic inflammation should include dexamethasone plus either baricitinib or tocilizumab. These patients should receive only prophylactic dose heparin (unless contraindicated). Remdesivir should not be used in patients requiring mechanical ventilation.

BEYOND THE BOOK

BEYOND THE BOOK

Most U.S. states have a Department of Public Health webpage dedicated to providing COVID-19 information. Conduct a search to find your state's page and familiarize yourself with the categories of information contained within.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a widespread, life-threatening infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). An epidemiological alert was placed with the World Health Organization (WHO) on December 31st, 2019 after several patients in Wuhan, China were diagnosed with an unexplained pneumonia.[1] The WHO declared a pandemic on March 11, 2020.[2] In the first year of existence, SARS-CoV-2 infected over 83 million people worldwide resulting in 1.82 million deaths.[3] Remarkably, scientists developed multiple effective vaccines to prevent SARS-CoV-2 infection within a year of virus isolation and sequencing.[4–7] COVID-19 vaccination is one of the most important global public health measures to stop the exponential spread of infection and to prevent significant morbidity and mortality. Hundreds of pharmacological agents have been evaluated for COVID-19 prevention and/or treatment with limited success. Therapies with proven efficacy are limited to passive immunity via monoclonal antibodies, three antiviral agents, and multiple agents targeting the inflammatory cascade in severe illness. The approach to clinical management of COVID-19 is based on staging the severity of illness.

ETIOLOGY AND EPIDEMIOLOGY

SARS-CoV-2 is a single-stranded positive-sense RNA virus belonging to the family *Coronaviridae* and the genus *Betacoronavirus*.[8] The term "coronavirus" stems from the Latin root *corona-*, meaning "crown" or "halo,"—so named after the characteristic spike proteins which surround the surface of the virus. Other disease outbreaks caused by betacoronaviruses include those due to Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

1) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

The original source of SARS-CoV-2 infection in humans remains unknown; however, many early cases were associated with exposure to an animal market in Wuhan, China.[9] Theorized origins under investigation include either direct transmission from an infected animal to humans (eg, bat to human), indirect transmission through an intermediate host (eg, bat to pangolin to human), or introduction to humans through cold or food chain products or a laboratory incident. The closest known viral sequence is that of the RaTG13 virus found in a horseshoe bat, which shares 96.2% homology with SARS-CoV-2.[8]

COVID-19 quickly spread from China to countries throughout the world including those in Europe, the Middle East, and the Americas. COVID-19 has since been reported on all continents, representing over 560 million reported cases and 6.3 million reported deaths worldwide from the start of the pandemic through July 2022.[10] Due to underreporting of cases, the actual number of total COVID-19 cases worldwide from the start of the pandemic through November 2021 is estimated to be much higher at 3.8 billion infections (including reinfections) among an estimated 3.4 billion individuals.[11] Approximately 44% of the global population contracted COVID-19 at least once during this period. Notably this was prior to the emergence of the Omicron variant (described below), which has been the most infectious variant to date, and responsible for the largest surges in infections worldwide.

Within the United States, the Centers for Disease Control and Prevention (CDC) describes 87.6 million reported cases of COVID-19 and 1 million reported COVID-19 deaths from the start of the pandemic through July 2022.[12] Considering underreporting of cases, the CDC estimated the actual cumulative incidence of COVID-19 in the United States during the time period from February 2020 to September 2021 was still higher at 146 million total infections, 124 million symptomatic infections, 7.5 million hospitalizations, and 921,000 deaths.[13] The estimated COVID-19 infection rate was 44,650 cases per 100,000, suggesting COVID-19 may have infected over 40% of the US population during this period, a number similar to those reported globally. Individuals aged 18 to 49 years were estimated to comprise the highest proportion of both total (51%) and symptomatic COVID-19 infections (52%); however, elderly individuals aged 65 years or older were estimated to comprise the highest percentage of hospitalized patients (43%) and COVID-19 deaths (77%).

Within the United States, COVID-19 incidence rates to date have been characterized by at least five distinct surges. The first surge in March and April 2020 represented the initial rapid spread of the virus to “hot spots,” such as the state of New York. The second surge in July and August of 2020 was characterized by more regional transmission, especially across southern states such as Florida, Arizona, Texas, and California. Subsequent surges were generally widespread throughout the country, including the third surge from November 2020 to January 2021, the fourth surge from August to September 2021 associated with the emergence of the Delta variant, and the fifth and largest surge from December 2021 to January 2022 associated with the emergence of the Omicron variant (BA.1 lineage). A sixth surge is ongoing as of April 2022 due to the emergence of the Omicron BA.2 lineage. Cases have remained elevated through August 2022 (at the time of this chapter’s publication) with the subsequent displacement of the BA.2 lineage with the BA.5 lineage. Further discussion of SARS-COV-2 variants and lineages is provided below.

SARS COV-2 VARIANTS

As COVID-19 continues to spread, the virus is evolving in its human host. This has led to the emergence of SARS-CoV-2 variants and lineages. The CDC defines a SARS-CoV-2 variant by the presence of one or more mutations, or single changes, in a virus’ genome, or genetic code. It defines a SARS-CoV-2 lineage as a group of closely related viruses with a common ancestor.[14] To facilitate discussion with nonscientific audiences, successful variants are often referred to by an assigned label from the World Health Organization (WHO) consisting of a letter from the Greek alphabet, such as Alpha, Beta, and Gamma. A lineage within a specific WHO label is often referred to as a “subvariant” or “sublineage.” For example, the Omicron variant consists of at least seven lineages to date: B.1.1.529, BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5.

The CDC further categorizes a SARS-CoV-2 variant into four classifications based on their potential impact on COVID-19 countermeasures, including vaccines, therapeutics, or diagnostics. The two most important of these classifications are variant of interest (VOI) and variant of concern (VOC). VOIs are novel variants that contain specific genetic mutations that may be associated with changes to receptor binding, reduced neutralization by antibodies from previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, and/or predicted increased transmissibility, immune evasion, or disease severity. A VOI is elevated to a VOC if evidence of such deleterious impacts is demonstrated to a significant degree. To date, there have been five VOCs, including the Omicron variant and its many sublineages outlined above.

The proportion of new COVID-19 infections comprised by each variant changes rapidly in a local region.[14] As new variants emerge and circulate, the variant with the fastest growth rate among the population generally becomes the most common variant in a local region, often over a period of a few weeks. Faster viral growth rates can be due to higher transmissibility (or infectivity), improved ability to evade the immune system, or both. The Alpha variant, circulating in the United States in the spring of 2021, was 43% to 90% more transmissible than prior variants.[15] The Delta variant then emerged in the United States around August 2021 and was 63% to 167% more transmissible than the Alpha variant, likely due in part to significantly higher viral loads (6.2 times higher).[16] The Delta variant also resulted in more severe illness, with approximately double the risk of hospitalization compared to the Alpha variant.[17] The Omicron variant (specifically the BA.1 lineage) demonstrated increased immune evasion compared to the Delta variant, but also appeared to result in less severe illness with 80% lower odds of hospitalization.[18,19] This decreased severity of illness is due to decreased virulence as well as increased immunity in the population from prior infection and/or vaccination. Other Omicron lineages have continued to emerge due to further enhanced immune evasion. As of August 2022, the Omicron BA.5 lineage is now the most predominant variant in the United States, comprising 86% of new cases.

Variant testing on an individual patient’s virus is not readily available for clinical decision-making. However, variant testing is done over time as part of routine public health surveillance. Clinicians typically use reported public health data on currently circulating variants, which may lag by one to four weeks, to determine the most likely variant and/or lineage responsible for an individual patient case. Readers should refer to resources from the CDC for the latest information on SARS-CoV-2 variants.

RISK FACTORS FOR SEVERE DISEASE

The risk of severe disease or mortality from COVID-19 significantly increases with specific factors, with the strongest being older age.[21] When compared to adults aged 18 to 39 years, the risk of a COVID-19 death is 2.2 times higher in adults aged 40 to 49 years, 4.3 times higher in those aged 50 to 64 years, 6.7 times higher in those aged 65 to 74 years, 8.5 times higher in those aged 75 to 84 years, and 10.6 times higher in those aged 85 years and older.[22] Adults aged 65 years or older represent over 75% of COVID-19 deaths in the United States and adults 50 years or older represent over 93% of COVID-19 deaths.[23] Male sex is independently associated with severe disease compared to female sex, demonstrating a 17% higher risk of intensive care unit admission and a 31% higher risk of death.[24] Presence of at least one underlying medical condition is also a predictor of progression to severe COVID-19; the risk increases with the number of comorbid conditions. Knowing whether a patient is at high risk for severe COVID-19 is an important component of assessing an individual patient’s eligibility for COVID-19 therapies.

Belonging to specific racial or ethnic groups is also associated with a higher risk of severe COVID-19 and mortality.[12,23,25] As of July 2022, people of Hispanic ethnicity comprised 28% of COVID-19 deaths in the United States adjusted for age, while only comprising 19.6% of the US population. A similar trend was also found in non-Hispanic Blacks (21.6% and 12.8%, respectively). As a comparison, non-Hispanic Whites comprised 43.3% of COVID-19 deaths adjusted for age while comprising 58.2% of the US population.[26] Lastly, individuals with disabilities, including intellectual disabilities, experience an increased incidence of COVID-19 and risk of hospitalization or death.[27,28]

The imbalance in the burden of COVID-19 demonstrates health inequities present across the United States. Understanding and addressing the structural barriers driving these inequities is a key component of public health efforts to combat COVID-19. Such barriers impact the social determinants including discrimination, poor healthcare access and use, disproportionately higher representation in essential occupations such as farms, factories, grocery stores, public transportation, and healthcare facilities, gaps in education, income, and wealth, and a greater tendency to live in crowded housing.[29]

Pediatric patients are more likely to have asymptomatic or mild COVID-19 illness.[30] Due to the high prevalence of asymptomatic infection in this population, the true incidence of COVID-19 infection is likely underestimated. In one study of children aged 5 to 17 years diagnosed with COVID-19, 58% reported at least one symptom, 5% reported no symptoms, and symptom data was missing or unknown in the remaining 37%. Only 1.2% of school-aged children required hospitalization, 0.1% required intensive care, and <0.01% died from COVID-19.[31]

PATHOPHYSIOLOGY

The primary route of transmission of SARS-CoV-2 is direct person-to-person respiratory transmission via infected particles (ie, droplets and aerosols). Aerosols and droplets containing SARS-CoV-2 are generated from everyday

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

activities, eg, talking or singing, in addition to coughing and sneezing. Risk of transmission is greatest for individuals in close contact (less than 6 ft apart), especially while indoors. Thus, physical distancing, face masks, and increased ventilation are all associated with decreased transmission. Hand washing is also a central component of infection prevention. Outdoor transmission is very uncommon, highlighting the importance of adequate ventilation to circulate the surrounding air.[32] Contact with contaminated surfaces or fomites, eg, doorknobs, clothing, is a rare route of transmission.[33]

Evaluation and management of COVID-19 is based on clinical severity, yet the severity of an individual case often takes days to weeks to become fully evident. This protracted pathophysiology of COVID-19 is a significant driver of both its high infectivity as well as its high morbidity and mortality. The time from virus exposure to symptom onset with COVID-19, ie, the incubation period, ranges from 2 to 14 days and typically 4 to 5 days.[34,35] In one study 97.5% of patients developed symptoms by 11.5 days from exposure.[35] The incubation period may be shorter with the Omicron variant, with a more rapid onset of infection occurring at a median of 3 days (range 0-8 days).[36]

A patient is deemed presymptomatic if they are infected with SARS-CoV-2 but are not yet experiencing symptoms; infected patients who never experience symptoms are deemed asymptomatic. Earlier in the pandemic the majority of COVID-19 transmission (48%-62%) occurred from presymptomatic carriers as this is early in the disease course (1-3 days prior to symptom onset) when SARS-CoV-2 viral loads are high and patients shed significant amounts of replication-competent virus, but patients do not feel ill.[37] The timing of transmission in the Omicron era (where symptom onset is faster) has not been elucidated. Replication-competent virus has infrequently been recovered greater than 10 days following symptom onset in mild-to-moderate COVID-19 or greater than 20 days after symptom onset in severe COVID-19.[38]

COVID-19 disease progression occurs in three phases of increasing severity: (i) early infection, (ii) pulmonary phase, and (iii) hyperinflammation.[39] Notably, not all patients progress through each phase. Early infection is characterized by inoculation, incubation, viral replication, and mild symptoms (eg, fever, cough, shortness of breath). Following inhalation or other contact with SARS-CoV-2, the virus' spike protein (or S protein) gains entry into the host by binding to angiotensin-converting enzyme-2 (ACE2) receptors present on the surface of cells in the respiratory tract, eg, nasal and bronchial epithelial cells and alveolar type II pneumocytes. The virus may also directly infect other human epithelial cells expressing ACE2, such as capillary endothelial cells also in the alveoli or endothelial cells in the small intestine. Another receptor, type II cellular transmembrane serine protease (TMPRSS2), is vital to this interaction with ACE2. It activates the spike protein and cleaves ACE2 which allows for fusion of the viral envelope with the host cell membrane and further endocytosis of the spike protein-ACE2 complex. Once inside the cell, viral RNA is released into the cytoplasm and the virus uses host cell machinery to replicate and form new virions, which then bud off the infected host cell via exocytosis or bursting of the host cell. The new virions then travel to infect neighboring cells in the body and/or enter the bloodstream.[8,37,40]

The pulmonary phase is characterized by localized inflammation of the lung with continued viral replication and moderate symptoms. Development of hypoxia, ie, an oxygen saturation of less than or equal to 94% (0.94), is a key sign which is associated with a poorer prognosis and helps determine eligibility for certain therapies. Thus, this second phase can be subdivided into phase IIa without hypoxia and phase IIb with hypoxia.[8] Hypoxia is the result of impaired gas exchange due to alveolar damage from localized pulmonary inflammation. Such inflammation is driven in part by loss of the anti-inflammatory effects of ACE2 on the renin-angiotensin-aldosterone system. Local ACE2 expression is decreased following endocytosis in the form of the SARS-CoV-2 virion-ACE2 complex. Infected endothelial cells also drive local inflammation via activation of innate, cellular, and humoral immune responses. Monocytes and neutrophils are recruited to the site of infection and potent cytokines such as interleukin-6 (IL-6) are released by activated macrophages and other immune cells. Pulmonary infiltration of the immune system in this phase is often recognized as bilateral ground glass opacities and/or consolidations on chest radiograph or computed tomography.[8,37,40]

The third phase of hyperinflammation is characterized by marked systemic inflammation and severe symptoms. The release of high levels of cytokines, sometimes called a "cytokine storm," leads to dilation of the pulmonary vascular bed with corresponding vascular permeability and leakage, thickening and fibrosis of the alveolar wall, edema filling the alveolar sacs, and thrombus formation (both microthrombi in capillaries and pulmonary emboli in larger vessels of the lungs), which all contribute to pulmonary ischemia and damage. Most COVID-19 deaths are attributable to this cascade leading to acute respiratory distress syndrome (ARDS) with hypoxic respiratory failure. Many critically ill COVID-19 patients also suffer significant injury to one or more additional organ systems, such as the heart, brain, liver, kidneys, and gastrointestinal tract. This may be due to direct cytotoxic injury from the virus given high expression of ACE2 in the endothelial cells of these organs. Organ injury may also be the result of systemic inflammation, cytokine release, and/or thrombosis in local tissues.[8,40] The coagulopathy seen in critically ill patients is a distinct feature of COVID-19 and can appear similar to disseminated intravascular coagulation (DIC). Other manifestations of end-organ damage include acute complications of the cardiac and cardiovascular system (eg dysrrythmias, myocardial infarction, heart failure, cardiogenic shock) as well as thromboembolic (eg, pulmonary embolism, deep venous thromboembolism) and neurologic complications (eg, encephalopathy).

