Coronavirus Disease 2019 (COVID-19) Management

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Author: David J Cennimo, MD, FAAP, FACP, FIDSA, AAHIVS; Chief Editor: Michael Stuart Bronze, MD

Overview

Practice Essentials

Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China.[1] It was initially reported to the WHO on December 31, 2019. On January 30, 2020, the WHO declared the COVID-19 outbreak a global health emergency.[2, 3] On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009.[4]

Illness caused by SARS-CoV-2 was termed COVID-19 by the WHO, the acronym derived from "coronavirus disease 2019." The name was chosen to avoid stigmatizing the virus's origins in terms of populations, geography, or animal associations.[5, 6] On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses issued a statement announcing an official designation for the novel virus: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[7]

The CDC estimates that SARS-CoV-2 entered the United States in late January or early February 2020, establishing low-level community spread before being noticed.[8] Since that time, the United States has experienced widespread infections, with over 49 million reported cases and more than 785,000 deaths reported as of December 6, 2021.

On April 3, 2020, the CDC issued a recommendation that the general public, even those without symptoms, should begin wearing face coverings in public settings where social-distancing measures are difficult to maintain to abate the spread of COVID-19.[9]

The CDC had postulated that large numbers of patients could require medical care concurrently, resulting in overloaded public health and healthcare systems and, potentially, elevated rates of hospitalizations and deaths. The CDC advised that nonpharmaceutical interventions (NPIs) are the most important response strategy for delaying viral spread and reducing disease impact. Unfortunately, these concerns have been proven accurate.

The feasibility and implications of suppression and mitigation strategies have been rigorously analyzed and are being encouraged or enforced by many governments to slow or halt viral transmission. Population-wide social distancing plus other interventions (eg, home self-isolation, school and business closures) are strongly advised. These policies may be required for long periods to avoid rebound viral transmission.[10]

As the United States is experiencing another surge of COVID-19 infections, the CDC has intensified its recommendations for transmission mitigation. They recommend all unvaccinated individuals wear masks in public indoor settings. On the basis of evidence regarding emerging variants of concern (See Virology), CDC recommends that persons who are fully vaccinated also wear masks in public indoor settings in areas with substantial or high transmission. Fully vaccinated individuals might consider wearing a mask in public indoor areas, regardless of transmission level, if they or someone in their home is immunocompromised, is at increased risk for severe disease, or is unvaccinated (including children younger than 12 years who are ineligible for vaccination).[11]

The CDC recommends physical distancing, avoiding nonessential indoor spaces, postponing travel until fully vaccinated, enhanced ventilation, and hand hygiene.[12, 13]

According to the CDC, individuals at high risk for infection include persons in areas with ongoing local transmission, healthcare workers caring for patients with COVID-19, close contacts of infected persons, and travelers returning from locations where local spread has been reported.

The CDC has published a summary of evidence of comorbidities that are supported by meta-analysis/systematic review that have a significant association with risk of severe COVID-19 illness. These include the following conditions[14] :

- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Diabetes mellitus, type 1 and type 2
- Heart conditions (eg, heart failure, coronary artery disease, cardiomyopathies)
- Immunocompromised state from solid organ transplant
- Obesity (BMI 30 kg/m ^{2} or greater)
- Pregnancy
- Smoking, current or former

Comorbidities that are supported by mostly observational (eg, cohort, case-control, or cross-sectional) studies include[14] :

- Children with certain underlying conditions
- Down syndrome
- HIV (human immunodeficiency virus)

- Neurologic conditions, including dementia
- Overweight (BMI 25 to less than 30 kg/m ^{2})
- Other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension)
- Sickle cell disease
- Solid organ or blood stem cell transplantation
- Substance use disorders
- Use of corticosteroids or other immunosuppressive medications

Comorbidities that are supported by mostly case series, case reports, or, if other study design or the sample size is small include[14] :

- Cystic fibrosis
- Thalassemia

Comorbidities supported by mixed evidence include[14] :

- Asthma
- Hypertension
- Immune deficiencies
- Liver disease

Such individuals should consider the following precautions[14] :

- Stock up on supplies.
- Avoid close contact with sick people.
- Wash hands often.
- Stay home as much as possible in locations where COVID-19 is spreading.
- Develop a plan in case of illness.

Signs and symptoms

Presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness and mortality. Symptoms may develop 2 days to 2 weeks after exposure to the virus.[15] In a pooled analysis of 181 confirmed cases of COVID-19 outside Wuhan, China, the mean incubation period was 5.1 days and 97.5% of individuals who developed symptoms did so within 11.5 days of infection.[16]

Wu and McGoogan reported that, among 72,314 COVID-19 cases reported to the Chinese CDC (CCDC), 81% were mild (absent or mild pneumonia), 14% were severe (hypoxia, dyspnea, >50% lung involvement within 24-48 hours), 5% were critical (shock, respiratory failure, multiorgan dysfunction), and 2.3% were fatal. Multiple reports from around the globe have subsequently confirmed these patterns of presentation.[17]

The following symptoms may indicate COVID-19[15] :

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Other reported symptoms have included the following:

- Sputum production
- Malaise
- Respiratory distress
- Neurologic (eg, headache, altered mentality)

The most common serious manifestation of COVID-19 appears to be pneumonia.

A complete or partial loss of the sense of smell (anosmia) has been reported as a potential history finding in patients eventually diagnosed with COVID-19.[18] A phone survey of outpatients with mildly symptomatic COVID-19 found that 64.4% (130 of 202) reported any altered sense of smell or taste.[19]

Diagnosis

COVID-19 should be considered a possibility (1) in patients with respiratory tract symptoms and newly onset fever or (2) in patients with severe lower respiratory tract symptoms with no clear cause. Suspicion is increased if such patients have been in an area with community transmission of SARS-CoV-2 or have been in close contact with an individual with confirmed or suspected COVID-19 in the preceding 14 days.

Microbiologic (PCR or antigen) testing is required for definitive diagnosis.

Patients who do not require emergency care are encouraged to contact their healthcare provider by phone. Patients with suspected COVID-19 who present to a healthcare facility should trigger infection-control measures. These patients should be evaluated in a private room with the door closed (an airborne infection isolation room is ideal) and instructed to wear a surgical mask. All other standard contact and airborne precautions should be observed, and treating healthcare personnel should wear eye protection.[20]

Management

Utilization of programs established by the FDA to allow clinicians access to investigational therapies during the pandemic has been essential. The expanded access (EA) and emergency use authorization (EUA) programs allowed for rapid deployment of potential therapies for investigation and investigational therapies with emerging evidence. A review by Rizk et al describes the role for each of these measures and their importance to providing medical countermeasures in the event of infectious disease and other threats.[21]

Remdesivir, an antiviral agent, was the first drug to gain full FDA approval for treatment of COVID-19 in October 2020. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg.[22] An emergency use authorization (EUA) remains in place to treat children younger than 12 years who weigh at least 3.5 kg.[23]

The first vaccine to gain full FDA approval was mRNA-COVID-19 vaccine (Comirnaty; Pfizer) in August 2021.

EUAs have been issued for other vaccines, monoclonal-directed antibodies, convalescent plasma, baricitinib (a Janus kinase inhibitor), and tocilizumab (an interleukin-6 inhibitor) in the United States. A full list of EUAs and access to the Fact Sheets for Healthcare Providers is available from the FDA.

Use of corticosteroids improves survival in hospitalized patients with severe COVID-19 disease requiring supplemental oxygen, with the greatest benefit shown in those requiring mechanical ventilation.[24]

Infected patients should receive supportive care to help alleviate symptoms. Vital organ function should be supported in severe cases.[25]

Numerous collaborative efforts to discover and evaluate effectiveness of antivirals, immunotherapies, monoclonal antibodies, and vaccines have rapidly emerged. Guidelines and reviews of pharmacotherapy for COVID-19 have been published.[25, 26, 27, 28, 29]

Background

Coronaviruses comprise a vast family of viruses, seven of which are known to cause disease in humans. Some coronaviruses that typically infect animals have evolved to infect humans. SARS-CoV-2 is likely one such virus, postulated to have originated in a large animal and seafood market.

Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) also are caused by coronaviruses that “jumped” from animals to humans. More

than 8000 individuals developed SARS, nearly 800 of whom died of the illness (mortality rate, approximately 10%), before it was controlled in 2003.[30] MERS continues to resurface in sporadic cases. A total of 2465 laboratory-confirmed cases of MERS have been reported since 2012, resulting in 850 deaths (mortality rate, 34.5%).[31]

Route of Transmission

The principal mode by which people are infected with SARS-CoV-2 is through exposure to respiratory droplets carrying infectious virus (generally within a space of 6 feet). Additional methods include contact transmission (eg, shaking hands) and airborne transmission of droplets that linger in the air over long distances (usually greater than 6 feet).[32, 33, 34] Virus released in respiratory secretions (eg, during coughing, sneezing, talking) can infect other individuals via contact with mucous membranes.

On July 9, 2020, the WHO issued an update stating that airborne transmission may play a role in the spread of COVID-19, particularly involving “super spreader” events in confined spaces such as bars, although they stressed a lack of such evidence in medical settings. Thus, they emphasized the importance of social distancing and masks in prevention.[34]

The virus can also persist on surfaces to varying durations and degrees of infectivity, although this is not believed to be the main route of transmission.[32] One study found that SARS-CoV-2 remained detectable for up to 72 hours on some surfaces despite decreasing infectivity over time. Notably, the study reported that no viable SARS-CoV-2 was measured after 4 hours on copper or after 24 hours on cardboard.[35]

In a separate study, Chin and colleagues found the virus was very susceptible to high heat (70°C). At room temperature and moderate (65%) humidity, no infectious virus could be recovered from printing and tissue papers after a 3-hour incubation period or from wood and cloth by day 2. On treated smooth surfaces, infectious virus became undetectable from glass by day 4 and from stainless steel and plastic by day 7. “Strikingly, a detectable level of infectious virus could still be present on the outer layer of a surgical mask on day 7 (~0.1% of the original inoculum).”[36] Contact with fomites is thought to be less significant than person-to-person spread as a means of transmission.[32]

Viral shedding

The duration of viral shedding varies significantly and may depend on severity. Among 137 survivors of COVID-19, viral shedding based on testing of oropharyngeal samples ranged from 8 to 37 days, with a median of 20 days.[37] A different study found that repeated viral RNA tests using nasopharyngeal swabs were negative in 90% of cases among 21 patients with mild illness, whereas results were positive for longer durations

in patients with severe COVID-19.[38] In an evaluation of patients recovering from severe COVID-19, Zhou and colleagues found a median shedding duration of 31 days (range, 18-48 days).[39] These studies have all used PCR detection as a proxy for viral shedding. The Korean CDC, investigating a cohort of patients who had prolonged PCR positivity, determined that infectious virus was not present.[40] These findings were incorporated into the CDC guidance on the duration of isolation following COVID-19 infection.

Additionally, patients with profound immunosuppression (eg, following hematopoietic stem-cell transplantation, receiving cellular therapies) may shed viable SARS-CoV-2 for at least 2 months.[41, 42]

SARS-CoV-2 has been found in the semen of men with acute infection, as well as in some male patients who have recovered.[43]

Asymptomatic/presymptomatic SARS-CoV-2 infection and its role in transmission

Oran and Topol published a narrative review of multiple studies on asymptomatic SARS-CoV-2 infection. Such studies and news articles reported rates of asymptomatic infection in several worldwide cohorts, including resident populations from Iceland and Italy, passengers and crew aboard the cruise ship Diamond Princess, homeless persons in Boston and Los Angeles, obstetric patients in New York City, and crew aboard the USS Theodore Roosevelt and Charles de Gaulle aircraft carriers, among several others. Almost half (40-45%) of SARS-CoV-2 infections were asymptomatic.[44]

Utilizing a decision analytical model, Johansson et al from the CDC assessed transmission from presymptomatic, never symptomatic, and symptomatic individuals across various scenarios to determine the infectious period of transmitting SARS-CoV-2. Results from their base case determined 59% of all transmission came from asymptomatic transmission, 35% from presymptomatic individuals and 24% from individuals who never developed symptoms. They estimate at least 50% of new SARSCoV-2 infections originated from exposure to individuals with infection, but without symptoms.[45]

Zou and colleagues followed viral expression through infection via nasal and throat swabs in a small cohort of patients. They found increases in viral loads at the time that the patients became symptomatic. One patient never developed symptoms but was shedding virus beginning at day 7 after presumed infection.[46]

Epidemiology

Coronavirus outbreak and pandemic

As of December 6, 2021, confirmed COVID-19 infections number over 265 million individuals worldwide and have resulted in over 5.2 million deaths.[47]

In the United States, over 49 million reported cases of COVID-19 have been confirmed as of December 6, 2021, resulting in over 785,000 deaths.[48] The pandemic caused approximately 375,000 deaths in the United States during 2020. The age-adjusted death rate increased by 15.9% in 2020, making it the third leading cause of death after heart disease and cancer.[49] Beginning in late March 2020, the United States had more confirmed infections than any other country in the world.[47, 50] The United States also has the most confirmed deaths in the world, followed by Brazil, India, and Mexico.[47]

An interactive map of confirmed cases can be found here.

Health disparities

Communities of color have been disproportionally devastated by COVID-19 in the United States and in Europe. Data from New Orleans illustrated these disparities. African Americans represent 31% of the population but 76.9% of the hospitalizations and 70.8% of the deaths.[51]

The reasons are still being elucidated, but data suggest the cumulative effects of health disparities are the driving force. The prevalence of chronic (high- risk) medical conditions is higher, and access to healthcare may be less available. Finally, socioeconomic status may decrease the ability to isolate and avoid infection.[52, 53]

The overall age-adjusted death rate increased by 15.9% in 2020. Death rates were highest among non-Hispanic Black persons and non-Hispanic American Indian or Alaska Native persons.[49]

CDC maintains a COVID-19 Data Tracker for near real time updates.

Young Adults

Outcomes from COVID-19 disease in young adults have been described by Cunningham and colleagues. Of 3200 adults aged 18 to 34 years hospitalized in the United States with COVID-19, 21% were admitted to the ICU, 10% required mechanical ventilation, and 3% died. Comorbidities included obesity (33%; 25% overall were morbidly obese), diabetes (18%), and hypertension (16%). Independent predictors of death or mechanical ventilation included hypertension, male sex, and morbid obesity. Young adults with multiple risk factors for poor outcomes from COVID-19 compared similarly to middle-aged adults without such risk factors.[54]

A study from South Korea found that older children and adolescents are more likely to transmit SARS CoV-19 to family members than are younger children. The researchers reported that the highest infection rate (18.6%) was in household contacts of patients

with COVID-19 aged 10 to 19 years, and the lowest rate (5.3%) was in household contacts of those aged 0 to 9 years.[55] Teenagers have been the source of clusters of cases, illustrating the role of older children.[56]

COVID-19 in children

Data continue to emerge regarding the incidence and effects of COVID-19, especially for severe disease. A severe multisystem inflammatory syndrome linked to COVID-19 infection has been described in children.[57, 58, 59, 60]

The American Academy of Pediatrics (AAP) reports children represent 17.1% of all cases in the 49 states reporting by age; over 7 million children have tested positive in the United States since the onset of the pandemic as of December 2, 2021. This represents an overall rate of 9344 cases per 100,000 children. During the 2-week period of November 18 to December 2, 2021, there was a 4% increase in the cumulated number of children who tested positive, representing 264,850 new cases. In the week from November 25 to December 2, 2021, cases in children numbered 133,022 and represented 22.4% of the new weekly cases. Children were 1.7% to 4% of total reported hospitalizations, and 0.1% to 1.9% of all child COVID-19 cases resulted in hospitalization.[61]

AAP has issued interim guidance for follow-up care of children following a SARS-CoV-2 infection.

In the United States, a modeling study found one child loses a parent or caregiver for every four COVID-19 associated deaths. From April 1, 2020 through June 30, 2021, more than 140,000 children younger than 18 years in the United States lost a parent, custodial grandparent, or grandparent caregiver who provided the child's home and basic needs, including love, security, and daily care. Overall, the study shows that approximately one of 500 children in the United States has experienced COVID-19-associated orphanhood or the death of a grandparent caregiver. The study also revealed racial, ethnic, and geographic disparities in COVID-19-associated death of caregivers – children of racial and ethnic minorities accounted for 65% of those who lost a primary caregiver due to the pandemic.[62]

In September 2020, the CDC published the demographics of SARS-CoV-2-associated deaths among persons aged 21 years and younger. At the time of publication, approximately 6.5 million cases of SARS-CoV-2 infection and 190,000 associated deaths were reported in the United States. Persons younger than 21 years constitute 26% of the US population.[63]

Clinical characteristics and outcomes of hospitalized children and adolescents aged 1 month to 21 years with COVID-19 in the New York City area have been described. These observations alerted clinicians to rare, but severe illness in children. Of 67 children who tested positive for COVID-19, 21 (31.3%) were managed as outpatients. Among 46 hospitalized patients, 33 (72%) were admitted to the general pediatric

medical unit and 13 (28%) to the pediatric intensive care unit (PICU). Obesity and asthma were highly prevalent, but not significantly associated with PICU admission (P = .99).

Admission to the pediatric intensive care unit (PICU) was significantly associated with higher C-reactive protein, procalcitonin, and pro-B type natriuretic peptide levels and platelet counts (P < .05 for all). Patients in the PICU were more likely to require high-flow nasal cannula (P = .0001) and were more likely to have received remdesivir through compassionate release (P < .05). Severe sepsis and septic shock syndromes were observed in seven (53.8%) patients in the PICU. ARDS was observed in 10 (77%) PICU patients, six (46.2%) of whom required invasive mechanical ventilation for a median of 9 days. Of the 13 patients in the PICU, eight (61.5%) were discharged home, and four (30.7%) patients remained hospitalized on ventilatory support at day 14. One patient died after withdrawal of life-sustaining therapy associated with metastatic cancer.[64]

A case series of 91 children who tested positive for COVID-19 in South Korea showed 22% were asymptomatic during the entire observation period. Among 71 symptomatic cases, 47 children (66%) had unrecognized symptoms before diagnosis, 18 (25%) developed symptoms after diagnosis, and six (9%) were diagnosed at the time of symptom onset. Twenty-two children (24%) had lower respiratory tract infections. The mean (SD) duration of the presence of SARS-CoV-2 RNA in upper respiratory samples was 17.6 (6.7) days. These results lend more data to unapparent infections in children that may be associated with silent COVID-19 community transmission.[65]

An Expert Consensus Statement has been published that discusses diagnosis, treatment, and prevention of COVID-19 in children.

Multisystem inflammatory syndrome in children

Media reports and a health alert from the New York State Department of Health drew initial attention to a newly recognized multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Since then, MIS-C cases have been reported across the United States and Europe, and the American Academy of Pediatrics has published interim guidance.

Symptoms are reminiscent of Kawasaki disease, atypical Kawasaki disease, or toxic shock syndrome. All patients had persistent fevers, and more than half had rashes and abdominal complaints. Interestingly, respiratory symptoms were rarely described. Many patients did not have PCR results positive for COVID-19, but many had strong epidemiologic links with close contacts who tested positive. Furthermore, many had antibody tests positive for SARS-CoV-2. These findings suggest recent past infection, and this syndrome may be a postinfectious inflammatory syndrome. The CDC case definition requires:

An individual younger than 21 years presenting with fever ≥38.0°C for ≥24 hours, laboratory evidence of inflammation (including an elevated C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase [LDH], or interleukin 6 [IL-6], elevated neutrophils, reduced lymphocytes, and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); AND

- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

Jiang and colleagues reviewed the literature on MIS-C noting the multiple organ system involvement. Unlike classic Kawasaki Disease, the children tended to be older and those of Asian ethnicity tended to be spared.[66]

A case series compared 539 patients who had MIS-C with 577 children and adolescents who had severe COVID-19. The patients with MIS-C were typically younger (predominantly aged 6-12 years) and more likely to be non-Hispanic Black. They were less likely to have an underlying chronic medical condition, such as obesity. Severe cardiovascular or mucocutaneous involvement was more common in those with MIS-C. Patients with MIS-C also had higher neutrophil to lymphocyte ratios, higher CRP levels, and lower platelet counts than those with severe COVID-19.[67]

COVID-19 in pregnant individuals and neonates

The US COVID-19 PRIORITY study (Pregnancy coRonavIrus Outcomes RegIsTrY) pregnancy registry is open; the study has a dashboard for real time data.

The CDC COVID-NET data published in September 2020 reported that among 598 hospitalized pregnant patients with COVID-19, 55% were asymptomatic at admission. Severe illness occurred among symptomatic pregnant patients, including intensive care unit admissions (16%), mechanical ventilation (8%), and death (1%). Pregnancy losses occurred for 2% of pregnancies completed during COVID-19-associated hospitalizations, and were experienced by both symptomatic and asymptomatic individuals.[68]

A multicenter study involving 16 Spanish hospitals reported outcomes of 242 pregnant patients diagnosed with COVID-19 during the third trimester from March 13 to May 31, 2020. They and their 248 newborns were monitored until the infant was 1 month old. Pregnant patients with COVID-19 who were hospitalized had a higher risk for cesarean birth ($P = 0.027$). Newborns whose mothers were hospitalized for COVID-19 infection had a higher risk for premature delivery ($P = 0.006$). No infants died and no vertical or horizontal transmission was detected. Exclusive breastfeeding was reported for 41.7% of infants at discharge and 40.4% at 1 month.[69]

A cohort study of pregnant patients (n = 64) with severe or critical COVID-19 disease hospitalized at 12 US institutions between March 5, 2020, and April 20, 2020 has been published. At the time of the study, most (81%) received hydroxychloroquine; 7% of those with severe disease and 65% with critical disease received remdesivir. All of those with critical disease received either prophylactic or therapeutic anticoagulation. One case of maternal cardiac arrest occurred, but there were no cases of cardiomyopathy or death. Half (n = 32) delivered during their hospitalization (34% severe group; 85% critical group). Additionally, 88% with critical disease delivered preterm during their disease course, with 16 of 17 (94%) pregnant women giving birth through cesarean delivery. Overall, 15 of 20 (75%) with critical disease delivered preterm. There were no stillbirths or neonatal deaths or cases of vertical transmission.[70]

Adhikari and colleagues published a cohort study evaluating 252 pregnant patients with COVID-19 in Texas. Maternal illness at initial presentation was asymptomatic or mild in 95% of them, and 3% developed severe or critical illness. Compared with COVID negative pregnancies, there was no difference in the composite primary outcome of preterm birth, preeclampsia with severe features, or cesarean delivery for abnormal fetal heart rate. Early neonatal SARS-CoV-2 infection occurred in six of 188 tested infants,(3%) primarily born to asymptomatic or mildly symptomatic mothers. There were no placental pathologic differences by illness severity.[71]

Breastfeeding

A study by Chambers and colleagues found human milk is unlikely to transmit SARS-CoV-2 from infected mothers to infants. The study included 64 milk samples provided by 18 mothers infected with COVID-19. Samples were collected before and after COVID-19 diagnosis. No replication-competent virus was detectable in any of their milk samples compared with samples of human milk that were experimentally infected with SARS-CoV-2.[72]

Mothers or birthing parents who have been infected with SARS CoV-2 may have neutralizing antibodies expressed in their milk. In an evaluation of 37 milk samples from 18 women, 76% contained SARS-CoV-2-specific IgA, and 80% had SARS-CoV-2-specific IgG. 62% of the milk samples were able to neutralize SARS-CoV-2 infectivity in vitro. These results support recommendations to continue breastfeeding/chestfeeding with masking during mild-to-moderate maternal COVID-19 illness.[73]

COVID-19 in patients with HIV

Data for people with HIV and coronavirus are emerging. A multicenter registry has published outcomes for 286 patients with HIV who tested positive for COVID-19 between April 1 and July 1, 2020. Patient characteristics included mean age of 51.4 years, 25.9% were female, and 75.4% were African-American or Hispanic. Most patients (94.3%) were on antiretroviral therapy, 88.7% had HIV virologic suppression, and 80.8% had comorbidities. Within 30 days of positive SARS-CoV-2 testing, 164

(57.3%) patients were hospitalized, and 47 (16.5%) required ICU admission. Mortality rates were 9.4% (27/286) overall, 16.5% (27/164) among those hospitalized, and 51.5% (24/47) among those admitted to an ICU.[74]

Multiple case series have subsequently been published. Most suggest similar outcomes in patients living with HIV as the general patient population.[75, 76] Severe COVID-19 has been seen, however, suggesting that neither antiretroviral therapy of HIV infection are protective.[74, 77]

COVID-19 in clinicians

Among a sample of healthcare providers who routinely cared for patients with COVID-19 in 13 US academic medical centers from February 1, 2020, 6% had evidence of previous SARS-CoV-2 infection, with considerable variation by location that generally correlated with community cumulative incidence. Among participants who had positive test results for SARS-CoV-2 antibodies, approximately one third did not recall any symptoms consistent with an acute viral illness in the preceding months, nearly one half did not suspect that they previously had COVID-19, and approximately two thirds did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection.[78]

Prognosis

During January to December 2020, the estimated 2020 age-adjusted death rate increased for the first time since 2017, with an increase of 15.9% compared with 2019, from 715.2 to 828.7 deaths per 100,000 population. COVID-19 was the underlying or a contributing cause of 377,883 deaths (91.5 deaths per 100,000). COVID-19 death rates were highest among males, older adults, non-Hispanic American Indian or Alaska Native (AI/AN) persons, and Hispanic persons. Age-adjusted death rates was highest among Black (1105.3) and AI/AN persons (1024).[49]

COVID-19 deaths per 100,000 population in 2020 by age[49]

< 1 year: 1.1

1-4 years: 0.2

5-14 years: 0.2

15-24 years: 1.4

25-34 years: 5.5

35-44 years: 15.8

45-54 years: 44.2

55-64 years: 105.1

65-74 years: 249.2

75-84 years: 635.8

85 years or older: 1,797.8

Mortality and diabetes

Type 1 and type 2 diabetes are both independently associated with a significant increased odds of in-hospital death with COVID-19. In a nationwide analysis in England of 61,414,470 individuals in the registry alive as of February 19, 2020, 0.4% had a recorded diagnosis of type 1 diabetes and 4.7% of type 2 diabetes. A total of 23,804 COVID-19 deaths in England were reported as of May 11, 2020; one third were in people with diabetes, including 31.4% with type 2 diabetes and 1.5% with type 1 diabetes. Upon multivariate adjustment, the odds of in-hospital COVID-19 death were 3.5 for those with type 1 diabetes and 2.03 for those with type 2 diabetes, compared with deaths among individuals without known diabetes. Further adjustment for cardiovascular comorbidities found the odds ratios were still significantly elevated in both type 1 (2.86) and type 2 (1.81) diabetes.[79]

The CDC estimates diabetes is associated with a 20% increased odds of in-hospital mortality.[49]

Hospitalization and cardiometabolic conditions

O'Hearn et al estimate nearly two in three adults hospitalized for COVID-19 in the United States have associated cardiometabolic conditions including total obesity (BMI 30 kg/m2 or greater), diabetes mellitus, hypertension, and heart failure.[80]

Virology

The full genome of SARS-CoV-2 was first posted by Chinese health authorities soon after the initial detection, facilitating viral characterization and diagnosis. The CDC analyzed the genome from the first US patient who developed the infection on January 24, 2020, concluding that the sequence is nearly identical to the sequences reported by

China.[1] SARS-CoV-2 is a group 2b beta-coronavirus that has at least 70% similarity in genetic sequence to SARS-CoV.[31] Like MERS-CoV and SARS-CoV, SARS-CoV-2 originated in bats.[1]

VIral variants emerge when the virus develops one or more mutations that differentiate it from the predominant virus variants circulating in a population. The CDC surveillance of SARS-CoV-2 variants includes US COVID-19 cases caused by variants. The site also includes which mutations are associated with particular variants. The CDC has launched a genomic surveillance dashboard and a website tracking US COVID-19 case trends caused by variants. Researchers are studying how variants may or may not alter the extent of protection by available vaccines.

Variants of Concern in the United States

As mentioned, viruses such as SARS-CoV-2 are constantly changing. Among the hundreds of variants detected in the first year of the pandemic, the ones that are most concerning are the so-called variants of concern (VOCs). Researchers are continually studying how variants may or may not alter the extent of protection by avaible vaccines and antibody-directed therapies.

Omicron

The Omicron variant (B.1.1.529), initially identified in South Africa, was declared a variant of concern in the United States by the CDC November 30, 2021. This VOC contains several dozen mutations, including a large number in the spike gene, more than previous VOCs. These mutations include several associated with increased transmission. Facts regarding if this variant is more transmissible are not yet available; however, extrapolation from other variants and the mutations they include suggest Omicron may be more easily transmitted. As of early December, it is unclear how this variant will affect vaccine or monoclonal antibody treatment efficacy, although the available vaccines are expected to be effective at preventing severe illness, hospitalizations, and deaths.[81]

A preprinted, nonpeer reviewed article of routine surveillance data from South Africa suggests the Omicron variant may evade immunity from prior infection. Among 2,796,982 individuals with laboratory-confirmed SARS-CoV-2 who had a positive test result for SARS-CoV-2 at least 90 days before November 27, 2021, there were 35,670 suspected reinfections identified.[82]

Delta

The Delta variant (B.1.617.2) that was first identified in India became the dominant variant in the United States in mid-July 2021. This variant increases ACE binding and transmissibility. An approximate 6.8-fold decreased neutralization for mRNA vaccines and convalescent plasma has also been observed with the Delta variant.[83, 84] However, a study completed by Public Health England found the BNT162b2

vaccine was only slightly reduced from 93.7% with the B.1.1.7 variant to 88% for the Delta variant 2 weeks after the second dose.[85]

Mutations

Viral mutations may naturally occur anywhere in the SARS-CoV-2 genome. Unlike the human DNA genome, which is slow to mutate, RNA viruses can readily, and quickly, mutate. A mutation may alter the viral function (eg, enhance receptor binding), or may have no discernable function.

Mutations have been identified for the receptor-binding domain (RBD) on the spike protein of SARS-CoV-2. Several of these mutations display higher binding affinity to human ACE2, likely owing to enhanced structural stabilization of the RBD. Whether a mutation enhances viral transmission is a question to explore. Possible mechanisms of increased transmissibility include increased viral shedding, longer contagious interval, increased infectivity, or increased environmental stability.

Table 1. Examples of mutations and resulting actions (Open Table in a new window)

Mutation	Actions	Variants with Mutation
N501Y	Increased viral load	Alpha UK (B.1.117)
Del69-70	Increased ACE binding	Alpha UK (B.1.117); Omicron (B.1.1.529)
E484K	Increased transmission and virulence; decreased neutralization by vaccines and monoclonal antibodies When combined with other mutations, may result in an escape mutation	Beta South Africa (B.1.351), Gamma Brazil (P1), and Iota NYC (B.1.526 and B.1.526.1)
L452R	Monoclonal antibodies may be less effective	B.1.526.1, Epsilon California (B.1.427 and B.1.429), and Delta India (B.1.617 linages and sub-lineages)
D614G	Increased transmission	One of the first documented mutations in the United States after initially circulating in Europe. Included in nearly all variants of

		interest and variants of concern, including Delta and Omicron

Older Variants Monitored in the United States

Alpha

The CDC tracks variant proportions circulating in the United States and estimates the B.1.1.7 variant (Alpha) that was first detected in the United Kingdom accounted for over 44% of cases from January 2 to March 27, 2021. On April 7, 2021, the CDC announced B.1.1.7 was the dominant strain circulating in the United States. It was the dominant strain until mid-July 2021, when the Delta variant became the dominant strain.

A novel spike mutation with deletions of (delta)69/delta(70) has been shown to occur de novo on multiple occasions and to be maintained through sustained transmission in association with other mutations.[86] This is the source of intense scrutiny in Europe, especially in the United Kingdom. A recent VOC – 202012/01 (201/501Y.V1) contains the deletion 69-70 as well as several other mutations including: N501Y, A570D, D614G, P681H, T716I, S982A, D1118H. The variant is being investigated as a cause of rapid increase in case numbers, possibly due to increased viral loads and transmissibility. The N501Y mutation seems to increase viral loads 0.5 log.[87]

Additionally, VOC-202012/01 has mutations that appear to account for its enhanced transmission. The N501Y replacement on the spike protein has been shown to increase ACE2 binding and cell infectivity in animal models. The deletion at positions 69 and 70 of the spike protein (delta69-70) has been associated with diagnostic test failure for the ThermoFisher TaqPath probe targeting the spike protein. Therefore, British labs are using this test failure to identify the variant.[88]

Surveillance data from the UK national community testing (“Pillar 2”) showed a rapid increase in S-gene target failures (SGTF) in PCR testing for SARS-CoV-2 in November and December 2020. The R0 of this variant seems higher. At the same time that the transmission of the wild type virus was dropping, the variant increased, suggesting that the same recommendations (eg, masks, social distancing) may not be enough. The UK variant is also infecting more children (aged 19 years and younger) than the wild type, indicating that it may be more transmissible in children. This has raised concerns because a relative sparing of children has been observed to date. This variant is hypothesized to have a stronger ACE binding than the original variant, which was felt to have trouble infecting younger individuals as they express ACE to a lesser degree.[88]

Beta

The E484K mutation was found initially in the South Africa VOC (B.1.351 [Beta]) and also with the Brazil variants in late 2020, and was observed in the UK variant in early February 2021.

Position 484 and 501 mutations that are both present in the South African variant, and the combination is a concern that immune escape may occur. These mutations, among others, have combined to create the VOC B.1.351. The mutation at the 501 position changes the shape of the RBD by rotating it by 20 degrees to allow deeper binding. The mutation at the 484 position changes the RBD to a positive charge, and allows a higher affinity to the ACE2 receptor.[89]

Gamma

The Brazil VOC P.1 (Gamma) was responsible for an enormous second surge of infections. Sabino et al describe resurgence of COVID-19 in Manaus, Brazil in January 2021, despite a high seroprevalence. A study of blood donors indicated that 76% of the population had been infected with SARS-CoV-2 by October 2020. Hospitalizations for COVID-19 in Manaus numbered 3431 in January 1 to 19, 2021 compared with 552 for December 1 to 19, 2020. Hospitalizations had remained stable and low for 7 months prior to December 2020. Several postulated variables regarding this resurgence include waning titers to the original viral lineage and the high prevalence of the P.1 variant, which was first discovered in Manaus.[90] In addition, researchers are monitoring emergence of a second variant in Brazil, P.2, identified in Rio de Janeiro. As of September 21, 2021, the CDC lists P.2 as a variant being monitored.

Epsilon

VOCs B.1.427 (Epsilon) and B.1.429 (Epsilon) emerged in California. These variants accounted for 2.9% and 6.9% of variants circulating in the United States between January 2 to March 27, 2021. An approximate 20% increase in transmission has been observed with this variant.

Presentation

History

Presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness and mortality. Common symptoms include fever, cough, and shortness of breath.[15] Other symptoms, such as malaise and respiratory distress, have also been described.[31]

Symptoms may develop 2 days to 2 weeks after exposure to the virus.[15] A pooled analysis of 181 confirmed cases of COVID-19 outside Wuhan, China, found the mean incubation period was 5.1 days, and that 97.5% of individuals who developed symptoms did so within 11.5 days of infection.[16]

The following symptoms may indicate COVID-19[15] :

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Other reported symptomsinclude the following:

- Sputum production
- Malaise
- Respiratory distress
- Neurologic (eg, headache, altered mentality)

Wu and McGoogan reported that, among 72,314 COVID-19 cases reported to the CCDC, 81% were mild (absent or mild pneumonia), 14% were severe (hypoxia, dyspnea, >50% lung involvement within 24-48 hours), 5% were critical (shock, respiratory failure, multiorgan dysfunction), and 2.3% were fatal.[17] These general symptom distributions have been reconfirmed across multiple observations.[91, 92]

Clinicians evaluating patients with fever and acute respiratory illness should obtain information regarding travel history or exposure to an individual who recently returned from a country or US state experiencing active local transmission.[93]

Williamson and colleagues, in an analysis of 17 million patients, reaffirmed that severe COVID-19 and mortality was more common in males, older individuals, individuals in poverty, Black persons, and patients with medical conditions such as diabetes and severe asthma, among others.[94]

A multicenter observational cohort study conducted in Europe found frailty was a greater predictor of mortality than age or comorbidities.[95]

Type A blood has been suggested as a potential factor that predisposes to severe COVID-19, specifically in terms of increasing the risk for respiratory failure. Blood type O appears to confer a protective effect.[96, 97]

Patients with suspected COVID-19 should be reported immediately to infection-control personnel at their healthcare facility and the local or state health department. CDC guidance calls for the patient to be cared for with airborne and contact precautions (including eye shield) in place.[20] Patient candidates for such reporting include those with fever and symptoms of lower respiratory illness who have travelled from Wuhan City, China, within the preceding 14 days or who have been in contact with an individual under investigation for COVID-19 or a patient with laboratory-confirmed COVID-19 in the preceding 14 days.[93]

A complete or partial loss of the sense of smell (anosmia) has been reported as a potential history finding in patients eventually diagnosed with COVID-19.[18] A phone survey of outpatients with mildly symptomatic COVID-19 found that 64.4% (130 of 202) reported any altered sense of smell or taste.[19] In a European study of 72 patients with PCR results positive for COVID-19, 53 patients (74%) reported reduced olfaction, while 50 patients (69%) reported a reduced sense of taste. Forty-nine patients (68%) reported both symptoms.[98]

Physical Examination

Patients who are under investigation for COVID-19 should be evaluated in a private room with the door closed (an airborne infection isolation room is ideal) and asked to wear a surgical mask. All other standard contact and airborne precautions should be observed, and treating healthcare personnel should wear eye protection.[20]

The most common serious manifestation of COVID-19 upon initial presentation is pneumonia. Fever, cough, dyspnea, and abnormalities on chest imaging are common in these cases.[99, 100, 101, 102]

Huang and colleagues found that, among patients with pneumonia, 99% had fever, 70% reported fatigue, 59% had dry cough, 40% had anorexia, 35% experienced myalgias, 31% had dyspnea, and 27% had sputum production.[99]

Complications

Complications of COVID-19 include pneumonia, acute respiratory distress syndrome, cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, and multi-organ failure, among others.

Approximately 5% of patients with COVID-19, and 20% of those hospitalized, experience severe symptoms necessitating intensive care. The common complications among hospitalized patients include pneumonia (75%), ARDS (15%), AKI (9%), and acute liver injury (19%). Cardiac injury has been increasingly noted, including troponin elevation, acute heart failure, dysrhythmias, and myocarditis. Ten percent to 25 percent of hospitalized patients with COVID-19 experience prothrombotic coagulopathy resulting in venous and arterial thromboembolic events. Neurologic manifestations include impaired consciousness and stroke.

ICU case fatality is reported up to 40%.[91]

Long COVID

As the COVID-19 pandemic has matured, more patients have reported long-term, post-infection sequelae. Most patients recover fully, but those who do not have reported adverse symptoms such as fatigue, dyspnea, cough, anxiety, depression, inability to focus (ie, “brain fog”), gastrointestinal problems, sleep difficulties, joint pain, and chest pain lasting weeks to months after the acute illness. Long-term studies are underway to understand the nature of these complaints.[103]

Post-acute sequelae of SARS-CoV-2 (PASC) infection is the medical term for what is commonly called long COVID or "long haulers". The NIH includes discussion of persistent symptoms or organ dysfunction after acute COVID-19 within guidelines that discuss the clinical spectrum of the disease.[104]

The UK National Institute for Health and Care Excellence (NICE) issued guidelines on care of long COVID that define the syndrome as: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis.[105]

An international web-based survey of respondents (n = 3762) with suspected and confirmed COVID-19 from 56 countries tallied prevalence of 205 symptoms in 10 organ systems, with 66 symptoms traced over 7 months. The most frequent symptoms reported after 6 months were fatigue (77.7%), postexertional malaise (72.2%), and cognitive dysfunction (55.4%). Nearly 50% were unable to return to work 6 months after infection.[106]

A long-term follow-up study of adults with non-critical COVID-19 at 30 and 60 days post infection revealed ongoing symptoms in two thirds of patients. The most common symptoms included anosmia/ageusia in 28% (40/150) at day 30 and 23% (29/130) at day 60; dyspnea in 36.7% (55/150) of patients at day 30 and 30% (39/130) at day 60; and fatigue/weakness in 49.3% (74/150) at day 30 and 40% (52/130) at day 60.

Persistent symptoms at day 60 were significantly associated with age 40 to 60 years, hospital admission, and abnormal auscultation at symptom onset.[107]

A follow-up study of COVID-19 consequences in 1733 patients discharged from the hospital in Wuhan, China after 6 months reported fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety or depression (23%) were the most common symptoms. Lung function, as measured by CT showing interstitial change and 6-minute walking distance, was less than the lower limit of normal for 22% to 56% across different severity scales.[108]

A study of 55 patients from China looked at long-term pulmonary follow-up 3 months after discharge from a symptomatic COVID-19 illness. Patients' mean age was 47 years, 42% were female, and 85% had moderate disease. Only nine patients (16.4%) had underlying comorbidities including hypertension, diabetes mellitus, and cardiovascular diseases, but none had preexisting pulmonary disease. None of the patients required mechanical ventilation. At 3 months, 71% still had abnormal chest CT scans, most commonly showing interstitial thickening. Spirometry was also checked in all patients. Lung function abnormalities were detected in 25.5%. Anomalies were noted in total lung capacity of four patients (7.3%), FEV1 of six patients (11%), FVC of six patients (11%), DLCO of nine patients (16%), and small airway function in seven patients (12%), despite most patients having no respiratory complaints.[109]

These data are consistent with the findings of a study of 124 patients recovered from COVID-19 after 6 weeks in the Netherlands. The mean age was 59±14 years and 60% were male; 27 with mild, 51 with moderate, 26 with severe, and 20 with critical disease. Nearly all patients (99%) had improved imaging, but residual parenchymal abnormalities remained in 91% and correlated with reduced lung diffusion capacity in 42%. Twenty-two percent had low exercise capacity, 19% low fat-free mass index, and 36% had problems in mental and/or cognitive function.[110]

The long-term effects of COVID-19 have also been observed after mild infection treated in the outpatient setting. In a longitudinal cohort study at the University of Washington, 177 participants completed a survey a median of 169 days after their COVID-19 diagnosis. Almost 85% were never admitted for treatment. One third reported persistent symptoms, and a similar number reported worsened quality of life. The most common symptom was fatigue.[111]

Future public health implications

Public health implications for long COVID need to be examined, as reviewed by Datta, et al. As with other infections (eg, Lyme disease, syphilis, Ebola), late inflammatory and virologic sequelae may emerge. Accumulation of evidence beyond the acute infection and postacute hyperinflammatory illness is important to evaluate to gain a better understanding of the full spectrum of the disease.[112]

Thrombotic manifestations of severe COVID-19 are caused by the ability of SARS-CoV-2 to invade endothelial cells via angiotensin-converting enzyme-2 (ACE-2), which is expressed on the surface of endothelial cells. Subsequent endothelial inflammation, complement activation, thrombin generation, platelet and leukocyte recruitment, and the initiation of innate and adaptive immune responses culminate in immunothrombosis, and can ultimately cause microthrombotic complications (eg, DVT, PE, stroke).[113]

Kotecha et al describe patterns of myocardial injury in hospitalized patients with severe COVID-19 who had elevated troponin levels. During convalescence, myocarditis-like injury was observed, with limited extent and minimal functional consequence. However, in a proportion of patients, there was evidence of possible ongoing localized inflammation. Roughly 25% of patients had ischemic heart disease, of which two thirds had no previous history.[114]

Reinfection

Clinicians, infectious disease specialists, and public health experts are examining the potential for patient reinfection with the SARS CoV-2 virus.[115]

Cases of reinfection with SARS CoV-2 have emerged worldwide.[116] Several cases have shown differing viral genomes tested in the patient, which suggests reinfection rather than prolonged viral shedding.

A case report showed a 42-year-old male who was infected with SARS CoV-2 on March 21, 2020 after a workplace exposure. The patient had symptom resolution of symptoms after 10 days with continued good health for 51 days. On May 24, 2020, the patient presented with symptoms suggestive of COVID-19 after a new household exposure. Upon testing via SARS-CoV-2 RT-PCR, the patient had confirmed positive COVID-19 with several potential genetic variations that differed from the SARS-CoV-2 strain sequenced from the patient in March.[117]

In another case, a 33-year-old male in Hong Kong had contracted COVID-19 in March 2020, which was confirmed via saliva SARS-CoV-2 RT-PCR. The patient had symptom resolution along with two negative SARS-CoV-2 RT-PCR results by April 14, 2020. The patient experienced a second episode of COVID-19 in August 2020 after a trip to Spain. Although asymptomatic, the patient was tested upon returning to Hong Kong, and tested positive via SARS-CoV-2 RT-PCR. Genomic sequencing was performed on both RT-PCR specimens collected in March and August. The genomic analysis showed the two strains of SARS-CoV-2 (from March and August) belonged to different viral lineages, which suggests that the strain from the first episode differed from the strain in the second episode.[118]

The Collaborative Study COVID Recurrences (COCOREC) group in France reported 11 virologically-confirmed cases of patients with a second clinically- and virologically-confirmed acute COVID-19 episode between April 6, 2020 and May 14, 2020. The letter

does not describe confirmation with viral genomic sequencing to understand if the cases were a relapse of the initial infection or a new infection, however.[119]

Two cases of reinfection have emerged in the United States, a 25-year-old man from Nevada and a 42-year-old man in Virginia. These cases were confirmed by gene testing that showed different strains of the SARS-CoV-2 virus during the two infection episodes in each patient. In these cases, the patients experienced more severe symptoms during their second infections. It is unclear if the symptom severity experienced the second time were related to the virus or the how the patients' immune systems reacted. Vaccine development may need to take into account circulating viral strains.[116, 120]

These case reports give insight to the possibility of reinfection. Further research to determine the prevalence of COVID-19 reinfections is needed, including the frequency at which they occur and longevity of COVID-19 immunity.

Workup

Approach Considerations

Diagnostic testing for SARS-CoV-2 infection can be conducted by the CDC, state public health laboratories, hospitals using their own developed and validated tests, and some commercial reference laboratories.[121]

State health departments with a patient under investigation (PUI) should contact CDC's Emergency Operations Center (EOC) at 770-488-7100 for assistance with collection, storage, and shipment of clinical specimens for diagnostic testing. Specimens from the upper respiratory tract, lower respiratory tract, and serum should be collected to optimize the likelihood of detection.[93]

The FDA now recommends that nasal swabs that access just the front of the nose be used in symptomatic patients, allowing for (1) a more comfortable and simplified collection method and (2) self-collection at collection sites.[122]

Various organizations, including the CDC, have published guidelines on COVID-19.

Laboratory Studies

Signs and symptoms of coronavirus disease 2019 (COVID-19) may overlap with those of other respiratory infections; therefore, it is important to perform laboratory testing to

specifically identify symptomatic individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Three types of tests may be utilized to determine if an individual has been infected with SARS-CoV-2:

- Viral nucleic acid (RNA) detection
- Viral antigen detection
- Detection of antibodies to the virus

Viral tests (nucleic acid or antigen detection tests) are used to assess acute infection, whereas antibody tests provide evidence of prior infection with SARS-CoV-2. Home sample collection kits for COVID-19 testing have been available by prescription; in December 2020, the LabCorp Pixel COVID-19 Test Home Collection Kit became the first to receive an FDA EUA for nonprescription use.

The FDA has advised against the use of antibody tests to ascertain immunity or protection from COVID-19, particularly in patients who have been vaccinated against the disease. According to the agency, differences between antibodies that arise from prior SARS-CoV-2 infection and those induced by vaccination leave the tests unable to determine whether an individual has achieved protection through a vaccine.

Laboratory findings in patients with COVID-19

Leukopenia, leukocytosis, and lymphopenia were common among early cases.[31, 99]

Lactate dehydrogenase and ferritin levels are commonly elevated.[99]

Wu and colleagues[123] reported that, among 200 patients with COVID-19 who were hospitalized, older age, neutrophilia, and elevated lactate dehydrogenase and D-dimer levels increased the risks for ARDS and death.

CT Scanning

Chest computed tomography (CT) scanning in patients with COVID-19–associated pneumonia usually shows ground-glass opacification, possibly with consolidation. Some studies have reported that abnormalities on chest CT scans are usually bilateral, involve the lower lobes, and have a peripheral distribution. Pleural effusion, pleural thickening, and lymphadenopathy have also been reported, although with less frequency.[99, 124, 125]

Bai and colleagues reported the following common chest CT scanning features among 201 patients with CT abnormalities and positive RT-PCR results for COVID-19[126] :

- Peripheral distribution (80%)
- Ground-glass opacity (91%)
- Fine reticular opacity (56%)
- Vascular thickening (59%)

Less-common features on chest CT scanning included the following[126] :

- Central and peripheral distribution (14%)
- Pleural effusion (4.1%)
- Lymphadenopathy (2.7%)

The American College of Radiology (ACR) recommends against using CT scanning for screening or diagnosis but instead reserving it for management in hospitalized patients.[127]

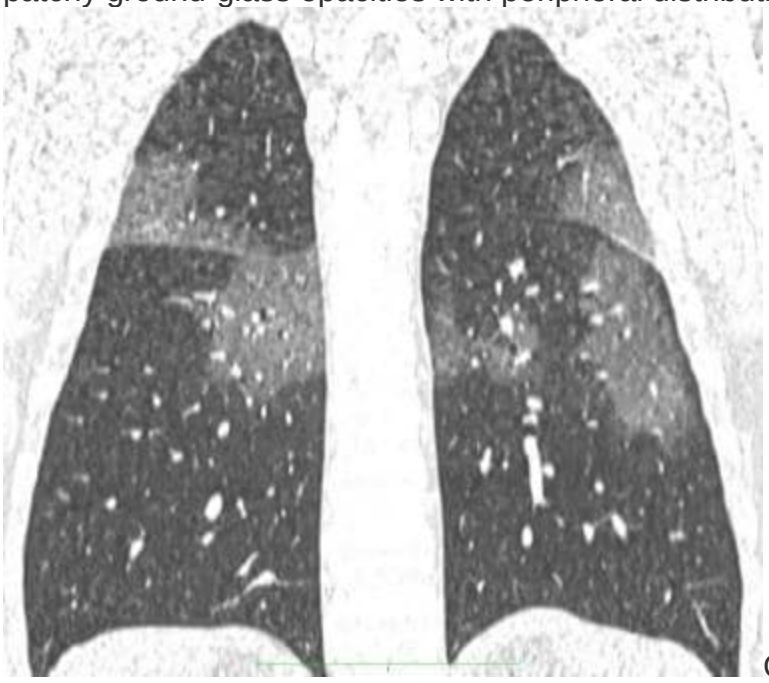
At least two studies have reported on manifestations of infection in apparently asymptomatic individuals. Hu and colleagues reported on 24 asymptomatic infected persons in whom chest CT scanning revealed ground-glass opacities/patchy shadowing in 50% of cases.[128] Wang and colleagues reported on 55 patients with asymptomatic infection, two thirds of whom had evidence of pneumonia as revealed by CT scanning.[129]

Progression of CT abnormalities

Li and colleagues recommend high-resolution CT scanning and reported the following CT changes over time in patients with COVID-19 among three Chinese hospitals:

- Early phase: Multiple small patchy shadows and interstitial changes begin to emerge in a distribution beginning near the pleura or bronchi rather than the pulmonary parenchyma.
- Progressive phase: The lesions enlarge and increase, evolving to multiple ground-glass opacities and infiltrating consolidation in both lungs.
- Severe phase: Massive pulmonary consolidations occur, while pleural effusion is rare.
- Dissipative phase: Ground-glass opacities and pulmonary consolidations are absorbed completely. The lesions begin evolving into fibrosis. [130]


Axial chest CT demonstrates patchy ground-glass opacities with peripheral distribution.

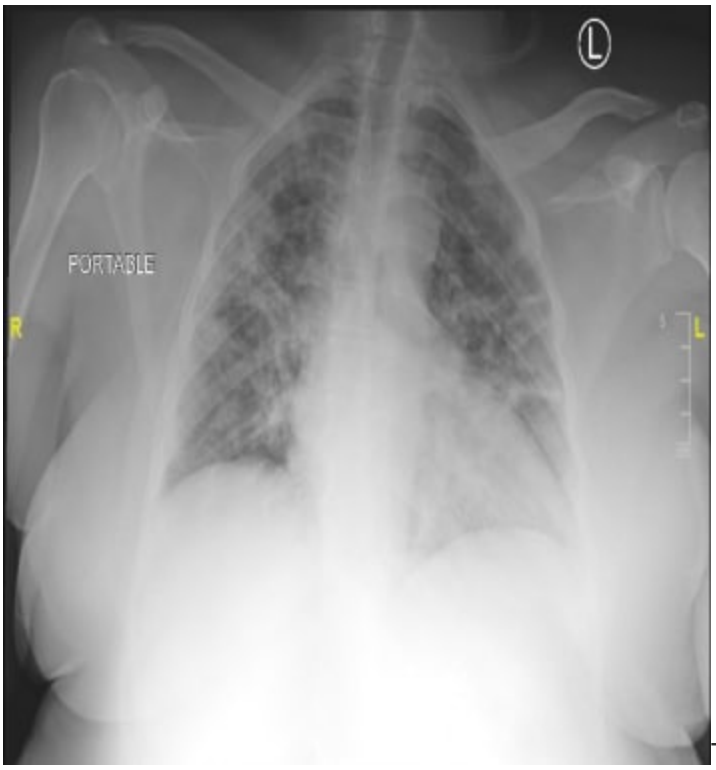

Coronal reconstruction chest CT of the same patient above, showing patchy ground-glass opacities.


Axial chest CT shows bilateral patchy consolidations (arrows), some with peripheral ground-glass opacity. Findings are in peripheral and subpleural distribution.

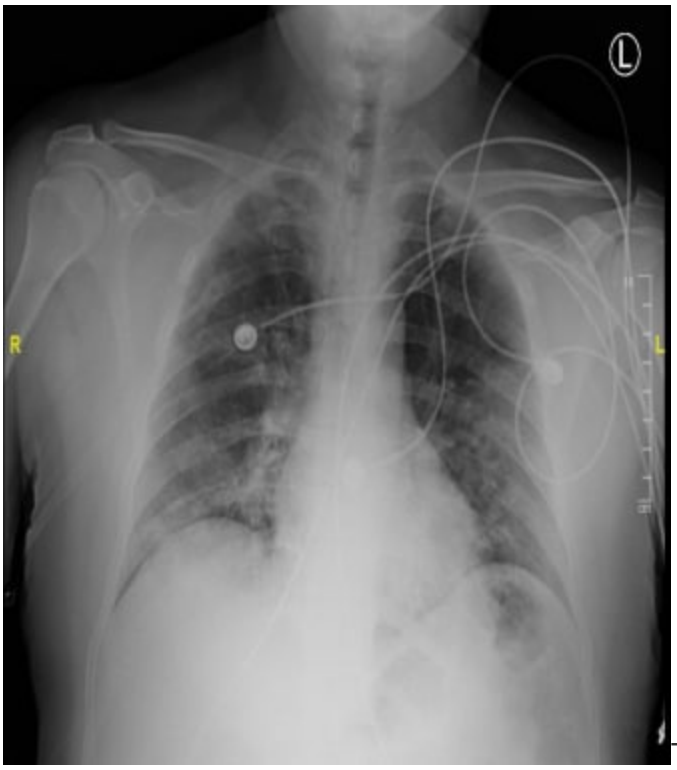
Chest Radiography

In a retrospective study of patients in Hong Kong with COVID-19, common abnormalities on chest radiography, when present, included consolidation (30 of 64 patients; 47%) and ground-glass opacities (33%). Consolidation was commonly bilateral and of lower zone distribution. Pleural effusion was an uncommon finding. Severity on chest radiography peaked 10 to 12 days after symptom onset.[131]

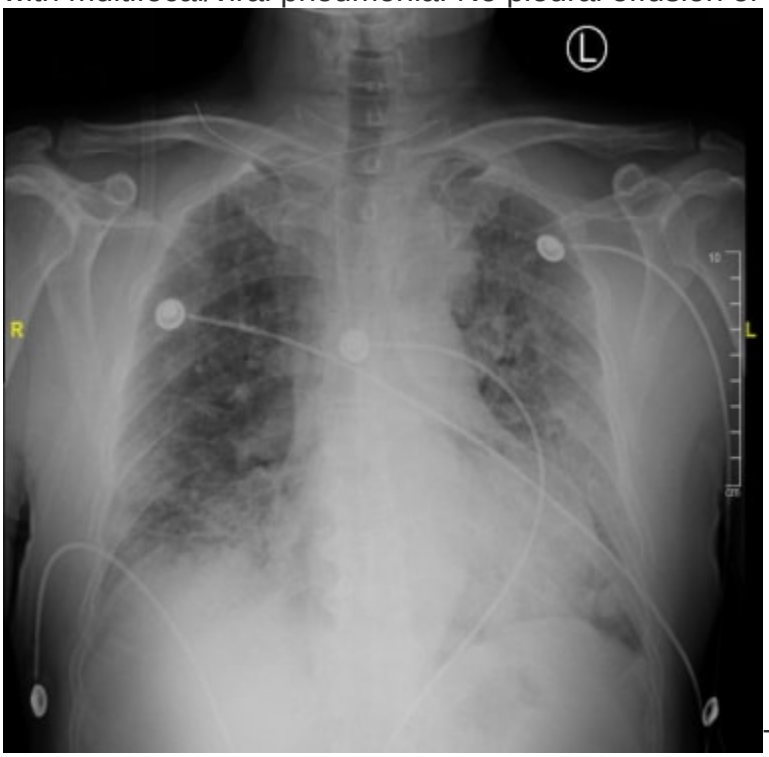
Chest radiography may reveal pulmonary infiltrates.[132]



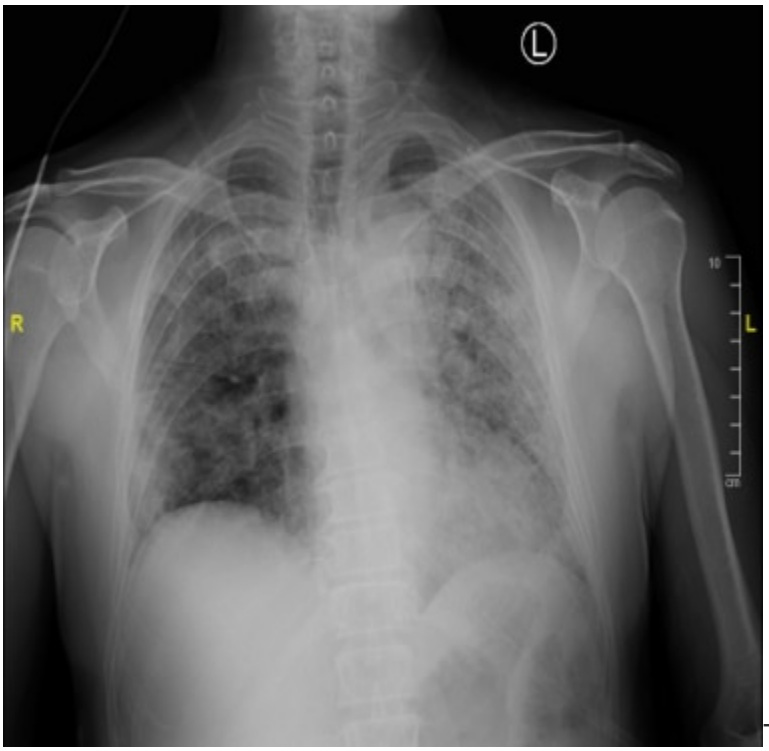
The heart is normal in size. There are diffuse, patchy opacities throughout both lungs, which may represent multifocal viral/bacterial pneumonia versus pulmonary edema. These opacities are particularly confluent along the periphery of the right lung. There is left midlung platelike atelectasis. Obscuration of the left costophrenic angle may represent consolidation versus a pleural effusion with atelectasis. There is no pneumothorax.



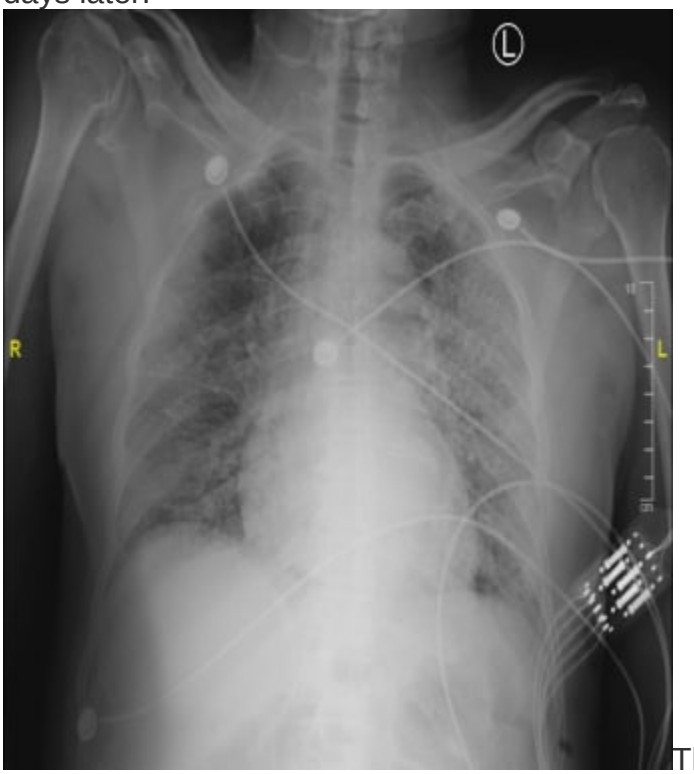
The heart is normal in size. There are bilateral hazy opacities, with lower lobe predominance. These findings are consistent with multifocal/viral pneumonia. No pleural effusion or pneumothorax are seen.



The heart is normal in size. Patchy opacities are seen throughout the lung fields. Patchy areas of consolidation at the right lung base partially silhouettes the right diaphragm. There is no effusion or pneumothorax. Degenerative changes of the thoracic spine are noted.



The same patient as above 10 days later.



The trachea is in midline. The cardiomediastinal silhouette is normal in size. There are diffuse hazy reticulonodular opacities in both lungs. Differential diagnoses include viral pneumonia, multifocal bacterial pneumonia or ARDS. There is no pleural effusion or pneumothorax.

Treatment

Approach Considerations

Utilization of programs established by the FDA to allow clinicians to gain access to investigational therapies during the pandemic has been essential. The expanded access (EA) and emergency use authorization (EUA) programs allowed for rapid deployment of potential therapies for investigation and investigational therapies with emerging evidence. A review by Rizk et al describes the role for each of these measures, and their importance to providing medical countermeasures in the event of infectious disease and other threats.[21]

Remdesivir, an antiviral agent, was the first drug to gain full FDA approval for treatment of COVID-19 in October 2020. It is indicated for treatment of COVID-19 disease in hospitalized adults and children 12 years and older who weigh at least 40 kg.[22] An emergency use authorization (EUA) remains in place for treating pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg.[23] An EUA for convalescent plasma was announced on August 23, 2020.[133] Numerous other antiviral agents, immunotherapies, and vaccines continue to be investigated and developed as potential therapies.

The first vaccine to gain full FDA approval was mRNA-COVID-19 vaccine (Comirnaty; Pfizer) in August 2021.

EUAs have been issued for vaccines, monoclonal-directed antibodies, convalescent plasma, baricitinib (a Janus kinase inhibitor), and tocilizumab (an interleukin-6 inhibitor) in the United States. A full list of EUAs and access to the Fact Sheets for Healthcare Providers are available from the FDA.

Use of corticosteroids improve survival in hospitalized patients with severe COVID-19 disease requiring supplemental oxygen, with the greatest benefit shown in those requiring mechanical ventilation.[24]

All infected patients should receive supportive care to help alleviate symptoms. Vital organ function should be supported in severe cases.[13]

Early in the outbreak, concerns emerged about nonsteroidal anti-inflammatory drugs (NSAIDs) potentially increasing the risk for adverse effects in individuals with COVID-19. However, in late April, the WHO took the position that NSAIDS do not increase the risk for adverse events or affect acute healthcare utilization, long-term survival, or quality of life.[134]

Numerous collaborative efforts to discover and evaluate effectiveness of antivirals, immunotherapies, monoclonal antibodies, and vaccines have rapidly emerged.

Guidelines and reviews of pharmacotherapy for COVID-19 have been published.[25, 26, 27, 28] The Milken Institute maintains a detailed COVID-19 Treatment and Vaccine Tracker of research and development progress.

Searching for effective therapies for COVID-19 infection is a complex process. Gordon and colleagues identified 332 high-confidence SARS-CoV-2 human protein-protein interactions. Among these, they identified 66 human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials, and/or preclinical compounds. As of March 22, 2020, these researchers are in the process of evaluating the potential efficacy of these drugs in live SARS-CoV-2 infection assays.[135]

The NIH Accelerating Covid-19 Therapeutics Interventions and Vaccines (ACTIV) trials public-private partnership to develop a coordinated research strategy has several ongoing protocols that are adaptive to the progression of standard care.

Another adaptive platform trial is the I-SPY COVID-19 Trial for treating critically ill patients. The clinical trial is designed to allow numerous investigational agents to be evaluated in the span of 4 to 6 months, compared with standard of care (supportive care for ARDS, remdesivir backbone therapy), depending on the time course of COVID-19 infections across the United States. As the trial proceeds and a better understanding of the underlying mechanisms of the COVID-19 illness emerges, expanded biomarker and data collection can be added as needed to further elucidate how agents are or are not working.[136]

How these potential COVID-19 treatments will translate to human use and efficacy is not easily or quickly understood. The question of whether some existing drugs that have shown in vitro antiviral activity might achieve adequate plasma pharmacokinetics with current approved doses was examined by Arshad and colleagues. The researchers identified in vitro anti–SARS-CoV-2 activity data from all available publications up to April 13, 2020, and recalculated an EC90 value for each drug. EC90 values were then expressed as a ratio to the achievable maximum plasma concentrations (Cmax) reported for each drug after administration of the approved dose to humans (Cmax/EC90 ratio). The researchers also calculated the unbound drug to tissue partition coefficient to predict lung concentrations that would exceed their reported EC50 levels.[137]

The WHO developed a blueprint of potential therapeutic candidates in January 2020. The WHO embarked on an ambitious global "megatrial" called SOLIDARITY in which confirmed cases of COVD-19 are randomly assigned to standard care or one of four active treatment arms (remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon beta-1a). In early July 2020, the treatment arms in hospitalized patients that included hydroxychloroquine, chloroquine, or lopinavir/ritonavir were discontinued owing to the drugs showing little or no reduction in mortality compared with standard of care.[138] Interim results released mid-October 2020 found the four aforementioned repurposed antiviral agents appeared to have little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality,

initiation of ventilation, and duration of hospital stay. The 28-day mortality was 12% (39% if already ventilated at randomization, 10% otherwise).[139]

The next phase of the trial, Solidarity PLUS, continued in August 2021. WHO announced over 600 hospitals in 52 countries will participate in testing three drugs (ie, artesunate, imatinib, infliximab). Patients will be randomized to standard of care (SOC) or SOC plus one of the study drugs. The drugs for the trial were donated by the manufacturers; however, approximate costs are $400/day for imatinib, $3,500 for a dose of infliximab, and $50,000 for a course of artesunate.

The urgent need for treatments during a pandemic can confound the interpretation of resulting outcomes of a therapy if data are not carefully collected and controlled. Andre Kalil, MD, MPH, writes of the detriment of drugs used as a single-group intervention without a concurrent control group that ultimately lead to no definitive conclusion of efficacy or safety.[140]

Rome and Avorn write about unintended consequences of allowing widening access to experimental therapies. First, efficacy is unknown and may be negligible, but, without appropriate studies, physicians will not have evidence on which to base judgement. Existing drugs with well-documented adverse effects (eg, hydroxychloroquine) subject patients to these risks without proof of clinical benefit. Expanded access of unproven drugs may delay implementation of randomized controlled trials. In addition, demand for unproven therapies can cause shortages of medications that are approved and indicated for other diseases, thereby leaving patients who rely on these drugs for chronic conditions without effective therapies.[141]

Drug shortages during the pandemic go beyond off-label prescribing of potential treatments for COVID-19. Drugs that are necessary for ventilated and critically ill patients and widespread use of inhalers used for COPD or asthma are in demand.[142, 143]

It is difficult to carefully evaluate the onslaught of information that has emerged regarding potential COVID-19 therapies within a few months' time in early 2020. A brief but detailed approach regarding how to evaluate resulting evidence of a study has been presented by F. Perry Wilson, MD, MSCE. By using the example of a case series of patients given hydroxychloroquine plus azithromycin, Wilson provides clinicians with a quick review of critical analyses.[144]

Related articles

The CDC has resources on global COVID-19 on its website.

For more information on investigational drugs and biologics being evaluated for COVID-19, see Treatment of Coronavirus Disease 2019 (COVID-19): Investigational Drugs and Other Therapies.

See the article Coronavirus Disease 2019 (COVID-19) in Emergency Medicine.

The Medscape article Acute Respiratory Distress Syndrome (ARDS) includes discussions of fluid management, noninvasive ventilation and high-flow nasal cannula, mechanical ventilation, and extracorporeal membrane oxygenation.

Some have raised concerns over whether patients with respiratory distress have presentations more like those of high-altitude pulmonary edema (HAPE) than ARDS.

See also the articles Viral Pneumonia, Respiratory Failure, Septic Shock, and Multiple Organ Dysfunction Syndrome in Sepsis.

Medscape resources describing relevant procedures are as follows:

Ventilator application techniques

- Bag-Valve-Mask Ventilation Technique (with video)
- Application of Noninvasive Ventilation
- Rapid Sequence Intubation Technique
- Nasotracheal Intubation Technique
- Lighted Stylet Assisted Tracheal Intubation

Ventilator management and monitoring

- Ventilator Management
- Ventilator Graphics
- Mechanical Ventilation: Initial Ventilator Settings
- Mechanical Ventilation: Alternative Modes of Mechanical Ventilation
- Mechanical Ventilation: Rapid Sequence Intubation

Respiratory conditions assessment and management

- Breath Sound Assessment
- Pulmonary Function Testing
- Respiratory Failure Treatment & Management
- Acute Respiratory Distress Syndrome Treatment & Management
- Barotrauma and Mechanical Ventilation
- Eucapnic Hyperventilation

Prevention

The FDA has granted EUAs for 3 SARS-CoV-2 vaccines since December, 2020. Two are mRNA vaccines – BNT-162b2 (Pfizer) and mRNA-1273 (Moderna), whereas the third is a viral vector vaccine – Ad26.COV2.S (Johnson & Johnson).

Avoidance is the principal method of deterrence.

General measures for prevention of viral respiratory infections include the following[13] :

- Handwashing with soap and water for at least 20 seconds. An alcohol-based hand sanitizer may be used if soap and water are unavailable.
- Individuals should avoid touching their eyes, nose, and mouth with unwashed hands.
- Individuals should avoid close contact with sick people.
- Sick people should stay at home (eg, from work, school).
- Coughs and sneezes should be covered with a tissue, followed by disposal of the tissue in the trash.

Frequently touched objects and surfaces should be cleaned and disinfected regularly.

Preventing/minimizing community spread of COVID-19

The CDC has recommended the below measures to mitigate community spread.[9, 145, 146]

All individuals in areas with prevalent COVID-19 should be vigilant for potential symptoms of infection and should stay home as much as possible, practicing social distancing (maintaining a distance of 6 feet from other persons) when leaving home is necessary.

Persons with an increased risk for infection—(1) individuals who have had close contact with a person with known or suspected COVID-19 or (2) international travelers (including travel on a cruise ship)—should observe increased precautions. These include (1) self-quarantine for at least 2 weeks (14 days) from the time of the last exposure and distancing (6 feet) from other persons at all times and (2) self-monitoring for cough, fever, or dyspnea with temperature checks twice a day.

On April 3, 2020, the CDC issued a recommendation that the general public, even those without symptoms, should begin wearing face coverings in public settings where social-distancing measures are difficult to maintain in order to abate the spread of COVID-19.[9]

Facemasks

In a 2020 study on the efficacy of facemasks in preventing acute respiratory infection, surgical masks worn by patients with such infections (rhinovirus, influenza, seasonal coronavirus [although not SARS-CoV-2 specifically]) were found to reduce the detection

of viral RNA in exhaled breaths and coughs. Specifically, surgical facemasks were found to significantly decreased detection of coronavirus RNA in aerosols and influenza virus RNA in respiratory droplets. The detection of coronavirus RNA in respiratory droplets also trended downward. Based on this study, the authors concluded that surgical facemasks could prevent the transmission of human coronaviruses and influenza when worn by symptomatic persons and that this may have implications in controlling the spread of COVID-19.[147]

In a 2016 systematic review and meta-analysis, Smith and colleagues found that N95 respirators did not confer a significant advantage over surgical masks in protecting healthcare workers from transmissible acute respiratory infections.[148]

Investigational agents for postexposure prophylaxis

PUL-042

PUL-042 (Pulmotech, MD Anderson Cancer Center, and Texas A&M) is a solution for nebulization with potential immunostimulating activity. It consists of two toll-like receptor (TLR) ligands: Pam2CSK4 acetate (Pam2), a TLR2/6 agonist, and the TLR9 agonist oligodeoxynucleotide M362.