Most COVID-19 patients recover from illness before progressing to the second or third phase (recovery time is usually within two weeks); however, those who do progress and require oxygen supplementation are typically hospitalized. Patients with mild-to-moderate disease managed in the outpatient setting should be closely monitored, as progression of symptoms to severe disease usually occurs approximately 1 week after initial symptom onset.[41] For patients who progress, time to resolution is longer and can be two to three months or longer for critically ill cases experiencing hyperinflammation. Long-term sequelae from COVID-19 can include permanent lung injury or other end-organ damage.[42]

Data regarding the rates of serious outcomes due to COVID-19 mainly stem from early in the pandemic and more contemporary data, in the setting of reduced severity with Omicron and increased preexisting immunity due to vaccination and/or previous infection, are lacking. Among 1.3 million confirmed COVID-19 cases in the United States from January through May 2020, 14% were hospitalized, 2% required intensive care, and 5% died.[43] A similar spectrum of disease severity was observed among 44,672 confirmed cases in China through February 2020, with 81% experiencing mild or moderate disease, 14% with severe disease, 5% with critical illness, and a case-fatality rate of 2.3%.[44] Specifically among the subset of patients hospitalized with COVID-19 early in the pandemic, the case-fatality rate was higher at 15% to 20%; yet it can vary widely based on differences in underlying risk factors within the local population, severity of illness, and potentially other factors such as local threshold for hospitalization.[37]

Due to suspected underreporting of COVID-19 cases, the infection-fatality rate (ie, estimated mortality rate among all individuals with infection) is expected to be much lower than the case-fatality rate (ie, mortality in documented cases). A meta-analysis found the infection mortality rate decreased from 0.47% in April 2020 to 0.31% in January 2021[46] potentially due to improved management of COVID-19 cases over time. With the ongoing evolution of SARS-CoV-2 variants (eg,. Omicron), the introduction of COVID-19 vaccines, and continued improvements in the management of COVID-19 infection, the entire spectrum of COVID-19 severity has likely decreased in severity over time resulting in a lower hospitalization rate and infection-fatality rate. Among hospitalized COVID-19 patients in the United States, the serious outcomes of intensive care unit admission, invasive mechanical ventilation, and mortality have all decreased significantly (about 40%-80%) from March 2020 to May 2022.[47] However, definitive data to confirm this trend are still needed.

Bacterial coinfection at the time of COVID-19 diagnosis is relatively rare at 5%.[48] If bacterial coinfection is diagnosed, the causative pathogen is typically *Staphylococcus aureus,* coagulase-negative staphylococci, or *Klebsiella* spp. The rate of secondary bacterial infection following presentation is higher at 13%.[48] Secondary invasive fungal infections (eg, invasive aspergillosis, mucormycosis, and candidiasis) have also been reported in about 5% to 6% of patients globally, with an increased risk among those with uncontrolled diabetes, critical illness, and/or receiving immunomodulatory therapy (eg, corticosteroids).[49,50] Clinicians should remain vigilant for secondary infections and pursue infectious work-up as clinically indicated.

Children and adolescents are at risk of a serious complication of COVID-19 termed multisystem inflammatory syndrome in children (MIS-C). MIS-C occurs in the period following acute infection with SARS-CoV-2 and is similar in presentation to Kawasaki disease. The incidence rate is rare, approximately 316 persons per 1,000,000 SARS-CoV-2 infections; however, the true incidence is unknown given the uncertainties surrounding the number of children who have been infected.[51] The risk of MIS-C was substantially lower (86%-88%) during the Omicron surge compared to prior Alpha and Delta surges and the risk was particularly lower in vaccinated versus unvaccinated patients.[52] The syndrome is characterized by fever, elevated laboratory markers for inflammation (eg, interleukin-6, tumor necrosis factor), and involvement of two or more organ systems in the presence of current or recent COVID-19 infection or exposure within four weeks and in the absence of alternative plausible diagnoses.[53,54] Other presenting signs and symptoms include abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, and, in severe cases, hypotension and shock. Examples of organ involvement include cardiac dysfunction (eg, myocarditis, cardiogenic shock) and renal dysfunction (eg, acute kidney injury). Sporadic reports of a similar phenomenon in adults, termed multisystem inflammatory syndrome in adults (MIS-A), have occurred. The majority of MIS-A patients were male (70%) and young adults (median age 21 years) and 36% were non-Hispanic Black individuals.[55] The most common symptoms were fever, hypotension, cardiac dysfunction, shortness of breath, and diarrhea. Among the 68% of patients with prior symptoms of a COVID-19-like illness, the median time to onset of MIS-A symptoms was 4 weeks.

While most patients' symptoms from acute COVID-19 infection resolve in a matter of weeks, a subset of patients suffer from prolonged symptoms for over 4 weeks and potentially for months or years. This complication is most commonly referred to as "long COVID," but goes by many other names including "post-COVID conditions," "long haul COVID," "postacute sequalae of COVID-19 (PASC)," and "chronic COVID."[56] Much of the initial awareness and knowledge of long COVID was derived from patient advocacy groups who then contributed to scientific research.[57] A uniform case definition is still lacking and reported symptoms can vary widely. The most common symptoms associated with long COVID include fatigue (85%-95%), self-reported "brain fog" which is also described as sluggish or fuzzy cognition (81%), dyspnea (46%-90%), headache (68%-76%), chest tightness (75%),

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

numbness/tingling (60%), dysgeusia (59%), myalgia (55%-65%), anosmia (40%-55%), depression/anxiety (47%), chest pain (37%-61%), and variation in heart rate and blood pressure (30%-55%).[58] The symptomatology is similar to that of other medical conditions that seem to develop postinfection, particularly myalgic encephalomyelitis/chronic fatigue syndrome.[59] Theorized causes of long COVID include: (1) persistence of SARS-CoV-2 in the tissues of the human body due to immune evasion, (2) damage from ongoing inflammation of the immune system, and (3) ongoing microvascular blood clots affecting the body's circulation.[60]

Long COVID seems to occur more often in individuals who experienced severe acute COVID-19, yet it can develop in anyone who has previously been infected, including asymptomatic individuals who may not realize they were infected.[56] The incidence of long COVID ranges from 4.5% to 10.8% among known COVID-19 cases.[61] Factors associated with a decreased risk of long COVID include initial infection with the Omicron variant (50%-75% lower risk than infection with the Delta variant) as well as COVID-19 vaccination.[61,62] Several health systems in the United States have started dedicated clinics to track and manage long COVID patients.

Lastly, additional research is needed to further elucidate the impact of COVID-19 on serious long-term health outcomes. In a large study of patients from the US Department of Veterans Affairs, the one-year risks and burdens of cardiovascular outcomes, like strokes, cardiac arrhythmias, myocardial infarction, heart failure, myocarditis, and thrombotic disorders, were significantly higher in patients who survived COVID-19 versus patients with no history of COVID-19.[63] Preliminary data suggest that repeat COVID-19 infections can further increase risk of severe outcomes such as cardiovascular disorders and mortality.[64]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: COVID-19[34,41,43,45,65,66]

General

- Wide range in clinical presentation and severity from asymptomatic, presymptomatic, mild illness, moderate illness, severe illness, or critical illness which can result in death.

Diagnosis

- Nucleic acid amplification tests (NAATs), such as real-time reverse transcription polymerase chain reaction (RT-PCR), are the gold standard diagnostic tests for COVID-19 infection.
  - NAATs detect the presence of genetic material of SARS-CoV-2 with high sensitivity and specificity, indicating active or recent infection.
  - Most are performed in a laboratory; some are available as point-of-care tests.
  - Limitations include inability to differentiate replicating virus capable of being transmitted to others from nonreplicating virus. Such distinction would require viral culture which is rarely pursued in clinical practice.
- SARS-CoV-2 antigen tests are an alternative diagnostic methodology.
  - These are immunoassays that detect a specific SARS-CoV-2 antigen and indicate active or recent infection.
  - Many are available as point-of-care tests with results available in minutes, and have become the most common method of testing in the United States.
  - Limitations include a lower sensitivity than most NAATs. Confirmatory testing with laboratory-based NAAT is necessary in certain instances (eg, a patient is symptomatic with a high clinical suspicion for COVID-19, but antigen testing is negative).
- Specimens for NAATs or antigen tests include nasopharyngeal, oropharyngeal, sputum, bronchoalveolar, or saliva samples. Acceptable specimens may vary by the specific test.
- Serologic tests for antibody against SARS-CoV-2 are complementary diagnostics which indicate past infection and/or vaccination.
  - Blood specimens are typically collected via fingerstick or venipuncture for analysis.
- Probable COVID-19 can be diagnosed by presence of a compatible syndrome in either the absence of viral testing or a negative test. False negative tests are most common early in infection.

Signs and Symptoms

- Following viral exposure, initial symptoms take a median of 4 to 5 days to develop (possibly shorter with newer variants) and can persist for weeks (or even months, especially in an immune compromised patient).
- Severity of the case may take days to weeks to become fully evident:
  - Median 7 days after initial symptom onset: 40% of patients will progress to feeling short of breath
  - Median 10 days after initial symptom onset: 14% of patients will progress to severe disease and 5% will progress to critical illness
  - The above reflect rates of progression and symptom evolution prior to Omicron introduction and widespread immunity. While severe and critical disease still occur, the incidence is lower and exact pathophysiological stages remain ill-defined
- Most common symptoms, often presenting together:
  - Runny nose (74%)
  - Headache (72%)
  - Sore throat (68%)
  - Sneezing (61%)
  - Cough (49%)
- Other common symptoms:
  - Fever and/or chills (30%-40% at presentation, up to 89% during hospitalization)
  - Fatigue (38%)
  - Sputum production (34%)
  - Muscle or body aches (30%-40%)
  - Shortness of breath (10%, up to 71% in hospitalized patients)

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

- Diarrhea (4%-19%), nausea or vomiting (5%-12%), abdominal pain (8%)
- New loss of taste or smell (8%, less common with newer variants)

- Critically ill cases resemble a "cytokine storm" with elevated blood concentrations of interleukin-1 (IL-1), IL-2, IL-6, granulocyte colony stimulating factor (G-CSF), and tumor necrosis factor alpha (TNF alpha), along with elevations of other inflammatory markers.
- Secondary bacterial infections and secondary invasive fungal infections may present in a small proportion of patients with COVID-19. Pursue infectious work up as clinically indicated based on risk factors, immune status, and hospitalization status.

Laboratory Tests

- Comprehensive metabolic panel
- Peripheral blood cell counts often low
- Inflammatory markers are often elevated (eg, C-reactive protein, lactate dehydrogenase, ferritin, creatine kinase)
- Coagulation studies are often abnormal
- Abnormalities become more numerous and pronounced with more severe disease

Other Diagnostic Tests

- Chest radiograph typically performed for patients presenting to the emergency department, computed tomography (CT) typically reserved for hospitalized patients with severe disease.
  - Abnormalities include multilobar ground glass opacities (56%), patchy shadowing (52%), or interstitial abnormalities (59% with chest radiograph, 86% with CT).
  - Asymptomatic patients may also have chest abnormalities on imaging.
- CT alone is not recommended for screening or first-line diagnosis of COVID-19 due to low specificity and issues related to infection control.[67]

PREVENTION

The best way to decrease morbidity and mortality associated with COVID-19 is to prevent infection through vaccination. Face masks, social distancing, and increased ventilation are also effective infection prevention strategies; hand washing and disinfectants may also have a role. Monoclonal antibodies have demonstrated effectiveness for primary prevention or postexposure prophylaxis of SARS-CoV-2 infection, but are currently only available for pre-exposure prophylaxis in immunosuppressed patients.[69,70]

Vaccination

SARS-CoV-2 vaccines were developed, distributed globally, and administered to patients within one year of virus identification. The usual timeline from the beginning of pre-clinical work to launch of a successful vaccine is over 10 years, demonstrating the remarkable scientific research efforts for COVID-19.[71] Vaccination prevented an estimated 19.8 million deaths from COVID-19 globally during the first year of vaccine availability, which represents a global reduction of 63% of the total deaths that would have occurred without vaccination.[72]

This section focuses on the vaccines utilized in the United States as of August 1, 2022. Four vaccines are available in the United States under either full Food and Drug Administration (FDA) approval or Emergency Use Authorization (EUA): two as a two-dose primary series using an mRNA technology platform (Pfizer, Moderna), one as a one-dose primary series using an adenovirus vector platform (Johnson & Johnson), and one as a two-dose primary series using an adjuvanted recombinant spike protein platform (Novovax). An additional dose (a third dose of an mRNA vaccine or a second dose of adenovirus vector vaccine) is recommended as part of the primary series for patients with moderately or severely immunocompromised who are less likely to respond to vaccination. As the Novovax vaccine was only approved in July 2022 and there are no data on the safety or efficacy of additional doses, there is currently no recommendation for additional doses in any patient population with this vaccine.

Although not the focus of this chapter, there are multiple other vaccines utilized internationally. A second adenovirus vector platform vaccine, AZD1222, is used in many countries globally as a two-dose primary series, but not in the United States. There are also multiple inactivated platform vaccines used internationally (eg, Sinovac, Covaxin, Coronavac, and BBIBP-CorV).

All of the currently available vaccines were designed based on the spike protein of the original strain of SARS-CoV-2. Booster doses have since been recommended due to a combination of waning immunity and increased immune evasion by some VOC (eg, the Omicron variant and its sublineages). While protection against symptomatic infection decreases over time from vaccination, the authorized vaccines, particularly when boosted with an additional dose(s) of an mRNA vaccine, continue to provide robust protection against severe disease, hospitalization, and death. In May 2022, unvaccinated individuals ≥5 years of age had twice the risk of testing positive for COVID-19 and six times the risk of dying from COVID-19 compared to people vaccinated with at least the primary series of COVID-19 vaccines.[73]

A booster vaccine dose is recommended for most people ≥5 months after completion of the primary series. Additionally, a second booster is now recommended for adults ≥50 years of age, to be given ≥4 months after the first booster (Table e132-1). Among this population (those aged ≥50 years), unvaccinated individuals had 29 times the risk of dying from COVID-19 in May 2022 compared to vaccinated individuals who received a primary series and two boosters.[73] All current booster recommendations from the CDC prefer the use of mRNA vaccines regardless of what was utilized for the primary series. This is due to an enhanced immune response and an improved safety profile with mRNA vaccines.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

TABLE e132-1

CDC Recommended Vaccine Schedule as of July 2022

	Age range	Dose	Primary Series	1st booster[a]	2nd booster[a]
Moderna (mRNA1273)	6 months – 5 years	25 µg	Two doses, 4-8 weeks apart	Not currently recommended	
	6-11	50 µg		Not currently recommended	
	12-17	100 µg		Not currently recommended	
	18-49	100 µg		≥5 months after dose 2	Not currently recommended
	≥50	100 µg		≥5 months after dose 2	≥4 months after dose 3
Pfizer (BNT162b2)	6 months – 4 years	3 µg	Three dose series, second dose 3-8 weeks after first, third dose ≥8 weeks after second	Not currently recommended	
	5-11	10 µg	Two doses, 3-8 weeks apart	≥5 months after dose 2	Not currently recommended
	12-49	30 µg			
	≥50	30 µg		≥5 months after dose 2	≥ 4 months after dose 3
Johnson and Johnson (Ad26.CoV2S)	18-49	0.5 mL	One dose	≥2 months after dose 1	Not currently recommended
	50+	0.5 mL	One dose	≥2 months after dose 1	≥ 4 months after dose 2
Novovax (NVX-CoV2373)	≥18	0.5 mL	Two doses, 3-8 weeks apart	Not currently recommended[b]	
Patients with moderate-to-severe immunocompromised					
	Age range	Dose	Primary Series	1st booster[c]	2nd booster[c]
Moderna (mRNA1273)	6 months – 5 years	25 µg	Three dose series, second dose 4 weeks after first, third dose ≥4 weeks after second	Not currently recommended	
	6-11	50 µg		Not currently recommended	
	12-17	100 µg		Not currently recommended	
	18-49	100 µg		≥3 months after dose 2	Not currently recommended
	≥50	100 µg			≥4 months after dose 3
Pfizer (BNT162b2)	6 months – 4 years	3 µg	Three dose series, second dose 3 weeks after first, third dose ≥8 weeks after second	Not currently recommended	
	5-11	10 µg	Three dose series, second dose 3 weeks after first, third dose ≥4 weeks after second	≥3 months after dose 3	≥4 months after dose 4
	12-49	30 µg			
	≥50	30 µg		≥3 months after dose 3	≥4 months after dose 4
Johnson and Johnson (Ad26.CoV2S)	≥18	0.5 mL	Two doses; dose 2 should be an mRNA vaccine ≥4 weeks after the first dose	≥2 months after dose 2	≥4 months after dose 3
Novovax (NVX-CoV2373)	≥18	0.5 mL	Two doses, 3-8 weeks apart	Not currently recommended[d]	

[a]Can mix and match between mRNA boosters, if possible mRNA vaccines are recommended for booster doses for patients with primary series of Johnson and Johnson given increase breadth of immune response and safety.

[b]Authorized on July 2022 as two-dose series; at time of chapter update nobody is eligible for booster doses. Anticipate recommendations will change in fall of 2022, so stay abreast of latest recommendations from the CDC.

[c]Can mix and match between mRNA boosters; if possible mRNA vaccines are recommended for booster doses for patients with primary series of Johnson and Johnson given increase breadth of immune response and safety.

[d]Authorized July 2022 as two-dose series with no data available surrounding an extra dose as part of primary series in those with moderate to severe immunocompromise; at time of chapter update, there is no recommendation for additional doses. Anticipate recommendations will change in fall of 2022, so stay abreast of latest recommendations from the CDC.