PUL-042 binds to and activates TLRs on lung epithelial cells. This induces the epithelial cells to produce peptides and reactive oxygen species (ROS) against pathogens in the lungs, including bacteria, fungi, and viruses. M362, through binding of the CpG motifs to TLR9 and subsequent TLR9-mediated signaling, initiates the innate immune system and activates macrophages, natural killer (NK) cells, B cells, and plasmacytoid dendritic cells; stimulates interferon-alpha production; and induces a T-helper 1 cells–mediated immune response. Pam2CSK4, through TLR2/6, activates the production of T-helper 2 cells, leading to the production of specific cytokines.[149]

In May 2020, the FDA approved initiation of two COVID-19 phase 2 clinical trials of PUL-042 at up to 20 US sites. The trials are for the prevention of infection with SARS-CoV-2 and the prevention of disease progression in patients with early COVID-19. In the first study, up to 4 doses of PUL-042 or placebo will be administered to 200 participants via inhalation over a 10-day period to evaluate the prevention of infection and reduction in severity of COVID-19. In the second study, 100 patients with early symptoms of COVID-19 will receive PUL-042 up to 3 times over 6 days. Each trial will monitor participants for 28 days to assess effectiveness and tolerability.[150, 151]

Antiviral Agents

Remdesivir

Remdesivir (Veklury) was the first drug approved by the FDA for treating the SARS-CoV-2 virus. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg. The broad-spectrum antiviral is a nucleotide analog prodrug.[22] Full approval was preceded by the US FDA issuing an EUA (emergency use authorization) on May 1, 2020.[152] Upon approval of remdesivir in adults and adolescents, the EUA was updated to maintain the ability for prescribers to treat pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg.[23]

The remdesivir EUA was expanded to include moderate disease August 28, 2020. This expands the previous authorization to treat all hospitalized patients with COVID-19 regardless of oxygen status.[153] A new drug application (NDA) for remdesivir was submitted to the FDA in August 2020. A phase 1b trial of an inhaled nebulized version was initiated in late June 2020 to determine if remdesivir can be used on an outpatient basis and at earlier stages of disease.[154] As of October 1, 2020, remdesivir is available from the distributor (ie, AmerisourceBergen). Wholesale acquisition cost is approximately $520/100-mg vial, totaling $3,120 for a 5-day treatment course.

Several phase 3 clinical trials have tested remdesivir for treatment of COVID-19. Positive results were seen with remdesivir after use by the University of Washington in the first case of COVID-19 documented on US soil in January 2020.[155] An adaptive randomized trial of remdesivir coordinated by the National Institute of Health (NCT04280705) was started first against placebo, but additional therapies were added to the protocol as evidence emerged and treatment evolved. The first experience with this study involved passengers of the Diamond Princess cruise ship in quarantine at the University of Nebraska Medical Center in February 2020 after returning to the United States from Japan following an on-board outbreak of COVID-19.[156] Trials of remdesivir for moderate and severe COVID-19 compared with standard of care and varying treatment durations are ongoing.

The initial EUA for remdesivir was based on preliminary data analysis of the Adaptive COVID-19 Treatment Trial (ACTT), and was announced April 29, 2020. The final analysis included 1,062 hospitalized patients with advanced COVID-19 and lung involvement, showing that patients treated with 10-days of remdesivir had a 31% faster time to recovery than those who received placebo (remdesivir, 10 days; placebo, 15 days; $P < 0.001$). Patients with severe disease ($n = 957$) had a median time to recovery of 11 days compared with 18 days for placebo. A statistically significant difference was not reached for mortality by day 15 (remdesivir 6.7% vs placebo 11.9%) or by day 29 (remdesivir 11.4% vs placebo 15.2%).[157]

The final ACTT-1 results for shortening the time to recovery differed from interim results from the WHO SOLIDARITY trial for remdesivir. These discordant conclusions are complicated and confusing as the SOLIDARITY trial included patients from ACTT-1.[139] An editorial by Harrington and colleagues[158] notes the complexity of the SOLIDARITY trial and the variation within and between countries in the standard of care and in the burden of disease in patients who arrive at hospitals. The authors also

mention that trials solely focused on remdesivir were able to observe nuanced outcomes (ie, ability to change the course of hospitalization), whereas the larger, simple randomized SOLIDARITY trial focused on more easily defined outcomes.

Similar to the SOLIDARITY trial, the DisCoVeRy open-labeled, multicenter trial did not show clinical benefit from use of remdesivir. The trial was conducted in 48 sited throughout Europe from March 22, 2020 to January 21, 2022. However, among the participants included in the SOLIDARITY trial, 219 (8%) of 2750 participants who were randomly assigned to receive remdesivir and 221 (5.4%) of 4088 randomly assigned to standard of care were shared by the DisCoVeRy trial. These shared patients between the 2 trials accounted for approximately 50% of DisCoVeRy participants (remdesivir plus SOC [n = 429]; SOC alone [n = 428]). Standard of care did not include dexamethasone until October 2021 in this trial.[159]

The open-label phase 3 SIMPLE trial (n = 397) in hospitalized patients with severe COVID-19 disease not requiring mechanical ventilation showed similar improvement in clinical status with the 5-day remdesivir regimen compared with the 10-day regimen on day 14 (odds ratio, 0.75). After adjustment for imbalances in baseline clinical status, patients receiving a 10-day course of remdesivir had a distribution in clinical status at day 14 that was similar to that of patients receiving a 5-day course (P = 0.14). The findings could significantly expand the number of patients who could be treated with the current supply of remdesivir. The trial is continuing with an enrollment goal of 6,000 patients.[160]

Similarly, the phase 3 SIMPLE II trial in patients with moderate COVID-19 disease (n = 596) showed that 5 days of remdesivir treatment had a statistically significant higher odds of a better clinical status distribution on Day 11 compared with those receiving standard care (odds ratio, 1.65; P = 0.02). Improvement on Day 11 did not differ between the 10-day remdesivir group and standard of care (P = 0.18).[161]

The phase 3 PINETREE trial evaluated remdesivir as a 3-day outpatient regimen in high-risk patients with COVID-19. An analysis of 562 patients showed an 87% reduction in risk for COVID-19 related hospitalization or all-cause death by Day 28 for remdesivir (0.7% [2/279]) compared with placebo (5.3% [15/283]) p = 0.008. Remdesivir was also associated with an 81% reduction in the risk of medical visits owing to COVID-19 or all-cause death (1.6% vs 8.3% with placebo; P = 0.002).[162]

Real-world analysis

Three retrospective real-world studies presented at the 2021 World Microbe Forum showed remdesivir-treated hospitalized patients had significantly lower risk for mortality compared with matched controls. The studies included 98,654 patients and results are summarized below.[163]

Aetion and HealthVerity: Remdesivir-treated patients (n = 24,856) had a 23% lower mortality risk compared with controls (n = 24,856), regardless of baseline oxygen

requirement from May 1, 2020 to May 3, 2021. Patients who received a 5-day regimen also had a significantly greater likelihood of discharge by day 28.

Premier Healthcare: Assessed mortality in hospitalized patients who were initiated remdesivir (n=28,855) within the first 2 days of hospitalization versus matched patients not receiving remdesivir (n=16,687) between August and November 2020. Patients were matched on baseline level of oxygenation, hospital, within a 2-month hospital admission period, and all stayed in the hospital for a minimum of 3 days after initiating treatment. Remdesivir-treated patients had a significantly lower risk of mortality at Day 14 ($p < 0.0001$) and Day 28 ($P = 0.003$) compared with those not given remdesivir.

SIMPLE-Severe: Compared outcomes in patients receiving 10-days of remdesivir in the extension phase of the open-label SIMPLE-Severe trial. Regardless of baseline oxygen requirements, treatment with remdesivir results in a 54% lower mortality risk at Day 28 compared with the control group ($P < 0.001$).

Remdesivir use in children

Remdesivir emergency use authorization includes pediatric dosing that was derived from pharmacokinetic data in healthy adults. Remdesivir has been available through compassionate use to children with severe COVID-19 since February 2020. A phase 2/3 trial (CARAVAN) of remdesivir was initiated in June 2020 to assess safety, tolerability, pharmacokinetics, and efficacy in children with moderate-to-severe COVID-19. CARAVAN is an open-label, single-arm study of remdesivir in children from birth to age 18 years.[164]

Data were presented on compassionate use of remdesivir in children at the virtual COVID-19 Conference held July 10-11, 2020. Most of the 77 children with severe COVID-19 improved with remdesivir. Clinical recovery was observed in 80% of children on ventilators or ECMO and in 87% of those not on invasive oxygen support.[165]

Remdesivir use in pregnant women

Outcomes in the first 86 pregnant women who were treated with remdesivir (March 21 to June 16, 2020)found high recovery rates. Recovery rates were high among women who received remdesivir (67 while pregnant and 19 on postpartum days 0-3). No new safety signals were observed. At baseline, 40% of pregnant women (median gestational age, 28 weeks) required invasive ventilation compared with 95% of postpartum women (median gestational age at delivery 30 weeks). Among pregnant women, 93% of those on mechanical ventilation were extubated, 93% recovered, and 90% were discharged. Among postpartum women, 89% were extubated, 89% recovered, and 84% were discharged. There was 1 maternal death attributed to underlying disease and no neonatal deaths.[166]

Data continue to emerge. A case series of 5 patients describes successful treatment and monitoring throughout treatment with remdesivir in pregnant women with COVID-19.[167]

Investigational Antivirals

Molnupiravir

An EUA for molnupiravir was requested in October 2021. The FDA's Antimicrobial Drugs Advisory Committee narrowly voted to recommend the FDA authorize molnupiravir for EUA on November 30, 2021.

Molnupiravir (MK-4482 [previously EIDD-2801]; Merck) is an oral antiviral agent that is a prodrug of the nucleoside derivative N4-hydroxycytidine. It elicits antiviral effects by introducing copying errors during viral RNA replication of the SARS-CoV-2 virus.

The phase 3 outpatient MOVe-OUT study (n = 1433) found molnupiravir reduced risk of hospitalization or death from 9.7% (68 of 699) in the placebo group to 6.8% (48 of 709) in the molnupiravir group for an absolute risk reduction of 3% (p = 0.02) and a relative risk reduction of 30%. Nine deaths were reported in the placebo group and one in the molnupiravir group. These data are consistent with the interim analysis.[168]

Molnupiravir is also being evaluated in a phase 3 trial for postexposure prophylaxis for individuals residing in the same household with someone who tests positive for SARS-CoV-2 in the phase 3 MOVE-AHEAD trial.[169]

Favipiravir

Favipiravir (Avigan, Reeqonus; Appili Therapeutics) is an oral antiviral that disrupts viral replication by selectively inhibiting RNA polymerase. An adaptive, multicenter, open label, randomized, phase 2/3 clinical trial of favipiravir compared with standard of care I hospitalized patients with moderate COVID-19 was conducted in Russia. Both dosing regimens of favipiravir demonstrated similar virologic response. Viral clearance on Day 5 was achieved in 25/40 (62.5%) patients on in the favipiravir group compared with 6/20 (30%) patients in the standard care group (P = 0.018). Viral clearance on Day 10 was achieved in 37/40 (92.5%) patients taking favipiravir compared with 16/20 (80%) in the standard care group (P = 0.155).[170]

The phase 3 PRESECO (PREventing SEvere COVID-19) study evaluated early treatment in patients with mild-to-moderate symptoms to prevent disease progression and hospitalization. Enrollment was completed in September 2021. The phase 3 PEPCO (Post Exposure Prophylaxis for COVID-19) study in asymptomatic individuals with direct exposure (within 72 hours) to an infected individual is ongoing.[171]

PF-07321332

Oral SARS-CoV2-3CL protease inhibitor in phase 2/3 clinical trial initiated Fall 2021. In the EPIC-PEP (Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis) trial, PF-07321332 (Pfizer) is coadministered with low-dose ritonavir for prevention of COVID-19 disease adult household contacts living with an individual with a confirmed symptomatic SARS-COV-2 infection.[172] The EPIC trials also include other ongoing trials, including one in SARS-CoV-2 infected patients who are at high risk of severe illness (including hospitalization or death).[173]

AT-527

AT-527 (Atea Pharmaceuticals) is an oral purine nucleotide prodrug designed to inhibit RNA polymerase enzyme. It has demonstrated in vitro and in vivo antiviral activity against several enveloped single-stranded RNA viruses, including human flaviviruses and coronaviruses. Phase 2 interim virology analysis reported in June 2021 included data from 62 of 70 hospitalized patients with moderate COVID-19 symptoms who received the drug or placebo BID for 5 days. On Day 2 of treatment, patients taking AT-527 had an 80% (0.7 log10) greater mean reduction from baseline viral load compared with placebo. No detectable levels of virus were observed at 2 weeks in 47% of the AT-527 group compared with 22% in the placebo group.[174]

Additional global trials for AT-527 include a phase 2 trial (MOONSONG) and phase 3 trial (MORNINGSKY) in outpatients with mild-to-moderate COVID-19 disease. Another phase 3 trial (MEADOWSPRING) is being conducted as a 6-month long-term follow-on study to evaluate the impact of prior administration of AT-527 on long COVID in patients previously enrolled in MORNINGSKY.

Clinical trials of existing drugs with antiviral properties

Nitazoxanide

Nitazoxanide extended-release tablets (NT-300; Romark Laboratories) inhibit replication of a broad range of respiratory viruses in cell cultures, including SARS-CoV-2. Two phase 3 trials for prevention of COVID-19 are being initiated in high-risk populations, including elderly residents of long-term care facilities and healthcare workers. In addition to the prevention studies, a third trial for early treatment of COVID-19 is planned.[175, 176] Another multicenter, randomized, double-blind phase 3 study was initiated in August 2020 for treatment of people aged 12 years and older with fever and respiratory symptoms consistent with COVID-19. Efficacy analyses will examine those participants who have laboratory-confirmed SARS-CoV-2 infection.[177]

Niclosamide

Niclosamide (FW-1002 [FirstWave Bio]; ANA001 [ANA Therapeutics]) is an anthelmintic agent used primarily for tapeworms for nearly 50 years. Niclosamide is thought to disrupt SARS-CoV-2 replication through S-phase kinase-associated protein 2 (SKP2)-inhibition, by preventing autophagy and blocking endocytosis.

A proprietary formulation that targets the viral reservoir in the gut to decrease prolonged infection and transmission has been developed, specifically to decrease gut viral load. It is being tested in a phase 2 trial.[178] A phase 2/3 trial is testing safety and the potential to improved outcomes and reduce hospital stay by reducing viral load.[179]

Other investigational antivirals continue to emerge.

Immunomodulators and Other Investigational Therapies

Various methods of immunomodulation are being quickly examined, mostly by repurposing existing drugs, in order blunt the hyperinflammation caused by cytokine release. Interleukin (IL) inhibitors, Janus kinase inhibitors, and interferons are just a few of the drugs that are in clinical trials. Ingraham and colleagues[180] provide a thorough explanation and diagram of the SARS-CoV-2 inflammatory pathway and potential therapeutic targets. A review of pharmaco-immunotherapy by Rizk and colleagues[181] summarizes the roles and relationships of innate immunity and adaptive immunity, along with immunomodulators (eg, interleukins, convalescent plasma, JAK inhibitors) prevent and control infection.

Interleukin Inhibitors

Interleukin (IL) inhibitors may ameliorate severe damage to lung tissue caused by cytokine release in patients with serious COVID-19 infections. Several studies have indicated a “cytokine storm” with release of IL-6, IL-1, IL-12, and IL-18, along with tumor necrosis factor alpha (TNFα) and other inflammatory mediators. The increased pulmonary inflammatory response may result in increased alveolar-capillary gas exchange, making oxygenation difficult in patients with severe illness.

Tocilizumab and other interleukin-6 inhibitors

IL-6 is a pleiotropic proinflammatory cytokine produced by various cell types, including lymphocytes, monocytes, and fibroblasts. SARS-CoV-2 infection induces a dose-dependent production of IL-6 from bronchial epithelial cells. This cascade of events is the rationale for studying IL-6 inhibitors.[182]

Tocilizumab was issued an EUA on June 24, 2021 for hospitalized adults and pediatric patients (aged 2 years and older) with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The Infectious Disease Society of America guidelines recommend tocilizumab in addition to standard of care (ie, steroids) among hospitalized adults with COVID-19 who have elevated markers of systemic inflammation.[25] The NIH guidelines recommend

use of tocilizumab (single IV dose of 8 mg/kg, up to 800 mg) in combination with dexamethasone in recently hospitalized patients who are exhibiting rapid respiratory decompensation caused by COVID-19.[183] These recommendations are based on the paucity of evidence from randomized clinical trials to show certainty of mortality reduction.

The EMPACTA trial found nonventilated hospitalized patients who received tocilizumab (n = 249) in the first 2 days of ICU admission had a lower risk of progression to mechanical ventilation or death by day 28 compared with those not treated with tocilizumab (n = 128) (12% vs 19.3% respectively). The data cutoff for this study was September 30, 2020. In the 7 days before the trial or during the trial, 200 patients in the tocilizumab group (80.3%) and 112 patients in the placebo group (87.5%) received systemic glucocorticoids and 55.4% and 67.2% of the patients received dexamethasone. Antiviral treatment was administered in 196 (78.7%) and 101 (78.9%), respectively, and 52.6% and 58.6% received remdesivir. However, there was no difference in incidence of death from any cause between the 2 groups.[184]

Results from the REMAP-CAP international adaptive trial evaluated efficacy of tocilizumab 8 mg/kg (n = 353), sarilumab 400 mg (n = 48), or control (n = 402) in critically ill hospitalized adults receiving organ support in intensive care. Hospital mortality at day 21 was 28% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab, and 35.8% (142/397) for control. Of note, corticosteroids became part of the standard of care midway through the trial. Estimates of the treatment effect for patients treated with either tocilizumab or sarilumab and corticosteroids in combination were greater than for any single intervention.[185]

The RECOVERY trial assessed use of 4,116 hospitalized adults with COVID-19 infection who received either tocilizumab (n = 2022) compared with standard of care (n = 2094) in the United Kingdom from April 23, 2020 to January 24, 2021. Among participants, 562 (14%) received invasive mechanical ventilation, 1686 (41%) received non-invasive respiratory support, and 1868 (45%) received no respiratory support other than oxygen. Median C-reactive protein was 143 mg/L and most patients (82% in both treatment groups) were receiving systemic corticosteroids at randomization. Tocilizumab mortality benefits were clearly seen among those who also received systemic corticosteroids. Patients in the tocilizumab group were more likely to be discharged from the hospital within 28 days (57% vs 50; $p < 0.0001$). Among those not receiving invasive mechanical ventilation at baseline, patients who received tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs 42%; $p < 0.0001$).[186]

Conversely, the COVACTA study, 452 with COVID-19 (oxygen saturation, 93% or less) were randomly assigned in a 2:1 ratio to receive 1 dose of tocilizumab or placebo. At day 28, no significant difference was observed for mortality between the tocilizumab group and placebo (19.7% vs 19.4%, respectively).[187]

An editorial by Rubin et al discusses the discordant results of the RECOVERY and REMAP-CAP trials compared with the COVACTA trial. One significant difference noted is that patients with severe disease, now almost universally receive glucocorticoids. Only a minority of patients in the COVACTA trial were treated with glucocorticoids. Fewer in the group that received tocilizumab (19.4%) than in the group that received placebo (28.5%) also received glucocorticoids. In contrast, 93% and 82% of all patients in REMAP-CAP and the RECOVERY trial, respectively, were receiving glucocorticoid therapy.[188]

Average wholesale price of tocilizumab is approximately $5000 for an 800-mg dose. Preliminary results for sarilumab have also been reported.

Interleukin-1 inhibitors

Hospitalized patients with COVID-19 at increased risk for respiratory failure showed significant improvement after treatment with anakinra compared with placebo, based on data from a phase 3, randomized, confirmatory trial (SAVE-MORE study; n = 594). Patients in each study arm also received standard of care treatment. Patients were identified by increased soluble urokinase plasminogen activator receptor (suPAR) serum levels, which is an early indicator of progressing respiratory failure. At 28 days, 204 (50.4%) of the anakinra-treated patients had fully recovered, with no detectable viral RNA, compared with 50 (26.5%) of the placebo-treated patients ($P < .0001$). In addition, significantly fewer patients in the anakinra group had died by 28 days (13 patients, 3.2%), compared with patients in the placebo group (13 patients, 6.9%).[189]

Endogenous IL-1 levels are elevated in individuals with COVID-19 and other conditions, such as severe CAR-T-cell–mediated cytokine-release syndrome. Anakinra has been used off-label for this indication. As of June 2020, the NIH guidelines note insufficient data to recommend for or against use of IL-1 inhibitors.[190]

Interleukin-7 inhibitors

The recombinant interleukin-7 inhibitor, CYT107 (RevImmune), increases T-cell production and corrects immune exhaustion. Several phase 2 clinical trials have been completed in France, Belgium, and the UK to assess immune reconstitution in lymphopenic patients with COVID-19.[191, 192, 193] Phase 2 trials were initiated in November 2020 in the United States.

JAK and NAK Inhibitors

Drugs that target numb-associated kinase (NAK) may mitigate systemic and alveolar inflammation in patients with COVID-19 pneumonia by inhibiting essential cytokine signaling involved in immune-mediated inflammatory response. In particular, NAK inhibition has been shown to reduce viral infection in vitro. ACE2 receptors are a point of cellular entry by COVID-19, which is then expressed in lung AT2 alveolar epithelial cells. A known regulator of endocytosis is the AP2-associated protein kinase-1 (AAK1).

The ability to disrupt AAK1 may interrupt intracellular entry of the virus. Baricitinib (Olumiant; Eli Lilly Co), a Janus kinase (JAK) inhibitor, is also identified as a NAK inhibitor with a particularly high affinity for AAK1.[194, 195, 196]

Baricitinib

Emergency use authorization (EUA) was issued by the FDA for baricitinib on November 19, 2020. The EUA is for use, in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized patients 2 years and older who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[197] The EUA was revised in July 2021 to allow use without remdesivir.

The NIAID Adaptive Covid-19 Treatment Trial (ACTT-2) evaluated the combination of baricitinib (4 mg PO daily up to 14 days) and remdesivir (100 mg IV daily up to 10 days) (515 patients) compared with remdesivir plus placebo (518 patients). Patients who received baricitinib had a median time to recovery of 7 days compared with 8 days with control (P = 0.03), and a 30% higher odds of improvement in clinical status at day 15. Those receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51). The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65). Incidence of serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; P = 0.03) There were also fewer new infections in patients who received baricitinib (5.9% vs. 11.2%; P =0 .003).[198]

The COV-BARRIER trial demonstrated baricitinib to be the first immunomodulatory treatment to reduce COVID-19 mortality in a placebo-controlled trial.[199] Results from the global COV-BARRIER phase 3 trial showed a reduced risk of death in hospitalized patients not on mechanical ventilation who received baricitinib 4 mg daily for up to 14 days when added to standard of care (SOC), compared with SOC alone at Day 28 (38.2% risk reduction in mortality; (62/764 [8.1%] baricitinib; 101/761 [13.3%] placebo; p = 0.0018). Progression to high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation did not reach statistical significance for baricitinib plus SOC compared with SOC alone (27.8% vs 30.5%; p = 0.0018). The 60-day all-cause mortality was 10% (n=79) for baricitinib and 15% (n=116) for placebo (p = 0.005). Serious adverse events occurred in 15% of the baricitinib group compared with 18% of those receiving placebo. Serious infections (9% vs 10%) and venous thromboembolic events (3% in each group) were similar between the 2 groups.[200]

The COV-BARRIER study was expanded to include patients on mechanical ventilation. Those who received baricitinib plus SOC and on mechanical ventilation or ECMO were 46% less likely to die by Day 28 compared with patients on SOC alone (p = 0.0296). The cumulative proportion among these patients who died by Day 28 was 39.2% (20/51) in the baricitinib arm compared with 58% in the placebo arm (29/50).[201]

Tofacitinib

Tofacitinib (Xeljanz), another JAK inhibitor, was evaluated in 289 hospitalized patients with COVID-19 pneumonia were randomized 1:1 at 15 sites in Brazil. Most patients (89.3%) received glucocorticoids during hospitalization. Cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29% in the placebo group (P = 0.04). Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group.[202]

Corticosteroids

The UK RECOVERY trial assessed the mortality rate at day 28 in hospitalized patients with COVID-19 who received low-dose dexamethasone 6 mg PO or IV daily for 10 days added to usual care. Patients were assigned to receive dexamethasone (n = 2104) plus usual care or usual care alone (n = 4321). Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (P< 0.001). In the dexamethasone group, the incidence of death was lower than in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs 41.4%) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs 26.2%), but not among those who were receiving no respiratory support at randomization (17.8% vs 14%).[24]

Corticosteroids are not generally recommended for treatment of viral pneumonia.[203] The benefit of corticosteroids in septic shock results from tempering the host immune response to bacterial toxin release. The incidence of shock in patients with COVID-19 is relatively low (5% of cases). It is more likely to produce cardiogenic shock from increased work of the heart need to distribute oxygenated blood supply and thoracic pressure from ventilation. Corticosteroids can induce harm through immunosuppressant effects during the treatment of infection and have failed to provide a benefit in other viral epidemics, such as respiratory syncytial virus (RSV) infection, influenza infection, SARS, and MERS.[204]

Early guidelines for management of critically ill adults with COVID-19 specified when to use low-dose corticosteroids and when to refrain from using corticosteroids. The recommendations depended on the precise clinical situation (eg, refractory shock, mechanically ventilated patients with ARDS); however, these particular recommendations were based on evidence listed as weak.[205] The results from the RECOVERY trial in June 2020 provided evidence for clinicians to consider when low-dose corticosteroids would be beneficial.[24]

Several trials examining use of corticosteroids for COVID-19 were halted after publication of the RECOVERY trial results; however, a prospective meta-analysis from the WHO rapid evidence appraisal for COVID-19 therapies (REACT) pooled data from 7 trials (eg, RECOVERY, REMAP-CAP, CoDEX, CAP COVID) that totaled 1703 patients (678 received corticosteroids and 1025 received usual care or placebo). An association between corticosteroids and reduced mortality was similar for dexamethasone and

hydrocortisone, suggesting the benefit is a general class effect of glucocorticoids. The 28-day mortality rate, the primary outcome, was significantly lower among corticosteroid users (32% absolute mortality for corticosteroids vs 40% assumed mortality for controls).[206] An accompanying editorial addresses the unanswered questions regarding these studies.[207]

The WHO guidelines for use of dexamethasone (6 mg IV or oral) or hydrocortisone (50 mg IV every 8 hours) for 7-10 days in the most seriously ill patients coincides with publication of the meta-analysis.[208]

Human Vasoactive Intestinal Polypeptides

Aviptadil (Zyesami; RLF-100; NeuroRx) is a synthetic vasoactive intestinal peptide (VIP) that prevents NMDA-induced caspase-3 activation in lungs and inhibits IL-6 and TNF-alpha production. An EUA was submitted to the FDA on June 1, 2021 to treat critically ill patients with COVID-19 infection and respiratory failure. Results from a phase 2b/3 trial (COVID-AIV) of IV aviptadil for treatment of respiratory failure in critically ill patients with COVID-19 demonstrated meaningful recovery at days 28 ($p = 0.014$) and 60 ($p = 0.013$) and survival ($P < 0.001$). Patients enrolled in the study had respiratory failure despite prior treatment with all approved medicines for COVID-19 including remdesivir. Other therapies administered included steroids, anticoagulants, and various monoclonal antibodies.Analysis of patients who remained in respiratory failure despite treatment with remdesivir identified a statistically significant ($P = .03$) 2.5-fold increased odds of being alive and free of respiratory failure and a statistically significant ($P = .006$) 4-fold higher odds of being alive at day 60 among patients treated with aviptadil compared with those treated with placebo. Although antiviral treatment has shown advantages in treating patients with earlier stages of COVID-19, aviptadil is the first to demonstrate increased recovery and survival in patients who have already progressed to respiratory failure.[209]

Aviptadil is being studied as part of the NIH's ACTIV-3 critical care protocol alone and in combination with remdesivir in hospitalized patients with ARDS.

Additionally, it is being studied as an inhaled treatment.[210]

SYK Inhibitors

Fostamatinib (Tavalisse; Rigel Pharmaceuticals) is a spleen tyrosine kinase (SYK) inhibitor that reduces signaling by Fc gamma receptor (FcγR) and c-type lectin receptor (CLR), which are drivers of proinflammatory cytokine release. It also reduces mucin-1 protein abundance, which is a biomarker used to predict ARDS development. It is approved in the U.S. for thrombocytopenia in patients with chronic immune thrombocytopenia (ITP). The active metabolite (R406) inhibits signal transduction of Fc-activating receptors and B-cell receptor to reduce antibody-mediated destruction of platelets.

The phase 2 NIH trial randomized 59 patients (30 to fostamatinib and 29 to placebo) in hospitalized patients with COVID-19 in addition to standard of care. There were 3 deaths that occurred by day 29, all receiving placebo. The mean change in ordinal score at day 15 was greater in the fostamatinib group (-3.6 ± 0.3 vs. -2.6 ± 0.4, P = .035) and the median length in the ICU was 3 days in the fostamatinib group compared with 7 days in placebo (P = .07). Differences in clinical improvement were most evident in patients with severe or critical disease (median days on oxygen, 10 vs. 28, P = .027).[211]

Interferons

Interferon is a natural antiviral part of the immune system. Interferon impairment is associated with the pathogenesis and severity of COVID-19 infection. The NIAID's Adaptive COVID-19 Treatment Trial (ACTT-3) compared SC interferon beta-1a (Rebif) plus remdesivir (n = 487) with remdesivir plus placebo (n = 482) in hospitalized patients. Results showed interferon beta-1a plus remdesivir was not superior to remdesivir alone. Additionally, in patients who required high-flow oxygen at baseline, adverse effects were higher in among those receiving remdesivir plus interferon beta-1a group compared with the remdesivir plus placebo (69% vs 39%). Serious adverse events in the interferon beta-1a plus remdesivir group were also higher compared with remdesivir alone (60% vs 24%).[212]

Miscellaneous Therapies

Nitric Oxide

The Society of Critical Care Medicine recommends against the routine use of iNO in patients with COVID-19 pneumonia. Instead, they suggest a trial only in mechanically ventilated patients with severe ARDS and hypoxemia despite other rescue strategies.[205] The cost of iNO is reported as exceeding $100/hour.

Statins

In addition to the cholesterol-lowering abilities of HMG-CoA reductase inhibitors (statins), they also decrease the inflammatory processes of atherosclerosis.[213] Because of this, questions have arisen whether statins may be beneficial to reduce inflammation associated with COVID-19. RCTs of statins as anti-inflammatory agents for viral infections are limited, and results have been mixed.

Two meta-analyses have shown opposing conclusions regarding outcomes of patients who were taking statins at the time of COVID-19 diagnosis.[214, 215] Randomized controlled trials are needed to examine the ability of statins to attenuate inflammation, presumably by inhibiting expression of the MYD88 gene, which is known to trigger inflammatory pathways.[216]

Adjunctive Nutritional Therapies

NIH guidelines state there are insufficient evidence to recommend either for or against use of vitamins C and D, and zinc for treatment of COVID-19. The guidelines recommend against using zinc supplementation above the recommended dietary allowance.

Vitamin and mineral supplements have been promoted for the treatment and prevention of respiratory viral infections; however, there is insufficient evidence to suggest a therapeutic role in treating COVID-19.[217]

Zinc

A retrospective analysis showed lack of a causal association between zinc and survival in hospitalized patients with COVID-19.[218]

Vitamin D

A study found individuals with untreated vitamin D deficiency were nearly twice as likely to test positive for COVID-19 compared with peers with adequate vitamin D levels. Among 489 individuals, vitamin D status was categorized as likely deficient for 124 participants (25%), likely sufficient for 287 (59%), and uncertain for 78 (16%). Seventy-one participants (15%) tested positive for COVID-19. In a multivariate analysis, a positive COVID-19 test was significantly more likely in those with likely vitamin D deficiency than in those with likely sufficient vitamin D levels (relative risk, 1.77; P = .02). Testing positive for COVID-19 was also associated with increasing age up to age 50 years (relative risk, 1.06; P = .02) and race other than White (relative risk, 2.54; P = .009).[219] It is unknown if vitamin D deficiency is the specific issue, as it is also associated with various conditions that are risk factors for severe COVID-19 conditions (eg, advanced age, cardiovascular disease, diabetes mellitus).[220]

Additional Investigational Drugs for ARDS/Cytokine Release

NIH immune modulators trial

In October 2020, the NIH launched an adaptive phase 3 trial (ACTIV-1 Immune Modulators) to assess safety and efficacy of 3 immune modulator agents in hospitalized patients with Covid-19. The three drugs are infliximab (Remicade), abatacept (Orencia), and cenicriviroc, a late-stage investigational drug for hepatic fibrosis associated with nonalcoholic steatohepatitis.

Infliximab

Monoclonal antibody that inhibits TNF, a proinflammatory cytokine that may cause excess inflammation during advanced stages of COVID-19. Initially approved in 1998 to treat various chronic autoimmune inflammatory diseases (eg, rheumatoid arthritis, psoriasis, inflammatory bowel diseases).

Abatacept

Selective T-cell costimulatory immunomodulator. The drug consists of the extracellular domain of human cytotoxic T cell-associated antigen 4 fused to a modified immunoglobulin. It works by preventing full activation of T cells, resulting in inhibition of the downstream inflammatory cascade.

Cenicriviroc

An immunomodulator that blocks 2 chemokine receptors, CCR2 and CCR5, shown to be closely involved with the respiratory sequelae of COVID-19 and of related viral infections. It is also part of the I-SPY COVID-19 clinical trial.[136] This study was discontinued due to futility at the recommendation of the Data and Safety Monitoring Board.

Colony-stimulating factors

Granulocyte-macrophage colony stimulating factor (GM-CSF) has been implicated in the pathogenesis of respiratory failure in patients with severe COVID-19 pneumonia and systemic hyperinflammation.

Lenzilumab

Lenzilumab (Humanigen) is a monoclonal antibody directed against GM-CSF. Results from a phase 3 trial (n = 520) found lenzilumab significantly improved survival without ventilation in hospitalized, hypoxic patients with COVID-19 pneumonia over and above treatment with remdesivir and/or corticosteroids. Those with CRP less than 150 mg/L and age younger than 85 years demonstrated an improvement in survival and had the greatest benefit.[221]

Additionally, lenzilumab is part of the NIH ACTIV-5/BET trial that is ongoing as of April 2021.

Sargramostim

Sargramostim (Leukine, rhuGM-CSF; Partner Therapeutics, Inc) is an inhaled colony-stimulating factor. Results of the phase 2 trial (iLeukPulm) of inhaled sargramostim plus standard of care (SOC) in 122 hospitalized patients with confirmed SARS-CoV-2 infection with acute hypoxemia requiring supplemental oxygen were release in late June 2021. Patients on inhaled sargramostim plus SOC showed an average improvement in oxygenation from baseline, as measured by P(A-a)O2, of 100 mm Hg (31%) compared

to 35 mm Hg (5%) on SOC alone (P = 0.033). Improved oxygenation was observed in 84% of sargramostim-treated patients, compared with 64% in the control arm (P = 0.023).[222] GM-CSF may reduce the risk for secondary infection, accelerate removal of debris caused by pathogens, and stimulate alveolar epithelial cell healing during lung injury.[223]

Gimsilumab

Gimsilumab (Riovant Sciences) is being studied in the phase 2 BREATHE clinical trial at Mt Sinai and Temple University is analyzing this monoclonal antibody that targets granulocyte macrophage-colony stimulating factor (GM-CSF) in patients with ARDS.[224]

Mavrilimumab

Mavrilimumab (Kiniksa Pharmaceuticals) is a fully humanized monoclonal antibody that targets granulocyte macrophage colony-stimulating factor (GM-CSF) receptor alpha. Results from an ongoing global phase 2/3 trial showed a significant reduction in need for mechanical ventilation and death in those receiving mavrilimumab. Mortality at day 29 was 21% in the placebo arm but just 8% in the combined mavrilimumab arms (P = .07).[225]

Otilimab

Otilimab (GlaxoSmithKline) is a humanized monoclonal anti-GM-CSF antibody under development for rheumatoid arthritis. A global, randomized trial (OSCAR; n = 806) compared a single 90-mg infusion of otilimab plus standard of care (SOC) with SOC alone in hospitalized adults with severe COVID-19 respiratory failure and systemic inflammation. At day 28, 71% of patients who received otilimab were alive and free of respiratory failure compared with 67% of SOC alone. Although this did not reach statistical significance in the entire population, benefit was observed those aged 70 years and older (P = 0.009). This age group also had a reduction of 14.4% in all-cause mortality at Day 60. These findings are being confirmed in a further cohort of patients aged 70 and older.[226]

Neurokinin-1 (NK-1) receptor antagonists

Tradipitant

Tradipitant (Vanda Pharmaceuticals) is an NK-1 receptor antagonist. The NK-1 receptor is genetically coded by TACR1 and it is the main receptor for substance P. The substance P NK-1 receptor system is involved in neuroinflammatory processes that lead to serious lung injury following numerous insults, including viral infections. ODYSSEY phase 3 trial in severe or critical COVID-19 infection reported an interim analysis on August 18, 2020. Patients who received tradipitant recovered earlier than those receiving placebo.[227, 228]

Aprepitant

Aprepitant (Cinvanti; Heron Therapeutics) is a substance P/neurokinin-1 (NK1) receptor antagonist. Substance P and its receptor, NK1, are distributed throughout the body in the cells of many tissues and organs, including the lungs. Phase 2 clinical study (GUARDS-1) initiated mid-July 2020 in early-hospitalized patients with COVID-19. Administration to these patients is expected to decrease production and release of inflammatory cytokines mediated by the binding of substance P to NK1 receptors, which could prevent the progression of lung injury to ARDS.[229]

Mesenchymal stem cells

Remestemcel-L

Remestemcel-L (Ryoncil; Mesoblast Ltd) is an allogeneic mesenchymal stem cell (MSC) product currently pending FDA approval for graft versus host disease (GVHD). On December 1, 2020, the FDA granted Fast Track designation for remestemcel-L in the treatment of ARDS due to COVID-19 infection. Fast Track designation is granted if a therapy demonstrates the potential to address unmet medical needs for a serious or life-threatening disease.[230]

As of December 2020, the phase 3 trial for COVID-19 ARDS has enrolled about 200 of the goal of 300 ventilator-dependent patients with moderate-to-severe ARDS. The trial's primary endpoint is overall mortality at Day 30, and the key secondary endpoint is days alive off ventilatory support through Day 60. Two interim analyses by the independent Data Safety Monitoring Board (DSMB) were completed after 90 and 135 patients were enrolled, with recommendations to continue the trial as planned. A third and final interim analysis is planned when 180 patients have completed 30 days of follow-up. A pilot study under emergency compassionate use at New York's Mt Sinai Hospital in March-April this year showed 9 of 12 ventilator-dependent patients with moderate-to-severe COVID-19 ARDS were successfully discharged from hospital a median of 10 days after receiving 2 intravenous doses of remestemcel-L. Theorized mechanism is down-regulation of proinflammatory cytokines.[230, 231]

PLX-PAD

PLX-PAD (Pluristem Therapeutics) contains allogeneic mesenchymal-like cells with immunomodulatory properties that induce the immune system's natural regulatory T cells and M2 macrophages. Initiating phase 2 study in mechanically ventilated patients with severe COVID-19.[232]

BM-Allo.MSC

BM-Allo.MSC (NantKwest, Inc) is a bone marrow-derived allogeneic mesenchymal stem cell product. IND for phase 1b trial initiating Q2 2020 in Los Angeles area hospitals.[233]

HB-adMSC

Autologous, adipose-derived mesenchymal stem cells (HB-adMSCs; Hope Biosciences) has been shown to attenuate systemic inflammation in phase 1/2 clinical trial for rheumatoid arthritis. Three phase 2 trials are in progress that include patients aged 50 years and older with preexisting health conditions or at high exposure risk, frontline healthcare workers or first responders, and a placebo-controlled study.[234]

hCT-MSCs

A multicenter trial using human cord tissue mesenchymal stromal cells (hCT-MSC) for children with multisystem inflammatory syndrome (MIS) was initiated in September 2020. The study will assess if infusion of hCT-MSCs are safe and can suppress the hyperinflammatory response associated with MIS. Duke University is coordinating the study, and is manufacturing the cells at the Robertson GMP cell laboratory.[235]

ExoFlo

ExoFlo (Direct Biologics) is a paracrine signaling exosome product isolated from human bone marrow MSCs. The EXIT COVID-19 phase 2 study is enrolling patients and was granted expanded access by the FDA to be provided to patients with ARDS.[236]

Phosphodiesterase inhibitors

Ibudilast

Ibudilast (MN-166; MediciNova) is a first-in-class, orally bioavailable, small molecule phosphodiesterases (PDE) 4 and 10 inhibitor and a macrophage migration inhibitory factor (MIF) inhibitor that suppresses proinflammatory cytokines and promotes neurotrophic factors. The drug has been approved in Japan and South Korea since 1989 to treat post-stroke complications and bronchial asthma. An IND for a phase 2 trial in the United States to prevent ARDS has been accepted by the FDA.[237]

Apremilast

Apremilast (Otezla; Amgen Inc) is a small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, which may indirectly modulate the production of inflammatory mediators. Part of the I-SPY COVID-19 clinical trial.[136]

Table 1. Investigational Drugs for ARDS/Cytokine Release Associated With COVID-19 (Open Table in a new window)

Therapy	Description
Ifenprodil (NP-120; Algernon Pharmaceuticals) [238]	N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist. NMDA is linked to inflammation and lung injury. An injectable and long-acting oral product are under production to begin clinical trials for COVID-19 and acute lung injury. The phase 2b part of the 2b/3 study completed enrollment mid-December 2020. Key findings were no mortality at Day 15 in ifenprodil treated patients compared with 3.3% in those in the standard of care (SOC) group. Oxygenation returned to normal at day 4 compared with day 9 in the treated vs SOC groups respectively.
Eculizumab (Soliris; Alexion) [239]	Modulates activity of terminal complement to prevent the formation of the membrane attack complex; 10-patient proof of concept completed; if 100-patient single-arm trial in the United States and Europe for 2 weeks shows a positive risk/benefit ratio, a 300-patient randomized controlled trial will proceed.
Ravulizumab (Ultomiris; Alexion) [240]	Monoclonal antibody that is a C5 complement inhibitor. Phase 3 randomized controlled trial in hospitalized adults with severe pneumonia or acute ARDS requiring mechanical ventilation was initiated in April 2020, but was paused in January 2021 owing to initial outcomes not showing efficacy. Another phase 3 trial (TACTIC-R) in the UK is studying use of earlier immune modulation in preventing disease progression.
ATYR1923 (aTyr Pharma, Inc) [241]	Phase 2 randomized, double-blind, placebo-controlled trial at up to 10 centers in the United States. In preclinical studies, ATYR1923 (a selective modulator of neuropilin-2) has been shown to down-

Therapy	Description
	regulate T-cell responses responsible for cytokine release.
BIO-11006 (Biomark Pharmaceuticals) [242]	Results of a phase 2a study for 38 ventilated patients with ARDS showed 43% reduction at day 28 in the all-cause mortality rate. This study was initiated in 2017. The company is in discussion with the FDA to proceed with a phase 3 trial.
Dociparstat sodium (DSTAT; Chimerix) [243]	Glycosaminoglycan derivative of heparin with anti-inflammatory properties, including the potential to address underlying causes of coagulation disorders. Phase 2/3 trial starting May 2020.
Opaganib (Yeliva; RedHill Biopharma Ltd) [244, 245]	Orally administered sphingosine kinase-2 (SK2) inhibitor that may inhibit viral replication and reduce levels of IL-6 and TNF-alpha. Nonclinical data indicate both antiviral and anti-inflammatory effects. As of December 2020, the phase 2/3 trial has enrolled more than 60% of participants, who are hospitalized patients with severe COVID-19 who have developed pneumonia and require supplemental oxygen.
Tranexamic acid (LB1148; Leading BioSciences, Inc) [246]	Oral/enteral protease inhibitor designed to preserve GI tract integrity and protect organs from proteases leaking from compromised mucosal barrier that can lead to ARDS. Phase 2 study announced May 15, 2020.

Therapy	Description
DAS181 (Ansun Biopharma) [247]	Recombinant sialidase drug is a fusion protein that cleaves sialic receptors. Phase 3 substudy for COVID-19 added to existing study for parainfluenza infection.
AT-001 (Applied Therapeutics) [248]	Aldose reductase inhibitor shown to prevent oxidative damage to cardiomyocytes and to decrease oxidative-induced damage.
CM4620-IE (Auxora; CalciMedica, Inc) [249]	Calcium release-activated calcium (CRAC) channel inhibitor that prevents CRAC channel overactivation, which can cause pulmonary endothelial damage and cytokine storm. Results in mid-July 2020 from a small randomized, controlled, open-label study showed CM4620-IE (n = 20) combined with standard of care therapy (n = 10) improved outcomes in patients with severe COVID-19 pneumonia, showing faster recovery (5 days vs 12 days), reduced use of invasive mechanical ventilation (18% vs 50%), and improved mortality rate (10% vs 20%) compared with standard of care alone. Part 2 of this trial will start late summer and will be a placebo-controlled trial, possibly including both remdesivir and dexamethasone.
Intranasal vazegepant (Biohaven Pharmaceuticals) [250]	Calcitonin gene-related peptide (CGRP) receptor antagonist. Received FDA may proceed letter to initiate phase 2 study. Acute lung injury induces up-regulation of transient receptor potential (TRP) channels, activating CGRP release. CGRP contributes to acute lung injury (pulmonary edema with acute-phase cytokine/mediator release, with immunologic milieu shift toward TH17 cytokines). A CGRP receptor antagonist may blunt the severe inflammatory response at the alveolar level, delaying

Therapy	Description
	or reversing the path toward oxygen desaturation, ARDS, requirement for supplemental oxygenation, artificial ventilation, or death.
Selinexor (Xpovio; Karyopharma Therapeutics) [251]	Selective inhibitor of nuclear export (SINE) that blocks the cellular protein exportin 1 (XPO1), which is involved in both replication of SARS-CoV-2 and the inflammatory response to the virus. An interim analysis indicated that the trial was unlikely to meet its prespecified primary endpoint across the entire patient population studied, and has since been discontinued. However, the results demonstrated encouraging antiviral and anti-inflammatory activity for a subset of treated patients with low baseline LDH or D-dimer.
EDP1815 (Evelo Biosciences; Rutgers University; Robert Wood Johnson University Hospital) [252, 253]	Phase 2/3 trials underway in the United States and United Kingdom to determine if early intervention with oral EDP1815 (under development for psoriasis) prevents progression of COVID-19 symptoms and complications in hospitalized patients ≥15 years with COVID-19 who presented at the ER within the preceding 36 hours. The drug showed marked activity on inflammatory markers (eg, IL-6, IL-8, TNF, IL-1b) in a phase 1b study.
VERU-111 (Veru, Inc) [254]	Microtubule depolymerization agent that has broad antiviral activity and has strong anti-inflammatory effects. As of August 2020, a phase 2 trial is underway for hospitalized patients with COVID-19 at high risk for ARDS.

Therapy	Description
Vascular leakage therapy (Q BioMed; Mannin Research) [255]	Targets the angiopoietin-Tie2 signaling pathway to reduce endothelial dysfunction.
Trans sodium crocetinate (TSC; Diffusion Pharmaceuticals) [256, 257]	TSC increases the diffusion rate of oxygen in aqueous solutions. Guidance has been received from the FDA for a phase 1b/2b clinical trial.
Rayaldee (calcifediol; OPKO Health) [258]	Extended-release formulation of calcifediol (25-hydroxyvitamin D3), a prohormone of the active form of vitamin D3. Phase 2 trial (REsCue) objective is to raise and maintain serum total 25-hydroxyvitamin D levels to mitigate COVID-19 severity. Raising serum levels is believed to enable macrophages.
Deupirfenidone (LYT-100; PureTech Bio) [259]	Deuterated form of pirfenidone, an approved anti-inflammatory and anti-fibrotic drug. Inhibits TGF-beta and TNF-alpha. Phase 2 trial initiated in December 2020 for long COVID syndrome to evaluate use for serious respiratory complications, including inflammation and fibrosis, that persist following resolution of SARS-CoV-2 infection.
OP-101 (Ashvattha Therapeutics) [260]	Selectively targets reactive macrophages to reduce inflammation and oxidative stress.
Vidofludimus calcium (IMU-838; Immunic Therapeutics) [261, 262]	Oral dihydroorotate dehydrogenase (DHODH) inhibitor. DHODH is located on the outer surface of the inner mitochondrial membrane. Inhibitors of this enzyme are used to treat autoimmune diseases. Phase 2 CALVID-1 clinical trial for hospitalized patients

Therapy	Description
	with moderate COVID-19. Another phase 2 trial (IONIC) in the UK combines vidofludimus with oseltamivir for moderate-to-severe COVID-19.
Vafidemstat (ORY-2001; Oryzon) [263]	Oral CNS lysine-specific histone demethylase 1 (LSD1) inhibitor. Phase 2 trial (ESCAPE) initiated in May 2020 to prevent progression to ARDS in severely ill patients with COVID-19.
Icosapent ethyl (Vascepa; Amarin Co) [264]	Randomized, open-label study (CardioLink-9; n = 100) focuses on reduction of circulating proinflammatory biomarkers (eg, high-sensitivity C-reactive protein [hsCRP, D-dimer) in COVID-infected outpatients. Patients in the icosapent ethyl group received a loading dose of 8 g/day for 3 days followed by 4 g/day for 11 days plus usual care. Icosapent ethyl showed a 25% reduction in hsCRP (p = 0.011) and a reduction in D-dimer (p = 0.048). Additionally, icosapent ethyl resulted in a significant 52% reduction of the total FLU-PRO prevalence score (flulike symptoms) compared with 24% reduction in the usual care group (p = 0.003).
Prazosin (Johns Hopkins) [265, 266]	Cytokine storm syndrome is accompanied by increased catecholamine release. This amplifies inflammation by enhancing IL-6 production through a signaling loop that requires the alpha1 adrenergic receptor. A clinical trial at Johns Hopkins University is using prazosin, an alpha1 receptor antagonist, to evaluate its effects to prevent cytokine storm.

Therapy	Description
Aspartyl-alanyl diketopiperazine (DA-DKP; AmpionTM; Ampio Pharmaceuticals) [267]	Low-molecular weight fraction of human serum albumin (developed for inflammation associated with osteoarthritis). Theorized to reduce inflammation by suppressing pro-inflammatory cytokine production in T-cells. Phase 1 trial results of IV Ampion or standard of care (eg, remdesivir and/or convalescent plasma) were evaluated in September 2020. IND granted for phase 1 trial of inhaled Ampion in September 2020.
Losmapimod (Fulcrum Therapeutics) [268]	Selective inhibitor of p38alpha/beta mitogen activated protein kinase (MAPK), which is known to mediate acute response to stress, including acute inflammation. FDA authorized a phase 3 trial (LOSVID) for hospitalized patients with COVID-19 at high risk. Losmapimod has been evaluated in phase 2 clinical trials for facioscapulohumeral muscular dystrophy (FSHD).
DUR-928 (Durect Corp) [269]	Endogenous epigenetic regulator. Preclinical trials have shown the drug regulates lipid metabolism, inflammation, and cell survival. The FDA accepted the IND application. A phase 2 study is planned for approximately 80 hospitalized patients with COVID-19 who have acute liver or kidney injury.
ATI-450 (Aclaris Therapeutics, Inc) [270]	IND approved mid-June 2020 for use in hospitalized patients with COVID-19. ATI-450 is an oral mitogen-activated protein kinase-activated protein kinase 2 (MAPKAPK2, or MK2) inhibitor that targets inflammatory cytokine expression. In a phase 1 clinical trial in healthy volunteers at the University of Kansas Medical Center, researchers used a first-in-human study using an ex vivo lipopolysaccharide (LPS) stimulation model that demonstrated a dose-

Therapy	Description
	dependent reduction of TNF-alpha, IL-1-beta, IL-6, and IL-8.
Leronlimab (Vyrologix; CytoDyn) [271, 272]	CCR5 antagonist. A phase 2 trial for mild-to-moderate COVID-19 is ongoing. The phase 3 trial in severe-to-critical patients is fully enrolled (n = 390) as of December 2020 and an open-label extension trial has been added to the protocol. Laboratory data following leronlimab administration in 15 patients showed increased CD8 T-lymphocyte percentages by day 3, normalization of CD4/CD8 ratios, and resolving cytokine production, including reduced IL-6 levels correlating with patient improvement.
Sarconeos (BIO101; Biophytis SA) [273]	Activates MAS, a component of the protective arm of the renin angiotensin system. Phase 2/3 trial (COVA) international trial assessing potential treatment for ARDS.
Abivertinib (Sorrento Therapeutics) [274]	Tyrosine kinase inhibitor with dual selective targeting of mutant forms of EGFR and BTK. Phase 2 trial starting late July 2020 in hospitalized patients with moderate-to-severe COVID-19 who have developing cytokine storm in the lungs.
Nangibotide (LR12; Inotrem S.A.) [275]	Immunotherapy that targets the triggering receptor expressed on myeloid cells-1 (TREM-1) protein pathway, a factor causing unbalanced inflammatory responses. Phase 2a clinical trial (ASTONISH) authorized in the United States, France, and Belgium for mechanically ventilated patients with COVID-19 who have systemic inflammation. Previous clinical

Therapy	Description
	studies demonstrated safety and tolerability in patients with septic shock.
Piclidenoson (Can-Fite BioPharma) [276]	A3 adenosine receptor (A3AR) agonist that elicits anti-inflammatory effects. Phase 2 trial planned in the United States to start late July 2020 involving hospitalized patients with moderate COVID-19.
LSALT peptide (MetaBlok™; Arch Biopartners) [277]	LSALT peptide that targets dipeptidase-1 (DPEP1), which is a vascular adhesion receptor for neutrophil recruitment in the lungs, liver, and kidney. The first US phase 2 trial will be at Broward Health Medical Center in Florida to treat complications in patients with COVID-19, including prevention of acute lung and/or kidney injury.
RLS-0071 (ReAlta Life Sciences) [278]	Animal model shows that RLS-0071 decreases inflammatory cytokines IL-1b, IL-6, and TNF-alpha. A phase 1 randomized, double-blind, placebo-controlled trial is planned to begin Q3 2020 in adults with COVID-19 pneumonia and early respiratory failure.
BLD-2660 (Blade Therapeutics) [279]	Antifibrotic agent. Targets a specific group of cysteine proteases called dimeric calpains (calpains 1, 2 and 9). Overactivity of dimeric calpains lead to inflammation and fibrosis. Phase 2 trial (CONQUER) in hospitalized patients (n = 120) with COVID pneumonia completed in September 2020.

Therapy	Description
EC-18 (Enzychem Lifesciences) [280]	Preclinical studies observed EC-18 to control neutrophil infiltration, thereby modulating the inflammatory cytokine and chemokine signaling. A phase 2 multicenter, randomized, double-blind, placebo-controlled study is being initiated in the US to evaluate the safety and efficacy of EC-18 in preventing the progression of COVID-19 infection to severe pneumonia or ARD.
SBI-101 (Sentien Biotechnologies) [281]	Biologic/device combination product designed to regulate inflammation and promote repair of injured tissue using allogeneic human mesenchymal stromal cells. The phase 1/2 study integrates SBI-101 into the renal replacement circuit for treatment up to 24 hours in patients with ARDS and acute kidney injury requiring renal replacement therapy (RRT).
Bacille Calmette-Guérin (BCG) vaccine (Baylor, Texas A&M, and Harvard Universities; MD Anderson and Cedars-Sinai Medical Centers) [282]	Areas with existing BCG vaccination programs appear to have lower incidence and mortality from COVID19. Study administers BCG vaccine to healthcare workers to see if reduces infection and disease severity during SARS-CoV-2 epidemic.
ARDS-003 (Tetra Bio-Pharma) [283]	Cannabinoid that specifically targets CB2 receptor. Phase 1 clinical trial planned to evaluate anti-inflammatory properties and reduce cytokine release to prevent ARDS.
CAP-1002 (Capricor Therapeutics) [284]	CAP-1002 consists of allogeneic cardiosphere-derived cells (CDCs), a type of cardiac cell therapy that has been shown in preclinical and clinical studies to exert potent immunomodulatory activity. CDCs releasing exosomes that are taken up largely

Therapy	Description
	by macrophages and T-cells and begin a cycle of repair. A phase 2 trial (INSPIRE) in hospitalized patients with severe or critical COVID-19 was initiated in late 2020.
Icatibant (Firazyr; Takeda Pharmaceuticals) [136]	Competitive antagonist selective for bradykinin B2 receptor. Bradykinin formation results in vascular leakage and edema. Part of the I-SPY COVID-19 clinical trial.
Razuprotafib (AKB-9778; Aerpio Pharmaceuticals) [136]	Tie2 activator that enhances endothelial function and stabilizes blood vessels, including pulmonary and renal vasculature. SC razuprotafib restores Tie2 activation and improves vascular stability in multiple animal models of vascular injury and inflammation, including lipopolysaccharide-induced pulmonary and renal injury, polymicrobial sepsis, and IL-2 induced cytokine storm. Part of the I-SPY COVID-19 clinical trial.
Fenretinide (LAU-7b; Laurent Pharmaceuticals) [285]	Synthetic retinoid shown to address the complex links between fatty acids metabolism and inflammatory signaling, which is distinct from the retinoid class MOA. Believed to work by modulating key membrane lipids in conjunction with proinflammatory pathways (eg, ERK1/2, NF-kappa-B, and cPLA2) needed for coronavirus entry, replication, and host defense evasion. It may also have antiviral properties. The phase 2 RESOLUTION trial in Canada has also gained FDA approval in August 2020 for an IND in the US.

Therapy	Description
Ebselen (SPI-1005; Sound Pharmaceuticals) [286]	Anti-inflammatory molecule that mimics and induces glutathione peroxidase. It reduces reactive oxygen and nitrogen species by first binding them to selenocysteine, and then reducing the selenic acid intermediate through a reduction with glutathione. May also inhibit viral replication. Phase 2 studies for moderate and severe COVID-19 infection initiated in Fall 2020.
Fostamatinib (Tavalisse; Rigel Pharmaceuticals) [211]	Spleen tyrosine kinase (SYK) inhibitor that reduces signaling by Fc gamma receptor (FcγR) and c-type lectin receptor (CLR), which are drivers of proinflammatory cytokine release. It also reduces mucin-1 protein abundance, which is a biomarker used to predict ARDS development. Part of the NIH ACTIV-4 Host Tissue phase 3 trial.
Vadadustat (Akebia Therapeutics) [287]	Oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor designed to mimic the physiologic effect of altitude on oxygen availability and increased RBC production. Approved in Japan for anemia owing to chronic kidney disease (in phase 3 trials in US). Phase 2 trial initiated at U of Texas Health Center in Houston for prevention and treatment of ARDS in hospitalized patients with COVID-19.
Ultramicronized palmitoylethanolamide (PEA; FSD201; FSD Pharma) [288]	Fatty acid amide studied for its anti-inflammatory and analgesic actions. Phase 2a trial expected to begin in October 2020 for hospitalized patients with documented COVID-19 disease.

Therapy	Description
EB05 (Edesa Biotech) [289]	Toll-like receptor 4 (TLR4) inhibitor. TLR4 is a key component of the innate immune system which functions to detect molecules generated by pathogens, acting upstream of cytokine storm and IL-6-mediated acute lung injury.
Fluvoxamine (Luvox) [290]	Preliminary double, randomized study of nonhospitalized adults with COVID-19 in community living environment showed no clinical deterioration at Day 15 compared with those taking placebo. Limited sample size with short follow-up. Clinical efficacy would require larger randomized trial. Theorized mechanisms include Sigma-1 receptor (S1R) activation (an endoplasmic reticulum chaperone protein), anti-inflammatory actions owing to S1R stimulation of inositol-requiring enzyme 1 alpha, and SSRI inhibition of platelet activation. Several trials are evaluating fluvoxamine's use for early treatment of COVID, including the TOGETHER clinical trial in Canada, COVID OUT trial at the University of Minnesota, and the Stop COVID 2 trial at Washington University. Fluvoxamine is also part of the NIH ACTIV-6 phase 3 trial.
Lanadelumab (Takeda) [291]	mAb that targets kallikrein. Inhibits kallikrein proteolytic activity to control excess bradykinin. Part of the COVID R&D alliance (Amgen, UCB SA, Takeda) to identify drugs that can reduce severity of COVID-19 in hospitalized patients by moderating the immune system.
Zilucoplan (UCB SA) [291]	Macrocyclic peptide inhibitor of complement C5. Part of the COVID R&D alliance (Amgen, UCB SA, Takeda) to identify drugs that can reduce severity of

Therapy	Description
	COVID-19 in hospitalized patients by moderating the immune system.
CRV431 (Hepion) [292]	Binds cyclophilin A, which blocks the binding of cyclophilin A to specific receptors on inflammatory cells. This decreases infiltration of the cells into the tissue and production of harmful inflammatory molecules, resulting in reduced lung inflammation. Phase 2 trial starting late 2020.
Ensifentrine (Verona Pharma) [293]	Phosphodiesterase (PDE) 3 and 4 inhibitor. Elicits both bronchodilator and anti-inflammatory activities. Delivered via pressurized metered-dose inhaler. Phase 2 trial in 45 patients completed January 2021.
TZLS-501 (Tiziana Life Sciences) [294]	Anti-interleukin-6 receptor monoclonal antibody in early development.
Apabetalone (Resverlogix Corp) [295]	Bromodomain and extra-terminal domain (BET) protein function is required for inflammation. BET inhibitors reversibly bind the bromodomains of BET proteins and prevent the protein-protein interaction between BET proteins and acetylated histones and transcription factors. Apabetalone, a BET inhibitor, reduces the expression of both ACE2 and DPP4 at the surface of human lung epithelial cells. Initiating open-label trials mid-2021 for apabetalone plus standard of care.

Investigational Immunotherapies

Bucillamine

Bucillamine (Revive Therapeutics) is an antirheumatic oral agent derived from tiopronin. It has been available in Japan and South Korea for over 30 years. N-acetyl-cysteine (NAC) has been shown to significantly attenuate clinical symptoms in respiratory viral infections in animals and humans, primarily via donation of thiols to increase antioxidant activity of cellular glutathione. Bucillamine has 2 thiol groups and its ability as a thiol donor is estimated to be 16 times that of NAC. A phase 3 trial for treatment of outpatients with mild-to-moderate COVID-19 at 40 sites in the United States is ongoing with an enrollment goal of 1000 participants. Interim analysis of 600-800 participants is expected in late 2021. The study was amended in late 2021 to evaluate inflammatory markers to complement in addition to viral load testing.[296]

Other immunotherapies are in early clinical trials.

Investigational Antibody-Directed Therapies

Monoclonal Antibodies

Information, including allocation, for monoclonal antibody treatments for COVID-19 granted emergency use authorization is located at the United States Public Health Emergency webpage.

Owing to the increase in variants of concern (VOC) in the United States, monoclonal antibodies that have gained emergency use authorization are continually tested to evaluate activity against VOCs.

Casirivimab plus imdevimab

An EUA was issued for intravenous coadministration of the monoclonal antibodies casirivimab and imdevimab (REGN-COV; Regeneron) on November 21, 2020 for treatment of mild-to-moderate COVID-19 in adults and pediatric patients aged 12 years and older who weigh at least 40 kg and are at high risk for progressing to severe COVID-19 and/or hospitalization.[297] The mixture is designed to bind to 2 points on the SARS-CoV-2 spike protein. As with bamlanivimab, administration of casirivimab and imdevimab has not shown benefit in hospitalized patients with severe COVID-19.

In June 2021, the EUA was updated with a lower recommended IV dose of casirivimab 600 mg and imdevimab 600 mg. This update also allowed for administration as a SC injection when an IV infusion is not feasible.

In July 2021, the EUA updated to include use as postexposure prophylaxis for individuals at high risk of progression to severe COVID-19, including hospitalization or

death, and are not fully vaccinated or are not expected to mount an adequate immune response.[298]

Treatment trials

Intravenous casirivimab and imdevimab reduced viral levels and improved symptoms in nearly 800 non-hospitalized patients with COVID-19 disease in a phase 2/3 trial. Results showed treatment with the 2 antibodies reduced COVID-19 related medical visits by 57% through day 29 (2.8% combined dose groups; 6.5% placebo; p = 0.024). In high risk patients (1 or more risk factor including age older than 50 years; body mass index greater than 30; cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) COVID-19 related medical visits were reduced by 72% (p = 0.0065).[299, 300]

A phase 3 trial (n = 4,567) in infected outpatients who were at high risk for hospitalization or severe COVID-19 disease found casirivimab plus imdevimab significantly reduced the risk of hospitalization or death. Risk was decreased by 70% with the 1200 mg IV dose (n = 827) and by 71% with 2400 mg IV (n = 1,849) compared with placebo (n = 1,843).[301]

A phase 3 trial showed casirivimab plus imdevimab significantly reduced viral load within 7 days of treatment in seronegative patients hospitalized with COVID-19 who did not require high-flow oxygen or mechanical ventilation at baseline. Risk of death or mechanical ventilation decreased by approximately 50% after 1 week following treatment with the antibody cocktail. Seronegative patients (n = 217) had much higher viral loads than those who had already developed their own antibodies (seropositive [n = 270]) to SARS-CoV-2 at the time of randomization. In seronegative patients, the antibody cocktail reduced the time-weighted average daily viral load through day 7 by -0.54 log10 copies/mL, and through day 11 by -0.63 log10 copies/mL (nominal p = 0.002 for combined doses). As expected, the clinical and virologic benefit of the antibody cocktail was limited in seropositive patients.[302, 303]

The much larger UK-based RECOVERY trial showed reduced 28-day mortality among hospital patients who were seronegative at baseline for antibodies. Between September 18, 2020 and May 22, 2021, 9785 patients were randomly allocated to receive usual care plus casirivimab/imdevimab or usual care alone, including 3153 (32%) seronegative patients, 5272 (54%) seropositive patients, and 1360 (14%) patients with unknown baseline antibody status. In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to casirivimab/imdevimab and 451 (30%) of 1520 patients allocated to usual care died within 28 days (p = 0.001). In an analysis involving all randomized patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to casirivimab/imdevimab and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (p = 0.17). The proportional effect of mortality differed significantly between seropositive and seronegative patients for those who received the monoclonal antibody combination (p = 0.001).[304]

Prevention trials

A phase 3 trial showed risk reduction of symptomatic SARS-CoV-2 infection of household contacts administered casirivimab and imdevimab following exposure through day 29 (relative risk reduction, 81.4%; $p < 0.001$). Participants received either a single 1,200-mg SC dose of casirivimab and imdevimab (n = 753) or placebo (n=752) within 96 hours following exposure. Risk of symptomatic infection was decreased by 71.9% in the first week, and 92.6% in subsequent weeks. Among individuals who developed symptomatic infections, those who received casirivimab and imdevimab cleared the virus faster and had a shorter duration of symptoms compared with placebo.[298]

Sotrovimab

Sotrovimab (VIR-7831; VIR Biotechnology; GlaxoSmithKline) is a mAb that binds to conserved epitope of the spiked protein of SARS-CoV-1 and SARS-CoV-2, thereby indicating unlikelihood of mutational escape. This is supported by a preclinical trial showing it retained ability to neutralize SARS-CoV-2 variants (ie, B.1.1.7, B.1.351, P.1).[305] The FDA granted emergency use authorization on May 26, 2021.

The EUA submission was based on an interim analysis of the COMET-ICE phase 3 trial. The trial evaluated sotrovimab as monotherapy for early treatment of COVID-19 in adults at high risk of hospitalization or death. The interim analysis demonstrated an 85% reduction in hospitalization or death in those who received a single IV dose of VIR-7831 (n = 291) compared with placebo (n = 292) ($p = 0.002$).[306]

Results from a phase 2 trial (BLAZE-4) of a single IV dose of VIR-7831 coadministered with bamlanivimab in low-risk adults with mild-to-moderate COVID-19 demonstrated a 70% ($p < 0.001$) relative reduction in persistently high viral load at day 7 compared with placebo.[307]

IM administration

Additional trials for VIR-7831 include comparison of IM and IV administration in low-risk adults (COMET-PEAK), IM use in high-risk adults (COMET-TAIL), and IM administration in uninfected adults to prevent symptomatic infection (COMET-STAR).

The randomized, multi-center, open-label COMET-TAIL phase 3 trial demonstrated IM administration was noninferior to IV administration for early treatment of mild-to-moderate COVID-19 in high-risk, outpatient adults and adolescents aged 12 years of age and older.

Bamlanivimab plus etesevimab

Bamlanivimab and etesevimab (LY-CoV555; Eli Lilly & Co, AbCellera) are neutralizing IgG1 monoclonal antibodies (mAb) directed against the spike protein of SARS-CoV-2

designed to block viral attachment and entry into human cells, thus neutralizing the virus, potentially preventing and treating COVID-19. Emergency use authorization of bamlanivimab and etesevimab is for treatment of mild-to-moderate COVID-19 in adults and children, including neonates, with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Treatment trials

The EUA for treatment was based on results from the phase 3 BLAZE-1 trial. A total of 1035 patients underwent randomization and received an IV infusion of bamlanivimab plus etesevimab or placebo. By day 29, a total of 11 of 518 patients (2.1%) in the bamlanivimab plus etesevimab group had a COVID-19–related hospitalization or death from any cause, compared with 36 of 517 patients (7%) in the placebo group ($P < 0.001$). No deaths occurred in the bamlanivimab plus etesevimab group. Ten deaths occurred in the placebo group, 9 of which were designated by the trial investigators as COVID-1919–related. At day 7, a greater reduction from baseline in the log viral load was observed among patients who received bamlanivimab plus etesevimab than among those who received placebo ($P < 0.001$).[308]

Postexposure prophylaxis

The EUA for bamlanivimab plus etesevimab was updated to include postexposure prophylaxis in certain individuals on September 16, 2021. Specifically, postexposure prophylaxis is indicated for patients aged 12 years and older and weigh at least 40 kg who are:

- at high risk for progression to severe COVID-19 and are not fully vaccinated or
- who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination and have been exposed to an infected individual or at high risk of exposure to an infected individual (eg, nursing home)

Inclusion of this indication in the EUA was based on the BLAZE-2 phase 3 trial that enrolled residents and staff of 74 skilled nursing and assisted living facilities in the United States with at least 1 confirmed SARS-CoV-2 index case from August 2 to November 20, 2020. Participants were randomized to receive a single IV infusion of bamlanivimab, 4200 mg (n = 588), or placebo (n = 587). Bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (8.5% vs 15.2%; $P < 0.001$). Five deaths attributed to COVID-19 were reported by day 57; all occurred in the placebo group.[309]

BRII-196/BRII-198

An EUA was submitted to the FDA in early October 2021 for BRII-196/BRII-198 (Brii Biosciences Ltd) to reduce the risk of hospitalization and death in individuals with COVID-19.

Phase 3 results from the NIH ACTIV-2 trial of outpatients with mild COVID-19 treated with BRII-196/BRII-198 demonstrated a 78% reduction in relative risk as measured by hospitalizations or death compared with placebo ($p < 0.00001$). Among patients who received treatment with BRII-196/BRII-198 within 5 days of symptom onset, 2% (4/196) progressed to hospitalization or death, compared with 11% (21/197) in the placebo arm. Similarly, 2% (5/222) of subjects who received treatment with BRII-196/BRII-198 at 6-10 days following symptom onset progressed to hospitalization or death, compared with 11% (24/222) of those receiving placebo. The analysis also showed no deaths in the treatment arm versus 8 deaths in the placebo arm through day 28. There was1 death in each arm during the post 28-day follow up.[310]

Tixagevimab plus cilgavimab

An EUA was submitted to the FDA in early October 2021 for the long-acting antibodies (LAAB) tixagevimab plus cilgavimab (AZD7442; AstraZeneca) for use as preexposure prophylaxis or treatment of symptomatic COVID-19.