Decisions regarding additional boosters for the fall of 2022 and beyond are currently being considered. It is anticipated that the booster recommendations for the fall of 2022 will be for bivalent vaccines directed toward both the original SARS-CoV-2 virus and the Omicron subvariants BA.4/BA.5. Importantly, this is a dynamic situation and subject to change. Pharmacists and other healthcare providers should reference the CDC for the most recent information regarding COVID-19 vaccines, the need for booster doses, and vaccine efficacy against VOC.[74]

mRNA Vaccines

SARS-CoV-2 ushered the first successful mRNA vaccines into widespread use in patients. Although no mRNA vaccines were FDA-approved prior to COVID-19, the mRNA platform was previously studied in multiple phase 1 and 2 trials for other viruses, which helped accelerate SARS-CoV-2 vaccine development. mRNA vaccines encode the SARS-CoV-2 spike protein, allowing ribosomes within antigen presenting cells to translate the genetic material and present it to the immune system to stimulate an immune response. The mRNA administered is noninfectious and cannot be integrated into human DNA. mRNA is inherently unstable and these vaccines are therefore formulated within lipid nanoparticles to avoid rapid extracellular breakdown.[71] Two mRNA vaccines are currently available globally. In the United States, mRNA vaccines are preferred over viral vector vaccines for both the primary series and booster doses due to increased efficacy against infection and severe disease, a broadened immune response, and a more favorable safety profile.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

BNT162b2 (Pfizer/BioNtech)

BNT162b2 is an mRNA vaccine that encodes the full length prefusion spike protein for SARS-CoV-2. It is US FDA approved for adults ≥16 years of age as a two-dose primary series. It received EUA for use as a two-dose primary series in patients aged 5 to 15 years of age, a three-dose primary series in children aged 6 months to 4 years, a booster dose in patients ≥5 years of age, and a second booster for adults ≥50 years of age. Furthermore, it has been authorized to give an additional dose as part of the primary series (ie, three-dose primary series) to moderate or severely immunocompromised individuals at least 4 weeks after the second dose (Table e132-1).

Initial authorization resulted from the findings of a phase 3 randomized clinical trial enrolling 43,448 patients 16 years of age or older in 152 sites worldwide who received two 30-µg doses of BNT162b2 or placebo on day 0 and day 21.[6] Symptomatic COVID-19 ≥7 days after the second dose occurred in 0.04% participants receiving the vaccine compared with 0.89% participants receiving placebo for a vaccine efficacy (VE) of 95% (95% CI 90.3-97.6). Only one case of severe COVID-19 occurred in a vaccine recipient (compared to nine cases in placebo recipients), and 0 vaccinated patients required hospitalization.

Adverse events were largely mild to moderate in nature and more likely to occur in younger patients. Systemic reactions were more common after the second dose. Common adverse events were injection site pain (83%), fatigue (59%), headache (52%), myalgia (37%), chills (35%), and fever (16%). Most reactions resolved within 1 to 2 days after vaccination.

Results from a randomized, placebo-controlled trial of BNT162b2 in adolescents (12-15 years of age) demonstrated similar findings. Confirmed COVID-19 ≥7 days after the second dose occurred in 1.6% participants who received placebo compared to 0% who received vaccine for an estimated VE of 100% (95% CI 75.3-100). Adverse events in adolescents were similar in frequency and severity to those described above for participants aged 16 to 25 years.[76]

Lower doses of BNT162b2 are now authorized for children from 6 months to 11 years of age (Table e132-1). These authorizations were based primarily on a combination of immunobridging and safety data, which is common methodology for approval of pediatric vaccines. In these analyses, a two-dose series of 10 µg (1/3 the adult dose) for children aged 5 to 11 years and a three-dose series of 3 µg (1/10 the adult dose) demonstrated a similar immune response and safety profile to the standard 30 µg dose that demonstrated clinical efficacy in those aged 16 to 25 years.[77]

mRNA1273 (Moderna)

mRNA1273 is an mRNA vaccine encoding the full length prefusion spike protein for SARS-CoV-2. This vaccine received US FDA approval as a two-dose primary series in adults 18 years of age or older.[78] It received EUA as a two-dose primary series in patients aged 6 months to 17 years of age, a booster dose in patients ≥18 years of age, and a second booster for adults ≥50 years of age. Furthermore, it is authorized to give an additional dose as part of the primary series (ie, three-dose primary series) to moderate or severely immunocompromised individuals at least 4 weeks after the second dose (Table e132-1).

Initial approval stemmed from a phase 3 trial that enrolled approximately 30,000 patients 18 years of age or older to receive two doses of 100-µg mRNA1273 or placebo on day 0 and day 28.[4] Symptomatic COVID-19 ≥14 days after the second dose, occurred in 0.08% participants receiving vaccine compared to 1.3% participants receiving placebo, resulting in a VE of 94.1% (95% CI 89.6-96.8). Secondary outcomes included symptomatic COVID-19 ≥14 days after the first dose (225 vs 11 cases; VE 95.2%), and severe disease (0 vs 30 cases in vaccine and placebo recipients, respectively).

Adverse reactions were generally mild to moderate in nature, more common in younger patients, and more frequent and severe following the second dose. After the second dose, injection site reactions were the most common adverse event occurring in 89% of patients, followed by fatigue (65%), myalgia (58%), chills (44%), and fever (16%).

mRNA1273 has recently received EUA as a two-dose primary series for children aged 6 months to 17 years. Similarly to BNT162b2, these authorizations were primarily based on immunobridging and safety data. The authorized dose for adolescents aged 12 to 17 years is the same (100 µg) as that for adults ≥18 years of age. The authorized dose is 50 µg (1/2 the adult dose) for children aged 6 to 11 years and 25 µg (1/4 the adult dose) for children aged 6 months to 5 years (Table e132-1).

Real-World Safety with mRNA Vaccines

Although not observed in the clinical trials, reports of allergic reactions with administration of both mRNA vaccines surfaced soon after the global vaccination campaign commenced. Ten million doses of BNT162b2 and 7.5 million doses of mRNA1273 were administered to Americans from December 14, 2020, through January 18, 2021, and reported in the CDC vaccine adverse event reporting system (VAERS). Sixty-six cases of anaphylaxis were reported for a rate of 4.7 cases per million doses with BNT162b2 and 2.5 cases per million doses of mRNA1273.[79] In a separate analysis within one health system of 64,900 healthcare workers who received their first dose of an mRNA vaccine, sixteen had an anaphylactic reaction for a rate of 247 cases per million doses.[80] All cases in this series resolved without shock or the need for endotracheal intubation. Ten (63%) of the patients experiencing anaphylactic reaction had a history of prior allergic reactions and five (31%) had a history of anaphylaxis. While anaphylaxis is a rare adverse event, it is important to counsel patients prior to vaccination and provide close monitoring for 15 to 30 minutes after receipt of an mRNA vaccine, especially in patients with a prior history of significant allergic reactions. Pharmacists and patients should also be aware that a delayed (median onset 8 days), large rash at the injection site has been observed following receipt of mRNA1273. These rashes can be managed supportively (ice, antihistamines, topical/systemic corticosteroids) and are not a contraindication to receive subsequent doses of the vaccine, even though they may recur with additional doses.[81] This rash resolves after a median of 6 days.

Real-world evidence has also demonstrated an association between mRNA vaccines (both BNT162b2 and mRNA1273) and myocarditis, more frequently seen with the second dose and in younger males. Median time to symptom (eg, chest pain, shortness of breath, palpitations) onset is 2 days and occurs within 7 days for most patients. Rates of myocarditis following the second dose are estimated at 40.6 cases per 1 million vaccinations in males aged 12 to 29, compared to 2.4 cases per 1 million vaccinations in males ≥30 years of age. Comparative rates in females are 4.2 and 1 cases per 1 million vaccinations, respectively.[53] The highest rates appear to occur with dose 2 in young males aged 12 to 24 years (46, 76, and 39 cases per million in the 12- to 15-, 16- to 17-, and 18- to 24-year-old age groups, respectively). To date, myocarditis rates with booster doses appear lower than with second doses. Additionally, increasing the interval between the first and second doses and/or preferential use of BNT162b2 over mRNA1273 in these high-risk age groups may decrease the incidence of myocarditis. In contrast to viral myocarditis, myocarditis associated with mRNA vaccines rarely requires ICU level care or has a fulminant course and cardiac recovery occurs rapidly in nearly all cases.[82] The US FDA Advisory Committee on Immunization Practices recommends vaccination in all eligible children, stating the benefit of vaccination outweighs the risk for all age groups.[83]

Viral Vectored Vaccines

Viral vectored vaccines consist of either nonpathogenic or mildly pathogenic adenovirus vectors with altered genetic material to include the SARS-CoV-2 spike protein. The viral vectors are engineered so once the adenovirus enters a human cell, it does not replicate and cause disease; however, the DNA from the vector encoding the spike protein can be synthesized into mRNA. The synthesized mRNA then follows the same process as mRNA vaccines to stimulate an immune response directed toward the SARS-CoV-2 spike protein.

Ad26.CoV2S (Johnson & Johnson/Janssen)

Ad26.CoV2S is a replication-deficient human adenovirus type 26 vector that expresses a stabilized variant of the full-length SARS-CoV-2 spike protein.[87] This vaccine received US FDA EUA as a single dose in adults 18 years of age or older.[88] It is also authorized for use as a booster dose in adults ≥18 years of age at least 2 months after the initial dose and a second booster dose in adults ≥ 50 years of age at least 4 months after the first booster dose (Table e132-1). As previously mentioned, the CDC preferentially recommends booster doses, even in patients who received their primary series with Ad26.CoV2S, with mRNA vaccines due to enhanced safety and efficacy.

In the phase 3 trial, primary efficacy analyses were performed in 39,321 seronegative patients randomized 1:1 to receive vaccine or placebo, with a median follow-up time of 2 months postvaccination.[7] Vaccination was associated with a significant decrease in the incidence of moderate or severe infection 14 days (VE 66.9% (95% CI 59.0-73.4)) and 28 days (VE 66.1% (95% CI 55.0 –74.8)) after the dose was administered. Numerically higher rates of efficacy were demonstrated when limited to severe disease cases, and no hospitalizations or deaths related to COVID-19 occurred ≥28 days after vaccination. Five deaths related to COVID-19 occurred in the placebo arm.

The most common adverse events were injection site pain (49%), headache (39%), fatigue (38%), and myalgia (33%). Consistent with mRNA vaccines, these occurred less frequently in patients 60 years of age or older. Of note, there was a numerical imbalance (11 vs 3) in thromboembolic events in vaccinated patients in the trial. Postmarketing surveillance data of 14.1 million vaccinated Americans identified 54 cases of a potentially life-threatening thrombosis with thrombocytopenia syndrome (TTS), which most commonly presented as cerebral venous sinus thrombosis (CVST).[89] The median onset is 8 (range 6-15) days postvaccination and appears to occur most

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

frequently in women 18 to 49 years of age.[90,91] Per the CDC, the estimated incidence of TTS in women aged 18 to 49 years is 7 cases per 1 million vaccinations, with the highest incidence (9-10 cases per 1 million vaccinations) in women aged 30 to 49 years.[89] While the initial symptoms of CVST may be similar to systemic reactions to vaccination (ie, severe headache), the timing of the onset of symptoms (1-2 weeks after vaccination with TTS vs 1-2 days after vaccination for systemic reactogenicity symptoms) is an important counseling point for patients. The pathology of TTS is similar to that described with heparin-induced thrombocytopenia and thrombosis, and TTS is associated with the viral vector vaccine platform as a similar phenomenon has been demonstrated with AZD1222 internationally. Additionally, an association between receipt of Ad26.CoV2S and Guillain-Barré syndrome (GBS) has been demonstrated, with an estimated incidence of 8 cases per 1 million vaccinations. Given these potentially life-threatening cases of TTS occurring in a small percentage of patients receiving Ad26.CoV2S, combined with superior efficacy and ample supply of the mRNA vaccines, the CDC made a preferential recommendation in December 2021 for use of mRNA vaccines over Ad26.CoV2S for both the primary series and booster doses. However, for patients who are unable to tolerate or unwilling to take mRNA vaccines, Ad26.CoV2S is an acceptable alternative.

NVX-CoV2373 (Novavax)

NVX-CoV2373 consists of a full-length, prefusion stabilized SARS-CoV-2 recombinant spike protein antigen adjuvanted with Matrix-M to boost immune response to the spike protein. It is authorized as a two-dose primary series (Table e132-1) based on the results of a randomized, observer-blinded, placebo-controlled trial in 25,452 participants in the United States and Mexico.[92] Patients received two doses of either 5 µg of NVX-CoV2373 or placebo 21 days apart. Confirmed SARS-CoV-2 infection ≥7 days after the second dose occurred in 0.08% participants in the vaccine group compared to 0.78% in the placebo arm, for a VE of 90.4% (95% CI 82.9-94.6). All four severe cases of COVID-19 occurred in placebo recipients.

Adverse events were more commonly observed in the vaccine group compared to placebo and were more frequently observed after the second dose. Common adverse events after the second dose included injection site tenderness (73%) and pain (60%), fatigue (50%), muscle pain (48%), and headache (44%).

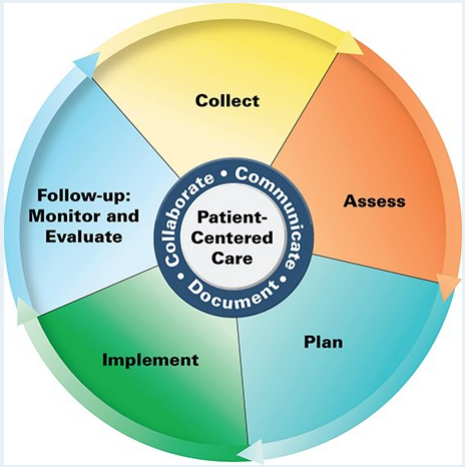
Monoclonal Antibodies: Evusheld™ (Tixagevimab Co-packaged with Cilgavimab)

Monoclonal antibodies are a form of passive immunity targeting the SARS-CoV-2 spike protein.[97] They neutralize cellular viral entry and recruit immune system effector cells to eradicate virus. As of August 2022, the only monoclonal antibody available for pre-exposure prophylaxis or prevention of COVID-19 is the combination of tixagevimab co-packaged with cilgavimab (AZD7442, Evusheld™, AstraZeneca). Both neutralizing antibodies have a prolonged half-life of approximately 90 days, making them candidates for sustained disease prevention. In a randomized, clinical trial of 5,197 patients, receipt of tixagevimab and cilgavimab resulted in a relative risk reduction of 82.8% for developing symptomatic COVID-19 compared to placebo.[70] Additionally, 5 cases of severe or critical COVID-19 and 2 deaths occurred in the placebo group whereas no patients experienced either of these outcomes in the antibody group. Tixagevimab co-packaged with cilgavimab received EUA for pre-exposure prophylaxis of COVID-19 in patients aged 12 years of age and older who are immunocompromised and may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available vaccine is not recommended due to history of severe allergy to any vaccine component. The recommended dosing strategy is 300-mg tixagevimab plus 300-mg cilgavimab, given as two injections in a large muscle (eg, gluteus, thigh), every 6 months.