Preexposure prophylaxis

The EUA submission was based on results from the phase 3, multicenter PROVENT trial that enrolled 5197 unvaccinated participants, of which 75% had comorbidities that placed them at increased risk for severe COVID-19. Participants were randomized 2:1 to receive a one-time dose of tixagevimab IM and cilgavimab IM (n = 3460 or saline placebo (n = 1737). In the primary efficacy analysis, risk of developing symptomatic COVID-19 was reduced by 77% with tixagevimab plus cilgavimab compared with placebo ($p < 0.001$). No cases of severe COVID-19 or COVID-19–related deaths were reported in the study drug arm; in the placebo group, 1 case of severe/critical COVID-19 and 2 COVID-19–related deaths were reported.[311]

Treatment

In the TACKLE phase 3 trial (primary analysis n = 822), outpatients with confirmed COVID-19 who had been symptomatic for 7 days or less received either tixagevimab plus cilgavimab 600 mg IM or placebo. Tixagevimab plus cilgavimab reduced the risk of developing severe COVID-19 or death by 50% compared with placebo (18/407 vs 37/415, respectively). In those administered tixagevimab plus cilgavimab within 5 days of symptom onset, the risk was reduces by 67% compared with placebo (9/253 vs 27/251, respectively).[312]

ADG20

ADG20 (Adagio Therapeutics) it a long-acting mAb that elicits high potency and broad neutralization against SARS-CoV-2 and additional clade 1 sarbecoviruses, by targeting a highly conserved epitope in the receptor binding domain. Phase 2/3 trials for prevention (EVADE) and treatment (STAMP) are in late stages. It is administered as a single IM injection.[313, 314]

Convalescent Plasma

An expanded access (EA) program for convalescent plasma was initiated in early April 2020.[133] The FDA granted emergency use authorization (EUA) on August 23, 2020 for use of convalescent plasma in hospitalized patients with COVID-19.[315] Convalescent plasma contains antibody-rich plasma products collected from eligible donors who have recovered from COVID-19. Clinical trial results have been disappointing with early use in high-risk outpatients,[316] and also in hospitalized patients with advanced disease.[317] Very early use in nursing home settings continue to be investigated.

The NIH halted its trial of convalescent plasma in emergency departments for treatment of high-risk outpatients with mild symptoms as of March 2021 after interim results showed use with 1 week after symptom onset did not prevent disease progression. Final results of the SIREN-C3PO trial (n= 511) showed disease progression occurred in 77/257 patients (30%) in the convalescent-plasma group and in 81/254 patients (31.9%) in the placebo group.[316]

The REMAP-CAP investigators concluded that among critically ill adults with confirmed COVID-19, treatment with 2 units of high-titer, ABO-compatible convalescent plasma had a low likelihood of providing improvement in the number of organ support–free days. The study's primary end point was organ support–free days (days alive and free of intensive care unit–based organ support) up to day 21. Among 2011 participants who were randomized, 1990 (99%) completed the trial. The convalescent plasma intervention was stopped after the prespecified criterion for futility was met. Median number of organ support–free days was 0 in the convalescent plasma group and 3 in the no convalescent plasma group. The in-hospital mortality rate was 37.3% (401/1075) for the convalescent plasma group and 38.4% (347/904) for the no convalescent plasma group and the median number of days alive and free of organ support was 14 for each group.[317]

NIH and IDSA guidelines[25, 318] continue to be updated as evidence from randomized, controlled trials emerge.

Vaccines

The mRNA vaccine (Comirnaty; Pfizer) gained full FDA approval August 23, 2021. Two other SARS-CoV-2 vaccines are available in the United States through emergency use authorizations – mRNA-1273 (Moderna) and a viral vector vaccine – Ad26.COV2.S (Johnson & Johnson). For full discussion regarding vaccines, see COVID-19 Vaccines.

The genetic sequence of SARS-CoV-2 was published on January 11, 2020. The rapid emergence of research and collaboration among scientists and biopharmaceutical

manufacturers followed. Various methods are used for vaccine discovery and manufacturing.

In addition to the complexity of finding the most effective vaccine candidates, the production process is also important for manufacturing the vaccine to the scale needed globally. Other variable that increase complexity of distribution include storage requirements (eg, frozen vs refrigerated) and if more than a single injection is required for optimal immunity. Several technological methods (eg, DNA, RNA, inactivated, viral vector, protein subunit) are available for vaccine development. Vaccine attributes (eg, number of doses, speed of development, scalability) depends on the type of technological method employed. For example, the mRNA vaccine platforms allow for rapid development.[319, 320]

Antithrombotics

COVID-19 is a systemic illness that adversely affects various organ systems. A review of COVID-19 hypercoagulopathy aptly describes both microangiopathy and local thrombus formation, and a systemic coagulation defect leading to large vessel thrombosis and major thromboembolic complications, including pulmonary embolism, in critically ill patients.[321] While sepsis is recognized to activate the coagulation system, the precise mechanism by which COVID-19 inflammation affects coagulopathy is not fully understood.[322]

Several retrospective cohort studies have described use of therapeutic and prophylactic anticoagulant doses in critically ill hospitalized patients with COVID-19. No difference in 28-day mortality was observed for 46 patients empirically treated with therapeutic anticoagulant doses compared with 95 patients who received standard DVT prophylaxis doses, including those with D-dimer levels greater than 2 mcg/mL. In this study, day 0 was the day of intubation, therefore, they did not evaluate all patients who received empiric therapeutic anticoagulation at the time of diagnosis to see if progression to intubation was improved.[323]

In contrast to the above findings, a retrospective cohort study showed a median 21 day survival for patients requiring mechanical ventilation who received therapeutic anticoagulation compared with 9 days for those who received DVT prophylaxis.[324]

NIH Trial

Current guidelines include thrombosis prophylaxis (typically with low-molecular-weight heparin [LMWH]) for hospitalized patients. The NIH ACTIV trial includes an arm (ACTIV-4) for use of antithrombotics in the outpatient (trial closed as of June 2021), inpatient, and convalescent settings.

The 3 adaptive clinical trials within ACTIV-4 include preventing, treating, and addressing COVID-19-associated coagulopathy (CAC). Additionally, a goal to understand the effects of CAC across patient populations – inpatient, outpatient, and convalescent.

Outpatient trial

For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for the prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial.

The ACTIV-4B was initiated mid-2020 to investigate whether anticoagulants or antithrombotic therapy can reduce life-threatening cardiovascular or pulmonary complications in newly diagnosed patients with COVID-19 who do not require hospital admission. Participants were randomized to take either a placebo, aspirin, or a low or therapeutic dose of apixaban. The outpatient thrombosis prevention study was halted as the researchers concluded that among mildly symptomatic but clinically stable COVID-19 outpatients a week or more since the time of diagnosis, rates of major cardio-pulmonary complications are very low and do not justify preventive anticoagulant or antiplatelet therapy unless otherwise clinically indicated.[325]

Inpatient trial

Investigates an approach aimed at preventing clotting events and improving outcomes in hospitalized patients with COVID-19. Results published in August 2021 found full-dose anticoagulation (ie, therapeutic dose parenteral anticoagulation with SC low-molecular weight heparin [LMWH] or IV unfractionated heparin) reduced the need for organ support in moderately ill hospitalized patients (n = 2,219), but not in critically ill patients (n = 1,098). Additionally, full dose anticoagulation in critically ill patients, and may cause harm compared with those give usual-care thromboprophylaxis (ie, thromboprophylactic dose anticoagulation according to local practice). Among moderately ill patients, researchers found that the likelihood of full-dose heparin to reduce the need for organ support compared to those who received low-dose heparin was 98.6%. To ensure adequate separation between the study groups the dose of heparin/LMWH used in the usual care arm did not equal more than half of the approved therapeutic dose for that agent for the treatment of venous thromboembolism. These results emphasize the need to stratify patients with different disease severity within clinical trials.[326, 327]

Convalescent trial

Investigates safety and efficacy apixaban administered to patients who have been discharged from the hospital or are convalescing in reducing thrombotic complications (eg, MI, stroke, DVT, PE, death). Patients will be assessed for these complications within 45 days of being hospitalized for moderate and severe COVID-19.

Investigational antithrombotics

AB201

AB201 (ARCA Biopharma) is a recombinant nematode anticoagulant protein c2 (rNAPc2) that specifically inhibits tissue factor (TF)/factor VIIa complex and has anticoagulant, anti-inflammatory, and potential antiviral properties. TF plays a central role in inflammatory response to viral infections. The phase 2b/3 clinical trial (ASPEN-COVID-19) completed enrollment (n = 160). The trial randomized 2 AB201 dosage regimens compared with heparin in hospitalized SARS-CoV-2 positive patients with an elevated D-dimer level. The primary endpoint was change in D-dimer level from baseline to Day 8. The phase 3 trial design is contingent upon phase 2b results.[328]

Renin Angiotensin System Blockade and COVID-19

SARS-CoV-2 is known to utilize angiotensin-converting enzyme 2 (ACE2) receptors for entry into target cells.[329] Data are limited concerning whether to continue or discontinue drugs that inhibit the renin-angiotensin-aldosterone system (RAAS), namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).

The first randomized study to compare continuing vs stopping (ACEIs) or ARBs receptor for patients with COVID-19 has shown no difference in key outcomes between the 2 approaches. A similar 30-day mortality rate was observed for patients who continued and those who suspended ACE inhibitor/ARB therapy, at 2.8% and 2.7%, respectively (hazard ratio, 0.97).[330]

The BRACE Corona trial design further explains the 2 hypotheses.[330]

- One hypothesis suggests that use of these drugs could be harmful by increasing the expression of ACE2 receptors (which the SARS-CoV-2 virus uses to gain entry into cells), thus potentially enhancing viral binding and viral entry.
- The other suggests that ACE inhibitors and ARBs could be protective by reducing production of angiotensin II and enhancing the generation of angiotensin 1-7, which attenuates inflammation and fibrosis and therefore could attenuate lung injury.

Concern arose regarding appropriateness of continuation of ACEIs and ARBs in patients with COVID-19 after early reports noted an association between disease severity and comorbidities such as hypertension, cardiovascular disease, and diabetes, which are often treated with ACEIs and ARBs. The reason for this association remains unclear.[331, 332]

The speculated mechanism for detrimental effect of ACEIs and ARBs is related to ACE2. It was therefore hypothesized that any agent that increases expression of ACE2

could potentially increase susceptibility to severe COVID-19 by improving viral cellular entry;[332] however, physiologically, ACE2 also converts angiotensin 2 to angiotensin 1-7, which leads to vasodilation and may protect against lung injury by lowering angiotensin 2 receptor binding.[331, 333] It is therefore uncertain whether an increased expression of ACE2 receptors would worsen or mitigate the effects of SARS-CoV-2 in human lungs.

Vaduganathan and colleagues note that data in humans are limited, so it is difficult to support or negate the opposing theories regarding RAAS inhibitors. They offer an alternate hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. As mentioned, ACE2 acts as a counterregulatory enzyme that degrades angiotensin 2 to angiotensin 1-7. SARS-CoV-2 not only appears to gain initial entry through ACE2 but also down-regulates ACE2 expression, possibly mitigating the counterregulatory effects of ACE2.[334]

There are also conflicting data regarding whether ACEIs and ARBs increase ACE2 levels. Some studies in animals have suggested that ACEIs and ARBs increase expression of ACE2,[335, 336, 337] while other studies have not shown this effect.[338, 339]

As uncertainty remains regarding whether ACEIs and/or ARBs increase ACE2 expression and how this effect may influence outcomes in patients with COVID-19, cardiology societies have largely recommended against initiating or discontinuing these medications based solely on active SARS-CoV-2 infection.[340, 341]

A systematic review and meta-analysis found use of ACEIs or ARBs was not associated with a higher risk of mortality among patients with COVID-19 with hypertension or multiple comorbidities, supporting recommendations of medical societies to continue use of these agents to control underlying conditions.[342]

Diabetes and COVID-19

High plasma glucose levels and diabetes mellitus (DM) are known risk factors for pneumonia.[343, 344] Potential mechanisms that may increase the susceptibility for COVID-19 in patients with DM include the following[345] :

- Higher-affinity cellular binding and efficient virus entry
- Decreased viral clearance
- Diminished T-cell function
- Increased susceptibility to hyperinflammation and cytokine storm syndrome
- Presence of cardiovascular disease

SARS-CoV-2 is known to utilize angiotensin-converting enzyme 2 (ACE2) receptors for entry into target cells. Insulin administration attenuates ACE2 expression, while hypoglycemic agents (eg, glucagonlike peptide 1 [GLP-1] agonists, thiazolidinediones) up-regulate ACE2.[345] Dipeptidyl peptidase 4 (DPP-4) is highly involved in glucose and insulin metabolism, as well as in immune regulation. This protein was shown to be a functional receptor for Middle East respiratory syndrome coronavirus (MERS-CoV), and protein modeling suggests that it may play a similar role with SARS-CoV-2, the virus responsible for COVID-19.[346]

The relationship between diabetes, coronavirus infections, ACE2, and DPP-4 has been reviewed by Drucker.[344] Important clinical conclusions of the review include the following:

- Hospitalization is more common for acute COVID-19 among patients with diabetes and obesity.
- Diabetic medications need to be reevaluated upon admission.
- Insulin is the glucose-lowering therapy of choice, not DPP-4 inhibitors or GLP-1 receptor agonists, in patients with diabetes who are hospitalized with acute COVID-19.

Therapies Determined Ineffective

Hydroxychloroquine and chloroquine

On June 15, 2020, the FDA revoked the emergency use authorization (EUA) for hydroxychloroquine and chloroquine donated to the Strategic National Stockpile to be used for treating certain hospitalized patients with COVID-19 when a clinical trial was unavailable or participation in a clinical trial was not feasible.[347]

Based on its ongoing analysis of the EUA and emerging scientific data, the FDA determined that hydroxychloroquine is unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other potential serious adverse effects, the known and potential benefits of hydroxychloroquine no longer outweigh the known and potential risks for the EUA.

Although additional clinical trials may continue to evaluate potential benefit, the FDA determined the EUA was no longer appropriate.

Additionally, the NIH halted the Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic Disease (ORCHID) study on June 20, 2020. After the fourth analysis that included more than 470 participants, the NIH data and safety monitoring board determined that, while there was no harm, the

study drug was very unlikely to be beneficial to hospitalized patients with COVID-19.[348]

Hydroxychloroquine and chloroquine are widely used antimalarial drugs that elicit immunomodulatory effects and are therefore also used to treat autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis). As inhibitors of heme polymerase, they are also believed to have additional antiviral activity via alkalinization of the phagolysosome, which inhibits the pH-dependent steps of viral replication. Wang and colleagues[349] reported that chloroquine effectively inhibits SARS-CoV-2 in vitro. The pharmacological activity of chloroquine and hydroxychloroquine was tested using SARS-CoV-2–infected Vero cells. Physiologically based pharmacokinetic models (PBPK) were conducted for each drug. Hydroxychloroquine was found to be more potent than chloroquine in vitro. Based on PBPK models, the authors recommend a loading dose of hydroxychloroquine 400 mg PO BID, followed by 200 mg BID for 4 days.[350]

Published reports stemming from the worldwide outbreak of COVID-19 have evaluated the potential usefulness of these drugs in controlling cytokine release syndrome in critically ill patients. Owing to widely varying dosage regimens, disease severity, measured outcomes, and lack of control groups, efficacy data have been largely inconclusive.

Hydroxychloroquine plus azithromycin

Opposing conclusions by French researchers regarding viral clearance and clinical benefit with the regimen of hydroxychloroquine plus azithromycin have been published.[351, 352, 353]

A small prospective study (11 consecutive hospitalized participants; mean age, 58.7 years) found no evidence of a strong antiviral activity or clinical benefit conferred by hydroxychloroquine plus azithromycin.[353]

In direct contrast to the aforementioned results, another study in France evaluated patients treated with hydroxychloroquine (n=26) against a control group (n=16) who received standard of care. After dropping 6 patients from the analysis for having incomplete data, the 20 remaining patients receiving hydroxychloroquine (200 mg PO q8h) had improved nasopharyngeal clearance of the virus on day 6 (70% [14/20] vs 12.5% [2/16]).[351] This is an unusual approach to reporting results because the clinical correlation with nasopharyngeal clearance on day 6 is unknown and several patients changed status within a few days of that endpoint (converting from negative back to positive). The choice of that particular endpoint was also not explained by the authors, yet 4 of the 6 excluded patients had adverse outcomes (admission to ICU or death) at that time but were not counted in the analysis. Furthermore, patients who refused to consent to the study group were included in the control arm, indicating unorthodox study enrollment.

Nonhospitalized patients with early COVID-19

Hydroxychloroquine did not improve outcomes when administered to outpatient adults (n = 423) with early COVID-19. Change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (P = 0.117). At 14 days, 24% (49 of 201) of participants receiving hydroxychloroquine had ongoing symptoms compared with 30% (59 of 194) receiving placebo (P = 0.21). Medication adverse effects occurred in 43% (92 of 212) of participants receiving hydroxychloroquine compared with 22% (46 of 211) receiving placebo (P< 0.001). Among patients receiving placebo, 10 were hospitalized (two cases unrelated to COVID-19), one of whom died. Among patients receiving hydroxychloroquine, four were hospitalized and one nonhospitalized patient died (P = 0.29).[354]

Clinical trials evaluating prevention

Various clinical trials in the United States were initiated to determine if hydroxychloroquine reduces the rate of infection when used by individuals at high risk for exposure, such as high-risk healthcare workers, first responders, and individuals who share a home with a COVID-19–positive individual.[355, 356, 357, 358, 359, 360]

Results from the PATCH trial (n=125) did not show any benefit of hydroxychloroquine to reduce infection among healthcare workers compared with placebo.[357]

Another study rerolled 1483 healthcare workers, of which 79% performed aerosol-generating procedures did not show a difference in preventing infection with once or twice weekly hydroxychloroquine compared with placebo. The incidence of SARS-CoV-2 laboratory-confirmed or symptomatic compatible illness was 0.27 events per person-year with once-weekly and 0.28 events per person-year with twice-weekly hydroxychloroquine compared with 0.38 events per person-year with placebo (P = 0.18 and 0.22 respectively).[361]

Results from a double-blind randomized trial (n = 821) from the University of Minnesota found no benefit of hydroxychloroquine (n = 414) in preventing illness due to COVID-19 compared with placebo (n = 407) when used as postexposure prophylaxis in asymptomatic participants within 4 days following high-risk or moderate-risk exposure. Overall, 87.6% of participants had high-risk exposures without eye shields and surgical masks or respirators. New COVID-19 (either PCR-confirmed or symptomatically compatible) developed in 107 participants (13%) during the 14-day follow-up. Incidence of new illness compatible with COVID-19 did not differ significantly between those receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]) (P = 0.35).[362]

QT prolongation with hydroxychloroquine and azithromycin

Chloroquine, hydroxychloroquine, and azithromycin each carry the warning of QT prolongation and can be associated with an increased risk of cardiac death when used

in a broader population.[363] Because of this risk, the American College of Cardiology, American Heart Association, and the Heart Rhythm Society have published a thorough discussion of the arrhythmogenicity of hydroxychloroquine and azithromycin that includes a suggested protocol for clinical research QT assessment and monitoring when the two drugs are coadministered.[364, 365]

A Brazilian study comparing chloroquine high-dose (600 mg PO BID for 10 days) and low-dose (450 mg BID for 1 day, then 450 mg/day for 4 days) observed QT prolongation in 25% of patients in the high-dose group. All patients received other drugs (ie, azithromycin, oseltamivir) that may contribute to prolonged QT.[366]

An increased 30-day risk of cardiovascular mortality, chest pain/angina, and heart failure was observed with the addition of azithromycin to hydroxychloroquine from an analysis of pooled data from Japan, Europe, and the United States. The analysis compared use of hydroxychloroquine, sulfamethoxazole, or the combinations of hydroxychloroquine plus amoxicillin or hydroxychloroquine plus azithromycin.[367]

Doxycycline

A few case reports and small case series have speculated on a use for doxycycline in COVID-19. Most seem to have been searching for an antibacterial to replace azithromycin for use in combination with hydroxychloroquine. In general, the use of HCQ has been abandoned. The anti-inflammatory effects of doxycycline were also postulated to moderate the cytokine surge of COVID-19 and provide some benefits. However, the data on corticosteroid use has returned, and is convincing and strongly suggests their use. It is unclear that doxycycline would provide further benefits. Finally, concomitant bacterial infection during acute COVID-19 is proving to be rare decreasing the utility of antibacterial drugs. Overall, there does not appear to be a routine role for doxycycline.

Lopinavir/ritonavir

The NIH Panel for COVID-19 Treatment Guidelines recommend against the use of lopinavir/ritonavir or other HIV protease inhibitors, owing to unfavorable pharmacodynamics and because clinical trials have not demonstrated a clinical benefit in patients with COVID-19.[368]

The Infectious Diseases Society of America (IDSA) guidelines recommend against the use of lopinavir/ritonavir. The guidelines also mention the risk for severe cutaneous reactions, QT prolongation, and the potential for drug interactions owing to CYP3A inhibition.[25]

The RECOVERY trial concluded no beneficial effect was observed in hospitalized patients with COVID-19 who were randomized to receive lopinavir/ritonavir (n = 1616) compared with those who received standard care (n = 3424). No significant difference for 28-day mortality was shown. Overall, 374 (23%) patients allocated to

lopinavir/ritonavir and 767 (22%) patients allocated to usual care died within 28 days (P = 0.60). No evidence was found for beneficial effects on the risk of progression to mechanical ventilation or length of hospital stay.[369]

The WHO discontinued use of lopinavir/ritonavir in the SOLIDARITY trial in hospitalized patients on July 4, 2020.[138] Interim results released mid-October 2020 found lopinavir/ritonavir (with or without interferon) appeared to have little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. Death rate ratios were: lopinavir, 1.00 (P = 0.97; 148/1399 vs 146/1372) and lopinavir plus interferon, 1.16 (P = 0.11; 243/2050 vs 216/2050).[139]

In a randomized, controlled, open-label trial of hospitalized adults (n=199) with confirmed SARS-CoV-2 infection, recruited patients had an oxygen saturation of 94% or less on ambient air or PaO2 of less than 300 mm Hg and were receiving a range of ventilatory support modes (eg, no support, mechanical ventilation, extracorporeal membrane oxygenation [ECMO]). These patients were randomized to receive lopinavir/ritonavir 400 mg/100 mg PO BID for 14 days added to standard care (n=99) or standard care alone (n=100). Time to clinical improvement did not differ between the two groups (median, 16 days). The mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%) but did not reach statistical significance.[370] An editorial accompanies this study that is informative in regard to the extraordinary circumstances of conducting such a study in the midst of the outbreak.[371]

Another study (n = 86) that compared lopinavir/ritonavir or umifenovir monotherapy with standard care in patients with mild-to-moderate COVID-19 showed no statistical difference between each treatment group.[372]

A multicenter study in Hong Kong compared 14 days of triple therapy (n = 86) (lopinavir/ritonavir [400 mg/100 mg q12h], ribavirin [400 mg q12h], interferon beta1b [8 million IU x 3 doses q48h]) with lopinavir/ritonavir alone (n = 41). Triple therapy significantly shortened the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19.[373]

Average wholesale price (AWP) for a course of lopinavir/ritonavir at this dose is $575.

Ivermectin

NIH COVID-19 guidelines for ivermectin provide analysis of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19. The guidelines concluded most of these studies had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. Ivermectin has been shown to inhibit SAR-COV-2 in cell cultures; however, available pharmacokinetic data from clinically relevant and excessive dosing studies

indicate that the SARS-CoV-2 inhibitory concentrations for ivermectin are not likely attainable in humans.[374]

Chaccour and colleagues raised concerns regarding ivermectin-associated neurotoxicity, particularly in patients with a hyperinflammatory state possible with COVID-19. In addition, drug interactions with potent CYP3A4 inhibitors (eg, ritonavir) warrant careful consideration of coadministered drugs. Finally, evidence suggests that ivermectin plasma levels with meaningful activity against COVID-19 would not be achieved without potentially toxic increases in ivermectin doses in humans. More data are needed to assess pulmonary tissue levels in humans.[375]

A prospective study (n = 400) of adults with mild COVID-19 were randomized 1:1 to receive ivermectin 300 mcg/kg/day for 5 days or placebo. Use of ivermectin did not show a significantly shorten duration of symptoms compared with placebo (p = 0.53).[376]

Table 4. Other therapies determined ineffective (Open Table in a new window)

Therapy	Comment
Merimepodib (antiviral; BioSig Technologies) [377]	Phase 2 trial in combination with remdesivir in advanced disease (NCT04410354).
Acalabrutinib (Calquence; AstraZeneca) [378]	Phase 2 trial (CALAVI US) of Bruton kinase inhibitor in hospitalized patients to ameliorate excessive inflammation (NCT04380688).
Ruxolitinib (Jakafi) [379]	Data from the RUXCOVID study (n = 432) showed treatment with ruxolitinib plus standard-of-care did not prevent complications in patients with COVID-19 associated cytokine storm.
Umifenovir (Arbidol) [372, 380]	Antiviral drug that binds to hemagglutinin protein; it is used in China and Russia to treat influenza. In a structural and molecular dynamics study, Vankadari corroborated that the drug target for umifenovir is the spike glycoproteins of SARS-CoV-2, similar to

Therapy	Comment
	that of H3N2. A retrospective study of non-ICU hospitalized patients (n = 81) with COVID-19 conducted in China did not show an improved prognosis or accelerated viral clearance. Another study (n = 86) that compared lopinavir/ritonavir or umifenovir monotherapy with standard care in patients with mild-to-moderate COVID-19 showed no statistical difference between each treatment group.
Colchicine	UK RECOVERY trial stopped the colchicine arm upon advice from its independent data monitoring committee for lack of efficacy in hospitalized patients with COVID-19.
Ciclesonide inhaled (Alvesco) [381]	Phase 3 outpatient randomized controlled trial demonstrated that ciclesonide did not achieve the primary efficacy endpoint of reduced time to alleviation of all COVID-19–related symptoms.

QT Prolongation with Potential COVID-19 Pharmacotherapies

Chloroquine, hydroxychloroquine, and azithromycin each carry the warning of QT prolongation and can be associated with an increased risk of cardiac death when used in a broader population.[363] Because of this risk, the American College of Cardiology, American Heart Association, and the Heart Rhythm Society have published a thorough discussion on the arrhythmogenicity of hydroxychloroquine and azithromycin, including a suggested protocol for clinical research QT assessment and monitoring when the two drugs are coadministered.[364, 365]

Giudicessi and colleagues[382] have published guidance for evaluating the torsadogenic potential of chloroquine, hydroxychloroquine, lopinavir/ritonavir, and azithromycin. Chloroquine and hydroxychloroquine block the potassium channel, specifically KCNH2-encoded HERG/Kv11.1. Additional modifiable risk factors (eg, treatment duration, other QT-prolonging drugs, hypocalcemia, hypokalemia,

hypomagnesemia) and nonmodifiable risk factors (eg, acute coronary syndrome, renal failure, congenital long QT syndrome, hypoglycemia, female sex, age ≥65 years) for QT prolongation may further increase the risk. Some of the modifiable and nonmodifiable risk factors may be caused by or exacerbated by severe illness.

A cohort study was performed from March 1 through April 7, 2020, to characterize the risk and degree of QT prolongation in patients with COVID-19 who received hydroxychloroquine, with or without azithromycin. Among 90 patients given hydroxychloroquine, 53 received concomitant azithromycin. Seven patients (19%) who received hydroxychloroquine monotherapy developed prolonged QTc of 500 milliseconds or more, and 3 patients (3%) had a change in QTc of 60 milliseconds or more. Of those who received concomitant azithromycin, 11 of 53 (21%) had prolonged QTc of 500 milliseconds or more, and 7 of 53 (13 %) had a change in QTc of 60 milliseconds or more. Clinicians should carefully monitor QTc and concomitant medication usage if considering using hydroxychloroquine.[383]

A retrospective study reviewed 84 consecutive adult patients hospitalized with COVID-19 and treated with hydroxychloroquine plus azithromycin. The QTc increased by greater than 40 ms in 30% of patients. In 11% of patients, QTc increased to more than 500 ms, which is considered a high risk for arrhythmia. The researcher noted that development of acute renal failure, but not baseline QTc, was a strong predictor of extreme QTc prolongation.[384]

A Brazilian study (n=81) compared chloroquine high-dose (600 mg PO BID for 10 days) and low-dose (450 mg BID for 1 day, then 450 mg/day for 4 days). A positive COVID-19 infection was confirmed by RT-PCR in 40 of 81 patients. In addition, all patients received ceftriaxone and azithromycin. Oseltamivir was also prescribed in 89% of patients. Prolonged QT interval (> 500 msec) was observed in 25% of the high-dose group, along with a trend toward higher lethality (17%) compared with lower dose. this prompted the investigators to prematurely halt use of the high-dose treatment arm, noting that azithromycin and oseltamivir can also contribute to prolonged QT interval. The fatality rate was 13.5%. In 14 patients with paired samples, respiratory secretions at day 4 showed negative results in only one patient.[366]

An increased 30-day risk of cardiovascular mortality, chest pain/angina, and heart failure was observed with the addition of azithromycin to hydroxychloroquine. Pooled data from 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, United Kingdom, and the United States were analyzed for adverse effects of hydroxychloroquine, sulfasalazine, or the combinations of hydroxychloroquine plus azithromycin or amoxicillin. Overall, 956,374 and 310,350 users of hydroxychloroquine and sulfasalazine, respectively, and 323,122 and 351,956 users of hydroxychloroquine-azithromycin and hydroxychloroquine-amoxicillin, respectively, were included in the analysis.[367]

Investigational Devices

Blood purification devices

Several extracorporeal blood purification filters (eg, CytoSorb, oXiris, Seraph 100 Microbind, Spectra Optia Apheresis) have received emergency use authorization from the FDA for the treatment of severe COVID-19 pneumonia in patients with respiratory failure. The devices have various purposes, including use in continuous renal replacement therapy or in reduction of proinflammatory cytokines levels.[385]

Nanosponges

Cellular nanosponges made from plasma membranes derived from human lung epithelial type II cells or human macrophages have been evaluated in vitro. The nanosponges display the same protein receptors required by SARS-CoV-2 for cellular entry and act as decoys to bind the virus. In addition, acute toxicity was evaluated in vivo in mice by intratracheal administration.[386]

Guidelines

Guidelines Summary

Numerous clinical guidelines have been issued for COVID-19. The following guidelines have been summarized at Medscape's COVID-19 Clinical Guidelines center:

- COVID-19 Enforcement Policy for Sterilizers, Disinfectant Devices, and Air Purifiers (FDA, 2020): 2020 COVID-19 guidance for industry and FDA staff
- OSHA Guidance on Preparing the Workplace for COVID-19 (2020): 2020 guidance on preparing the workplace for coronavirus disease 2019 (COVID-19) by the Occupational Safety and Health Administration (OSHA)
- COVID-19 Breast Cancer Patient Triage Guidelines (CPBCC): Guidelines on surgical triage of patients with breast cancer by the COVID 19 Pandemic Breast Cancer Consortium
- Procedures in Known/Suspected COVID-19 (ASA, 2020): 2020 guidelines on performing procedures on patients with known or suspected COVID-19 by the American Society of Anesthesiologists (ASA)
- COVID-19–Related Airway Management Clinical Practice Guidelines (SIAARTI/EAMS, 2020): 2020 clinical practice guidelines from the SIAARTI Airway Research Group and the European Airway Management Society on coronavirus disease 2019 (COVID-19)–related airway management.
- Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19): Panel consisting of 36 experts from

12 countries compiled 54 evidence-based statements for clinicians caring for patients with severe COVID-19 infection

- Belgium Task Force on Supportive Care and Antiviral/Immunologic Treatment of Hospitalized Patients With Suspected or Confirmed COVID-19 (2020): 2020 interim clinical guidance by the Belgium Task Force for supportive care and antiviral/immunologic therapy for adults with suspected or confirmed coronavirus disease 2019 (COVID-19).
- COVID-19 Ventilation Clinical Practice Guidelines (2020): COVID-19 ventilation clinical practice guidelines by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine
- Guidance on Obstetric COVID-19 (ISUOG, 2020): Guidance on the management of COVID-19 infection during pregnancy, childbirth, and the neonatal period, from the International Society of Ultrasound in Obstetrics and Gynecology
- Control of COVID-19 in Nursing Homes Guidelines (2020): 2020 guidelines on infection control and prevention of COVID-19 in nursing homes by the Centers for Medicare & Medicaid Services (CMS)
- FDA Face Mask and Respirator Policy in COVID-19 (2020): 2020 guidelines on enforcement policy for face masks and respirators by the US Food and Drug Administration (FDA)
- Rapid COVID-19 Clinical Practice Guidelines (2020): Rapid COVID-19 clinical practice guidelines by Wuhan University Novel Coronavirus Management & Research Team and China International Exchange & Promotive Association for Medical and Health Care.
- Guidance on Cardiac Implications of COVID-19 (ACC, 2020): 2020 guidance by the American College of Cardiology regarding the cardiac implications of COVID-19
- COVID-19 Guidance for Ophthalmologists (AAO, 2020): 2020 COVID-19 guidance for urgent and nonurgent patient care in ophthalmology.
- Guidance on Containing Spread of COVID-19 (CMS, 2020): Guidance for hospitals on how to identify at-risk patients, screen for COVID-19, and monitor or restrict health care facility staff, from the Centers for Medicare & Medicaid Services
- COVID-19 Sample Collection and Testing: Clinical Practice Guidelines (CDC, 2020): 2020 clinical practice guidelines from the Centers for Disease Control and Prevention on the collection, handling, and testing of specimens for the diagnosis of coronavirus disease 2019 (COVID-19).
- Guidelines for Evaluating and Testing Persons Under Investigation for COVID-19 (CDC, 2020): 2020 clinical practice guidelines on evaluating and testing persons under investigation for coronavirus disease 2019 (COVID-19) by the Centers for Disease Control and Prevention (CDC)
- Caring for Children and Youth with Special Health Care Needs During the COVID-19 Pandemic: 2020 clinical practice guidelines from the American Academy of Pediatrics. Provides discussion and resources for parents and caregivers of children with special needs regarding how to minimize infection risk, support from health and related service providers, and school decisions.

Information regarding COVID-19 is rapidly emerging and evolving. For the latest information, see the following:

- Clinical trials
- Public health information
- Research information

CDC Evaluating and Testing Persons Under Investigation (PUI) for COVID-19 Clinical Guidelines

The CDC has issued interim guidance for the COVID-19 outbreak, including evaluation and testing of persons under investigation (PUIs) for COVID-19.[387]

Criteria to guide evaluation and testing of patients under investigation for COVID-19

Clinicians should work with state and local health departments to coordinate testing. The FDA has authorized COVID-19 diagnostic testing to be made available in clinical laboratories, expanding the capacity for clinicians to consider testing symptomatic patients.

The decision to administer COVID-19 testing should be based on clinical judgment, along with the presence of compatible signs and symptoms. The CDC now recommends that COVID-19 be considered a possibility in patients with severe respiratory illness regardless of travel history or exposure to individuals with confirmed infection. The most common symptoms in patients with confirmed COVID-19 have included fever and/or symptoms of acute respiratory illness, including breathing difficulties and cough.

Patient groups in whom COVID-19 testing may be prioritized include the following:

1. Hospitalized patients with compatible signs and symptoms in the interest of infection control
2. High-risk symptomatic patients (eg, older patients and patients with underlying conditions that place them at higher likelihood of a poor outcome)
3. Symptomatic patients who have had close contact with an individual with suspected or confirmed COVID-19 or who have traveled from affected geographic areas within 14 days of symptom onset

Clinicians should also consider epidemiologic factors when deciding whether to test for COVID-19. Other causes of respiratory illness (eg, influenza) should be ruled out.

Patients with mild illness who are otherwise healthy should stay home and coordinate clinical management with their healthcare provider over the phone. Patients with severe

symptoms (eg, breathing difficulty) should seek immediate care. High-risk patients (older individuals and immunocompromised patients or those with underlying medical conditions) should be encouraged to contact their healthcare provider in the case of any illness, even if mild.[387]

Reporting, testing, and specimen collection

In the event that a patient is classified a PUI for COVID-19, infection-control personnel at the healthcare facility should immediately be notified. Upon identification of a PUI, state health departments should immediately complete a PUI and Case Report form and can contact CDC's Emergency Operations Center (EOC) at 770-488-7100 for assistance.

Currently, diagnostic testing for COVID-19 is being performed at state public health laboratories and the CDC. Testing for other respiratory pathogens should not delay specimen testing for COVID-19.

The CDC recommends collecting and testing upper respiratory specimens (oropharyngeal and nasopharyngeal swabs) and lower respiratory specimens (sputum, if possible) in patients with a productive cough for initial diagnostic testing. Sputum induction is not indicated. If clinically indicated, a lower respiratory tract aspirate or bronchoalveolar lavage sample should be collected and tested. Once a PUI is identified, specimens should be collected as soon as possible.[387]

CDC Sample Collection and Testing Guidelines for COVID-19

In March 2020, the CDC published interim guidelines regarding the collection, handling, and testing of clinical specimens for the diagnosis of COVID-19.[388]

Collection and evaluation of an upper respiratory nasopharyngeal swab (NP) is recommended for initial COVID-19 testing.