In this trial,[70] a numerically higher proportion of patients who received tixagevimab and cilgavimab experienced a cardiac-related serious adverse event (0.6% vs 0.2%). However, all patients had cardiac risk factors and/or a prior history of cardiovascular disease upon trial entry. It is not known if the serious cardiac adverse events are related to tixagevimab and cilgavimab or underlying medical conditions. History of cardiovascular disease is not a contraindication to receiving tixagevimab and cilgavimab; however, patients should receive appropriate counseling about possible risks and monitoring for cardiac events postinjection.[98]

PATIENT CARE PROCESS

PATIENT CARE PROCESS



Collect

- Patient characteristics: age, sex, race/ethnicity, social living arrangements, travel history, current health status (eg, chief complaint), past and present medical history, underlying medical conditions, allergies
- Medication history: Nonprescription medications, herbal products, dietary supplements, prescription medications (including prior antiviral or other antimicrobial use), vaccination history
- Subjective data
  - Signs and symptoms including cough, sore throat, rhinorrhea, sneezing, fever, shortness of breath, diarrhea, and new loss of taste or smell
  - Date of symptom onset
  - Vaccination history including timing, number of doses, and type of vaccine received
- Objective data
  - Vitals: Blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature, oxygen saturation, need for supplemental oxygen, height, weight
  - Labs: Complete metabolic panel including serum creatinine (SCr), liver function tests; complete blood count with differential; markers of inflammation (C-reactive protein, D-dimer, ferritin)
  - Microbiologic & Molecular Testing Data: Molecular, antigenic, and/or serologic viral testing; other microbiologic testing for bacterial or fungal infections (if available)

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy
Monash University
Access Provided by:
SILVERCHAIR INFORMATION SYSTEMS

- Radiographic Imaging, eg, chest x-ray, computed tomography (CT) of the chest

Assess

- Assess any recent exposure to an individual with COVID-19 or other high-risk activities for exposure to SARS-CoV-2
- Assess COVID-19 vaccination status, including which vaccine was utilized for primary series and if any boosters were received
- Determine severity of illness (eg, Oxygen saturation, radiographic evidence of pulmonary infiltrates, hemodynamic stability) and setting in which patient will receive care for COVID-19 (ie, outpatient vs inpatient)
- Determine underlying medical conditions or other risk factors for progression to severe COVID-19 (eg, age, sex, comorbidities, immunocompromised status, race/ethnicity)
- Assess duration of symptoms and whether patient is within various eligibility windows for certain therapeutic options (eg, within 5 days of symptom onset for oral antiviral therapy)
- Assess potential medication drug interactions and whether they require a dosage adjustment, a temporary discontinuation of concomitant medications, or whether they are contraindications that preclude the use of certain COVID-19 therapeutic options
- Assess baseline renal function for drug dosing and safety monitoring
- Assess baseline liver function for safety of drug therapy and progression of disease
- Determine likelihood of coinfection of the respiratory tract (typically very low likelihood)
- For uninfected patients, determine eligibility for vaccinations and/or pre-exposure prophylaxis with monoclonal antibody therapy as prevention of infection

Plan *

- Outpatient (nonhospitalized) Management:
  - Initiate appropriate oral antiviral therapy, intravenous antiviral therapy, or intravenous monoclonal antibody therapy based on assessment
  - Recommend supportive care for symptom management as indicated
- Inpatient (hospitalized) Management:
  - Initiate remdesivir as antiviral therapy based on severity of illness, if appropriate
  - Initiate immunomodulatory therapy (eg, corticosteroids) based on severity of illness, if appropriate
- Management in All Settings:
  - Determine goals of therapy, monitoring parameters to determine efficacy and safety of each therapy, and frequency and timing of follow-up
  - Determine appropriate antibiotic or antifungal therapy for secondary bacterial or fungal infection (if applicable), with an associated monitoring plan
  - Determine appropriate management strategy for drug interactions and/or drug dosing based on end-organ function
  - Patient education (eg, infection prevention practices, purpose of treatment, drug-specific information, medication administration, adverse event counseling, informed consent for clinical trials)
  - Recommend vaccinations and/or other prophylaxis as indicated for prevention once patient has recovered from acute illness

Implement*

- Facilitate prescribing, dispensing, and administration of disease-appropriate pharmacotherapy, as applicable
- If bacterial or fungal coinfection suspected, initiate empiric antibiotic or antifungal therapy and de-escalate to narrower-spectrum antimicrobials or discontinue as appropriate based on clinical response and microbiologic data
- Ensure all necessary monitoring parameters are determined
- Provide patient education regarding all elements of treatment plan
- Coordinate care to provide recommended vaccinations or other prophylaxis once patient has recovered from acute illness

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms (eg, cough, sore throat, fever, shortness of breath, hypoxia)
- Presence of adverse effects (eg, infusion-related reactions, dysgeusia, transaminitis, gastrointestinal disturbance, secondary infections, hyperglycemia)
- Regulatory reporting (eg, MedWatch, VAERS)
- Evaluate availability of resources and patient readiness to prevent further transmission

*** Collaborate with patient, caregivers, and other healthcare professionals.**

TREATMENT

Desired Outcomes and General Approach to Treatment

The US FDA has approved one intravenous antiviral agent, remdesivir, for treatment of COVID-19.[99] Other agents that have demonstrated efficacy for COVID-19 include monoclonal antibodies, oral antivirals (ie, ritonavir-boosted nirmatrelvir, molnupiravir) and immunomodulatory therapies (eg, corticosteroids, tocilizumab, baricitinib). Table e132-2 outlines which treatments should be considered for each severity stage of COVID-19 and Tables e132-3 and e132-4 summarize dosing, monitoring, and counseling considerations for drugs recommended for outpatient (Table e132-3) and inpatient (Table e132-4) management of COVID-19. Pharmacotherapy early in the course of illness (during the early infection and/or pulmonary phases) is focused on minimizing viral replication by either supplementing the immune response to eradicate the virus (ie, monoclonal antibodies) or directly

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

inhibiting viral replication (ie, remdesivir, nirmatrelvir/ritonavir, molnupiravir). If patients progress to more severe stages, characterized by progressive hypoxia, radiographic abnormalities, and/or organ failure, pharmacotherapy employed at these later time points is focused on immune modulation (ie, corticosteroids, IL-6 inhibitors, Janus kinase inhibitors) to help blunt the hyperinflammatory phase which could otherwise cause significant end-organ damage, morbidity, and mortality.

TABLE e132-2

Treatment Recommendations by Disease Severity and Patient Location

Severity of Illness	Defining Characteristics	Patient Location	Symptom Management	Nirmatrelvir/ritonavir	Bebtelovimab	Remdesivir	Corticosteroids	Tocilizumab	Baricitinib	Therapeutic Anticoagulation	Notes
Mild to Moderate, Not Hospitalized	Not requiring supplemental oxygen above baseline needs	Outpatient or Emergency Department	Yes	Patients at high risk of hospitalization per FDA EUA criteria	Patients at high risk of hospitalization per FDA EUA criteria.	Patients at high risk of hospitalization per FDA EUA criteria (3-day therapy).	No	No	No	No	Patients breathing ambient air should not receive corticosteroids. Patients should not receive more than one EUA therapy, and choice between those available is based on patient characteristics and preferences, drug interactions, and drug availability Molnupiravir may be considered if ninrmaltrevir/ritonavir, remdesivir, and bebtelovimab are all unavailable. There is an unclear benefit to fluvoxamine, and it should not be routinely recommended. Colchicine, ivermectin, hydroxychloroquine, azithromycin, and inhaled corticosteroids are not recommended.
Moderate	Not requiring supplemental oxygen above baseline needs Radiographic evidence of pneumonia	Hospitalized	Yes	No	Patients hospitalized for reasons other than COVID-19 and incidentally found to have COVID-19 may be eligible.	Not routinely recommended; consider in high-risk patients (3-5 day therapy).	No	No	No	Therapeutic anticoagulation should be avoided unless otherwise indicated for thrombosis treatment	Patients breathing ambient air should not receive corticosteroids. High-risk patients include those with profound immunosuppression (e.g., solid organ or hematopoietic cell transplantation, ongoing graft-versus-host-disease, receipt of B- or T-cell depleting therapy, receipt of CAR-T, neutropenia, actively receiving chemotherapy for malignancy, CD4 < 200 cells/mm^3 [0.2 × 10^9/L])
Severe	Requiring supplemental oxygen above baseline needs or noninvasive ventilation	Hospitalized	Yes	No	No	Low-flow O_2: Yes (5-day therapy) HFNC or NIV: No	Yes	Yes (see notes)	Yes (see notes)	Low-flow O2: Yes HFNC or NIV: Therapeutic anticoagulation should be avoided unless otherwise indicated for thrombosis treatment	Discontinue corticosteroid if supplemental oxygen no longer required. Either tocilizumab or baricitinib should only be administered in combination with corticosteroids. Patients should not receive both tocilizumab and

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

											baricitinib. Tocilizumab or baricitinib is recommended in patients who have rapidly increasing oxygen needs and require HFNC or NIV and/or who have significantly increased markers of inflammation (e.g., CRP ≥75 mg/L).
Severe-Critical	Mechanically ventilated, ECMO, septic shock, and/or multiple organ dysfunction	Hospitalized	Yes	No	No	No	Yes	Yes (see notes)	Yes (see notes)	Therapeutic anticoagulation should be avoided unless otherwise indicated for thrombosis treatment	Large, randomized trials demonstrated no benefit of remdesivir and possible harm of therapeutic anticoagulation in patients requiring mechanical ventilation. Discontinue corticosteroid if supplemental oxygen no longer required. Either tocilizumab or baricitinib should only be administered in combination with corticosteroids. Benefit has not been established in patients not receiving corticosteroids. Patients should not receive both tocilizumab and baricitinib. Tocilizumab or baricitinib are recommended for recently intubated patients who have not already received one of these agents during their admission.

CAR-T, chimeric antigen receptor T-cell therapy; CRP, C-reactive protein; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; SpO2, oxygen saturation.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy®
Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

TABLE e132-3

Dosing, Monitoring, and Counseling for Drugs Recommended for Outpatients with Mild-Moderate COVID-19 at High-Risk for Progression to Severe Disease

Drug	Dose	Duration	Drug Interactions	Adverse Events	Treatment Pearls
Preferred					
Bebtelovimab	175 mg IV	Once	None	Infusion-related reactions	Can be infused as rapidly as over 30 seconds; Authorized for use within 7 days of symptom onset
Nirmatrelvir/Ritonavir	300 mg / 100 mg PO twice daily	5 Days	Strong CYP3A4 and PGP inhibitor— many interactions, utilize interaction checker and work closely with providers to optimize treatment plan	Dysgeusia Diarrhea	Requires renal dose adjustments and not authorized for use if estimated glomerular filtrate rate < 30 mL/min (0.5 mL/s); Authorized for use within 5 days of symptom onset
Remdesivir	200 mg IV on day 1, then 100 mg IV once daily Pediatric patients 3-40 kg: 5 mg/kg/dose IV on day 1 (max dose = 200 mg), followed by 2.5 mg/kg/dose IV once daily (max dose = 100 mg)	Three Days	Chloroquine and hydroxychloroquine may diminish therapeutic effect of remdesivir (Theoretical interaction listed in package insert based on *in vitro* analysis with non-SARS viruses; no clinical data to date to support a clinically relevant impact of coadministration)	Elevated LFTs, Infusion reaction, Bradycardia, Hypotension	Authorized for use within 7 days of symptom onset
Alternative					
Molnupiravir	800 mg orally twice daily	5 days	None	Diarrhea Nausea Dizziness	Do not use in pregnancy/breastfeeding; Counsel patients with reproductive potential about need to use effective contraception; Authorized for use within 7 days of symptom onset

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

TABLE e132-4

Dosing, Monitoring, and Counseling for Drugs Recommended for Inpatients with COVID-19

Drug	Dose	Duration	Drug Interactions	Adverse Events	Treatment pearls
Remdesivir	Adults: 200 mg IV on day 1, followed by 100 mg IV once daily Pediatric patients 3-40 kg: 5 mg/kg/dose IV on day 1 (max dose = 200 mg), followed by 2.5 mg/kg/dose IV once daily (max dose = 100 mg)	5 days or until hospital discharge. Guidelines state may extend to 10 days if no substantial improvement by day 5, although data are lacking for this, and it is not routinely done in clinical practice.	Chloroquine and hydroxychloroquine may diminish therapeutic effect of remdesivir (Theoretical interaction listed in package insert based on *in vitro* analysis with non-SARS viruses; no clinical data to date to support a clinically relevant impact of coadministration)	Elevated LFTs Infusion reaction, Bradycardia, Hypotension	Patients should not be kept in the hospital to complete remdesivir therapy. Patients medically ready for discharge should be discharged. Use lyophilized powder product only for pediatrics (less SBECD, see text).
Dexamethasone	Adults: 6 mg IV or orally once daily Pediatrics: 0.15 mg/kg orally or IV once daily (max dose = 6 mg)	10 days or until hospital discharge or until patient is no longer requiring oxygen support	Moderate CYP3A4 inducer	Hyperglycemia, Fluid retention, Leukocytosis, Dermatologic, Adrenal suppression, Gastrointestinal hemorrhage or perforation, Amyotrophy, Myopathy	Higher doses of 10-20 mg per day were evaluated in smaller trials for patients with severe ARDS; however, these doses are not currently recommended as there is no additional benefit.
Tocilizumab	8 mg/kg IV once based on actual body weight (max dose = 800 mg)	Once	May increase metabolism of CYP3A4 substrates Caution with other immunosuppressive therapies	Bacterial infection, Hypersensitivity	Gastrointestinal, hepatic, and hematologic effects seen with prolonged therapy (when used for rheumatoid arthritis)
Baricitinib	4 mg orally daily	14 days or until hospital discharge	Caution with other immunosuppressive therapies	Bacterial infection, Increased aminotransferases, Venous thrombus embolism	Renal dose adjustment needed

For those treated in the outpatient setting, the goals of treatment are to prevent progression to severe disease requiring hospitalization or death and hasten symptom resolution. For those treated in the hospital (ie, inpatient setting), the primary goals of therapy are survival, to prevent the need for mechanical ventilation or intensive care unit admission, and to shorten length of hospital stay.

Nonpharmacologic Therapy

Patients infected with SARS-CoV-2 with mild to moderate symptomatic COVID-19 should isolate at home for at least 5 days, where day 0 is the first day of symptoms or a positive test.[100] Day 1 is the first full day after symptoms developed or test specimen was collected. Isolation can end after 5 full days in patients who are fever-free for 24 hours and whose symptoms are improving or those who were asymptomatic. Patients should wear a well-fitting mask and avoid travel until day 10. Immunocompromised patients should isolate for at least 10 days and discuss with their doctor before ending isolation. Isolation requirements may vary with each SARS-CoV-2 variant; healthcare providers should refer to the CDC isolation guide for the latest information.

Wherever possible, separate rooms, bathrooms, and household items should be used by the infected patient during this time frame, and everyone in the household should wear a well-fitting mask. During this period of isolation, patients are encouraged to monitor their blood oxygen saturation using a home pulse oximeter and seek healthcare if oxygen saturation levels fall to 94% (0.94) or below. Patients should also seek healthcare if symptoms worsen, especially if breathing becomes more difficult. Adequate sleep, fluid intake, and low levels of activity are encouraged. Symptom control with cough/throat lozenges, warm tea, soup, and nonprescription nonsteroidal anti-inflammatory drugs (NSAIDs) or antipyretics (ie, acetaminophen) are appropriate as needed.

Pharmacologic Therapy

The pandemic resulted in an explosion of investigational therapies. There are thousands of clinical trials registered with the US National Library of Medicine under the search term “SARS-CoV-2.” Many pharmacological agents demonstrate potent *in vitro* antiviral activity and/or immunomodulatory properties; however, few are subsequently found to be clinically effective in human trials.

OUTPATIENT TREATMENT

Outpatient treatment options are summarized in Table e132-3. As of July 1, 2022, four agents are authorized or approved for outpatient treatment of COVID-19: nirmatrelvir/ritonavir, remdesivir, molnupiravir, and bebtelovimab

Antiviral Therapy

There are three available anti-SARS-CoV-2 antiviral therapies available for outpatient use, two of which are available as a 5-day oral course (nirmatrelvir/ritonavir and molnupiravir) and one as a 3-day intravenous regimen (remdesivir). Importantly, both oral antivirals are authorized for use within 5 days of symptom onset, whereas remdesivir is authorized for use within 7 days from symptom onset in outpatients with mild-moderate COVID-19 at high risk for progression to severe disease.

Nirmatrelvir/ritonavir (Paxlovid)

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Nirmatrelvir is an oral SARS-CoV-2 main protease (or 3C-like or 3CL protease) inhibitor. It is coadministered with ritonavir, which serves as a strong CYP 3A4 inhibitor, significantly increasing the half-life and plasma concentrations of nirmatrelvir, to allow twice daily dosing. The SARS-CoV-2 main protease is responsible for facilitating proteolysis, a process that converts large nonfunctional polypeptides into functional proteins which facilitate viral replication.

The primary efficacy data that led to EUA for nirmatrelvir/ritonavir was the EPIC-HR trial comparing 300 mg / 100 mg of oral nirmatrelvir/ritonavir twice daily to placebo in high-risk outpatients with mild to moderate COVID-19.[101] Patients were eligible for inclusion in this trial if they had symptomatic mild to moderate disease, were unvaccinated, had a symptom onset no more than 5 days prior to randomization, and had at least one characteristic (eg, age, obesity) or comorbidity (eg, cardiovascular disease, chronic lung disease) that put them at high risk for progression to severe disease. Receipt of nirmatrelvir/ritonavir was associated with an 88% relative reduction in hospitalization or death compared to placebo. Side effects more commonly seen in the nirmatrelvir/ritonavir arm were dysgeusia (4.5% vs 0.2%) and diarrhea (1.3% vs 0.2%).

Nirmatrelvir/ritonavir is currently authorized as a 300 mg / 100mg twice daily oral five-day course if started within 5 days of symptom onset for outpatients with mild-moderate COVID-19 at high risk for progression to severe disease and is recommended as first-line therapy in both the NIH and IDSA guidelines for this indication. For patients with an estimated glomerular filtration rate (eGFR) between 30 to 59 mL/min (0.5 to 0.99 mL/s), the dose should be reduced to 150 mg / 100mg by mouth twice daily, and it is currently not authorized for use in patients with an eGFR <30 mL/min (0.5 mL/s). The most common side effect is significant taste disturbances, which real world evidence has suggested occurs in roughly half of treated patients. As ritonavir is a significant CYP3A4 and P-glycoprotein (PGP) inhibitor, many drug interactions exist and pharmacists must work closely with providers to ensure optimal management of concomitant medications.