If an oropharyngeal swab (OP) is collected, it should be combined in the same tube as the NP; however, OPs are a lower priority than NPs.

Only patients with a productive cough should undergo sputum collection. Sputum induction is not recommended.

If lower respiratory tract specimens are available, they should also be tested.

If clinically indicated (eg, if the patient is undergoing invasive mechanical ventilation), collection and testing of a lower respiratory tract aspirate or bronchoalveolar lavage sample should be performed.

Once a possible COVID-19 case has been identified, specimen collection should be performed as soon as possible, regardless of when the individual's symptoms began.

Proper infection control must be maintained during specimen collection.

Lower respiratory tract specimens

Bronchoalveolar lavage, tracheal aspirate

Two to 3 mL should be collected in a sterile, leak-proof, screw-cap sputum collection cup or sterile, dry container.

Sputum

The patient should rinse their mouth with water and then expectorate deep cough sputum directly into a sterile, leak-proof, screw-cap sputum collection cup or sterile, dry container.

Upper respiratory tract specimens

Nasopharyngeal swab/oropharyngeal swab

Only synthetic fiber swabs with plastic shafts should be used. Calcium alginate swabs or swabs with wooden shafts—both of which may contain substances that inactivate some viruses and inhibit PCR testing—should not be used. Swabs should be placed immediately in sterile tubes containing 2-3 mL of viral transport media. In general, the CDC recommends that only an NP should be collected. If an OP is collected as well, it should be combined at collection with the NP in a single vial.

To collect an NP, the swab should be inserted into the nostril parallel to the palate, reaching a depth equal to the distance from the nostrils to the ear's outer opening. To absorb secretions, the swab should be left in place for several seconds. It should then be slowly removed while the clinician rotates it.

In collecting an OP (eg, a throat swab), the posterior pharynx should be swabbed, with avoidance of the tongue.

Nasopharyngeal wash/aspirate or nasal aspirate

Two to 3 mL should be collected in a sterile, leak-proof, screw-cap sputum collection cup or sterile, dry container.

Storage

Specimens should be stored at 2-8°C for up to 72 hours after collection. If testing or shipping may be delayed, the specimens should be stored at -70°C or below.

Shipping

Packaging, shipping, and transportation of specimens must be performed as designated in the current edition of the International Air Transport Association (IATA) Dangerous Goods Regulations. Specimens should be stored at 2-8°C and shipped overnight to the CDC on ice pack. Specimens frozen at -70°C should be shipped overnight to the CDC on dry ice.

Guidance for Hospitals on Containing Spread of COVID-19

The guideline on coronavirus disease (COVID-19) infection control and prevention for hospitals was released on March 4, 2020 by the Centers for Medicare & Medicaid Services.[389]

Hospitals should monitor the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/index.html) for up-to-date information and resources.

Hospitals should contact their local health department if they have questions or suspect a patient or healthcare provider (HCP) has COVID-19.

Hospitals should have plans for monitoring healthcare personnel with exposure to patients with known or suspected COVID-19. Additional information about monitoring healthcare personnel is available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html .

Risk assessment and screening

Older adults and those with underlying chronic medical conditions or immunocompromised state may be at highest risk for severe outcomes. This should be considered in the decision to monitor the patient as an outpatient or inpatient.

Hospitals should identify visitors and patients at risk for having COVID-19 infection before or immediately upon arrival to the healthcare facility. They should ask patients about the following:

- Fever or symptoms of a respiratory infection, such as a cough and sore throat
- International travel within the last 14 days to restricted countries (For updated information on restricted countries, visit https://www.cdc.gov/coronavirus/2019-ncov/travelers/index.html.)
- Contact with someone with known or suspected COVID-19

For patients identified as at-risk, implement respiratory hygiene and cough etiquette (ie, placing a face mask over the patient's nose and mouth) and isolate the patient in an examination room with the door closed.

If the patient cannot be immediately moved to an examination room, ensure they are not allowed to wait among other patients seeking care. Identify a separate, well-ventilated space that allows waiting patients to be separated by 6 or more feet, with easy access to respiratory hygiene supplies. In some settings, medically stable patients might opt to wait in a personal vehicle or outside the healthcare facility where they can be contacted by mobile phone when they can be evaluated.

Inform infection prevention and control services, local and state public health authorities, and other healthcare facility staff as appropriate about the presence of a person under investigation for COVID-19.

Additional guidance for evaluating patients in the United States for COVID-19 can be found on the CDC COVID-19 Web site.

Provide supplies for respiratory hygiene and cough etiquette, including 60%-95% alcohol-based hand sanitizer (ABHS), tissues, no-touch receptacles for disposal, facemasks, and tissues at healthcare facility entrances, waiting rooms, patient check-ins, etc.

Monitoring or restriction of healthcare facility staff

The same screening performed for visitors should be performed for hospital staff.

HCP who have signs and symptoms of a respiratory infection should not report to work.

Any staff that develop signs and symptoms of a respiratory infection while on the job should do the following:

- Immediately stop work, put on a facemask, and self-isolate at home.
- Inform the hospital's infection prevention specialist and include information on individuals, equipment, and locations with which the person came into contact.
- Contact and follow the local health department recommendations for next steps (eg, testing, locations for treatment).

Refer to the CDC guidance for exposures that might warrant restricting asymptomatic health care personnel from reporting to work (https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-risk-assesment-hcp.html).

Hospitals should contact their local health department for questions and frequently review the CDC website dedicated to COVID-19 for health care professionals: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html.

Patient placement and infection prevention and control for known or suspected COVID-19 cases

Patient placement and other detailed infection prevention and control recommendations regarding hand hygiene, transmission-based precautions, environmental cleaning and disinfection, managing visitors, and monitoring and managing health care personnel are available in the CDC Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID-19) or Persons under Investigation for COVID-19 in Healthcare Settings.

Patients may not require hospitalization and can be managed at home if they are able to comply with monitoring requests. More information is available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html.

Patients with known or suspected COVID-19 should continue to receive the intervention appropriate for the severity of their illness and overall clinical condition. Because some procedures create high risks for transmission (eg, intubation), additional precautions include the following:

- HCP should wear all recommended personal protective equipment (PPE).
- The number of HCP present should be limited to essential personnel.
- The room should be cleaned and disinfected in accordance with environmental infection control guidelines.

Additional information about performing aerosol-generating procedures is available at https://www.cdc.gov/coronavirus/2019-ncov/infection-control/controlrecommendations.html.

The decision to discontinue transmission-based precautions for hospitalized patients with COVID-19 should be made on a case-by-case basis in consultation with clinicians, infection prevention and control specialists, and public health officials. This decision should consider disease severity, illness signs and symptoms, and results of laboratory testing for COVID-19 in respiratory specimens.

More detailed information about criteria to discontinue transmission-based precautions are available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html.

Visitation rights

Medicare regulations require a hospital to have written policies and procedures regarding the visitation rights of patients, including those setting forth any clinically necessary or reasonable restriction or limitation that the hospital may need to place on such rights and the reasons for the clinical restriction or limitation, such as infection control concerns.

Patients must be informed of their visitation rights and the clinical restrictions or limitations on visitation.

The development of such policies and procedures require hospitals to focus efforts on preventing and controlling infections, not just between patients and personnel, but also between individuals across the entire hospital setting (for example, among patients, staff, and visitors), as well as between the hospital and other healthcare institutions and settings and between patients and the healthcare environment.

Hospitals should work with their local, state, and federal public health agencies to develop appropriate preparedness and response strategies for communicable threats.

Hospital discharge

The decision to discharge a patient from the hospital should be based on the clinical condition of the patient. If transmission-based precautions must be continued in the subsequent setting, the receiving facility must be able to implement all recommended infection prevention and control measures.

Although patients COVID-19 who have mild symptoms may be managed at home, the decision to discharge to home should take into account the patient's ability to adhere to isolation recommendations, as well as the potential risk of secondary transmission to household members with immunocompromising conditions.

Medicare's Discharge Planning Regulations (updated in November 2019) require that the hospital assess the patient's needs for post-hospital services and the availability of such services. When a patient is discharged, all necessary medical information (including communicable diseases) must be provided to any post-acute service provider. For patients with COVID-19, this must be communicated to the receiving service provider prior to discharge/transfer and to the healthcare transport personnel.

American Academy of Pediatrics Guidance on Management of Infants Born to Mothers with COVID-19

The American Academy of Pediatrics Committee on Fetus and Newborn, Section on Neonatal Perinatal Medicine, and Committee on Infectious Diseases has issued guidance on the management of infants born to mothers with COVID-19.[390, 391]

Early evidence has shown low rates of peripartum SARS-CoV-2 transmission and uncertainty concerning in utero viral transmission.

Neonates can be infected by SARS-CoV-2 after birth. Because of their immature immune systems, they are vulnerable to serious respiratory viral infections. SARS-CoV-2 may be able to cause severe disease in neonates.

Precautions during delivery

A gown and gloves should be worn by birth attendants, along with an N95 respiratory mask plus goggles or an air-purifying respirator that protects the eyes.

Delayed cord clamping

Transplacental viral transmission from mother to newborn has not been clearly demonstrated, so delayed cord clamping can continue per normal center practices. The mother can briefly hold the newborn during delayed cord clamping if infection-control precautions are observed.

Room-in of mother and well newborn

This is controversial. Some information has shown good outcomes among most newborns exposed to mothers with COVID-19, although some infants have developed severe illness. The safest approach is to minimize the infection risk via separation, at least temporarily, allowing time for the mother to become less infectious. If the mother chooses against separation or other factors preclude separation, infection risks should be minimized with distancing (at least 6 feet between mother and newborn) and provision of hands-on care to the infant by a noninfected caregiver. Mothers who provide hands-on care should wear a facemask and observe proper hand hygiene.

Breastfeeding

Breastfeeding is strongly supported as the best choice for infant feeding. Breastmilk is unlikely to transmit SARS-CoV-2. Mothers with COVID-19 may express breast milk after appropriate hand and breast hygiene to be fed to the newborn by caregivers without COVID-19. Mothers who opt for nursing should observe strict precautions, including use of a facemask and breast and hand hygiene.

Neonatal intensive care

If the newborn requires intensive care and respiratory support, admission to a single-patient room with negative room pressure is optimal. If multiple newborns with exposure to COVID-19 must be treated in the same room, they should be kept at least six feet apart and/or kept in temperature-controlled isolettes.

Care providers should wear gowns and gloves, along with an N95 respiratory mask plus goggles or an air-purifying respirator that protects the eyes to treat infants who require supplemental oxygen at more than 2 LPM, continuous positive airway pressure, or mechanical ventilation.

Neonatal testing for COVID-19

Following birth, newborns born to mothers with COVID-19 should be bathed to remove virus from the skin. Newborns should undergo testing for SARS-CoV-2 at 24 hours and 48 hours (if still at the birth facility) after birth. Centers with limited testing resources can make testing decisions on a case-by-case basis.

Newborn discharge

Newborns born to mothers with COVID-19 should be discharged per the hospital's normal criteria. Early discharge is not necessary.

Newborns who test positive for SARS-CoV-2 but are asymptomatic should undergo frequent outpatient follow-up (via phone, telemedicine, or office visit) through 14 days after birth. Infection-control precautions should be observed at home and in the outpatient office.

Infants who test negative for SARS-CoV-2 are likely to be discharged to the care of individuals who have COVID-19 or who have been exposed to COVID-19. All potential caregivers should receive infection-prevention instructions. Following hospital discharge, mothers with COVID-19 should stay at least 6 feet away from their newborns. If a closer proximity is required, the mother should wear a mask and observe hand hygiene for newborn care until (1) her temperature has normalized for 72 hours without antipyretic therapy and (2) at least 10 days has passed since the onset of symptoms. If the mother has asymptomatic SARS-CoV-2 infection (identified with obstetric screening tests), she should wait at least 10 days from the positive test or until two consecutive tests administered more than 24 hours apart show negative results.

Newborns who cannot undergo SARS-CoV-2 testing should be treated as infected for an observation period of 14 days. The mother should still observe the precautions detailed above.

NICU visitation

Access to NICUs during the COVID-19 pandemic is limited. Mothers and partners with confirmed or suspected COVID-19 (PUIs) should not enter the NICU until their status is resolved and transmission is no longer a risk.

NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

Pharmacologic management based on COVID-19 disease severity

Outpatient or hospitalized (but not requiring oxygen)

- No specific antiviral or immunomodulatory therapy recommended
- The Panel recommends against use of dexamethasone
- Also see remdesivir for use in hospitalized patients with moderate COVID-19

Hospitalized and requires supplemental oxygen (but not by high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO)

- Remdesivir 200 mg IV x 1, then 100 mg IV qDay for 4 days or until hospital discharge, whichever comes first, OR
- Remdesivir plus dexamethasone 6 mg IV/PO qDay for up to 10 days or until hospital discharge, whichever comes first
- If remdesivir cannot be used, dexamethasone may be used instead

Hospitalized and requires oxygen by high-flow device or noninvasive ventilation

- Dexamethasone plus remdesivir at doses and durations above OR
- Dexamethasone

Hospitalized and requires invasive mechanical ventilation or ECMO

- Dexamethasone at doses and duration above OR
- Dexamethasone plus remdesivir for patient recently intubated

Antiviral therapy

Remdesivir

Because remdesivir supplies are limited, the Panel recommends prioritizing remdesivir for use in hospitalized patients with COVID-19 who require supplemental oxygen, but who do not require oxygen delivery by high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Five days of remdesivir treatment is recommended in hospitalized patients with severe COVID-19 who are not intubated. The optimal duration of remdesivir treatment is undetermined in mechanically ventilated patients, patients on ECMO, and patients in whom improvement is inadequate after 5 days of therapy.

The data are insufficient to recommend for or against remdesivir in patients with mild or moderate COVID-19.

Chloroquine or hydroxychloroquine

The Panel recommends against chloroquine or hydroxychloroquine with or without azithromycin in the treatment of COVID-19 outside the context of a clinical trial.

The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19.

Other antivirals

The Panel recommends against (1) hydroxychloroquine plus azithromycin, (2) lopinavir/ritonavir, and (3) other HIV protease inhibitors except in a clinical trial.

Tocilizumab

The Panel recommends use of tocilizumab (single IV dose of 8 mg/kg, up to 800 mg) in combination with dexamethasone in recently hospitalized patients who are exhibiting rapid respiratory decompensation caused by COVID-19. These patients include:

- Recently hospitalized patients who have been admitted to the ICU within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO2/30 L/min of oxygen flow) (BIIa); or
- Recently hospitalized patients (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation (BIIa) (eg, C-reactive protein 75 mg/L or greater)

Corticosteroids

The Panel recommends dexamethasone (6 mg/day for up to 10 days) in patients with COVID-19 who are mechanically ventilated and in patients who require supplemental oxygen but are not mechanically ventilated.

The Panel recommends against dexamethasone in patients with COVID-19 who do not require supplemental oxygen.

If dexamethasone is not available, the Panel recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone.

Convalescent plasma

The FDA granted emergency use authorization (EUA) on August 23, 2020 for use of convalescent plasma in hospitalized patients with COVID-19.[133] Convalescent plasma contains antibody-rich plasma products collected from eligible donors who have recovered from COVID-19.

The NIH COVID-19 Guidelines Panel further evaluated the Mayo Clinic's expanded access (EA) program data and further reviewed subgroups. Among patients who were not intubated, 11% of those who received convalescent plasma with high antibody titers died within 7 days of transfusion compared with 14% of those who received

convalescent plasma with low antibody titers. Among those who were intubated, there was no difference in 7-day survival.

Based on the available evidence, the panel determined the following [318] :

- There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.
- Adverse effects of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications.
- Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19.
- Prospective, well-controlled, adequately powered, randomized trials are needed.

The NIH halted its trial of convalescent plasma in emergency departments for treatment of patients with mild symptoms as of March 2021. The second planned interim analysis of the trial data determined that while the convalescent plasma intervention caused no harm, it was unlikely to benefit this group of patients.

NIH COVID-19 Treatment Guidelines[392]

Care of Critically Ill Patients with COVID-19

Potential Antiviral Drugs Under Evaluation for the Treatment of COVID-19

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

Considerations for certain Concomitant Medications in Patients with COVID-19

Infectious Diseases Society of America (IDSA) Management Guidelines

The Infectious Diseases Society of America (IDSA) has formed a multidisciplinary guideline panel to provide treatment recommendations for coronavirus disease 2019 (COVID-19).[25] Refer to the IDSA guidelines for the most recent version.

Antivirals

Remdesivir

- Remdesivir is approved the FDA for treatment of COVID-19 in hospitalized adults and pediatric patients aged 12 years and older who weigh at least 40 kg.
- Emergency use authorization (EUA) has also been issued for use in hospitalized children aged 12 years or younger weighing 3.5 kg to less than 40 kg.

- Consideration in contingency or crisis capacity settings (ie, limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

Ivermectin

- Insufficient data exist to recommend.
- Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19, in either ambulatory or hospitalized patients.

Strong recommendation against use

- Hydroxychloroquine or chloroquine with or without azithromycin: In patients with COVID-19, the panel recommends against hydroxychloroquine/chloroquine. Strong recommendation, moderate certainty of evidence.
- Lopinavir/ritonavir and other HIV protease inhibitors
- Hydroxychloroquine/chloroquine plus azithromycin: In patients with COVID-19, the panel suggests against hydroxychloroquine/chloroquine plus azithromycin. Strong recommendation, low certainty of evidence.
- Combination of lopinavir/ritonavir: In hospitalized patients with severe COVID-19, the panel recommends against the combination of lopinavir/ritonavir. Strong recommendation, moderate certainty of evidence.

Corticosteroids

Corticosteroids used in patients with COVID-19 include the following:

- Hospitalized critically ill patients: The panel recommends glucocorticoids over no glucocorticoids (dexamethasone 6 mg IV or PO for 10 days, or until discharge). Strong recommendation, moderate certainty of evidence.
- Hospitalized patients with severe, but noncritical COVID-19: The panel suggests corticosteroids rather than no corticosteroids. Conditional recommendation, moderate certainty of evidence.
- Hospitalized patients with nonsevere COVID-19: The Panel suggests against use of glucocorticoids. Conditional recommendation, low certainty of evidence.

Immunomodulators

Baricitinib

- Among hospitalized adults with severe COVID-19 having elevated inflammatory markers, but not on invasive mechanical ventilation, the IDSA panel suggests baricitinib rather than no baricitinib.

- Among hospitalized patients with severe COVID-19 who cannot receive corticosteroids because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone.
- The FDA issued and EUA for baricitinib for use in combination with remdesivir for treatment of COVID-19 in hospitalized patients aged 2 years and older who require supplemental oxygen, invasive mechanical ventilation, or ECMO.

Tocilizumab and other IL-6 inhibitors

- Tocilizumab: In hospitalized adults with COVID-19 who have elevated markers of systemic inflammation, the panel suggests tocilizumab in addition to standard of care (ie, steroids) rather than standard of care alone. Conditional recommendation, low certainty of evidence.
- Sarilumab: Preliminary data (preprint) from a trial with 45 patients receiving sarilumab; data are limited to offer recommendation.

Anti-SARS-CoV-2 antibody products

Monoclonal directed antibodies

- The FDA issued EUAs for nonhospitalized patients with mild-to-moderate COVID-19 disease who are at high risk of disease progression.
- Consider local variant susceptibility when choosing of the most appropriate neutralizing antibody therapy.

Convalescent plasma

- The FDA issued an EUA for use in hospitalized patients.
- Hospitalized patients: IDSA guideline panel suggests against COVID-19 convalescent plasma (low certainty of evidence).
- Ambulatory patients with mild-to-moderate disease: IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial (knowledge gap)

Famotidine

Famotidine may also be administered to patients with COVID-19, as follows:

- In hospitalized patients with severe COVID-19, the panel suggests against famotidine for the sole intent of COVID-19 treatment outside the context of a clinical trial
- Conditional recommendation, very low certainty of evidence.

Thromboembolism Prevention and Treatment

American College of Chest Physicians

Guideline summary is as follows[393] :

- In the absence of contraindications, all acutely hospitalized patients with COVID-19 should receive thromboprophylaxis therapy.
- Low-molecular-weight heparin (LMWH) or fondaparinux should be used for thromboprophylaxis over unfractionated heparin and direct oral anticoagulants.
- Data are insufficient to justify routine increased-intensity anticoagulant dosing in hospitalized or critically ill patients with COVID-19.
- Recommend only inpatient thromboprophylaxis for patients with COVID-19.
- In critically ill patients with COVID-19, suggest against routine ultrasonographic screening for asymptomatic deep vein thrombosis (DVT).
- In critically ill patients with COVID-19 who have proximal DVT or pulmonary embolism, recommend parenteral anticoagulation therapy with therapeutic weight-adjusted LMWH or fondaparinux over unfractionated heparin.

International Society on Thrombosis and Haemostasis

Guideline summary is as follows [394] :

- In hospitalized patients, measure D-dimers, prothrombin time, and platelet count (and possibly fibrinogen).
- The guidelines include an algorithm for management of coagulopathy based on laboratory markers.
- Monitoring for septic coagulopathy can be helpful in determining prognosis in patients with COVID-19 requiring hospital admission.
- Use of LMWH to protect critically ill patients against venous thromboembolism appears to improve prognosis.

National Institutes of Health Antithrombotic Therapy in Patients with COVID-19

Guideline summary is as follows [395] :

- Measure hematologic and coagulation parameters (eg, D-dimers, PT, platelet count, fibrinogen) in hospitalized patients.
- Patients on anticoagulant or antiplatelet therapies for underlying conditions should continue these medications if they receive a diagnosis of COVID-19.
- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults, unless contraindicated.
- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis.

- In hospitalized patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function or of sudden localized loss of peripheral perfusion.
- Nonhospitalized patients with COVID-19: Anticoagulants and antiplatelet therapy should not be initiated for prevention of VTE or arterial thrombosis unless the patient has other indications for the therapy or is participating in a clinical trial.

Medication

Medication Summary

Remdesivir (Veklury) was the first drug approved by the FDA for treating the SARS-CoV-2 virus. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg.[22] The broad-spectrum antiviral is a nucleotide analog prodrug. Full approval was preceded by the US FDA issued an EUA (emergency use authorization) on May 1, 2020 to allow prescribing of remdesivir for severe COVID-19 (confirmed or suspected) in hospitalized adults and children prior to approval.[152] Upon approval of remdesivir in adults and adolescents, the EUA was updated to maintain the ability for prescribers to treat pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg.[23]

The first vaccine to gain full FDA approval was mRNA-COVID-19 vaccine (Comirnaty; Pfizer) in August 2021.

Investigational treatments include other antiviral agents, vaccines, immunomodulators, monoclonal antibodies, convalescent plasma, and antithrombotics. Several of the above therapies and vaccines have been granted emergency use authorization by the FDA.

Vaccines

Class Summary

The FDA has granted emergency use authorization for the vaccines listed below.

COVID-19 vaccine, mRNA-Pfizer (Comirnaty)

August 23, 2021: Granted full approval by the FDA for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals aged 16 years and older. Administered IM as a 2-dose series 3 weeks apart.

May 10, 2021: Emergency use authorization (EUA) granted for adolescents aged 12-15 years.

August 12, 2021: EUA granted for third dose for individuals aged 12 years and older who have undergone solid organ transplantation or have conditions with equivalent level of immunocompromise.

September 22, 2021: FDA revised the EUA to include a single booster dose for individuals aged 65 years and older, individuals aged 18 to 64 years at high risk for severe COVID-19, and those aged 18 to 64 years whose frequent institutional or occupational exposure to SARS-CoV-2 puts them at high risk of serious complications of COVID-19 including severe COVID-19.

COVID-19 vaccine, mRNA-Moderna (mRNA-1273)

December 18, 2020: Emergency use authorization (EUA) issued by FDA for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals aged ≥18 years. Administered IM as a 2-dose series 1 month apart. The vaccine was submitted mid-2021 to the FDA to review for full approval.

COVID-19 vaccine, viral vector-Janssen (Ad26.COV2.S [Johnson & Johnson])

February 27, 2021: Emergency use authorization (EUA) issued by FDA for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals aged ≥18 years. Administered IM as a single dose.

Monoclonal Antibodies

Class Summary

Recombinant neutralizing human IgG1-kappa monoclonal antibodies (mAb) exert their effect by binding to various sites on the SARS-CoV-2 spike protein. All are indicated for mild-to-moderate COVID-19 disease in adults and adolescents who are at high risk for progressing to severe COVID-19 and/or hospitalization.

Casirivimab/imdevimab (REGEN-COV)

FDA granted EUA November 21, 2020. Casirivimab and imdevimab IV solution are each supplied in individual single-dose vials and are admixed in the same IV bag. May also be administered SC when an IV infusion is not feasible. In July 2021, the EUA updated to include use as postexposure prophylaxis for individuals at high risk of progression to severe COVID-19, including hospitalization or death, and are not fully vaccinated or are not expected to mount an adequate immune response.

Sotrovimab

FDA granted EUA May 26, 2021. Binds to conserved epitope of the spiked protein of SARS-CoV-1 and SARS-CoV-2, thereby indicating unlikelihood of mutational escape.

Bamlanivimab and etesevimab

EUA for treatment of treatment or postexposure prophylaxis of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients, including neonates, with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progressing to severe COVID-19, including hospitalization or death. Etesevimab and bamlanivimab are prepared by admixing each dose within the same IV bag. Etesevimab and bamlanivimab bind to different but overlapping epitopes in the receptor-binding domain of the S-protein. In clinical trials, bamlanivimab and etesevimab administered together resulted in fewer treatment-emergent variants relative to bamlanivimab administered alone.

Corticosteroids

Class Summary

NIH guidelines for COVID-19 recommends use of dexamethasone to reduce mortality in hospitalized patients who are mechanically ventilated or those requiring supplemental oxygen without mechanical ventilation.[392] These recommendations are based on results of the RECOVERY trial.[24]

If dexamethasone is unavailable, use alternant glucocorticoids (eg, prednisone, methylprednisolone, or hydrocortisone).[392]

Dexamethasone

Decreases inflammation by suppressing migration of polymorphonuclear leukocytes (PMNs) and reducing capillary permeability; stabilizes cell and lysosomal membranes.

Prednisone (Deltasone)

Consider use if dexamethasone is unavailable. Available as oral formulation.

Methylprednisolone (A-Methapred, DepoMedrol, Medrol)

Consider use if dexamethasone is unavailable. Available as IV formulation.

Hydrocortisone

Consider use if dexamethasone is unavailable. Available as oral or IV formulations.

Antiviral Agents

Class Summary

Remdesivir is the first drug approved by the FDA for COVID-19.

Remdesivir (Veklury)

Adenosine nucleotide prodrug that distributes into cells, where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Inhibits SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. It is indicated. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg. An EUA is approved for pediatric patients weighing 3.5 kg to less than 40 kg or children younger than 12 years who weigh at least 3.5 kg.

Immunomodulators

Class Summary

Immunomodulators plus other treatment modalities (eg, remdesivir, glucocorticoids) may be considered for hospitalized patients with severe COVID-19 to blunt the hyperinflammation caused by cytokine release.

Tocilizumab (Actemra)

June 24, 2021: Emergency use authorization (EUA) issued by the FDA for treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (aged >2 years) who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO.

Baricitinib (Olumiant)

November 19, 2020: Emergency use authorization (EUA) issued by the FDA for use, in combination with remdesivir, for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized patients aged ≥2 years who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). The EUA was revised in July 2021 to allow use with or without remdesivir.

Questions & Answers

Overview

How does diabetes affect mortality risk for coronavirus disease 2019 (COVID-19)?

Is the genome of SARS-CoV-2 (coronavirus) known?

Have any mutations been discovered for SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19)?

Presentation

What are the possible symptoms of coronavirus disease 2019 (COVID-19)?

How long do coronavirus disease 2019 (COVID-19) symptoms take to develop?

What is the incubation period for coronavirus disease 2019 (COVID-19)?

Are symptoms of coronavirus disease 2019 (COVID-19) in children common?

How common is asymptomatic coronavirus disease 2019 (COVID-19)?

What are important history details when evaluating a patient for coronavirus disease 2019 (COVID-19)?

What were the most common presentations of coronavirus disease 2019 (COVID-19) in China?

Does blood type affect coronavirus 2019 (COVID-19) severity?

What is the most common serious symptom of coronavirus disease 2019 (COVID-19)?

How should a patient under investigation for coronavirus disease 2019 (COVID-19) be evaluated in healthcare settings?

What are the potential complications of coronavirus disease 2019 (COVID-19)?

What is the clinical progression of coronavirus disease 2019 (COVID-19)?

Workup

Where are diagnostic tests for coronavirus disease 2019 (COVID-19) processed?

Should coronavirus disease 2019 (COVID-2019) testing be repeated if PCR results are negative?

Is an antibody test available for coronavirus disease 2019 (COVID-19)?

How is molecular testing used in the diagnosis of coronavirus disease 2019 (COVID-19)?

Can viral culture be used to diagnose coronavirus disease 2019 (COVID-19)?

What are common lab features in patients with coronavirus disease 2019 (COVID-19)?

What type of test is used to evaluate for coronavirus disease 2019 (COVID-19)?

What is the significance of a positive SARS-CoV-2 test result after clinical resolution of coronavirus disease 2019 (COVID-19)?

Which clinical specimen samples are best for coronavirus disease 2019 (COVID-19) testing?

Are there any signs of coronavirus disease 2019 (COVID-19) in seemingly asymptomatic patients?

What is the role of CT scanning in the diagnosis of coronavirus disease 2019 (COVID-19)?

What is the role of chest radiography in the diagnosis of coronavirus disease 2019 (COVID-19)?

Treatment

Are nonsteroidal anti-inflammatory drugs (NSAIDS) safe in persons with coronavirus disease 2019 (COVID-19)?

How is coronavirus disease 2019 (COVID-19) treated?

Are any drugs available for coronavirus disease 2019 (COVID-19) postexposure prophylaxis?

Is a coronavirus disease 2019 (COVID-19) vaccine available?

How can community spread of coronavirus disease 2019 (COVID-19) be prevented/minimized?

What is the roles of the antiparasitic drug niclosamide in the treatment of coronavirus disease 2019 (COVID-19)?

What is the role of the antiviral drug remdesivir in the treatment of coronavirus disease 2019 (COVID-19)?

Why is diabetes a risk factor for coronavirus disease 2019 (COVID-19)?

What are the role of the antivirals lopinavir/ritonavir and ivermectin in the treatment of coronavirus disease 2019 (COVID-19)?

What are the roles of hydroxychloroquine and chloroquine in the treatment of coronavirus disease 2019 (COVID-19)?

What is the role of hydroxychloroquine plus azithromycin in the treatment of coronavirus disease 2019 (COVID-19)?

Which drugs being studied for the treatment of coronavirus disease 2019 (COVID-19) are associated with QT prolongation and an increased risk of cardiac death?

What is the role of blood purification devices in the treatment of coronavirus disease 2019 (COVID-19)?

What is the role of nanosponges in the treatment of coronavirus disease 2019 (COVID-19)?

Which vaccines are being investigated for coronavirus disease 2019 (COVID-19) prevention?

Guidelines

What guidelines are available for coronavirus disease 2019 (COVID-19)?

What are the CDC criteria to guide evaluation and testing of patients under investigation for coronavirus disease 2019 (COVID-19)?

What are the CDC's sample collection and testing guidelines for coronavirus disease 2019 (COVID-19)?

What are the guidelines for containing hospital spread of coronavirus disease 2019 (COVID-19)?

What are the AAP guidelines for management of infants born to mothers with coronavirus disease 2019 (COVID-19)?

What are the thromboembolism prevention and treatment guidelines in patients with coronavirus disease 2019 (COVID-19)?

What are the CDC guidelines for reporting, testing, and specimen collection for coronavirus disease 2019 (COVID-19)?

Medications

Which medications in the drug class Vaccines are used in the treatment of Coronavirus Disease 2019 (COVID-19)?

Which medications in the drug class Monoclonal Antibodies are used in the treatment of Coronavirus Disease 2019 (COVID-19)?

Which medications in the drug class Corticosteroids are used in the treatment of Coronavirus Disease 2019 (COVID-19)?

Which medications in the drug class Antiviral Agents are used in the treatment of Coronavirus Disease 2019 (COVID-19)?

Which medications in the drug class Immunomodulators are used in the treatment of Coronavirus Disease 2019 (COVID-19)?

Contributor Information and Disclosures

Author

David J Cennimo, MD, FAAP, FACP, FIDSA, AAHIVS Associate Professor of Medicine and Pediatrics, Adult and Pediatric Infectious Diseases, Rutgers New Jersey Medical School

David J Cennimo, MD, FAAP, FACP, FIDSA, AAHIVS is a member of the following medical societies: American Academy of HIV Medicine, American Academy of Pediatrics, American College of Physicians, American Medical Association, HIV Medicine Association, Infectious Diseases Society of America, Medical Society of New Jersey, Pediatric Infectious Diseases Society

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Coauthor(s)

Scott J Bergman, PharmD, FCCP, FIDSA, BCPS, BCIDP Antimicrobial Stewardship Program Coordinator, Infectious Diseases Pharmacy Residency Program Director, Department of Pharmaceutical and Nutrition Care, Division of Infectious Diseases, Nebraska Medicine; Clinical Associate Professor, Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center

Scott J Bergman, PharmD, FCCP, FIDSA, BCPS, BCIDP is a member of the following medical societies: American Association of Colleges of Pharmacy, American College of Clinical Pharmacy, American Pharmacists Association, American Society for Microbiology, American Society of Health-System Pharmacists, Infectious Diseases

Society of America, Society of Infectious Diseases Pharmacists

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Keith M Olsen, PharmD, FCCP, FCCM Dean and Professor, College of Pharmacy, University of Nebraska Medical Center

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Specialty Editor Board

Mary L Windle, PharmD Adjunct Associate Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference

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Chief Editor

Michael Stuart Bronze, MD David Ross Boyd Professor and Chairman, Department of Medicine, Stewart G Wolf Endowed Chair in Internal Medicine, Department of Medicine, University of Oklahoma Health Science Center; Master of the American College of Physicians; Fellow, Infectious Diseases Society of America; Fellow of the Royal College of Physicians, London

Michael Stuart Bronze, MD is a member of the following medical societies: Alpha Omega Alpha, American College of Physicians, American Medical Association, Association of Professors of Medicine, Infectious Diseases Society of America, Oklahoma State Medical Association, Southern Society for Clinical Investigation

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Additional Contributors

Molly Marie Miller, PharmD Pharmacy Resident, Nebraska Medicine

Molly Marie Miller, PharmD is a member of the following medical societies: American College of Clinical Pharmacy, American Pharmacists Association, American Society of Health-System Pharmacists, Nebraska Pharmacists Association, Society of Infectious Diseases Pharmacists

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References

1. CDC. 2019 Novel Coronavirus, Wuhan, China. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/about/index.html. January 26, 2020; Accessed: December 1, 2021.
2. Gallegos A. WHO Declares Public Health Emergency for Novel Coronavirus. Medscape Medical News. Available at https://www.medscape.com/viewarticle/924596. January 30, 2020; Accessed: December 1, 2021.
3. Ramzy A, McNeil DG. W.H.O. Declares Global Emergency as Wuhan Coronavirus Spreads. The New York Times. Available at https://nyti.ms/2RER70M. January 30, 2020; Accessed: December 1, 2021.
4. The New York Times. Coronavirus Live Updates: W.H.O. Declares Pandemic as Number of Infected Countries Grows. The New York Times. Available at https://www.nytimes.com/2020/03/11/world/coronavirus-news.html#link-682e5b06. March 11, 2020; Accessed: December 1, 2021.
5. Coronavirus Updates: The Illness Now Has a Name: COVID-19. The New York Times. Available at https://www.nytimes.com/2020/02/11/world/asia/coronavirus-china.html. February 11, 2020; Accessed: December 1, 2021.
6. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available at https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. February 11, 2020; Accessed: December 1, 2021.
7. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. Available at https://doi.org/10.1101/2020.02.07.937862. February 11, 2020; Accessed: December 1, 2021.
8. CDC COVID-19 Response Team, Jorden MA, Rudman SL, et al. Evidence for Limited Early Spread of COVID-19 Within the United States, January-February 2020. MMWR. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. May 29, 2020; Accessed: December 1, 2021.
9. CDC. Coronavirus Disease 2019 (COVID-19): Recommendations for Cloth Face Covers. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html. April 3, 2020; Accessed: December 1, 2021.
10. Ferguson NM, Laydon D, Nedjati-Gilani G, Imai N, Ainslie K, Baguelin M, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College COVID-19 Response Team. Available at https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf. 2020 Mar 16; Accessed: December 1, 2021.
11. Christie A, Brooks JT, Hicks LA, et al. Guidance for Implementing COVID-19 Prevention Strategies in the Context of Varying Community Transmission Levels and Vaccination Coverage. MMWR Morb Mortal Wkly Rep. 2021. 70:1044–1047. [Full Text].
12. Honein MA, Christie A, Rose DA, et al. Summary of guidance for public health strategies to address high levels of community transmission of SARS-CoV-2 and

related deaths, December 2020. MMWR Morb Mortal Wkly Rep. 2020 Dec 04. [Full Text].
13. Centers for Disease Control and Prevention. How to Protect Yourself & Others. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. November 29, 2021; Accessed: December 1, 2021.
14. CDC. Underlying medical conditions associated with high risk for severe COVID-19: Information for healthcare providers. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. 2021 Mar 29; Accessed: December 1, 2021.
15. CDC. Symptoms of Coronavirus. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. May 13, 2020; Accessed: December 1, 2021.
16. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med. 2020 Mar 10. [Medline].
17. 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 Feb 24. [Medline].
18. Rabin RC. Lost Sense of Smell May Be Peculiar Clue to Coronavirus Infection. The New York Times. Available at https://www.nytimes.com/2020/03/22/health/coronavirus-symptoms-smell-taste.html. March 22, 2020; Accessed: December 1, 2021.
19. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA. 2020 Apr 22. [Medline].
20. CDC. 2019 Novel Coronavirus, Wuhan, China: Interim Healthcare Infection Prevention and Control Recommendations for Patients Under Investigation for 2019 Novel Coronavirus. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/infection-control.html. January 18, 2020; Accessed: December 1, 2021.
21. Rizk JG, Forthal DN, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, et al. Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic. Drug Discov Today. 2020 Nov 27. [Medline]. [Full Text].
22. FDA. FDA Approves First Treatment for COVID-19. FDA.gov. 2020 Oct 22. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.
23. FDA. Fact sheet for healthcare providers emergency use authorization (EUA) of Veklury (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weight at least 3.5 kg. fda.gov. Available at https://www.fda.gov/media/137566/download. October, 2020 (revised); Accessed: December 1, 2021.
24. RECOVERY Collaborative Group., Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Feb 25. 384 (8):693-704. [Medline]. [Full Text].

25. [Guideline] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. IDSA. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. 2021 Oct 01; Accessed: October 6, 2021.
26. McCreary EK, Pogue JM. COVID-19 Treatment: A Review of Early and Emerging Options. Open Forum Infectious Diseases (OFID). 2020 Mar 23. [Full Text].
27. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 Apr 13. [Medline]. [Full Text].
28. Barlow A, Landolf KM, Barlow B, Yeung SYA, Heavner JJ, Claassen CW, et al. Review of Emerging Pharmacotherapy for the Treatment of Coronavirus Disease 2019. Pharmacotherapy. 2020 Apr 7. [Medline]. [Full Text].
29. Jomah S, Asdaq SMB, Al-Yamani MJ. Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review. J Infect Public Health. 2020 Aug 3. [Medline]. [Full Text].
30. Abutaleb Y. How the new coronavirus differs from SARS, measles and Ebola. The Washington Post. Available at https://www.washingtonpost.com/health/how-the-new-coronavirus-differs-from-sars-measles-and-ebola/2020/01/23/aac6bb06-3e1b-11ea-b90d-5652806c3b3a_story.html. January 23, 2020; Accessed: December 1, 2021.
31. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020 Jan 14. 91:264-266. [Medline].
32. CDC. Coronavirus Disease 2019: Scientific Brief: SARS-CoV-2 and Potential Airborne Transmission. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html. 2020 Oct 05; Accessed: December 1, 2021.
33. Morawska L, Milton DK. It is Time to Address Airborne Transmission of COVID-19. Clin Infect Dis. 2020 Jul 6. [Medline].
34. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. World Health Organization. Available at https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions. July 9, 2020; Accessed: December 1, 2021.
35. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med. 2020 Mar 17. [Medline].
36. Chin AWH, Chu JTS, Perera MRA, et al. Stability of SARS-CoV-2 in different environmental conditions. The Lancet Microbe. April 2, 2020. [Full Text].
37. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11. [Medline].
38. Liu Y, Yan LM, Wan L, Xiang TX, Le A, Liu JM, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020 Mar 19. [Medline].

39. Zhou B, She J, Wang Y, Ma X. The duration of viral shedding of discharged patients with severe COVID-19. Clin Infect Dis. 2020 Apr 17. [Medline].
40. Mole B. Recovered COVID-19 patients test positive but not infectious, data finds. Ars Technica. Available at https://arstechnica.com/science/2020/05/feared-reactivation-of-covid-19-infections-disputed-by-new-data/. May 19, 2020; Accessed: December 1, 2021.
41. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. N Engl J Med. 2020 Dec 24. 383 (26):2586-2588. [Medline]. [Full Text].
42. Baang JH, Smith C, Mirabelli C, Valesano AL, Manthei DM, Bachman M, et al. Prolonged SARS-CoV-2 replication in an immunocompromised patient. J Infect Dis. 2020 Oct 22. [Medline]. [Full Text].
43. Li D, Jin M, Bao P, Zhao W, Zhang S. Clinical Characteristics and Results of Semen Tests Among Men With Coronavirus Disease 2019. JAMA Netw Open. 2020 May 1. 3 (5):e208292. [Medline].
44. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. Ann Intern Med. 2020 Sep 1. 173 (5):362-367. [Medline]. [Full Text].
45. Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. JAMA Netw Open. 2021 Jan 4. 4 (1):e2035057. [Medline]. [Full Text].
46. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020 Feb 19. [Medline].
47. WHO Coronavirus Disease (COVID-19) Dashboard. World Health Organization. Available at https://covid19.who.int/. 2021 Dec 06; Accessed: December 6, 2021.
48. CDC. Coronavirus Disease 2019 (COVID-19) – Cases in the U.S. Centers for Disease Control and Prevention (CDC). Available at https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days. 2021 Dec 06; Accessed: December 6, 2021.
49. Ahmad FB, Cisewski JA, Miniño A, Anderson RN. Provisional Mortality Data – United States, 2020. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly. 2021 Mar 31. [Full Text].
50. Feuer W, Higgins-Dunn N, Lovelace B. US now has more coronavirus cases than either China or Italy. CNBC. Available at https://www.cnbc.com/2020/03/26/usa-now-has-more-coronavirus-cases-than-either-china-or-italy.html. March 26, 2020; Accessed: December 1, 2021.
51. Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and Mortality among Black Patients and White Patients with Covid-19. N Engl J Med. 2020 Jun 25. 382 (26):2534-2543. [Medline]. [Full Text].
52. Zelner J, Trangucci R, Naraharisetti R, Cao A, Malosh R, Broen K, et al. Racial disparities in COVID-19 mortality are driven by unequal infection risks. Clin Infect Dis. 2020 Nov 21. [Medline]. [Full Text].
53. Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The Disproportionate Impact of COVID-19 on Racial and Ethnic Minorities in the United States. Clin Infect Dis. 2020 Jun 20. [Medline]. [Full Text].

54. Cunningham JW, Vaduganathan M, Claggett BL, Jering KS, Bhatt AS, Rosenthal N, et al. Clinical Outcomes in Young US Adults Hospitalized With COVID-19. JAMA Intern Med. 2020 Sep 9. [Medline]. [Full Text].
55. Park YJ, Choe YJ, Park O, and the, COVID-19 National Emergency Response Center, Epidemiology and Case Management Team. Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020. Emerg Infect Dis. 2020 Oct. 26 (10):2465-2468. [Medline]. [Full Text].
56. Schwartz NG, Moorman AC, Makaretz A, Chang KT, Chu VT, Szablewski CM, et al. Adolescent with COVID-19 as the Source of an Outbreak at a 3-Week Family Gathering - Four States, June-July 2020. MMWR Morb Mortal Wkly Rep. 2020 Oct 9. 69 (40):1457-1459. [Medline]. [Full Text].
57. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. JAMA Pediatr. 2020 Apr 22. [Medline].
58. Aronoff SC, Hall A, Del Vecchio MT. The Natural History of SARS-Cov-2 Related Multisystem Inflammatory Syndrome in Children (MIS-C): A Systematic Review. J Pediatric Infect Dis Soc. 2020 Sep 14. [Medline]. [Full Text].
59. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine. 2020 Jul. 24:100433. [Medline]. [Full Text].
60. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinicalMedicine. 2020 Sep 4. 100527. [Medline]. [Full Text].
61. Children and COVID-19: State-Level Data Report. American Academy of Pediatrics. Available at https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/. 2021 Dec 02; Accessed: December 6, 2021.
62. Hillis SD, Blenkinsop A, Villaveces A, Annor FB, Liburd L, Massetti GM, et al. COVID-19-Associated Orphanhood and Caregiver Death in the United States. Pediatrics. 2021 Oct 7. [Medline]. [Full Text].
63. Bixler D, Miller AD, Mattison CP, and the, Pediatric Mortality Investigation Team. SARS-CoV-2-Associated Deaths Among Persons Aged MMWR Morb Mortal Wkly Rep</i>. 2020 Sep 18. 69 (37):1324-1329. [Medline]. [Full Text].
64. Chao JY, Derespina KR, Herold BC, Goldman DL, Aldrich M, Weingarten J, et al. Clinical Characteristics and Outcomes of Hospitalized and Critically Ill Children and Adolescents with Coronavirus Disease 2019 at a Tertiary Care Medical Center in New York City. J Pediatr. 2020 Aug. 223:14-19.e2. [Medline]. [Full Text].
65. Han MS, Choi EH, Chang SH, Jin BL, Lee EJ, Kim BN, et al. Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea. JAMA Pediatr. 2020 Aug 28. [Medline]. [Full Text].
66. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020 Nov. 20 (11):e276-e288. [Medline].
67. Feldstein LR, Tenforde MW, Friedman KG, and the, Overcoming COVID-19 Investigators. Characteristics and Outcomes of US Children and Adolescents With

Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19. JAMA. 2021 Feb 24. [Medline]. [Full Text].
68. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 – COVID-NET, 13 states, March 1-August 22, 2020. MMWR Morb Mort Wkly Rep. 2020 Sep 18. [Full Text].
69. Marín Gabriel MA, Reyne Vergeli M, Caserío Carbonero S, Sole L, Carrizosa Molina T, Rivero Calle I, et al. Maternal, Perinatal and Neonatal Outcomes With COVID-19: A Multicenter Study of 242 Pregnancies and Their 248 Infant Newborns During Their First Month of Life. Pediatr Infect Dis J. 2020 Sep 11. [Medline].
70. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM. 2020 Aug. 2 (3):100134. [Medline]. [Full Text].
71. Adhikari EH, Moreno W, Zofkie AC, MacDonald L, McIntire DD, Collins RRJ, et al. Pregnancy Outcomes Among Women With and Without Severe Acute Respiratory Syndrome Coronavirus 2 Infection. JAMA Netw Open. 2020 Nov 2. 3 (11):e2029256. [Medline].
72. Chambers C, Krogstad P, Bertrand K, Contreras D, Tobin NH, Bode L, et al. Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women. JAMA. 2020 Aug 19. [Medline]. [Full Text].
73. Pace RM, Williams JE, Järvinen KM, Belfort MB, Pace CD, Lackey KA, et al. COVID-19 and human milk: SARS-CoV-2, antibodies, and neutralizing capacity. medRxiv. 2020 Sep 18. [Medline].
74. Dandachi D, Geiger G, Montgomery MW, and the, HIV-COVID-19 consortium. Characteristics, Comorbidities, and Outcomes in a Multicenter Registry of Patients with HIV and Coronavirus Disease-19. Clin Infect Dis. 2020 Sep 9. [Medline]. [Full Text].
75. Okoh AK, Bishburg E, Grinberg S, Nagarakanti S. COVID-19 Pneumonia in Patients With HIV: A Case Series. J Acquir Immune Defic Syndr. 2020 Sep 1. 85 (1):e4-e5. [Medline]. [Full Text].
76. Karmen-Tuohy S, Carlucci PM, Zervou FN, Zacharioudakis IM, Rebick G, Klein E, et al. Outcomes Among HIV-Positive Patients Hospitalized With COVID-19. J Acquir Immune Defic Syndr. 2020 Sep 1. 85 (1):6-10. [Medline]. [Full Text].
77. Ho HE, Peluso MJ, Margus C, Matias Lopes JP, He C, Gaisa MM, et al. Clinical outcomes and immunologic characteristics of Covid-19 in people with HIV. J Infect Dis. 2020 Jun 30. [Medline]. [Full Text].
78. Self WH, Tenforde MW, Stubblefield WB, and the, CDC COVID-19 Response Team IVY Network. Seroprevalence of SARS-CoV-2 among frontline health care personnel in a multistate hospital network – 13 academic medical centers, April-June 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 31. 69:[Full Text].
79. Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol. 2020 Aug 13. [Medline]. [Full Text].
80. O'Hearn M, Liu J, Cudhea F, Micha R, Mozaffarian D. Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A

Comparative Risk Assessment Analysis. J Am Heart Assoc. 2021 Feb. 10 (5):e019259. [Medline]. [Full Text].
81. Rubin EJ, Baden LR, Karim SSA, Morrissey S. Audio Interview: The Omicron Variant of SARS-CoV-2. N Engl J Med. 2021 Dec 02. 385:[Full Text].
82. Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa. medRxiv. 2021 Dec 02. [Full Text].
83. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv. 2021 May 03. [Full Text].
84. Edara VV, Lai L, Sahoo MK, Floyd K, Sibai M, Solis D, et al. Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant. bioRxiv. 2021 May 10. [Full Text].
85. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med. 2021 Jul 21. [Medline]. [Full Text].
86. Kemp SA, Harvey WT, Lytras S, and the, COVID-19 Genomics UK (COG-UK) consortium. Recurrent emergence and transmission of a SARS-CoV-2 Spike deletion H69/V70. BioRxiv. 2020 Dec 21. [Full Text].
87. New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) statements and meeting minutes for SARS-CoV-2 variants (VUI-202012/01 [B.1.1.7]). www.gov.uk/government. Available at https://www.gov.uk/government/groups/new-and-emerging-respiratory-virus-threats-advisory-group. 2020 Dec 23; Accessed: December 1, 2021.
88. Volz E, Mishra S, Chand M, Barrett JC, Johnson R, Geidelberg L, et al. Report 42 - Transmission of SARS-CoV-2 Lineage B.1.1.7 in England: Insights from linking epidemiological and genetic data. Imperial College London, MRC Centre for Global Infectious Disease Analysis. Available at https://www.imperial.ac.uk/media/imperial-college/medicine/mrc-gida/2020-12-31-COVID19-Report-42-Preprint-VOC.pdf. 2020 Dec 31; Accessed: December 1, 2021.
89. Nelson G, Oleksandr B, Spilman P, Niazi K, Rabizadeh S, Soon-Shiong P. Molecular dynamic simulation reveals E484K mutation enhances spike RBD-ACE2 affinity and the combination of E484K, K417N and N401Y mutations (501Y.V2 variant) induces conformational change greater than N401Y mutant alone, potentially resulting in an escape mutant. bioRxiv. 2021 Jan 13. [Full Text].
90. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. Lancet. 2021 Jan 27. [Full Text].
91. 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 Aug 25. 324 (8):782-793. [Medline].
92. Burke RM, Killerby ME, Newton S, Ashworth CE, Berns AL, Brennan S, et al. Symptom Profiles of a Convenience Sample of Patients with COVID-19 - United States, January-April 2020. MMWR Morb Mortal Wkly Rep. 2020 Jul 17. 69 (28):904-908. [Medline].

93. CDC. Healthcare Workers: Information on COVID-19. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/index.html. March 31, 2021 (updated); Accessed: December 1, 2021.
94. Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. Nature. 2020 Jul 8. [Medline].
95. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study. Lancet Public Health. 2020 Jun 30. [Medline].
96. Ellinghaus D, Degenhardt F, Bujanda L, et al. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis. medRxiv. Available at https://www.medrxiv.org/content/10.1101/2020.05.31.20114991v1. June 2, 2020; Accessed: December 1, 2021.
97. Ellinghaus D, Degenhardt F, Bujanda L, et al. Genomewide Association Study of Severe Covid-19 With Respiratory Failure. NEJM. 2020 Jun 17. [Medline]. [Full Text].
98. Luers JC, Rokohl AC, Loreck N, Wawer Matos PA, Augustin M, Dewald F, et al. Olfactory and Gustatory Dysfunction in Coronavirus Disease 19 (COVID-19). Clin Infect Dis. 2020 May 1. [Medline].
99. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Jan 24. [Medline].
100. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Feb 28. [Medline].
101. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15. 395 (10223):507-513. [Medline].
102. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Feb 7. [Medline].
103. CDC. Long-Term Effects of COVID-19. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html. 2020 Nov 13; Accessed: December 1, 2021.
104. [Guideline] COVID-19 Treatment Guidelines Panel. Clinical Spectrum of SARS-CoV-2 Infection. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. October 19, 2021 (updated); Accessed: December 1, 2021.
105. [Guideline] COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence (NICE). Available at https://www.nice.org.uk/guidance/NG188. 2020 Dec 18; Accessed: December 1, 2021.
106. Davis HE, Assaf GS, McCorkell L, Wie H, Low RJ, Re'em Y, et al. Characterizing Long COVIC in an international cohort: 7 months of symptoms and their impact. medRxiv. 2020 Dec 27. [Full Text].
107. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2020 Oct 5. [Medline]. [Full Text].

108. Huang C, Huang L, Wang Y, Xia L, Ren L, Xiaoying G, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021 Jan 08. [Full Text].
109. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine. 2020 Aug. 25:100463. [Medline]. [Full Text].
110. van den Borst B, Peters JB, Brink M, Schoon Y, Bleeker-Rovers CP, Schers H, et al. Comprehensive health assessment three months after recovery from acute COVID-19. Clin Infect Dis. 2020 Nov 21. [Medline]. [Full Text].
111. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA Netw Open. 2021 Feb 1. 4 (2):e210830. [Medline].
112. Datta SD, Talwar A, Lee JT. A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. JAMA. 2020 Dec 8. 324 (22):2251-2252. [Medline]. [Full Text].
113. McFadyen JD, Stevens H, Peter K. The Emerging Threat of (Micro)Thrombosis in COVID-19 and Its Therapeutic Implications. Circ Res. 2020 Jul 31. 127 (4):571-587. [Medline]. [Full Text].
114. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J. 2021 Feb 18. [Medline]. [Full Text].
115. Kang H, Wang Y, Tong Z, Liu X. Retest positive for SARS-CoV-2 RNA of "recovered" patients with COVID-19: Persistence, sampling issues, or re-infection?. J Med Virol. 2020 Jun 3. [Medline]. [Full Text].
116. Goodman B. First Confirmed Cases of COVID-19 Reinfections in US. Medscape Medical News. 2020 Oct 12. Available at https://www.medscape.com/viewarticle/939003.
117. Larson D, Brodniak SL, Voegtly LJ, Cer RZ, Glang LA, Malagon FJ, et al. A Case of Early Re-infection with SARS-CoV-2. Clin Infect Dis. 2020 Sep 19. [Medline]. [Full Text].
118. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis. 2020 Aug 25. [Medline]. [Full Text].
119. Gousseff M, Penot P, Gallay L, in behalf of the COCOREC study group. Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound?. J Infect. 2020 Jun 30. [Medline]. [Full Text].
120. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, rawford N, Gorzalski A, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Inf Dis. 2020 Oct 12. [Full Text].
121. CDC. 2019 Novel Coronavirus, Wuhan, China: Frequently Asked Questions and Answers. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/faq.html. October 19, 2021; Accessed: December 1, 2021.

122. FDA. Coronavirus (COVID-19) Update: Daily Roundup. fda.gov. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup. March 23, 2020; Accessed: December 1, 2021.
123. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13. [Medline].
124. Shi H, Han X, Jiang N, Cao Y, Alwalid O, Gu J, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020 Feb 24. [Medline].
125. Zhao W, Zhong Z, Xie X, Yu Q, Liu J. Relation Between Chest CT Findings and Clinical Conditions of Coronavirus Disease (COVID-19) Pneumonia: A Multicenter Study. AJR Am J Roentgenol. 2020 Mar 3. 1-6. [Medline].
126. Bai HX, Hsieh B, Xiong Z, Halsey K, Choi JW, Tran TML, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020 Mar 10. 200823. [Medline].
127. ACR. 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. March 22, 2020; Accessed: December 1, 2021.
128. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020 Mar 4. [Medline].
129. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. J Infect Dis. 2020 Mar 17. [Medline].
130. Li M, Lei P, Zeng B, Li Z, Yu P, Fan B, et al. Coronavirus Disease (COVID-19): Spectrum of CT Findings and Temporal Progression of the Disease. Acad Radiol. 2020 Mar 20. [Medline].
131. Wong HYF, Lam HYS, Fong AH, Leung ST, Chin TW, Lo CSY, et al. Frequency and Distribution of Chest Radiographic Findings in COVID-19 Positive Patients. Radiology. 2019 Mar 27. 201160. [Medline].
132. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of Unknown Etiology in Wuhan, China: Potential for International Spread Via Commercial Air Travel. J Travel Med. 2020 Jan 14. [Medline].
133. FDA News Release. FDA Reissues Emergency Use Authorization for Convalescent Plasma. U.S. Food and Drug Administration. Available at https://www.fda.gov/media/141477/download. 2020 Nov 30; Accessed: December 1, 2021.
134. WHO. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. WHO. Available at https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19. April 19, 2020; Accessed: December 1, 2021.
135. Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, O'Mera MJ, et al. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and

Potential Drug-Repurposing. bioRxiv. Available at https://www.biorxiv.org/content/10.1101/2020.03.22.002386v1. 2020 Mar 22; Accessed: December 1, 2021.
136. I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients (I-SPY_COVID). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04488081. 2020 Aug 12; Accessed: December 1, 2021.
137. Arshad U, Pertinez H, Box H, Tatham L, Rajoki RKR, Curley P, et al. Prioritisation of potential anti-SARS-CoV-2 drug repurposing opportunities based on ability to achieve adequate target site concentrations derived from their established human pharmacokinetics. medRxiv. 2020 Apr 22. [Full Text].
138. World Health Organization. “Solidarity” clinical trial for COVID-19 treatments. WHO. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. 2020 Oct 16; Accessed: December 1, 2021.
139. WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2020 Dec 2. [Medline]. [Full Text].
140. Kalil AC. Treating COVID-19-Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics. JAMA. 2020 Mar 24. [Medline]. [Full Text].
141. Rome BN, Avorn J. Drug Evaluation during the Covid-19 Pandemic. N Engl J Med. 2020 Apr 14. [Medline]. [Full Text].
142. Frellick M. Key Drugs Join PPEs on List of Front-Line Shortages. Medscape Medical News. 2020 Apr 02. Available at https://www.medscape.com/viewarticle/928039.
143. Live Updates: Which Drugs Are In Shortage Because of COVID-19?. GoodRx. Available at https://www.goodrx.com/blog/covid-19-drug-shortages-updates/. July 13, 2020; Accessed: December 1, 2021.
144. Wilson FP. Hydroxychloroquine for COVID-19: What’s the Evidence? (Commentary). Medscape Medical News and Perspectives. 2020 Mar 25. Available at https://www.medscape.com/viewarticle/927342.
145. CDC. Coronavirus Disease 2019 (COVID-19): Community-Related Exposures. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html. March 1, 2021 (updated); Accessed: December 1, 2021.
146. CDC. Coronavirus Disease 2019 (COVID-19): Travel-Associated Exposures. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/php/risk-assessment.html. November 5, 2021 (updated); Accessed: December 1, 2021.
147. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nat Med. 2020. [Full Text].
148. Smith JD, MacDougall CC, Johnstone J, Copes RA, Schwartz B, Garber GE. Effectiveness of N95 respirators versus surgical masks in protecting health care workers from acute respiratory infection: a systematic review and meta-analysis. CMAJ. 2016 May 17. 188 (8):567-574. [Medline].

149. TLR 2/6/9 agonist PUL-042. NCI Drug Dictionary. Available at https://www.cancer.gov/publications/dictionaries/cancer-drug/def/tlr-2-6-9-agonist-pul-042. Accessed: December 1, 2021.
150. The Use PUL-042 Inhalation Solution to Prevent COVID-19 in Adults Exposed to SARS-CoV-2. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04313023. 2020 Mar 24; Accessed: December 1, 2021.
151. The Use of PUL-042 Inhalation Solution to Reduce the Severity of COVID-19 in Adults Positive for SARS-CoV-2 Infection. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04312997?term=PUL-042&cond=COVID&cntry=US&draw=2&rank=2. 2020 May 07; Accessed: December 1, 2021.
152. FDA. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. fda.gov. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. May 01, 2020; Accessed: December 1, 2021.
153. COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19. US Food and Drug Administration. 2020 Aug 28. Available at https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklury-remdesivir-include-all-hospitalized?utm_campaign=FDA%20Broadens%20Emergency%20Use%20Authorization%20for%20Veklury%20%28Remdesivir%29%20to%.
154. Study in participants with early stage coronavirus disease 2019 (COVID-19) to evaluate the safety, efficacy, and pharmacokinetics of remdesivir administered by inhalation. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04539262. 2020 Dec 09; Accessed: December 1, 2021.
155. Holshue ML, DeBolt C, Lindquist S, and, the Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5. 382 (10):929-936. [Medline].
156. National Institutes of Health. NIH clinical trial of remdesivir to treat COVID-19 begins. U.S. Department of Health and Human Services. Available at https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins. 2020 Feb 25; Accessed: March 24, 2020.
157. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Oct 8. [Medline]. [Full Text].
158. Harrington DP, Baden LR, Hogan JW. A Large, Simple Trial Leading to Complex Questions. N Engl J Med. 2020 Dec 2. [Medline]. [Full Text].
159. Ader F, Bouscambert-Duchamp M, Hites M, and the, DisCoVeRy Study Group. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis. 2021 Sep 14. [Medline]. [Full Text].

160. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. November 5, 2020. 383:1827-1837. [Medline]. [Full Text].
161. Spinner CD, Gottlieb RL, Criner GJ, and the, GS-US-540-5774 Investigators. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2020 Aug 21. [Medline]. [Full Text].
162. Hill JA, Paredes R, Vaca C, Mera J, Webb BJ, Perez G, et al. Remdesivir for the treatment of high-risk non-hospitalized individuals with COVID-19: A randomized, double-blind, placebo-controlled trial (abstract). Presented at IDWeek, the 10th annual meeting the Infectious Disease Society of America, September 30, 2021.
163. Gilead's Veklury (remdesivir) associated with reduction in mortality rate in hospitalized patients with COVID-19 across three analyses of large retrospective real-world data sets. Gilead. 2021 Jun 21. Available at https://www.gilead.com/news-and-press/press-room/press-releases/2021/6/gileads-veklury-remdesivir-associated-with-a-reduction-in-mortality-rate-in-hospitalized-patients-with-covid19-across-three-analyses-of-large-ret.
164. Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04431453. 2020 Jun 01; Accessed: December 1, 2021.
165. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. 2020 Sep 12. [Medline]. [Full Text].
166. Burwick RM, Yawetz S, Stephenson KE, Collier AY, Sen P, Blackburn BG, et al. Compassionate Use of Remdesivir in Pregnant Women with Severe Covid-19. Clin Infect Dis. 2020 Oct 8. [Medline]. [Full Text].
167. McCoy JA, Short WR, Srinivas SK, Levine LD, Hirshberg A. Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women at a United States academic center. Am J Obstet Gynecol MFM. 2020 Aug. 2 (3):100164. [Medline]. [Full Text].
168. Fischer W, Eron JJ, Holman W, Cohen S, Fang L, Szewczyk LJ, et al. Molnupiravir, an oral antiviral treatment for COVID-19. medRxiv. 2021 Jun 17. [Full Text].
169. Study of MK-4482 for prevention of coronavirus disease 2019 (COVID-19) in adults (MK-4482-013) (MOVe-AHEAD). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04939428. 2021 Nov 29; Accessed: November 30, 2021.
170. Ivashchenko AA, Dmitriev KA, Vostokova NV, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. Clin Infect Dis. 2020 Aug 9. [Medline]. [Full Text].
171. Oral favipiravir compared to placebo in subjects with mild COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04346628. 2020 Oct 05; Accessed: December 1, 2021.

172. A post-exposure prophylaxis study of PF-07321332/ritonavir in adult household contacts of an individual with symptomatic COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT05047601. 2021 Sep 24; Accessed: September 26, 2021.
173. A study of PF-07321332/ritonavir in nonhospitalized high risk adult participants with COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04960202. 2021 Sep 21; Accessed: September 27, 2021.
174. Atea Pharmaceuticals provides clinical and corporate update and reports second quarter 2021 financial results. Atea Pharmaceuticals. Available at https://ir.ateapharma.com/news-releases/news-release-details/atea-pharmaceuticals-provides-clinical-and-corporate-update-and. 2021 Aug 12; Accessed: December 1, 2021.
175. Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Post-Exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses in Elderly Residents of Long-Term Care Facilities (LTCF). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04343248?term=nitazoxanide&recrs=ab&cond=COVID&draw=2&rank=6. 2020 Apr 16; Accessed: December 1, 2021.
176. Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Pre- or Post Exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04359680?term=nitazoxanide&recrs=ab&cond=COVID&draw=2&rank=5. 2020 Apr 24; Accessed: December 1, 2021.
177. Romark initiates new phase 3 clinical trial of NT-300 for the treatment of COVID-19. Romark Pharmaceuticals. Available at https://www.romark.com/romark-initiates-new-phase-3-clinical-trial-of-nt-300-for-the-treatment-of-covid-19/. 2020 Aug 11; Accessed: December 1, 2021.
178. Niclosamide in moderate COVID-19. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04436458. 2020 Jun 18; Accessed: December 1, 2021.
179. ANA Therapeutics begins phase 2/3 clinical trial of proprietary oral niclosamide formulation to treat COVID-19. Businesswire. Available at https://www.businesswire.com/news/home/20201026005569/en/ANA-Therapeutics-Begins-Phase-23-Clinical-Trial-of-Proprietary-Oral-Niclosamide-Formulation-to-Treat-COVID-19. 2020 Oct 26; Accessed: December 1, 2021.
180. Ingraham NE, Lotfi-Emran S, Thielen BK, Techar K, Morris RS, Holtan SG, et al. Immunomodulation in COVID-19. Lancet Respir Med. 2020 May 4. [Medline]. [Full Text].
181. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs. 2020 Sep. 80 (13):1267-1292. [Medline]. [Full Text].
182. Wagner JL, Veve MP, Barber KE. Using IL-6 inhibitors to treat COVID-19. ContagionLive. Available at https://www.contagionlive.com/publications/contagion/2020/august/using-il6-inhibitors-to-treat-covid19?ekey=c2NiZXJnbWFuQG5lYnJhc2thbWVkLmNvbQ. 2020 Aug 17; Accessed: December 1, 2021.

183. [Guideline] NIH. The COVID-19 Treatment Guidelines Panel's Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19. COVID-19 Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/interleukin-6-inhibitors/. 2021 Mar 05; Accessed: December 1, 2021.
184. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jan 7. 384 (1):20-30. [Medline]. [Full Text].
185. REMAP-CAP Investigators., Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Apr 22. 384 (16):1491-1502. [Medline]. [Full Text].
186. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1. 397 (10285):1637-1645. [Medline]. [Full Text].
187. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021 Apr 22. 384 (16):1503-1516. [Medline]. [Full Text].
188. Rubin EJ, Longo DL, Baden LR. Interleukin-6 Receptor Inhibition in Covid-19 - Cooling the Inflammatory Soup. N Engl J Med. 2021 Apr 22. 384 (16):1564-1565. [Medline]. [Full Text].
189. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med. 2021 Sep 3. [Medline]. [Full Text].
190. [Guideline] NIH. Interleukin-1 Inhibitors. COVID-19 Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/interleukin-1-inhibitors/. 2020 Jul 17; Accessed: September 8, 2021.
191. Intereukin-7 to improve clinical outcomes in lymphopenic patients with COVID-19 infection FR BL Cohort (ILIAD-7-FR). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04407689. 2020 Jun 22; Accessed: December 1, 2021.
192. Interleukin-7 (CYT107 to improve clinical outcomes in lymphopenic patients with COVID-19 infection UK cohort (ILIAD-7-UK). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04379076. 2020 May 15; Accessed: December 1, 2021.
193. Laterre PF, François B, Collienne C, Hantson P, Jeannet R, Remy KE, et al. Association of Interleukin 7 Immunotherapy With Lymphocyte Counts Among Patients With Severe Coronavirus Disease 2019 (COVID-19). JAMA Netw Open. 2020 Jul 1. 3 (7):e2016485. [Medline]. [Full Text].
194. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020 Apr. 20 (4):400-402. [Medline]. [Full Text].
195. Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020 Feb 15. 395 (10223):e30-e31. [Medline]. [Full Text].

196. Stebbing J, Krishnan V, de Bono S, Ottaviani S, Casalini G, Richarson PJ, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. 2020 Apr 15. [Full Text].
197. FDA. Fact sheet for healthcare providers emergency use authorization (EUA) of baricitinib. fda.gov. Available at https://www.fda.gov/media/143823/download. November 2020; Accessed: December 1, 2021.
198. Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2020 Dec 11. [Medline]. [Full Text].
199. Kalil AC, Stebbing J. Baricitinib: the first immunomodulatory treatment to reduce COVID-19 mortality in a placebo-controlled trial. Lancet Respir Med. 2021 Aug 31. [Medline]. [Full Text].
200. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, 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 Aug 31. [Medline]. [Full Text].
201. Lilly and Incyte's baricitinib reduced deaths among patients with COVID-19 receiving invasive mechanical ventilation. Lilly. Available at https://investor.lilly.com/news-releases/news-release-details/lilly-and-incytes-baricitinib-reduced-deaths-among-patients. 2021 Aug 03; Accessed: December 1, 2021.
202. Guimarães PO, Quirk D, Furtado RH, and the STOP-COVID Trial Investigators. Tofacitinib in patients hospitalized with COVID-19 pneumonia. N Engl J Med. 2021 Jun 16. [Medline]. [Full Text].
203. [Guideline] Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. World Health Organization. Available at https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. 2020 Mar 13; Accessed: March 24, 2020.
204. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020 Feb 15. 395 (10223):473-475. [Medline].
205. [Guideline] Alhazzani W, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Crit Care Med. 2021 Mar 1. 49 (3):e219-e234. [Medline]. [Full Text].
206. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2. [Medline]. [Full Text].
207. Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic. JAMA. 2020 Sep 2. [Medline]. [Full Text].
208. [Guideline] WHO. Corticosteroids for COVID-19 – Living Guidance. World Health Organization. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. 2020 Sep 02; Accessed: December 1, 2021.

209. NRx Pharmaceuticals identifies significantly higher likelihood of surviving and recovering from critical COVID-19 in Zyesami (aviptadil) treated patients previously administered remdesivir. NeuroRx Pharmaceuticals. 2021 November 29. Available at https://www.nrxpharma.com/nrx-pharmaceuticals-identifies-significantly-higher-likelihood-of-surviving-and-recovering-from-critical-covid-19-in-zyesami-aviptadil-treated-patients-previously-administered-remdesivir/.
210. Inhaled aviptadil for the treatment of moderate and severe COVID-19 (AVICOVID-2). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04360096. 2021 Mar 11; Accessed: December 1, 2021.
211. Strich JR, Tian X, Samour M, King CS, Shlobin O, Reger R, et al. Fostamatinib for the treatment of hospitalized adults with COVD-19 A randomized trial. Clin Infect Dis. 2021 Sep 1. [Medline]. [Full Text].
212. Kalil AC, Mehta AK, Patterson TF, and the, ACTT-3 study group members. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 Oct 18. [Medline]. [Full Text].
213. Schönbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents?. Circulation. 2004 Jun 1. 109 (21 Suppl 1):II18-26. [Medline]. [Full Text].
214. Hariyanto TI, Kurniawan A. Statin therapy did not improved the in-hospital outcome of coronavirus disease 2019 (COVID-19) infection. Diabetes Metab Syndr. 2020 Aug 26. 14(6):1613-1615. [Medline]. [Full Text].
215. Kow CS, Hasan SS. Meta-analysis of Effect of Statins in Patients with COVID-19. Am J Cardiol. 2020 Aug 12. [Medline]. [Full Text].
216. Castiglione V, Chiriacò M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. Eur Heart J Cardiovasc Pharmacother. 2020 Jul 1. 6 (4):258-259. [Medline]. [Full Text].
217. [Guideline] NIH. Covid-19 Treatment Guidelines - Adjunctive Therapy. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/adjunctive-therapy/. 2020 Jul 17; Accessed: December 1, 2021.
218. Yao JS, Paguio JA, Dee EC, Tan HC, Moulick A, Milazzo C, et al. The minimal effect of zinc on the survival of hospitalized patients with Covid-19: an observational study. Chest. 2020 Jul 22. [Medline]. [Full Text].
219. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. JAMA Netw Open. 2020 Sep 1. 3 (9):e2019722. [Medline]. [Full Text].
220. Sahota O. Understanding vitamin D deficiency. Age Ageing. 2014 Sep. 43 (5):589-91. [Medline]. [Full Text].
221. Temesgen Z, Burger CD, Baker J, Polk C, Libertin C, Kelley C, et al. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: Results from the LIVE-AIR phase 3 randomized double-blind placebo-controlled trial. medRxiv. 2021 May 05. [Full Text].
222. Second randomized trial of Leukine (sargramostim) in COVID-19 demonstrates improvement in lung function. PTx, Partner Therapeutics. Available at

https://www.partnertx.com/second-randomized-trial-of-leukine-sargramostim-in-covid-19-demonstrates-improvement-in-lung-function/. 2021 Jun 28; Accessed: December 1, 2021.
223. Study of sargramostim in patients with COVID-19 (iLeukPulm). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04411680. 2021 Jun 21; Accessed: June 28, 2021.
224. A study to assess the efficacy and safety of gimsilumab in subjects with lung injury or acute respiratory distress syndrome secondary to coronavirus disease 2019. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04351243?term=gimsilumab&draw=2&rank=1. 2020 Dec 03; Accessed: March 31, 2021.
225. Pupim L, Wang TS, Hudock K, Denson J, Fourie N, Hercilla Vasquez L, et al. Mavrilimumab improves outcomes in phase 2 trial in non-mechanically-ventilated patients with severe COVID-19 pneumonia and systemic hyperinflammation. Presented at the 2021 European Congress of Rheumatology. Ann Rheum Dis. 2021 Jun 05. [Full Text].
226. Patel J, Beishuizen A , Ruiz XB, Boughanmi H, Cahn A, Criner GJ, et al. A randomized trial of otilimab in severe COVID-19 pneumonia (OSCAR). medRxiv. 2021 Apr 17. [Full Text].
227. A Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy of Tradipitant in Treating Inflammatory Lung Injury and Improving Clinical Outcomes Associated With Severe or Critical COVID-19. (NCT04326426). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04326426?term=tradipitant&cond=COVID&draw=2&rank=1. 2020 Mar 30; Accessed: December 1, 2021.
228. Vanda Pharmaceuticals' interim analysis from ODYSSEY study shows tradipitant may accelerate clinical improvement in patients with COVID-19 pneumonia. Vanda Pharmaceuticals. Available at https://vandapharmaceuticalsinc.gcs-web.com/node/14256/pdf. 2020 Aug 18; Accessed: December 1, 2021.
229. Aprepitant injectable emulsion in patients with COVID-19 (GUARDS-1). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04470622. 2020 Jul 17; Accessed: December 1, 2021.
230. FDA grants fast track designation for remestemcel-L in the treatment of acute respiratory distress syndrome due to COVID-19. Mesoblast. 2020 Dec 01. Available at http://investorsmedia.mesoblast.com/static-files/046bf826-c5bf-4606-a0b2-0420f8c7a933.
231. MSCs in COVID-19 ARDS. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04371393. 2020 Nov 06; Accessed: December 1, 2021.
232. U.S. FDA clears Pluristem's IND application for phase II COVID-19 study. Pluristem Therapeutics, Inc. 2020 May 08. Available at https://www.pluristem.com/wp-content/uploads/2020/05/FDA-Clearance-COVID-19-FINAL.pdf.
233. NantKwest announces FDA authorization of IND application for mesenchymal stem cell product for the treatment of severe COVID-19 patients. NantKwest. 2020 May 18. Available at https://nantkwest.com/nantkwest-announces-fda-authorization-

of-ind-application-for-mesenchymal-stem-cell-product-for-the-treatment-of-severe-covid-19-patients/.
234. Efficacy and safety study of allogeneic HB-adMSCs for the treatment of COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04362189. 2020 Aug 12; Accessed: December 1, 2021.
235. FDA approves study to investigate the use of cell therapy to treat COVID-19 related multisystem inflammatory syndrome in children (MIS-C). PR Newswire. 2020 Sep 16. Available at https://www.prnewswire.com/news-releases/fda-approves-study-to-investigate-the-use-of-cell-therapy-to-treat-covid-19-related-multisystem-inflammatory-syndrome-in-children-mis-c-301131904.html.
236. Extracellular vesicle infusion therapy for severe COVID-19 (EXIT COVID-19). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04493242. 2020 Jul 30; Accessed: December 1, 2021.
237. MediciNova announces opening of investigational new drug application for MN-166 (ibudilast) for prevention of acute respiratory distress syndrome in patients with COVID-19. MediciNova. 2020 Jul 01. Available at https://investors.medicinova.com/news-releases/news-release-details/medicinova-announces-opening-investigational-new-drug-1.
238. Safety and efficacy of NP-120 (ifenprodil) for the treatment of hospitalized patient with confirmed COVID-19 disease. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04382924. 2020 Dec 10; Accessed: December 1, 2021.
239. Eculizumab (Soliris) in Covid-19 Infected Patients (SOLID-C19). ClinicialTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04288713. 2020 Mar 30; Accessed: December 1, 2021.
240. Alexion provides update on phase 3 study of Ultomiris (ravulizumab-cwvz) in hospitalized patients with severe COVID-19. Alexion Pharmaceuticals, Inc. Available at https://ir.alexion.com/news-releases/news-release-details/alexion-provides-update-phase-3-study-ultomirisr-ravulizumab. 2021 Jan 13; Accessed: December 1, 2021.
241. Study to evaluate the safety and efficacy of ATYR1923 in patients with severe pneumonia related to COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04412668. 2020 Jun 04; Accessed: December 1, 2021.
242. Evaluation of Safety & Efficacy of BIO-11006 Inhalation Solution in Patients with ARDS. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT03202394?term=NCT03202394&draw=2&rank=1. 2018 Dec 06; Accessed: December 1, 2021.
243. Chimerix Announces Initiation of a Phase 2/3 Study of DSTAT in Acute Lung Injury for Patients with Severe COVID-19. Chimerix. Available at https://ir.chimerix.com/news-releases/news-release-details/chimerix-announces-initiation-phase-23-study-dstat-acute-lung. 2020 Apr 29; Accessed: December 1, 2021.
244. A study of opaganib in coronavirus disease 2019 pneumonia (COVID-19). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04414618. 2020 Jul 31; Accessed: December 1, 2021.

245. Opaganib, a sphingosine kinase-2 (SK2) inhibitor in COVID-19 pneumonia. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04467840. 2020 Jul 17; Accessed: December 1, 2021.
246. LB1148 Now Available for Investigational Use to Treat Pulmonary Dysfunction Associated with COVID-19 Pneumonia. Leading BioSciences. 2020 May 15. Available at https://www.globenewswire.com/news-release/2020/05/15/2034269/0/en/Leading-BioSciences-Receives-IND-Clearance-for-Phase-2-COVID-19-Study.html.
247. Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects (Substudy: DAS181 for COVID-19): RCT Study. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT03808922?term=DAS181&cond=COVID&draw=2&rank=4. 2020 Apr 17;
248. Applied Therapeutics Announces IND and Investigator-Initiated Studies of AT-001 in Critical COVID-19 Patients. Applied Therapeutics. 2020 Apr 02. Available at https://ir.appliedtherapeutics.com/news-releases/news-release-details/applied-therapeutics-announces-ind-and-investigator-initiated.
249. Miller J, Bruen C, Schnaus M, Zhang J, Ali S, Lind A, et al. Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: Results from a randomized controlled trial. Research Square. 2020 Jul 15. [Full Text].
250. Biohaven receives FDA may proceed letter to begin phase 2 trial of intranasal vazegepant to treat lung inflammation after COVID-19 infection. Biohaven Pharmaceuticals. 2020 Apr 09. Available at https://www.biohavenpharma.com/investors/news-events/press-releases/04-09-2020.
251. Evaluation of activity and safety of oral selinexor in participants with severe COVID-19 infection (coronavirus). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04349098. 2020 May 08; Accessed: December 1, 2021.
252. Evelo Biosciences, Rutgers University, and Robert Wood Johnson University Hospital Announce Submission of IND for a Phase 2 Study of EDP1815 in COVID-19 Patients. Evelo Biosciences. 2020 May 07. Available at http://ir.evelobio.com/news-releases/news-release-details/evelo-biosciences-rutgers-university-and-robert-wood-johnson.
253. Evelo Biosciences announces EDP1815 to advance into phase 2/3 TACTIC-E COVID-19 trial. Evelo Biosciences. 2020 Jun 22. Available at http://ir.evelobio.com/news-releases/news-release-details/evelo-biosciences-announces-edp1815-advance-phase-23-tactic-e.
254. VERU-111 suppresses key cytokines responsible for severe acute respiratory distress syndrome in COVID-19. Veru, Inc. 2020 Aug 04. Available at https://verupharma.com/news/veru-111-suppresses-key-cytokines-responsible-for-severe-acute-respiratory-distress-syndrome-in-covid-19/.
255. Q BioMed partner Mannin Research developing potential treatment for patients infected with coronavirus and other infectious diseases. Q BioMed. 2020 Feb 04. Available at https://qbiomed.com/news-and-media/news-2020/180-q-biomed-partner-mannin-research-developing-potential-treatment-for-patients-infected-with-coronavirus-and-other-infectious-diseases.

256. Diffusion Pharmaceuticals receives FDA guidance for international phase 1b/2b COVID-19 clinical program with TSC. Diffusion Pharmaceuticals. 2020 July 27. Available at https://investors.diffusionpharma.com/News/news-details/2020/Diffusion-Pharmaceuticals-Receives-FDA-Guidance-for-International-Phase-1b2b-COVID-19-Clinical-Program-with-TSC/default.aspx.
257. NCI drug Dictionary. Trans sodium crocetinate. NIH, National Cancer Institute. Available at https://www.cancer.gov/publications/dictionaries/cancer-drug/def/trans-sodium-crocetinate. Accessed: December 1, 2021.
258. FDA authorizes OPKO Health clinical trial evaluating Rayaldee in COVID-19 patients. OPKO Health. 2020 Jun 01. Available at https://www.opko.com/news-media/press-releases/detail/394/fda-authorizes-opko-health-clinical-trial-evaluating.
259. LYT-100 in Post-acute COVID-19 Respiratory Disease. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04652518. 2020 Dec 07; Accessed: December 11, 2020.
260. Ashvattha Therapeutics subsidiary Orpheris announces FDA agreement to initiate phase 2 study evaluating OP-101 in severe COVID-19 patients. Ashvattha Therapeutics. 2020 May 28. Available at http://avttx.com/ashvattha-therapeutics-subsidiary-orpheris-announces-fda-agreement-to-initiate-phase-2-study-evaluating-op-101-in-severe-covid-19-patients/.
261. A Study to Evaluate the Efficacy, Safety and Tolerability of IMU-838 as Addition to Investigator's Choice of Standard of Care Therapy, in Patients With Coronavirus Disease 19 (COVID-19). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04379271. 2020 May 11;
262. Immunic, Inc. announces first patients enrolled in investigator-sponsored phase 2 clinical trial of IMU-838 in combination with oseltamivir for the treatment of patients with moderate-to-severe COVID-19. Immunic, Inc. 2020 Jul 27. Available at https://www.immunic-therapeutics.com/2020/07/27/immunic-inc-announces-first-patients-enrolled-in-investigator-sponsored-phase-2-clinical-trial-of-imu-838-in-combination-with-oseltamivir-for-the-treatment-of-patients-with-moderate-to-severe-covid-19/.
263. Oryzon announces enrollment of first patient in ESCAPE: a Phase II clinical trial with vafidemstat in severely ill COVID-19 patients. Oryzon Genomics. 2020 May 18. Available at https://www.oryzon.com/sites/default/files/PRESS_RELEASE_13-2020.pdf.
264. Bhatt DL. First Human Trial of a Loading Dose of Icosapent Ethyl in Patients with COVID-19: Primary Results of the Vascepa COVID-19 CardioLink-9 Randomized Trial. Presented at the National Lipid Association Scientific Sessions December 12, 2020. [Full Text].
265. Prazosin to prevent COVID-19 (PREVENT-COVID Trial). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04365257. 2020 May 15; Accessed: June 16, 2020.
266. Konig MF, Powell M, Staedtke V, Bai RY, Thomas DL, Fischer N, et al. Preventing cytokine storm syndrome in COVID-19 using α-1 adrenergic receptor antagonists. J Clin Invest. 2020 May 26. [Medline]. [Full Text].

267. Study of Ampion for the treatment of adult COVID-19 patients requiring oxygen supplementation. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04456452. 2020 Jul 24;
268. Fulcrum Therapeutics Announces Initiation of Multi-Center Phase 3 (LOSVID) Trial with Losmapimod for Hospitalized COVID-19 Patients. Fulcrum Therapeutics. 2020 Jun 24. Available at https://ir.fulcrumtx.com/news-releases/news-release-details/fulcrum-therapeutics-announces-initiation-multi-center-phase-3.
269. Durect Corporation announces initiation of patient recruitment in phase 2 safety and efficacy study of DUR-928 in COVID-19 patients with acute liver or kidney injury. Durect Corporation. 2020 Jul 01. Available at https://investors.durect.com/news-releases/news-release-details/durect-corporation-announces-initiation-patient-recruitment?field_nir_news_date_value[min]=2020.
270. Aclaris Therapeutics Supports Investigator-Initiated Clinical Trial of ATI-450 for Cytokine Release Syndrome in Hospitalized Patients with COVID-19. Aclaris Therapeutics. 2020 Jun 17. Available at https://investor.aclaristx.com/news-releases/news-release-details/aclaris-therapeutics-supports-investigator-initiated-clinical.
271. Study to evaluate the efficacy and safety of leronlimab for mild to moderate COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04343651. 2020 Jun 11; Accessed: July 13, 2020.
272. Study to evaluate the efficacy and safety of leronlimab for patients with severe or critical coronavirus disease 2019 (COVID-19). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04347239. 2020 Jun 11; Accessed: July 13, 2020.
273. Biophytis receives FDA IND clearance for COVA, a phase 2/3 clinical trial with sarconeos (BIO101) for the treatment of patients with COVID-19 related respiratory failure. Biophytis. 2020 Jul 01. Available at https://www.biophytis.com/wp-content/uploads/2020/07/Biophytis-COVA-FDA-IND-Clearance-PR-EN-vF-.pdf.
274. FDA clears abivertinib for Phase 2 safety and efficacy study in hospitalized patients with moderate to severe COVID-19. Sorrento Therapeutics. 2020 July 20. Available at https://investors.sorrentotherapeutics.com/news-releases/news-release-details/fda-clears-abivertinib-phase-2-safety-and-efficacy-study.
275. Safety, tolerability and efficacy of nangibotide in mechanically ventilated patients with COVID-19 and features of systemic inflammation. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04429334. 2020 Jun 12; Accessed: July 23, 2020.
276. Can-Fite Submits Investigational New Drug Application to U.S. FDA for COVID-19 Phase II Study. Can-Fite BioPharma. 2020 Jul 27. Available at https://ir.canfite.com/press-releases/detail/917/can-fite-submits-investigational-new-drug-application-to-u-s-fda-for-covid-19-phase-ii-study.
277. LSALT peptide vs placebo to prevent ARDS and acute kidney injury in patients infected with SARS-CoV-2 (COVID-19). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04402957. 2020 Jun 16; Accessed: : July 28, 2020.

278. ReAlta Life Sciences announces U.S. FDA clearance of first investigational new drug application for RLS-0071. ReAlta Life Sciences. 2020 Jul 28. Available at https://realtalifesciences.com/realta-life-sciences-announces-u-s-fda-clearance-of-first-investigational-new-drug-application-for-rls-0071/.
279. Safety and antiviral activity of BLD-2660 in COVID-19 hospitalized subjects. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04334460. 2020 Sep 03; Accessed: September 15, 2020.
280. Enzychem Lifesciences announces FDA acceptance of phase 2 study of EC-18 in preventing acute respiratory distress Syndrome (ARDS) due to COVID-19 pneumonia. Enzychem Lifesciences. 2020 Aug 14. Available at https://www.enzychem.com/enzychem-lifesciences-announces-fda-acceptance-of-phase-2-study-of-ec-18-in-preventing-acute-respiratory-distress-syndrome-ards-due-to-covid-19-pneumonia/.
281. A study of cell therapy in COVID-19 subjects with acute kidney injury who are receiving renal replacement therapy. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04445220. 2020 Aug 13; Accessed: August 19, 2020.
282. BCG Vaccine for Health Care Workers as Defense Against COVID 19 (BADAS). ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04348370. 2020 May 27; Accessed: August 19, 2020.
283. Synthetic cannabinoid drug for COVID-19 approved for phase 1 clinical trials. Forbes. 2020 Aug 20. Available at https://www.forbes.com/sites/emilyearlenbaugh/2020/08/20/synthetic-cannabinoid-drug-for-covid-19-approved-for-phase-1-clinical-trials/#7b9374223329.
284. Intravenous infusion of CAP-1002 in patients with COVID-19 (INSPIRE). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04623671. 2020 Nov 24; Accessed: November 25, 2020.
285. Study of LAU-7b for the treatment of COVID-19 disease in adults (RESOLUTION). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04417257. 2020 Jul 17; Accessed: August 26, 2020.
286. SPI-1005 treatment in severe COVID-19 patients. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04483973. 2020 Jul 23; Accessed: September 14, 2020.
287. Vadadustat for the prevention and treatment of acute respiratory distress syndrome (ARDS) in hospitalized patients with coronavirus disease 2019 (COVID-19). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04478071. 2020 Sep 10; Accessed: September 22, 2020.
288. FSD Pharma begins Phase 2 clinical trial to evaluate FSD201 for the treatment of hospitalized COVID-19 patients. FSD Pharma Inc. 2020 Sep 28. Available at https://www.fsdpharma.com/news/fsd-pharma-begins-phase-2-clinical-trial-to-evaluate-fsd201-for-the-treatment-of-hospitalized-covid-19-patients/.
289. A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of EB05 + SOC vs. placebo + SOC in adult hospitalized patients with moderate to severe COVID-19. ClinicalTrials.gov. Available at

https://www.clinicaltrials.gov/ct2/show/NCT04401475. 2020 Jul 01; Accessed: October 26, 2020.
290. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA. 2020 Nov 12. [Medline]. [Full Text].
291. COVID R&D Alliance launches trial of Amgen, UCB, Takeda drugs. Reuters. 2020 Nov 30. Available at https://www.reuters.com/article/health-coronavirus-treatment-trial/covid-rd-alliance-launches-trial-of-amgen-ucb-takeda-drugs-idUSL1N2I31W4.
292. Hepion Pharmaceuticals announces FDA clearance of IND application for CRV431 for COVID-19. Hepion Pharmaceuticals. 2020 Dec 22. Available at https://hepionpharma.com/news/hepion-pharmaceuticals-announces-fda-clearance-of-ind-application-for-crv431-for-covi/4573734.
293. Study of ensifentrine or placebo delivered via pMDI in hospitalized patients with COVID-19. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04527471. 2020 Dec 14; Accessed: January 14, 2021.
294. Tiziana Life Sciences Announces an Expedited Clinical Development Plan for Its Anti-Interleukin-6-Receptor, a Fully Human Monoclonal Antibody, for the Treatment of COVID-19 Patients. Tiziana Life Sciences. 2021 Aug 04. Available at https://ir.tizianalifesciences.com/news-releases/news-release-details/tiziana-life-sci-plc-expedited-clinical-development-plan.
295. Gilham D, Smith AL, Fu L, Moore DY, Muralidharan A, Reid PM. Bromodomain and extraterminal protein inhibitor, apabetalone (RVX-208), reduces ACE2 expression and attenuates SARS-CoV-2 infection in vitro. bioRxiv. 2021 Mar 11. [Full Text].
296. Bucillamine in treatment of patients with COVID-19. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04504734. 2021 Nov 02; Accessed: December 6, 2021.
297. FDA. Fact sheet for health care providers emergency use authorization (EUA) of casirivimab and imdevimab. United States Food and Drug Administration. Available at https://www.fda.gov/media/143892/download. 2020 Nov 21; Accessed: November 21, 2020.
298. O'Brien MP, Forleo-Neto E, Musser BJ, and the, Covid-19 Phase 3 Prevention Trial Team. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med. 2021 Aug 4. [Medline]. [Full Text].
299. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med. 2020 Dec 17. [Medline]. [Full Text].
300. Regeneron's COVID-19 outpatient trial prospectively demonstrates that REGN-COV2 antibody cocktail significantly reduced virus levels and need for further medical attention. Regeneron. 2020 Oct 28. Available at https://investor.regeneron.com/news-releases/news-release-details/regenerons-covid-19-outpatient-trial-prospectively-demonstrates.
301. New REGEN-COV (casirivimab and imdevimab) data show supportive results in patients hospitalized with COVID-19. Regeneron Pharmaceuticals, Inc. 2021 Sep 30.

Available at https://www.prnewswire.com/news-releases/new-regen-cov-casirivimab-and-imdevimab-data-show-supportive-results-in-patients-hospitalized-with-covid-19-301388370.html.
302. Safety, tolerability, and efficacy of anti-spike (S) SARS-CoV-2 monoclonal antibodies for hospitalized adult patients with COVID-19. ClinicalTrials.gov. Available at https://clinicaltrials.gov/ct2/show/NCT04426695. 2021 Aug 26; Accessed: October62, 2021.
303. Regeneron announces encouraging initial data from COVID-19 antibody cocktail trial in hospitalized patients on low-flow oxygen. PRNewswire. 2020 Dec 29. Available at https://investor.regeneron.com/news-releases/news-release-details/regeneron-announces-encouraging-initial-data-covid-19-antibody.
304. RECOVERY Collaborative Group, Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. medRxiv. 2021 Jun 16. [Full Text].
305. Cathcart AL, Havenar-Daughton C, Lempp FA, Ma D, Schmid M, Agostini ML, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. bioRxiv. 2021 Mar 10. [Full Text].
306. Gupta A, Gonzalez-Rojas Y, Juarez E, and the, COMET-ICE Investigators. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021 Nov 18. 385 (21):1941-1950. [Medline]. [Full Text].
307. Lilly, VIR Biotechnology and GSK announce positive topline data from the phase 2 BLAZE-4 trial evaluating bamlanivimab with VIR-7831 in low-risk adults with COVID-19. VIR Biotechnology. 2021 Mar 29. [Full Text].
308. Dougan M, Nirula A, Azizad M, and the, BLAZE-1 Investigators. Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19. N Engl J Med. 2021 Oct 7. 385 (15):1382-1392. [Medline]. [Full Text].
309. Cohen MS, Nirula A, Mulligan MJ, and the, BLAZE-2 Investigators. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA. 2021 Jul 6. 326 (1):46-55. [Medline]. [Full Text].
310. Evering TH, Daar ES, et al. BRII-196/BRII-198 in the ACTIV-2 study of Outpatient Monoclonal Antibodies and Other Therapies. Presented virtually at IDWeek 2021. September 29-October 3, 2021.
311. Levin MJ, et al. PROVENT: Phase 3 study of efficacy and safety of AZD7442 (tixagevimab/cilgavimab) for pre-exposure prophylaxis of COVID-19 in adults. Presented virtually at IDWeek 2021. September 29-October 3, 2021.
312. AZD7442 reduced risk of developing severe COVID-19 or death in TACKLE Phase III outpatient treatment trial. AstraZeneca. 2021 Oct 11. Available at https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html.
313. Evaluation of ADG20 for the prevention of COVID-19 (EVADE). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04805671. 2021 Nov 02; Accessed: November 29, 2021.

314. Evaluation of ADG20 for the treatment of mild or moderate COVID-19 (STAMP). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04805671. 2021 Nov 05; Accessed: November 29, 2021.
315. Fact Sheet for Health Care Providers - Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients. US Food and Drug Administration. Available at https://www.fda.gov/media/141478/download. 2020 Aug 23; Accessed: August 23, 2020.
316. Korley FK, Durkalski-Mauldin V, Yeatts SD, and the, SIREN-C3PO Investigators. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. N Engl J Med. 2021 Aug 18. [Medline]. [Full Text].
317. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, McQuilten ZK, et al. Effect of Convalescent Plasma on Organ Support-Free Days in Critically Ill Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2021 Oct 4. [Medline].
318. NIH COVID-19 Treatment Guidelines Panel. Statement on the emergency use authorization of convalescent plasma for the treatment of COVID-19. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/. 2021 Apr 21; Accessed: October 6, 2021.
319. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med. 2020 May 21. 382 (21):1969-1973. [Medline]. [Full Text].
320. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: The current state of play. Paediatr Respir Rev. 2020 Sep. 35:43-49. [Medline]. [Full Text].
321. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of Coronavirus Disease 2019. Crit Care Med. 2020 Sep. 48 (9):1358-1364. [Medline]. [Full Text].
322. Katneni UK, Alexaki A, Hunt RC, Schiller T, DiCuccio M, Buehler PW, et al. Coagulopathy and Thrombosis as a Result of Severe COVID-19 Infection: A Microvascular Focus. Thromb Haemost. 2020 Aug 24. [Medline]. [Full Text].
323. Ferguson J, Volk S, Vondracek T, Flanigan J, Chernaik A. Empiric therapeutic anticoagulation and mortality in critically ill patients with respiratory failure from SARS-CoV-2: A retrospective cohort study. J Clin Pharmacol. 2020 Sep 3. [Medline]. [Full Text].
324. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020 Jul 7. 76 (1):122-124. [Medline]. [Full Text].
325. NIH ACTIV-4B COVID-19 outpatient thrombosis prevention trial ends early. Brigham Health. 2021 Jun 22. Available at https://www.brighamandwomens.org/about-bwh/newsroom/press-releases-detail?id=3925.
326. REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC Investigators, Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 4. [Medline]. [Full Text].

327. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 4. [Medline]. [Full Text].
328. Assessing Safety, Hospitalization and Efficacy of rNAPc2 in COVID-19 (ASPEN). ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04655586. 2021 Nov 03; Accessed: December 6, 2021.
329. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar. 579 (7798):270-273. [Medline]. [Full Text].
330. Lopes RD, Macedo AVS, de Barros E Silva PGM, Moll-Bernardes RJ, Feldman A, D'Andréa Saba Arruda G, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)--The BRACE CORONA Trial. Am Heart J. 2020 Aug. 226:49-59. [Medline]. [Full Text].
331. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, et al. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. Circulation. 2020 Mar 21. [Medline]. [Full Text].
332. Fang L, Karakiulakis G, Roth M. Correction to Lancet Respir Med 2020; 8: e21. Lancet Respir Med. 2020 Jun. 8 (6):e54. [Medline]. [Full Text].
333. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005 Aug. 11 (8):875-9. [Medline]. [Full Text].
334. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon S. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 2020 March 30. [Medline]. [Full Text].
335. Ishiyama Y, Gallagher PE, Averill DB, Tallant EA, Brosnihan KB, Ferrario CM. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. Hypertension. 2004 May. 43 (5):970-6. [Medline]. [Full Text].
336. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005 May 24. 111 (20):2605-10. [Medline]. [Full Text].
337. Klimas J, Olvedy M, Ochodnicka-Mackovicova K, Kruzliak P, Cacanyiova S, Kristek F, et al. Perinatally administered losartan augments renal ACE2 expression but not cardiac or renal Mas receptor in spontaneously hypertensive rats. J Cell Mol Med. 2015 Aug. 19 (8):1965-74. [Medline]. [Full Text].
338. Walters TE, Kalman JM, Patel SK, Mearns M, Velkoska E, Burrell LM. Angiotensin converting enzyme 2 activity and human atrial fibrillation: increased plasma angiotensin converting enzyme 2 activity is associated with atrial fibrillation and more advanced left atrial structural remodelling. Europace. 2017 Aug 1. 19 (8):1280-1287. [Medline]. [Full Text].
339. Burchill LJ, Velkoska E, Dean RG, Griggs K, Patel SK, Burrell LM. Combination renin-angiotensin system blockade and angiotensin-converting enzyme 2 in

experimental myocardial infarction: implications for future therapeutic directions. Clin Sci (Lond). 2012 Dec. 123 (11):649-58. [Medline].
340. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. J Card Fail. 2020 May. 26 (5):370. [Medline]. [Full Text].
341. Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JGF, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. Eur Heart J. 2020 May 14. 41 (19):1810-1817. [Medline]. [Full Text].
342. Baral R, Tsampasian V, Debski M, Moran B, Garg P, Clark A, et al. Association Between Renin-Angiotensin-Aldosterone System Inhibitors and Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021 Mar 1. 4 (3):e213594. [Medline]. [Full Text].
343. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015 Oct. 70 (10):984-9. [Medline]. [Full Text].
344. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020 Apr 15. [Medline]. [Full Text].
345. Muniyappa R, Gubbi S. COVID-19 Pandemic, Corona Viruses, and Diabetes Mellitus. Am J Physiol Endocrinol Metab. 2020 Mar 31. [Medline]. [Full Text].
346. DPP4 dipeptidyl peptidase 4. National Center for Biotechnology Information (NCBI). Available at https://www.ncbi.nlm.nih.gov/gene/1803. 2020 Apr 20; Accessed: 2020 Apr 21.
347. FDA. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. US Food and Drug Administration. 2020 Jun 15. Available at https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and.
348. NIH Media Advisory. NIH halts clinical trial of hydroxychloroquine. National Institutes of Health. 2020 Jun 20. Available at https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine.
349. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Feb 4. [Medline].
350. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. [Medline].
351. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial International Journal of Antimicrobial Agents (2020) (prepublication).
352. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb, Sevestre J, et al. Hydroxychloroquine-Azithromycin and COVID-19. Available at

https://www.mediterranee-infection.com/wp-content/uploads/2020/03/COVID-IHU-2-1.pdf. 2020 Mar 30;
353. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection. Med Mal Infect. 2020 Mar 30. [Medline]. [Full Text].
354. Skipper CP, Pastick KA, Engen NW, Bangdiwala AS, Abassi M, Lofgren SM, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med. 2020 Jul 16. [Medline]. [Full Text].
355. NIH begins clinical trial of hydroxychloroquine and azithromycin to treat COVID-19. National Institutes of Health. Available at https://www.nih.gov/news-events/news-releases/nih-begins-clinical-trial-hydroxychloroquine-azithromycin-treat-covid-19. 2020 May 14;
356. A5395: A randomized, double-blind, placebo-controlled trial to evaluate the efficacy of hydroxychloroquine and azithromycin to prevent hospitalization or death in persons with COVID-19. AIDS Clinical Trials Group. Available at https://actgnetwork.org/studies/a5395/. Accessed: 2020 May 15.
357. Abella, BS, Jolkovsky EL, Biney BT, and the Prevention and Treatment of COVID-19 With Hydroxychloroquine (PATCH) Investigators. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers – A randomized clinical trial. JAMA Int Med. 2020 Sep 30. [Full Text].
358. Hydroxychloroquine Post Exposure Prophylaxis for Coronavirus Disease (COVID-19) NCT04318444. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04318444. 2020 Apr 27;
359. Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP) NCT04363450. ClinicalTrials.gov. Available at https://www.clinicaltrials.gov/ct2/show/NCT04363450. 2020 Apr 29;
360. Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HERO-HCQ) NCT04334148. ClinicalTrials.gov. 2020 May 14. Available at https://clinicaltrials.gov/ct2/show/NCT04334148.
361. Rajasingham R, Bangdiwala AS, Nicol MR, Skipper CP, Pastick KA, Axelrod ML, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. Clin Infect Dis. 2020 Oct 17. [Medline]. [Full Text].
362. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. N Engl J Med. 2020 Jun 3. [Medline]. [Full Text].
363. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med. 2012 May 17. 366 (20):1881-90. [Medline]. [Full Text].
364. Simpson TF, Kovacs RJ, Stecker EC. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19. American College of Cardiology; Cardiology Magazine. Available at https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19. 2020 Mar 29; Accessed: April 1, 2020.

365. [Guideline] Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for Drug Interactions on QTc in Exploratory COVID-19 (Coronavirus Disease 2019) Treatment. Circulation. 2020 Apr 8. [Medline]. [Full Text].
366. Borba M, de Almeida Val F, Sampaio VS, Alexandre MA, Melo GC, Brito M, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). MedRxiv. 2020 Apr 11. [Full Text].
367. Lane JCE, Weaver J, Kostka K, Duarte-Salles T, Abrahao MTF, Alghoul H, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv. 2020 Apr 10. [Full Text].
368. [Guideline] NIH. Potential Antiviral Drugs Under Evaluation for the treatment of COVID-19. COVID-19 Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/. 2020 Jun 11; Accessed: June 16, 2020.
369. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial. The Lancet. 2020 Oct 05. [Full Text].
370. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18. [Medline]. [Full Text].
371. Baden LR, Rubin EJ. Covid-19 - The Search for Effective Therapy. N Engl J Med. 2020 Mar 18. [Medline]. [Full Text].
372. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and safety of lopinavir/ritonavir or Arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Med (from Cell Press). 2020 Apr 17. [Full Text].
373. Hung IFN, Lung KC, Tso EYK, Liu R, Chung TWH, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020 May 08. [Full Text].
374. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. Biotechnology & Biotechnological Equipment. 2020. 2020. 34(1):469-74. [Full Text].
375. Chaccour C, Hammann F, Ramón-García S, Rabinovich NR. Ivermectin and Novel Coronavirus Disease (COVID-19): Keeping Rigor in Times of Urgency. Am J Trop Med Hyg. 2020 Apr 16. [Medline]. [Full Text].
376. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. JAMA. 2021 Apr 13. 325 (14):1426-1435. [Medline]. [Full Text].
377. ViralClear halts its phase 2 hospitalized COVID-19 trial. BioSig Technologies. 2020 Oct 26. Available at https://www.biosig.com/news-media/press-releases/detail/234/viralclear-halts-its-phase-2-hospitalized-covid-19-trial.

378. Update on CALAVI phase II trials for Calquence in patients hospitalized with respiratory symptoms of COVID-19. AstraZeneca. 2020 Nov 12. Available at https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/update-on-calavi-phase-ii-trials-for-calquence-in-patients-hospitalised-with-respiratory-symptoms-of-covid-19.html.
379. Incyte Announces Results of Phase 3 RUXCOVID Study of Ruxolitinib (Jakafi) as a Treatment for Patients with COVID-19 Associated Cytokine Storm. Incyte Corp. 2020 Dec 14. [Full Text].
380. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Microbiol Infect. 2020 Jul. 26 (7):917-921. [Medline]. [Full Text].
381. Clemency BM, Varughese R, Gonzalez-Rojas Y, Morse CG, Phipatanakul W, Koster DJ, et al. Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Adolescents and Adults With Symptomatic COVID-19: A Randomized Clinical Trial. JAMA Intern Med. 2021 Nov 22. [Medline].
382. [Guideline] Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19. Mayo Clin Proc. 2020 Apr 07. [Full Text].
383. Mercuro NJ, Yen CF, Shim DJ, Maher TR, McCoy CM, Zimetbaum PJ, et al. Risk of QT Interval Prolongation Associated With Use of Hydroxychloroquine With or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 May 1. [Medline]. [Full Text].
384. Chorin E, Dai M, Shulman E, Wadhwani L, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv. 2020 Apr 03. [Full Text].
385. FDA Combating COVID-19 with Medical Devices. US Food and Drug Administration. Available at https://www.fda.gov/media/136702/download. 2020 Jun 15; Accessed: June 19, 2020.
386. Zhang Q, et al. Cellular nanosponges inhibit SARS-CoV-2 infectivity. Nano Lett. 2020 Jun 17. [Medline]. [Full Text].
387. [Guideline] Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Evaluating and Testing PUI. Centers for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html. March 9, 2020; Accessed: March 18, 2020.
388. [Guideline] Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). CDC. Available at https://www.cdc.gov/coronavirus/2019-nCoV/lab/guidelines-clinical-specimens.html. 2020 Nov 05; Accessed: November 16, 2020.
389. [Guideline] Center for Clinical Standards and Quality/Quality, Safety & Oversight Group. Guidance for Infection Control and Prevention Concerning Coronavirus Disease (COVID-19): FAQs and Considerations for Patient Triage, Placement and

Hospital