As of July 2022, the FDA has authorized pharmacist prescribing of nirmatrelvlir/ritonavir to patients who qualify for therapy per the EUA if there are no drug interactions requiring therapy modification present and renal and hepatic function can be assessed. Pharmacists are encouraged to work with primary care providers or specialists to determine appropriateness of therapy and/or plans for concomitant therapy modification for more medically complex patients who may benefit from nirmatrelvir/ritonavir.

Pharmacists should also counsel patients on the potential for COVID-19 rebound after completion of their course of nirmatrelvir/ritonavir. This condition describes when a patient has resolution of symptoms and a negative viral test with therapy and then experiences a return of symptoms and/or a new positive viral test around 2 to 8 days after initial recovery. It is currently unclear if this phenomenon may be part of the natural history of SARS-CoV-2 infection with Omicron or if it is related to nirmatrelvir/ritonavir therapy. The return of symptoms is typically mild and self-resolving in a median of 3 days and repeat therapy is generally not recommended. Importantly, patients are considered infectious during this rebound period, so they should be counseled to restart their isolation period and other countermeasures to prevent further transmission.

Remdesivir

Remdesivir is an intravenously administered monophosphoramidate prodrug of an adenosine analog.[102] Remdesivir is highly selective for viral polymerases which lowers risk of human toxicity, it has a long intracellular half-life allowing once daily dosing in humans, and it has a high barrier to viral resistance in laboratory studies.[103,104] Remdesivir works as a delayed chain terminator, halting viral replication. While remdesivir was FDA approved for the treatment of SARS-CoV-2 in hospitalized patients with severe COVID-19 in 2020 (described in detail below in inpatient treatment section), it received approval in early 2022 as a 3-day intravenous course for outpatients with mild to moderate COVID-19 at high-risk for progression to severe disease based on the results of the PINETREE study.[105] In this small, randomized controlled trial, high-risk unvaccinated patients who received a 3-day course (200 mg IV on day 1, 100 mg IV on day 2-3) of remdesivir demonstrated an 87% relative reduction in COVID-19–related hospitalization or death compared to placebo. Even though there are logistical hurdles with administering a 3-day course of intravenous therapy in the outpatient setting, approval was granted given the high degree of efficacy (similar to that documented with nirmatrelvir/ritonavir and monoclonal antibodies) and the limited therapeutic alternatives in the outpatient setting. Both the NIH and IDSA consider a 3-day course of intravenous remdesivir to be an appropriate first-line therapy for high-risk patients with mild-moderate COVID-19 in the outpatient setting.

Molnupiravir

Molnupiravir is an oral prodrug that is metabolized to a cytidine nucleoside analogue, which is ultimately incorporated into SARS-CoV-2 RNA by the viral RNA polymerase during replication. Incorporation of this analogue does not result in chain termination, but rather an accumulation of errors in the viral genome ultimately leading to the inability to replicate. The mechanism of action is known as viral error catastrophe or viral lethal mutagenesis.

Molnupiravir was granted EUA based on the results of the MOVE-OUT study which compared molnupiravir 800 mg given by mouth twice daily for 5days versus placebo in high-risk outpatients with mild to moderate COVID-19 presenting within 5 days of symptom onset.[106] In this trial receipt of molnupiravir was associated with a 30% relative reduction in hospitalization or death (6.8% in molnupiravir arm vs 9.7% in placebo arm; difference, 3.0 %; 95% CI, −5.9 to −0.1). Molnupiravir was well tolerated with no significant increase in adverse events compared to placebo.

Given the mechanism of action of molnupiravir, there are theoretical concerns related to mutagenic potential in humans; however, mutagenesis studies suggest there is a low risk for genotoxicity, particularly given the short duration of therapy. Molnupiravir has demonstrated teratogenicity in animals given supratherapeutic exposures, and it is therefore not advised to prescribe molnupiravir during pregnancy and to avoid breastfeeding while on therapy and for the four days following completion of therapy. Molnupiravir may affect bone and cartilage growth and therefore it is not authorized for use in patients under 18 years of age.

Molnupiravir is currently only authorized for use in high-risk outpatients with mild to moderate COVID-19 “for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.” The NIH and IDSA guidelines list molnupiravir as a second-line option for nonhospitalized patients.

Monoclonal Antibodies

As previously discussed, monoclonal antibodies are a form of passive immunity targeting the SARS-CoV-2 spike protein.[97] They neutralize cellular viral entry and recruit immune system effector cells to eradicate virus. Patients with COVID-19 normally seroconvert (ie, make antibodies) 1-3 weeks post-symptom onset. Importantly, the timing and degree of antibody production can vary among patients based on multiple factors, including severity of disease.[107] Additionally, patients will have varying degrees of neutralizing antibodies based on vaccination and/or previous infection status, with lower levels present the further out the patient is from either of these immune stimulating events. Monoclonal antibodies are likely to be most effective in patients who have yet to seroconvert or have lower amounts of neutralizing antibodies. Therefore, clinical trial data focus primarily on outpatient use of these agents early in disease to prevent progression to hospitalization or death.

Because available monoclonal antibodies target the spike protein of SARS-CoV-2, activity will vary as a function of circulating variants, as VOI and VOC are characterized by significant mutations in the spike protein which can negatively impact binding and inhibition by monoclonal antibodies. Multiple highly effective monoclonal antibody therapies, including bamlanivimab, bamlanivimab/etesivimab, casirivimab/imdevimab, and sotrovimab, were extensively utilized earlier in the pandemic, but are no longer recommended given the loss of activity against the Omicron variant and its sublineages. Bebtelovimab is currently the only anti-SARS-CoV-2 monoclonal antibody available under EUA by the FDA for outpatient use for mild to moderate SARS-CoV-2 infection in patients at high risk for progression of disease as it retains broad neutralizing activity against current sublineages of the Omicron variant. It is anticipated that as SARS-CoV-2 continues to evolve, the available monoclonal antibodies to prevent or treat COVID-19 will continue to change, and clinicians and students should stay abreast of the latest recommendations from the FDA, NIH, and IDSA for currently authorized monoclonal antibodies to inform treatment decisions.

Bebtelovimab

Bebtelovimab is a recombinant neutralizing human IgG1λ monoclonal antibody to the spike protein of SARS-CoV-2. It is currently authorized as a one-time 175-mg intravenous dose infused over at least 30 seconds. Unlike previously authorized monoclonal antibodies, bebtelovimab was not approved based on robust clinical trial data demonstrating a reduction in progression to hospitalization or death in high-risk outpatients with mild-moderate COVID-19 when compared to placebo, but rather phase 2 data show a significant reduction in viral load in standard risk patients receiving bebtelovimab and a small phase 2 study suggest similar outcomes compared to a previously approved monoclonal antibody combination, bamlanivimab/etesevimab. The reason for this accelerated pathway was due to potent *in vitro* activity against Omicron, safety demonstrated in the phase 2 studies, and the public health need as the emergence of Omicron compromised the efficacy of all other monoclonal antibodies used for treatment of COVID-19. The most common adverse events in patients who received bebtelovimab were infusion-related reactions, pruritis or rash at the site of infusion, and nausea and vomiting. However, these occurred in less than 1% of patients in the clinical trials. In real-world use, higher rates of infusion-related reactions have been reported to FDA MedWatch in pregnant patients, resulting in an update to the EUA in May 2022. Bebtelovimab is currently authorized for use within 7 days of symptom onset in outpatients with mild to moderate COVID-19 at high risk for progression to severe disease and is recommended by the NIH as alternative therapy when nirmatrelvir/ritonavir or remdesivir are not available or appropriate options.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University
Access Provided by:
SILVERCHAIR INFORMATION / SYSTEMS

Outpatient Therapy of Uncertain Benefit

Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) with high affinity for the σ-1 receptor (SIR). The SIR is a protein involved in cytokine production regulation, and agonism may reduce damaging inflammatory responses. To date 4 randomized, controlled trials with fluvoxamine have shown mixed results and it is not recommended for use now by the NIH or IDSA.[116–118]

Outpatient Therapies That Should Not Be Used

Ivermectin

Ivermectin is an orally administered antiparasitic agent used globally for treatment of onchocerciasis, strongyloidiasis, and scabies that has *in vitro* activity against several RNA viruses including SARS-CoV-2.[125,126] Most studies reporting benefit of ivermectin have not undergone peer review, have significant methodological flaws, and some have since been retracted making the supportive evidence of extremely poor quality. Ivermectin was initially evaluated in several observational and a few small, randomized trials for patients with COVID-19, with mixed results.[128] Subsequently, larger, randomized controlled trials comparing patients with mild COVID-19 who received ivermectin or placebo found no difference in time to symptom resolution or the need for prolonged emergency department observation or hospitalization.[129–132] Accordingly, the NIH recommends against the use of ivermectin for treatment of COVID-19 and the IDSA suggests against use outside the context of a clinical trial.[65,66]

Hydroxychloroquine or chloroquine

Chloroquine and hydroxychloroquine are orally administered antimalarial agents with anti-inflammatory and immunomodulatory properties and *in vitro* activity against SARS-CoV-2.[134] Early in the pandemic, hundreds of trials were launched to evaluate these agents for prevention and treatment of SARS-CoV-2 infection since these were relatively inexpensive and globally available drugs. Large, randomized trials of pre-exposure prophylaxis, postexposure prophylaxis, outpatient treatment, and inpatient treatment all demonstrated no benefit of hydroxychloroquine therapy or were halted for futility.[135–143] The WHO, NIH, and IDSA all make a strong recommendation against hydroxychloroquine (or chloroquine) use in patients with COVID-19.

Azithromycin

Azithromycin is an orally administered macrolide antibiotic that is commonly prescribed acutely for community-acquired pneumonia and chronic obstructive pulmonary disease exacerbations. It is used chronically as an anti-inflammatory agent in patients with cystic fibrosis. After small, controversial pilot studies of poor methodological quality suggested *in vitro* activity and potential *in vivo* efficacy of azithromycin for patients with COVID-19,[144,145] it was studied alone and in combination with hydroxychloroquine in several large, randomized trials for treatment of COVID-19.[146,147] No benefit was observed and therefore the NIH and IDSA recommend against its use.[65,66]

Inhaled Corticosteroids

Inhaled budesonide has been evaluated in multiple trials for outpatients with mild COVID-19 and may be associated with reduced time to symptom resolution and less need for medical visits, but the open label nature of the studies may impact subjective endpoints.[119,120] Subsequent small double-blinded studies with inhaled ciclesonide provided equivocal results, and an NIH-sponsored double-blinded study with inhaled fluticasone demonstrated no benefit in time to symptom resolution or the need for medical visits with therapy.[122,148] Neither the NIH nor IDSA recommend inhaled corticosteroids and in the absence of new supportive evidence, inhaled corticosteroids should not be recommended for outpatients with mild-to-moderate COVID-19, unless being used for an alternative indication.

Supplements

Nonprescription supplements including, but not limited to, vitamin D, vitamin C, vitamin K, zinc, and melatonin have all been evaluated for prevention and treatment of COVID-19.[149] No supplement has demonstrated benefit and should not be recommended outside of the context of a clinical trial.

INPATIENT TREATMENT

Remdesivir

The efficacy and safety of remdesivir for hospitalized patients has been evaluated in six randomized, clinical trials.[138,141,150–154] The major clinical trial data supportive of remdesivir use were the NIH sponsored Adaptive COVID-19 Treatment Trial (ACTT)-1 and the WHO sponsored SOLIDARITY trial. ACTT-1 enrolled 1,063 adult patients with severe COVID-19 to 10 days of intravenous remdesivir (*N*=541) or placebo (*N*=521).[141] Patients treated with remdesivir experienced shorter time to recovery, defined as either being discharged or ready for discharge, with a risk ratio [RR] for recovery of 1.29 (95% CI 1.12-1.49). The benefit of remdesivir was most pronounced in patients requiring low-flow supplemental oxygen at baseline, where receipt of remdesivir was associated with a 2-day improvement in time to recovery. No benefit was observed in patients breathing ambient air, receiving high-flow supplemental oxygen or noninvasive mechanical ventilation, or requiring mechanical ventilation. The 29-day mortality was 11.4% with remdesivir and 15.2% with placebo (HR 0.73; 95% CI 0.52-1.03). Consistent with ACTT-1, no benefit with remdesivir was demonstrated in an open-label trial of hospitalized patients ≥12 years of age with moderate COVID-19 (ie, not requiring supplemental oxygen).[152] Importantly, mortality rates were low in all treatment groups.

In the SOLIDARITY trial of 8,275 hospitalized patients with COVID-19, remdesivir treatment was associated with fewer deaths (11.9% vs 13.5%, RR 0·86 [0·76-0·98]) and less progression to mechanical ventilation compared to control among patients who did not require mechanical ventilation at enrollment (14·1% vs 15·7%, RR 0·88 [0·77-1·00]).[154] Conversely, no benefit was seen in patients on mechanical ventilation at baseline, a finding consistent with the ACTT-1 trial. Accordingly, the NIH and IDSA recommend remdesivir use in hospitalized patients requiring supplemental oxygen or noninvasive ventilation only (ie, it is not recommended for mechanically ventilated patients).[65,66]

The optimal duration of remdesivir therapy was investigated in the SIMPLE-1 trial.[151] There was no significant difference between a 5-day and a 10-day course of remdesivir. Subsequently, the currently recommended duration of therapy is 5 days, although patients stable for discharge should not remain in the hospital solely to complete 5 days of therapy.

Clinical trials and numerous case reports have reinforced the relative safety of remdesivir with most observed adverse events reported as serum aminotransferase elevations, gastrointestinal symptoms, acute kidney injury, and rash. Rates of adverse events reported in trials were similar to rates in patients receiving placebo. It is recommended to avoid initiation or to discontinue remdesivir in patients with alanine aminotransferase (ALT) greater than 10 times the upper limit of normal and signs and symptoms of liver inflammation.[99] However, clinical trials showed similar rates of aminotransferase elevation in remdesivir-treated patients compared to placebo, and therefore liver injury may be an artifact of COVID-19 disease rather than drug-induced. The manufacturer's labeling does not recommend use of remdesivir in patients with an eGFR less than 30 mL/minute (0.5 mL/s) since these patients were excluded from clinical trials and the drug formulation contains sulfobutylether-beta-cyclodextrin (SBECD), which can accumulate in patients with renal dysfunction. The clinical effects, if any, of SBECD accumulation are poorly described and no patient harm has been associated with SBECD. Remdesivir comes as both a solution and a powder product which contain 6-g SBECD per 100-mg remdesivir and 3-g SBECD per 100-mg remdesivir, respectively. Remdesivir has been used safely in patients with renal dysfunction, including hemodialysis, and therefore use should be considered for patients who may benefit from antiviral therapy regardless of renal function.[156,157]

Remdesivir is FDA approved for all hospitalized adults and children, including neonates. Dosing by age and weight is described in Table e132-2. Use in pregnant patients is safe and should be based on clinical judgment if benefit is deemed to outweigh risk.[158–160]

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

Systemic Corticosteroids

There was significant interest in and controversy surrounding corticosteroids for severe COVID-19 at the beginning of the pandemic. This stemmed from the evolving understanding of the hyperinflammatory pathogenesis in severe COVID-19 and the potential role of corticosteroids to blunt this pathway juxtaposed with data from patients with SARS-CoV-1 and MERS-CoV suggesting administration of corticosteroids was associated with delayed viral clearance and potentially worse outcomes. Importantly, all data in SARS-CoV-1 and MERS-CoV were from small, observational analyses with significant limitations and biases including confounding by indication (ie, sicker patients tend to be treated with steroids). Thus, these data for corticosteroids in previous coronavirus infections were largely uninterpretable and uninformative.

In a large randomized controlled trial of hospitalized patients with COVID-19, receipt of dexamethasone 6 mg either by mouth or intravenously for up to 10 days resulted in a lower 28-day mortality (22.9%) compared to standard care alone (25.7%) (RR 0.83, 95% CI 0.75-0.93) with the largest impact on 28-day mortality in patients who were receiving invasive mechanical ventilation.[161] A benefit was also demonstrated in patients requiring supplemental oxygen; however, there was no benefit seen in patients not requiring supplemental oxygen at baseline. There were no major safety concerns noted in patients receiving dexamethasone.

A meta-analysis of all clinical trials in severely ill hospitalized patients with COVID-19 confirmed a mortality benefit was demonstrated regardless of corticosteroid administered, dose utilized, or degree of oxygen requirement at baseline.[162] Treatment guidelines currently recommend dexamethasone 6 mg for up to 10 days for the management of hospitalized patients with COVID-19 requiring oxygen support. Corticosteroids are not recommended if patients do not require supplemental oxygen as there is concern for potential harm in that subset. Furthermore, it is unclear if systemic corticosteroids have a role in outpatient management of COVID-19 and should not be used in this patient population outside of a clinical trial.

Tocilizumab (Interleukin-6 Receptor Antagonists)

Tocilizumab is a humanized interleukin-6 receptor antagonist (IL-6ra) monoclonal antibody FDA approved for severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, giant cell arteritis, and life-threatening cytokine release syndrome induced by chimeric antigen receptor (CAR) T-cell therapy.[163] Sarilumab is another IL-6ra FDA-approved for rheumatoid arthritis. Tocilizumab was evaluated in multiple RCTs for treatment of severe COVID-19 after an early case series described a hyperinflammatory state in COVID-19 patients and improved clinical outcomes with tocilizumab use.[164] Early trials found no overall benefit to tocilizumab treatment, but these results were limited by inconsistent corticosteroid use, varying severity of illness in patients enrolled, uncontrolled timing of tocilizumab administration, and small sample sizes.[165–169] In a subsequent trial where tocilizumab or sarilumab were administered to critically ill patients within 24 hours of new requirement of respiratory or cardiovascular support, the receipt of either of these agents significantly improved days free of organ support and in-hospital mortality.[170] Tocilizumab and sarilumab were equally effective.[170] Greater than 80% of the patients in this study received corticosteroids, demonstrating the incremental benefit of IL-6 immunomodulation in addition to corticosteroids, which had been lacking from previous trials.

These results were supported by a subsequent study of tocilizumab in patients with oxygen saturation less than 92% (0.92) breathing ambient air or requiring any form of oxygen supplementation and evidence of hyperinflammation (ie, C reactive protein ≥75 mg/L). In this trial, where the majority of patients were receiving corticosteroids, receipt of tocilizumab resulted in significantly lower 28-day mortality.[171] Based on these two large trials, the NIH and the IDSA recommend tocilizumab (or baricitinib, see below) in addition to dexamethasone for patients with rapidly increasing oxygen requirements and significantly increased inflammatory markers, and the US FDA granted EUA.[65,66,172] A large meta-analysis from 27 trials confirmed that IL-6ra treatment is associated with lower 28-day all-cause mortality compared to usual care or placebo.[173] The totality of evidence is more robust for use of tocilizumab for patients with severe COVID-19; however, intravenous sarilumab may be an acceptable alternative if tocilizumab is unavailable.

Baricitinib (Janus Kinase Inhibitors)

Baricitinib is an orally administered Janus kinase (JAK)-1 and JAK-2 inhibitor that mitigates inflammation and is FDA-approved for treatment of rheumatoid arthritis. It may display antiviral activity by inhibiting viral endocytosis and prevent viral entry into human cells. Baricitinib plus remdesivir therapy resulted in a faster median time to recovery than placebo plus remdesivir (median 7 days vs 8 days) in hospitalized patients with COVID-19.[174] There was no difference in mortality, but the study may have been underpowered for this endpoint and receipt of baricitinib was associated with a decrease in progression to mechanical ventilation or death. A minority of patients in this trial received corticosteroids, making the results difficult to interpret in the context of standard care by the time the results were published. Adverse events were similar between groups.

Two larger trials have since assessed baricitinib for severe COVID-19 where receipt of corticosteroids was standard of care. In both of these trials receipt of baricitinib was associated with lower 28- and/or 60-day mortality.[175–177]

The NIH guidelines recommend either baricitinib or tocilizumab in addition to dexamethasone for hospitalized patients with rapidly increasing oxygen needs and systemic inflammation.[66] While data are limited, results with baricitinib and tocilizumab appear similar and there is no preference between agents per the NIH.[179] Another JAK inhibitor, tofacitinib can be used instead of baricitinib if baricitinib and tocilizumab are not available or feasible to use.[180]

Anticoagulation

Patients with severe COVID-19 often have prothrombotic abnormalities including elevated D-dimer, fibrinogen, and factor VIII along with decreased protein C, protein S, and antithrombin levels.[181,182] In addition to a systemic inflammatory response, SARS-CoV-2 binding to ACE-2 receptors can result in endothelial injury and thrombosis. While risk of a venous thromboembolism (VTE) is high in critically ill patients at baseline, it is unknown if patients with COVID-19 are at increased risk compared to other patients with acute illness.

“Intermediate dose” enoxaparin administered to patients in the ICU did not reduce mortality or VTE events compared to the standard prophylaxis dose, but more bleeding and thrombocytopenia in the intermediate dose group.[183] A trial comparing therapeutic anticoagulation to prophylaxis in critically ill patients demonstrated no benefit and a potential of harm due to increased rates of bleeding in patients receiving therapeutic dosing.[184] Antiplatelet therapy was also demonstrated to have a low likelihood of providing improvement in number of organ support-free days within 21 days in critically ill patients with COVID-19.[185]

Conversely, therapeutic-dose anticoagulation in moderately ill patients (ie, patients not requiring organ support) with heparin increased the probability of survival to hospital discharge and reduced the need for organ support, regardless of D dimer at enrollment.[186] In a separate trial that only enrolled moderately ill hospitalized patients with elevated D dimers, therapeutic enoxaparin was associated with lower all-cause mortality at day 28 compared to prophylactic heparin with similar rates of major bleeding.[187] Conversely, rivaroxaban treatment was not associated with improved clinical outcomes and was associated with more bleeding compared with prophylactic heparin in a similar patient population.[188]

The NIH recommends therapeutic heparin or low molecular weight heparin in nonpregnant, hospitalized patients with COVID-19 requiring supplemental oxygen, elevated D-dimer levels, and who are not at increased bleeding risk. For patients requiring high-flow supplemental oxygen, noninvasive or mechanical ventilation, or who do not require oxygen support, the NIH recommends prophylactic dose heparin only.

Hospitalized patients should not be routinely discharged on VTE prophylaxis outside the context of a clinical trial. It may be reasonable to discharge patients at low risk for bleeding and high risk for VTE (ie, high IMRPOVE VTE risk score) on extended VTE prophylaxis as per protocols for patients without COVID-19.[191,192] This is reflected in the NIH guidelines which recommend no anticoagulation for mild-moderately ill outpatients with COVID-19 and no other indication for VTE prophylaxis, except in the context of a clinical trial.[66]

EVALUATION OF THERAPEUTIC OUTCOMES

Monitor for resolution of signs and symptoms (eg, hypoxia, fever, cough, shortness of breath). Also monitor for any adverse events while on therapy (eg, transaminitis while on remdesivir; hyperglycemia, neurological sides effects, secondary infections while on corticosteroids). Report any adverse events while on with medication therapy to FDA MedWatch program and any adverse events following vaccine administration to FDA Vaccine Adverse Event Reporting System (VAERS), especially if serious or previously unreported. If patient improves such that they are no longer eligible for a specific therapy (eg, on dexamethasone, yet no longer requiring supplemental oxygen), be sure to modify or discontinue therapy as needed. Upon resolution of their illness, encourage preventive measures such as vaccination, wearing a mask, social distancing, increased ventilation, and handwashing for

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

the patient, their family, and/or other members of their household.

CONCLUSIONS

It is important to pause and reflect on key lessons learned from the COVID-19 pandemic. Perhaps the most notable is the importance of following evidence-based medicine when considering therapeutic options for patients. While it can be difficult to withhold readily available therapies that may be considered low risk for patients, SARS-CoV-2 has re-emphasized the need to prioritize enrollment into randomized clinical trials to robustly assess if therapies are effective. Patients were given millions of doses of ineffective medications throughout the pandemic which led not only to unnecessary adverse events, but also delayed identification of therapeutic solutions. To date, only a handful of therapies have proven efficacious for the treatment of COVID-19, and prevention through vaccination and nonpharmacologic interventions remain paramount. Importantly, prevention and management of SARS-CoV-2 are rapidly dynamic areas and students are encouraged to reference the recommendations and guidance from the NIH, IDSA, and CDC for the latest information.

ABBREVIATIONS

ALT	alanine aminotransferase
CP	convalescent plasma
CT	computed tomography
CVST	cerebral venous sinus thrombosis
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
MIS-C	multisystem inflammatory syndrome in children
MIS-A	multisystem inflammatory syndrome in adults
RBD	receptor binding domain
SBECD	sulfobutylether-beta-cyclodextrin
TTS	thrombosis with thrombocytopenia syndrome
ULN	upper limit of normal
VAERS	Vaccine Adverse Event Reporting System
VE	vaccine efficacy
VITT	vaccine-induced thrombotic thrombocytopenia
VOC	variant of concern
VOI	variant of interest
VTE	venous thromboembolism

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi: 10.1016/S0140-6736(20)30183-5.

2. Listings of WHO's response to COVID-19. World Health Organization. Available at https://www.who.int/news/item/29-06-2020-covidtimeline. Accessed July 16, 2021.

3. COVID-19 Dashboard by the Center for Systems Science and Engineering. Johns Hopkins University. Available at https://coronavirus.jhu.edu/map.html. Accessed December 31, 2020.

4. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021;384(5):403–416. doi: 10.1056/NEJMoa2035389.

5. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99–111. doi: 10.1016/S0140-6736(20)32661-1.

6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020;383(27):2603–2615. 10.1056/NEJMoa2034577.

7. Sadoff J, Gray G, Vandebosch A, et al. Safety and efficacy of eingle-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021;384(23):2187–2201. 10.1056/NEJMoa2101544.

8. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: a comprehensive review. *J Med Virol* 2021;93(1):275–299. (In eng). doi: 10.1002/jmv.26254.

9. WHO-convened global study of origins of SARS-CoV-2: China Part. World Health Organization. Available at https://www.who.int/publications/i/item/who-convened-global-study-of-origins-of-sars-cov-2-china-part. Accessed April 30, 2021.

10. Johns Hopkins University COVID-19 Dashboard. Available at https://coronavirus.jhu.edu/map.html. Accessed July 24, 2022.

11. Estimating global, regional, and national daily and cumulative infections with SARS-CoV-2 through Nov 14, 2021: a statistical analysis. *Lancet*. 2022;399(10344):2351–2380. (In eng). doi: 10.1016/s0140-6736(22)00484-6.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

12. COVID Data Tracker. Centers for Disease Control and Prevention. Available at https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed July 16, 2021.

13. Estimated Disease Burden of COVID-19. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html. Accessed July 24, 2022.

14. SARS-CoV-2 Variant Classifications and Definitions. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html. Accessed July 1, 2022.

15. Davies NG, Abbott S, Barnard RC, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science*. 2021;372(6538):eabg3055. doi: 10.1126/science.abg3055.

16. Earnest R, Uddin R, Matluk N, et al. Comparative transmissibility of SARS-CoV-2 variants Delta and Alpha in New England, USA. *Cell Rep Med.* 2022;3(4):100583. (In eng). doi: 10.1016/j.xcrm.2022.100583.

17. Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis.* 2022;22(1):35–42. (In eng). doi: 10.1016/s1473-3099(21)00475-8.

18. Grabowski F, Kochańczyk M, Lipniacki T. The spread of SARS-CoV-2 variant Omicron with a doubling time of 2.0–3.3 days can be explained by immune evasion. *Viruses* 2022;14(2 10.3390/v14020294.

19. Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. *Lancet*. 2022;399(10323):437–446. (In eng). doi: 10.1016/s0140-6736(22)00017-4.

20. Walensky R. The Path Forward: A Federal Perspective on the COVID-19 Response. United States of America Senate Committee Hearing. Available at https://www.help.senate.gov/hearings/the-path-forward-a-federal-perspective-on-the-covid-19-response. Accessed July 20, 2021.

21. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. Accessed July 1, 2022.

22. CDC COVID Tracker: Demographic Trends of COVID-19 cases and deaths in the US reported to CDC. Available at https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed July 24, 2022.

23. People with Certain Medical Conditions. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Accessed July 16, 2021.

24. Pennington AF, Kompaniyets L, Summers AD, et al. Risk of clinical severity by age and race/ethnicity among adults hospitalized for COVID-19—United States, March–September 2020. *Open Forum Infectious Diseases* 2021;8(2):ofaa638. 10.1093/ofid/ofaa638.

25. Flook M, Jackson C, Vasileiou E, et al. Informing the public health response to COVID-19: a systematic review of risk factors for disease, severity, and mortality. *BMC Infectious Diseases*. 2021;21(1):342. (In eng). doi: 10.1186/s12879-021-05992-1.

26. Health Disparities. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/nchs/nvss/vsrr/covid19/health_disparities.htm. Accessed April 26, 2021.

27. Gleason, et al. The Devastating Impact of Covid-19 on Individuals with Intellectual Disabilities in the United States. 2021 Mar. Available at https://catalyst.nejm.org/doi/full/10.1056/CAT.21.0051.

28. Yuan Y. COVID-19 cases and hospitalizations among Medicare beneficiaries with and without disabilities — United States, January 1, 2020–November 20, 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:791–796. [PubMed: 35709015]

29. Health Equity Considerations and Racial and Ethnic Minority Groups. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html. Accessed April 26, 2021.

30. Jurado Hernández JL, Álvarez Orozco IF. COVID-19 in children: respiratory involvement and some differences with the adults. *Front Pediatr* 2021;9:622240. 10.3389/fped.2021.622240.

31. Leeb RT. COVID-19 trends among school-aged children — United States, March 1–September 19, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1410–1415. [PubMed: 33001869]

32. Greenhalgh T, Jimenez JL, Prather KA, Tufekci Z, Fisman D, Schooley R. Ten scientific reasons in support of airborne transmission of SARS-CoV-2. *Lancet*. 2021;0(0) (In English). doi: 10.1016/S0140-6736(21)00869-2.

33. Science Brief: SARS-CoV-2 and Surface (Fomite) Transmission for Indoor Community Environments. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/surface-transmission.html. Accessed July 16, 2021.

34. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708–1720. (In eng). doi: 10.1056/NEJMoa2002032.

35. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of Coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med* 2020;172(9):577–582. (In eng). doi: 10.7326/M20-0504.

36. Brandal LT, MacDonald E, Veneti L, et al. Outbreak caused by the SARS-CoV-2 Omicron variant in Norway, November to December 2021. *Euro Surveill.* 2021;26(50) (In eng). doi: 10.2807/1560-7917.Es.2021.26.50.2101147.

37. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of Coronavirus disease 2019 (COVID-19): a review. *JAMA.* 2020;324(8):782–793. (In eng). doi: 10.1001/jama.2020.12839.

38. Interim Guidance on Ending Isolation and Precautions for Adults with COVID-19. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html. Accessed April 30, 2021.

39. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405–407. (In eng). doi: 10.1016/j.healun.2020.03.012.

40. Bourgonje AR, Abdulle AE, Timens W, et al. Angiotensin-converting enzyme-2 (ACE2), SARS-CoV-2 and pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol*. 2020. doi: 10.1002/path.5471.

41. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. *N Engl J Med.* 2020;383(25):2451–2460. (In eng). doi: 10.1056/NEJMcp2009575.

42. Leung TYM, Chan AYL, Chan EW, et al. Short- and potential long-term adverse health outcomes of COVID-19: a rapid review. *Emerg Microbes Infect.* 2020;9(1):2190–2199. (In eng). doi: 10.1080/22221751.2020.1825914.

43. Stokes EK. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(In en-us). doi: 10.15585/mmwr.mm6924e2.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

44. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323(13):1239–1242. (In eng). doi: 10.1001/jama.2020.2648.

45. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ.* 2020;369. doi: 10.1136/bmj.m1985.

46. Variation in the COVID-19 infection-fatality ratio by age, time, and geography during the pre-vaccine era: a systematic analysis. *Lancet*. 2022;399(10334):1469–1488. (In eng). doi: 10.1016/s0140-6736(21)02867-1.

47. Centers for Disease Control and Prevention. COVID Data Tracker: Disease severity among hospitalized patients. Available at https://covid.cdc.gov/covid-data-tracker/#hospitalizations-severity. Accessed July 24, 2022.

48. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect.* 2020;26(12):1622–1629. (In eng). doi: 10.1016/j.cmi.2020.07.016.

49. Song G, Liang G, Liu W. Fungal co-infections associated with global COVID-19 pandemic: a clinical and diagnostic perspective from China. *Mycopathologia* 2020;185(4):599–606. (In eng). doi: 10.1007/s11046-020-00462-9.

50. Sen M, Honavar SG, Bansal R, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol.* 2021;69(7):1670–1692. (In eng). doi: 10.4103/ijo.IJO_1565_21.

51. Payne AB, Gilani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Network Open* 2021;4(6):e2116420. (In eng). doi: 10.1001/jamanetworkopen.2021.16420.

52. Holm M, Espenhain L, Glenthøj J, et al. Risk and phenotype of multisystem inflammatory syndrome in vaccinated and unvaccinated Danish children before and during the Omicron wave. *JAMA Pediatr* 2022;176(8):821–823. (In eng). doi: 10.1001/jamapediatrics.2022.2206.

53. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *The Lancet Infectious Diseases*. 2020;20(11):e276–e288. (In eng). doi: 10.1016/S1473-3099(20)30651-4.

54. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance. American Academy of Pediatrics. Available at https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/. Accessed April 30, 2021.

55. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: a systematic review. *JAMA Netw Open* 2021;4(9):e2126456. (In eng). doi: 10.1001/jamanetworkopen.2021.26456.

56. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. 11 Jul 2022. Available at https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. Accessed July 24, 2022.

57. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? *ERJ Open Res.* 2020;6(4) (In eng). doi: 10.1183/23120541.00542-2020.

58. Graham EL, Clark JR, Orban ZS, et al. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 “long haulers”. *Ann Clin Transl Neurol.* 2021 (In eng). doi: 10.1002/acn3.51350.

59. Wong TL, Weitzer DJ. Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a systemic review and comparison of clinical presentation and symptomatology. *Medicina (Kaunas)* 2021;57(5) (In eng). doi: 10.3390/medicina57050418.

60. Couzin-Frankel J. Clues to long COVID. *Science*. Jun 2022. Available at https://www.science.org/content/article/what-causes-long-covid-three-leading-theories?cookieSet=1. Accessed July 1, 2022.

61. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*. 2022;399(10343):2263–2264. (In eng). doi: 10.1016/s0140-6736(22)00941-2.

62. Azzolini E, Levi R, Sarti R, et al. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA* 2022 (In eng). doi: 10.1001/jama.2022.11691.

63. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med.* 2022;28(3):583–590. (In eng). doi: 10.1038/s41591-022-01689-3.

64. Ziyad Al-Aly, Benjamin Bowe, Yan Xie, et al. Outcomes of SARS-CoV-2 Reinfection, 17 June 2022, PREPRINT (Version 1) Available at Research Square https://doi.org/10.21203/rs.3.rs-1749502/v1.

65. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.4.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed July 19, 2021.

66. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 19 July 2021.

67. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. American College of Radiology. Available at https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection. Accessed 30 Apr 2021.

68. Garcia-Vidal C, Sanjuan G, Moreno-García E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect.* 2021;27(1):83–88. (In eng). doi: 10.1016/j.cmi.2020.07.041.

69. Cohen MS, Nirula A, Mulligan M, et al. for BLAZE-2 study team. Bamlanivimab prevents COVID-19 morbidity and mortality in nursing-home setting. Oral abstract #121. Presented at Virtual CROI 2021.

70. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (Tixagevimab-Cilgavimab) for Prevention of Covid-19. *N Engl J Med.* 2022;386(23):2188–2200. (In eng). doi: 10.1056/NEJMoa2116620.

71. Krammer F. SARS-CoV-2 vaccines in development. *Nature*. 2020;586(7830):516–527. doi: 10.1038/s41586-020-2798-3.

72. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis.* 2022. doi: https://doi.org/10.1016/S1473-3099(22)00320-6.

73. Centers for Disease Control and Prevention. Rates of COVID-19 Cases and Deaths by Vaccination Status. Available at https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status. Accessed July 24, 2022.

74. COVID-19 Vaccination. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/vaccines/covid-19/index.html. Accessed July 20, 2021.

75. FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS). EMERGENCY USE AUTHORIZATION (EUA) OF THE PFIZER-BIONTECH COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

2019 (COVID-19) United States Food and Drug Administration. Available at: https://www.fda.gov/media/144413/download. Accessed July 21, 2021.

76. Frenck RW Jr, Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *N Engl J Med.* 2021;385(3):239–250. doi: 10.1056/NEJMoa2107456.

77. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. *N Engl J Med.* 2022;386(1):35–46. (In eng). doi: 10.1056/NEJMoa2116298.

78. FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS). EMERGENCY USE AUTHORIZATION (EUA) OF THE MODERNA COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19). United States Food and Drug Administration. Available at https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-providers.pdf. Accessed 21 Jul 2021.

79. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US-December 14, 2020-January 18, 2021. *JAMA.* 2021;325(11):1101–1102. doi: 10.1001/jama.2021.1967.

80. Blumenthal KG, Robinson LB, Camargo CA Jr, et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. *JAMA.* 2021;325(15):1562–1565. doi: 10.1001/jama.2021.3976.

81. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. *N Engl J Med.* 2021;384(13):1273–1277. doi: 10.1056/NEJMc2102131.

82. Shimabukuro T. Update on myocardtitis following mRNA COVID-19 vaccination. Advisory Committee on Immunization Practices (ACIP). Available at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-COVID-Shimabukuro-508.pdf.

83. Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70(27):977–982. doi: 10.15585/mmwr.mm7027e2.

84. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:495–500. doi: http://dx.doi.org/10.15585/mmwr.mm7013e3external.

85. Jones NK, Rivett L, Seaman S, et al. Single-dose BNT162b2 vaccine protects against asymptomatic SARS-CoV-2 infection. *Elife*. 2021;10. doi: 10.7554/eLife.68808.

86. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. *N Engl J Med.* 2021. doi: 10.1056/NEJMc2107717.

87. Bos R, Rutten L, van der Lubbe JEM, et al. Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses. *NPJ Vaccines*. 2020;5:91. doi: 10.1038/s41541-020-00243-x.

88. FACT SHEET FOR HEALTHCARE PROVIDERS ADMINISTERING VACCINE (VACCINATION PROVIDERS). EMERGENCY USE AUTHORIZATION (EUA) OF THE JANSSEN COVID-19 VACCINE TO PREVENT CORONAVIRUS DISEASE 2019 (COVID-19). United States Food and Drug Administration. Available at https://www.alabamapublichealth.gov/immunization/assets/jj_factsheet_providers.pdf. Accessed 21 Jul 2021.

89. Oliver SE, Wallace M, See I, et al. Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices - United States, December 2021. *MMWR Morb Mortal Wkly Rep.* 2022;71(3):90–95. (In eng). doi: 10.15585/mmwr.mm7103a4.

90. Muir KL, Kallam A, Koepsell SA, Gundabolu K. Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination. *N Engl J Med.* 2021;384(20):1964–1965. doi: 10.1056/NEJMc2105869.

91. See I, Su JR, Lale A, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. *JAMA.* 2021;325(24):2448–2456. doi: 10.1001/jama.2021.7517.

92. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. *N Engl J Med.* 2022;386(6):531–543. (In eng). doi: 10.1056/NEJMoa2116185.

93. Ewer KJ, Barrett JR, Belij-Rammerstorfer S, et al. T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial. *Nat Med.* 2021;27(2):270–278. doi: 10.1038/s41591-020-01194-5.

94. von Hundelshausen P, Lorenz R, Siess W, Weber C. Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT): Targeting Pathomechanisms with Bruton Tyrosine Kinase Inhibitors. *Thromb Haemost.* 2021. doi: 10.1055/a-1481-3039.

95. Smadja DM, Yue QY, Chocron R, Sanchez O, Lillo-Le Louet A. Vaccination against COVID-19: insight from arterial and venous thrombosis occurrence using data from VigiBase. *Eur Respir J.* 2021;58(1). doi: 10.1183/13993003.00956-2021.

96. Heath PT, Galiza EP, Baxter DN, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med.* 2021. doi: 10.1056/NEJMoa2107659.

97. Jiang S, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. *Trends Immunol.* 2020;41(5):355–359. doi: 10.1016/j.it.2020.03.007.

98. Fact Sheet for Patients, Parents And Caregivers Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for Coronavirus Disease 2019 (COVID-19). U.S. Food and Drug Administration. Available at https://www.fda.gov/media/154702/download.

99. Veklury (remdesivir). Full Prescribing Information. Gilead Sciences, Inc. Available at https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf. Accessed July 19, 2021.

100. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html. Accessed July 21, 2021.

101. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med.* 2022;386(15):1397–1408. (In eng). doi: 10.1056/NEJMoa2118542.

102. Gordon CJ, Tchesnokov EP, Woolner E, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. *J Biol Chem.* 2020;295(20):6785–6797. doi: 10.1074/jbc.RA120.013679.

103. Siegel D, Hui HC, Doerffler E, et al. Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. *J Med Chem.* 2017;60(5):1648–1661. doi: 10.1021/acs.jmedchem.6b01594.

104. Agostini ML, Andres EL, Sims AC, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio.* 2018;9(2). doi: 10.1128/mBio.00221-18.

105. Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med.* 2022;386(4):305–315. (In eng). doi: 10.1056/NEJMoa2116846.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

106. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med.* 2022;386(6):509–520. (In eng). doi: 10.1056/NEJMoa2116044.

107. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell*. 2021;184(4):861–880. doi: 10.1016/j.cell.2021.01.007.

108. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Cocktail Clinical Outcomes Study in Covid-19 Outpatients. *medRxiv.* 2021:2021.05.19.21257469. doi: 10.1101/2021.05.19.21257469.

109. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. *N Engl J Med.* 2020 (In eng). doi: 10.1056/NEJMoa2035002.

110. Group RC, Horby PW, Mafham M, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv.* 2021:2021.06.15.21258542. doi: 10.1101/2021.06.15.21258542.

111. Jones BE, Brown-Augsburger PL, Corbett KS, et al. LY-CoV555, a rapidly isolated potent neutralizing antibody, provides protection in a non-human primate model of SARS-CoV-2 infection. *bioRxiv.* 2020 (In eng). doi: 10.1101/2020.09.30.318972.

112. Shi R, Shan C, Duan X, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature*. 2020;584(7819):120–124. doi: 10.1038/s41586-020-2381-y.

113. Gottlieb RL, Nirula A, Chen P, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(7):632–644. (In eng). doi: 10.1001/jama.2021.0202.

114. Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. *N Engl J Med.* 2021 (In eng). doi: 10.1056/NEJMoa2102685.

115. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab. United States Food and Drug Administration. Available at https://www.fda.gov/media/145802/download. Accessed July 19, 2021.

116. Lenze EJ, Mattar C, Zorumski CF, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(22):2292–2300. doi: 10.1001/jama.2020.22760.

117. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2022;10(1):e42–e51. (In eng). doi: 10.1016/s2214-109x(21)00448-4.

118. Lee TC, Vigod S, Bortolussi-Courval É, et al. Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization: A Systematic Review and Meta-analysis. *JAMA Network Open*. 2022;5(4):e226269–e226269. doi: 10.1001/jamanetworkopen.2022.6269.

119. Ramakrishnan S, Nicolau DV Jr, Langford B, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med.* 2021;9(7):763–772. doi: 10.1016/S2213-2600(21)00160-0.

120. Group PC, Yu L-M, Bafadhel M, et al. Inhaled budesonide for COVID-19 in people at higher risk of adverse outcomes in the community: interim analyses from the PRINCIPLE trial. *medRxiv.* 2021:2021.04.10.21254672. doi: 10.1101/2021.04.10.21254672.

121. Ezer N, Belga S, Daneman N, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. *BMJ.* 2021;375:e068060. (In eng). doi: 10.1136/bmj-2021-068060.

122. Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA Intern Med.* 2022;182(1):42–49. (In eng). doi: 10.1001/jamainternmed.2021.6759.

123. Tardif JC, Bouabdallaoui N, L'Allier PL, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. *Lancet Respir Med*. 2021 (In eng). doi: 10.1016/s2213-2600(21)00222-8.

124. Horby PW, Campbell M, Spata E, et al. RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv.* 2021:2021.05.18.21257267. doi: 10.1101/2021.05.18.21257267.

125. Sharun K, Dhama K, Patel SK, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. *Ann Clin Microbiol Antimicrob.* 2020;19(1):23. doi: 10.1186/s12941-020-00368-w.

126. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020;178:104787. doi: 10.1016/j.antiviral.2020.104787.

127. Jermain B, Hanafin PO, Cao Y, Lifschitz A, Lanusse C, Rao GG. Development of a Minimal Physiologically-Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing. *J Pharm Sci.* 2020;109(12):3574–3578. doi: 10.1016/j.xphs.2020.08.024.

128. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019: The Ivermectin in COVID Nineteen Study. *Chest*. 2021;159(1):85–92. doi: 10.1016/j.chest.2020.10.009.

129. Lopez-Medina E, Lopez P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *JAMA.* 2021;325(14):1426–1435. doi: 10.1001/jama.2021.3071.

130. Vallejos J, Zoni R, Bangher M, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. *BMC Infect Dis.* 2021;21(1):635. doi: 10.1186/s12879-021-06348-5.

131. Accelerating C-TI, Vaccines-6 Study G, Naggie S. Ivermectin for treatment of mild-to-moderate COVID-19 in the outpatient setting: a decentralized, placebo-controlled, randomized, platform clinical trial. *medRxiv* 2022:2022.06.10.22276252. doi: 10.1101/2022.06.10.22276252.

132. Reis, G, Silva, EASM, Silva, DCM, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. *N Engl J Med.* 2022;386(18):1721–1731. doi: 10.1056/NEJMoa2115869.

133. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov.* 2020;6:16. doi: 10.1038/s41421-020-0156-0.

134. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis.* 2003;3(11):722–727. doi: 10.1016/s1473-3099(03)00806-5.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

135. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as Pre-exposure Prophylaxis for Coronavirus Disease 2019 (COVID-19) in Healthcare Workers: A Randomized Trial. *Clin Infect Dis.* 2021;72(11):e835–e843. doi: 10.1093/cid/ciaa1571.

136. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. *Ann Intern Med.* 2020;173(8):623–631. doi: 10.7326/M20-4207.

137. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med.* 2020;383(6):517–525. doi: 10.1056/NEJMoa2016638.

138. Consortium WHOST, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med.* 2021;384(6):497–511. (In eng). doi: 10.1056/NEJMoa2023184.

139. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* 2020;369:m1849. doi: 10.1136/bmj.m1849.

140. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med.* 2020;383(21):2041–2052. doi: 10.1056/NEJMoa2019014.

141. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med.* 2020 (In eng). doi: 10.1056/NEJMoa2007764.

142. Group RC, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med.* 2020;383(21):2030–2040. doi: 10.1056/NEJMoa2022926.

143. Mitja O, Corbacho-Monne M, Ubals M, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. *N Engl J Med.* 2021;384(5):417–427. doi: 10.1056/NEJMoa2021801.

144. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;56(1):105949. doi: 10.1016/j.ijantimicag.2020.105949.

145. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis.* 2020;34:101663. doi: 10.1016/j.tmaid.2020.101663.

146. Horby PW, Roddick A, Spata E, et al. Azithromycin in Hospitalised Patients with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv.* 2020:2020.12.10.20245944. doi: 10.1101/2020.12.10.20245944.

147. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet*. 2020;396(10256):959–967. doi: 10.1016/S0140-6736(20)31862-6.

148. Naggie S. Inhaled Fluticasone for Outpatient Treatment of Covid-19: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial. *medRxiv.* 2022:2022.07.12.22277548. doi: 10.1101/2022.07.12.22277548.

149. Thomas S, Patel D, Bittel B, et al. Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Netw Open*. 2021;4(2):e210369. doi: 10.1001/jamanetworkopen.2021.0369.

150. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569–1578. (In eng). doi: 10.1016/s0140-6736(20)31022-9.

151. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med.* 2020;383(19):1827–1837. doi: 10.1056/NEJMoa2015301.

152. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048–1057. (In eng). doi: 10.1001/jama.2020.16349.

153. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ.* 2022;194(7):E242–e251. (In eng). doi: 10.1503/cmaj.211698.

154. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*. 2022;399(10339):1941–1953. (In eng). doi: 10.1016/s0140-6736(22)00519-0.

155. Rochwerg B, Agarwal A, Zeng L, et al. Remdesivir for severe covid-19: a clinical practice guideline. *BMJ.* 2020;370:m2924. (In eng). doi: 10.1136/bmj.m2924.

156. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A Valid Warning or Clinical Lore: an Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort. *Antimicrob Agents Chemother.* 2021;65(2). doi: 10.1128/AAC.02290-20.

157. Davis MR, Pham CU, Cies JJ. Remdesivir and GS-441524 plasma concentrations in patients with end-stage renal disease on haemodialysis. *J Antimicrob Chemother.* 2021;76(3):822–825. doi: 10.1093/jac/dkaa472.

158. Mendez-Echevarria A, Perez-Martinez A, Gonzalez Del Valle L, et al. Compassionate use of remdesivir in children with COVID-19. *Eur J Pediatr.* 2021;180(4):1317–1322. doi: 10.1007/s00431-020-03876-1.

159. Hopwood AJ, Jordan-Villegas A, Gutierrez LD, et al. Severe Acute Respiratory Syndrome Coronavirus-2 Pneumonia in a Newborn Treated With Remdesivir and Coronavirus Disease 2019 Convalescent Plasma. *J Pediatric Infect Dis Soc.* 2021;10(5):691–694. doi: 10.1093/jpids/piaa165.

160. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate Use of Remdesivir in Pregnant Women with Severe Covid-19. *Clin Infect Dis.* 2020. doi: 10.1093/cid/ciaa1466.

161. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021;384(8):693–704. doi: 10.1056/NEJMoa2021436.

162. Group WHOREAfC-TW, Sterne JAC, Murthy S, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA.* 2020;324(13):1330–1341. doi: 10.1001/jama.2020.17023.

163. Le RQ, Li L, Yuan W, et al. FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *Oncologist*. 2018;23(8):943–947. doi: 10.1634/theoncologist.2018-0028.

164. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A.* 2020;117(20):10970–10975. doi: 10.1073/pnas.2005615117.

165. Rosas IO, Brau N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. *N Engl J Med.* 2021;384(16):1503–1516. doi: 10.1056/NEJMoa2028700.

166. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 2021;181(1):24–31. doi: 10.1001/jamainternmed.2020.6615.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

167. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med.* 2021;384(1):20–30. doi: 10.1056/NEJMoa2030340.

168. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med.* 2020;383(24):2333–2344. doi: 10.1056/NEJMoa2028836.

169. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. *JAMA Intern Med.* 2021;181(1):32–40. doi: 10.1001/jamainternmed.2020.6820.

170. Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med.* 2021;384(16):1491–1502. doi: 10.1056/NEJMoa2100433.

171. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–1645. doi: 10.1016/S0140-6736(21)00676-0.

172. Fact Sheet For Health Care Providers Emergency Use Authorization (EUA) Of Actemra (tocilizumab). Available at https://www.fda.gov/media/150321/download. Accessed July 19, 2021.

173. Group WHOREAfC-TW, Shankar-Hari M, Vale CL, et al. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. *JAMA.* 2021. doi: 10.1001/jama.2021.11330.

174. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med.* 2021;384(9):795–807. doi: 10.1056/NEJMoa2031994.

175. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. *medRxiv.* 2021:2021.04.30.21255934. doi: 10.1101/2021.04.30.21255934.

176. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Med.* 2021;9(12):1407–1418. (In eng). doi: 10.1016/s2213-2600(21)00331-3.

177. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*. 2022;400(10349):359–368. (In eng). doi: 10.1016/s0140-6736(22)01109-6.

178. Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of Baricitinib. United States Food and Drug Administration. Available at http://pi.lilly.com/eua/baricitinib-eua-factsheet-hcp.pdf. Accessed July 19, 2021.

179. Karampitsakos T, Papaioannou O, Tsiri P, et al. Tocilizumab versus baricitinib in hospitalized patients with severe COVID-19: an open label, randomized controlled trial. *medRxiv.* 2022:2022.06.13.22276211. doi: 10.1101/2022.06.13.22276211.

180. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med.* 2021;385(5):406–415. (In eng). doi: 10.1056/NEJMoa2101643.

181. Goswami J, MacArthur TA, Sridharan M, et al. A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. *Shock*. 2021;55(6):700–716. doi: 10.1097/SHK.0000000000001680.

182. Piazza G, Morrow DA. Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19. *JAMA.* 2020;324(24):2548–2549. doi: 10.1001/jama.2020.23422.

183. Investigators I, Sadeghipour P, Talasaz AH, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. *JAMA.* 2021;325(16):1620–1630. doi: 10.1001/jama.2021.4152.

184. The R-C, a A, Investigators A, Zarychanski R. Therapeutic Anticoagulation in Critically Ill Patients with Covid-19 – Preliminary Report. *medRxiv.* 2021:2021.03.10.21252749. doi: 10.1101/2021.03.10.21252749.

185. Bradbury CA, Lawler PR, Stanworth SJ, et al. Effect of Antiplatelet Therapy on Survival and Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. *JAMA.* 2022;327(13):1247–1259. (In eng). doi: 10.1001/jama.2022.2910.

186. The Attacc A-a, Investigators R-C, Lawler PR, et al. Therapeutic Anticoagulation in Non-Critically Ill Patients with Covid-19. *medRxiv.* 2021:2021.05.13.21256846. doi: 10.1101/2021.05.13.21256846.

187. Sholzberg M, Tang GH, Rahhal H, et al. Heparin for Moderately Ill Patients with Covid-19. *medRxiv.* 2021:2021.07.08.21259351. doi: 10.1101/2021.07.08.21259351.

188. Lopes RD, de Barros ESPGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253–2263. doi: 10.1016/S0140-6736(21)01203-4.

189. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood*. 2020;136(11):1347–1350. doi: 10.1182/blood.2020008086.

190. Ramacciotti E, Agati LB, Calderaro D, et al. Medically Ill hospitalized Patients for COVID-19 THrombosis Extended ProphyLaxis with rivaroxaban ThErapy: Rationale and Design of the MICHELLE Trial. *Am Heart J.* 2021;242:115–122. (In eng). doi: 10.1016/j.ahj.2021.08.016.

191. Spyropoulos AC, Lipardi C, Xu J, et al. Modified IMPROVE VTE Risk Score and elevated D-Dimer identify a high venous thromboembolism risk in acutely ill medical population for extended thromboprophylaxis. *TH Open* 2020;4(1):e59–e65. 10.1055/s-0040-1705137.

192. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with Betrixaban in acutely ill medical patients. *N Engl J Med* 2016;375(6):534–544. 10.1056/NEJMoa1601747.

SELF-ASSESSMENT QUESTIONS

1. In which “phase” of COVID-19 are antiviral therapies most likely to be effective?

   A. Early infection.

   B. Pulmonary phase.

   C. Hyperinflammatory phase.

   D. There is no role for antiviral therapy in COVID-19.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

2. Which of the following risk factors has the greatest association with death from COVID-19?

   A. Male sex

   B. Diabetes

   C. Age ≥ 65

   D. History of COVID-19

3. What is the most common characteristic to date of the SARS-CoV-2 variants of concern (VOC)?

   A. More severe disease

   B. Enhanced transmission

   C. Remdesivir resistance

   D. Decreased efficacy of vaccines against hospitalization

4. Which of the following patients is most likely to have a systemic reactogenicity reaction (eg, headache, myalgias) to an mRNA vaccine?

   A. 22-year-old male receiving dose 2

   B. 68-year-old female receiving dose 1

   C. 35-year-old male receiving dose 1

   D. 77-year-old female receiving dose 2

5. Which of the following patients is at highest risk for myocarditis following an MRNA vaccine?

   A. 63-year-old male with a history of congestive heart failure

   B. 12-year-old female who plays soccer

   C. 19-year-old male in a college marching band

   D. 78-year-old female with a history of viral myocarditis

6. Which of the following patients is at greatest risk for thrombosis with thrombocytopenia syndrome (TTS) with Ad26.CoV2S (Johnson & Johnson)?

   A. 30-year-old male with history of spontaneous subarachnoid hemorrhage

   B. 38-year-old female with no significant past medical history

   C. 68-year-old female with history of multiple venous thromboembolic events

   D. 55-year-old man with congestive heart failure and atrial fibrillation receiving warfarin

7. Which of the following therapies is authorized for pre-exposure prophylaxis to prevent COVID-19 in those who are immunocompromised and may not mount an adequate immune response to COVID-19 vaccination?

   A. Remdesivir (3-day course)

   B. Tixagevimab-Cilgavimab

   C. Nirmatrelvir/ritonavir

   D. Hydroxychloroquine

8. JG is a 44-year-old male admitted to hospital with COVID-19. He has a new oxygen requirement of 3 L via nasal cannula and was started on remdesivir. By day 3, his fever resolved and he is breathing ambient air. What is the best course of action for completing his course of remdesivir?

   A. He should remain in the hospital for 2 more days to complete a 5-day course, as this was the minimally effective duration demonstrated in the clinical trials.

   B. JG should be discharged from the hospital and 2 days of remdesivir should be administered in the outpatient setting via a home infusion company.

   C. JG should be discharged and remdesivir should be discontinued.

   D. JG should be discharged on oral oseltamivir to complete 2 more days of antiviral therapy.

9. Which of the following laboratory values should be monitored for patients receiving remdesivir?

   A. Creatinine kinase

   B. Potassium

   C. Liver function tests

   D. Blood glucose

10. What COVID-19 patient listed below is most likely to benefit from tocilizumab treatment?

    A. A patient in the hyperinflammatory phase who was placed on mechanical ventilation a week ago, but has failed to improve

    B. A patient who was recently admitted to a medical ward, is currently only receiving remdesivir for COVID-19 management, and has had an increase in their oxygen needs from room air to 6 L via nasal cannula

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

C. A patient presenting to the emergency department with an elevated IL-6 serum concentration

D. A patient receiving remdesivir and dexamethasone on a medical ward who has an elevated CRP level and new, rapidly increasing oxygen requirements

11. A 68-year-old female with COVID-19 is admitted to the medical ward. She has extensive comorbidities but is doing relatively well with just a fever (39.4 °C) and is saturating 98% (0.98) on room air. The medical intern wants to start dexamethasone, what is the most appropriate response?

A. Dexamethasone is inappropriate in this patient, given that she is not requiring supplemental oxygen, and a benefit in this type of patient has not been demonstrated.

B. Dexamethasone should be started as soon as possible, as it has consistently demonstrated a mortality benefit in hospitalized patients with COVID-19.

C. Dexamethasone should be started with either tocilizumab or baricitinib as soon as possible.

D. Dexamethasone is appropriate, but it should not be administered without giving remdesivir as well.

12. In which of the following patient populations is therapeutic anticoagulation currently recommended as part of the management of their SARS CoV-2 infection?

A. An outpatient with mild-to-moderate COVID-19 at high risk for progression to severe illness

B. An inpatient with severe COVID-19 on low-flow supplemental oxygen

C. A critically ill mechanically ventilated patient with COVID-19

D. A low-risk patient without an alternative indication for anticoagulation after discharge from the hospital

13. EM is a 31-year-old unvaccinated female with morbid obesity presenting to her primary care physician with a cough and fever for 2 days. She tests positive for COVID-19 and is not taking any other medications. What is the best recommended treatment for EM now?

A. Fluvoxamine

B. Molnupiravir

C. Nirmatrelvir/ritonavir

D. Ivermectin

14. What adverse event is important to counsel patients about if they are starting nirmatrelvir/ritonavir?

A. Muscle pain/myopathy

B. Dysgeusia

C. Photosensitivity

D. Infusion-site reactions

15. JP is a 41-year-old male (169 kg) admitted to the medical intensive care unit. He was diagnosed 12 days ago with COVID-19. After spending 5 days at home, he presented to the Emergency Department with worsening dyspnea and fever. Now, on day 7 of hospitalization, he acutely worsened and required mechanical ventilation. He is receiving dexamethasone 6 mg IV every 24 hours (day 7 of steroid treatment) and recently completed 5 days of remdesivir. Baricitinib is not on your hospital formulary. What is the best treatment for JP now?

A. Give tocilizumab 1,350 mg IV once and increase dexamethasone to 10 mg IV twice daily

B. Give tocilizumab 800 mg IV once and increase dexamethasone to 10 mg IV twice daily

C. Give tocilizumab 1,350 mg IV once and continue dexamethasone 6 mg IV daily

D. Give tocilizumab 800 mg IV once and continue dexamethason e 6-mg IV daily

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Viral replication is highest early in infection. While viral replication can occur throughout the pulmonary phase, progression of illness in this phase is driven by localized pulmonary inflammation and hypoxia and anti-inflammatory therapies (ie, dexamethasone) improve mortality in these patients. Therapies directly targeting the virus (ie, monoclonal antibodies, remdesivir) are most effective early in the course of illness to prevent progression of illness. [Pathophysiology section; Monoclonal antibodies and remdesivir sections]

2. **C.** Greater than 80% of deaths and ~50% of hospitalizations for COVID-19 occur in patients ≥65 years of age. While males and patients with certain comorbidities (including diabetes) are at greater risk for severe disease, the association between advanced age and death is strongest. [Etiology and Epidemiology section]. Reinfection in patients with a history of COVID-19 remains relatively infrequent, and there is no indication that it is associated with more severe disease or death.

3. **B.** All variants of concern (VOC) to date have been associated with some degree of enhanced transmission. The Omicron variant has the greatest association [Etiology and Epidemiology section]. While there is concern for more severe disease with VOCs, this has only been seen with Delta, and evidence demonstrates that Omicron is associated with less severe disease relative to Delta. Mutations to the spike protein are common in VOC; however, this would not be expected to impact the activity of remdesivir, which inhibits SARS-CoV-2 polymerase. Finally, available data suggest vaccines that while efficacy against infection may be less with some VOC (notably Omicron lineages), efficacy against severe disease, hospitalization, and death remain robust.

4. **A.** Younger patients (≤55 years of age) are more likely to have systemic reactogenicity reactions than older adults, and it the frequency increases with the second dose [mRNA vaccine section].

5. **C.** Rates of myocarditis are highest in males aged 12 to 29 with mRNA vaccines. Rates in males ≥30 or females are over 10 times less frequent [real world safety of mRNA vaccines].

6. **B.** TTS has most frequently been demonstrated in females aged 18 to 49. This is no association with other comorbidities and/or with male patients [Ad26.CoV2S section].

7. **B.** Tixagevimab-Cilgavimab is the only agent that is currently authorized for pre-exposure prophylaxis, and is an important preventative strategy for patients who are immunocompromised [Prevention section: Monoclonal Antibodies: Evusheld™ (Tixagevimab co-packaged with cilgavimab)]. Neither remdesivir nor nirmatrelvir/ritonavir have been studied as a pre-exposure prophylaxis (nirmatrelvir/ritonavir was studied for postexposure prophylaxis, but failed to significantly reduce the incidence of COVID-19). Hydroxychloroquine has no role in the prevention or management of COVID-19.

8. **B.** A patient should not be kept in hospital to complete a course of remdesivir. In the clinical trials for remdesivir patients were not required to stay in hospital to complete their course [remdesivir section].

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

9. **C.** Although well tolerated in the clinical trials, remdesivir has been associated with elevations in aminotransferases in phase 1 studies and per the package insert, consideration should be given for discontinuation if ALT is greater than 10 times the upper limit of normal.

10. **D.** Patient D has all the characteristics of patients who benefitted most from tocilizumab in the clinical trials. Patient A is unlikely to have benefit given that they have been on the ventilator for a week, and the benefit of tocilizumab is likely lost at that point. While patient B has worsening oxygen status, they are not receiving dexamethasone, and tocilizumab has only been proven to be efficacious when added to corticosteroids. This patient could benefit from initiation of dexamethasone and then consideration could be given to the addition of tocilizumab at that point. To date, no association has been demonstrated with serum IL-6 concentration and effect of tocilizumab, so that laboratory value alone would not be an indication for tocilizumab in patient C.

11. **A.** Data do not currently exist suggesting a benefit in a patient not requiring supplemental oxygen, and the RECOVERY trial hinted at possible harm in this population.

12. **B.** The only patient population where a benefit to therapeutic anticoagulation has been definitively demonstrated, and subsequently recommended in guidelines, is in hospitalized patients not requiring end-organ support. While select data suggest a potential benefit in postdischarge patients, the recommendation is currently to only utilize outside of a clinical trial if patients have another indication for anticoagulation [Anticoagulation section].

13. **C.** Nirmatrelvir/ritonavir and molnupiravir have both demonstrated efficacy in reducing progression to hospitalization or death in outpatient with mild-moderate COVID-19. However, the efficacy demonstrated with nirmatrelvir/ritonavir was greater than that with molnupiravir, so that would be preferred. Molnupiravir should only be considered in patients where none of the first-line therapies (nirmatrelvir/ritonavir, remdesivir, or bebtelovimab) are not options. Ivermectin has been proven not to be efficacious for COVID-19, and while select evidence supports fluvoxamine, it is currently not recommended outside of a clinical trial given the mixed data.

14. **B.** Dysgeusia is a common side effect with nirmatrelvir/ritonavir and can be quite unpleasant for patients receiving this therapy. Counseling patients that this may occur is an important role of pharmacists.

15. **D.** The maximum dose of tocilizumab is 800 mg. Answers A and C are incorrect because this doses tocilizumab on the patient's total body weight without the dose cap. There are no data to support increasing the dose of dexamethasone, so answer B is also incorrect.

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University

Access Provided by:

SILVERCHAIR INFORMATION SYSTEMS

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University

Access Provided by:

SILVERCHAIR INFORMATION SYSTEMS

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University

Access Provided by:

SILVERCHAIR INFORMATION SYSTEMS

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University

Access Provided by:

SILVERCHAIR INFORMATION SYSTEMS

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239
Chapter e132: Coronavirus Disease (COVID-19), Jason M. Pogue; Erin K. McCreary; Julie Ann Justo
©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

ACCESS Pharmacy

Monash University

Access Provided by:

SILVERCHAIR INFORMATION SYSTEMS

Downloaded 2024-2-2 12:1 A Your IP is 130.194.219.239

©2024 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility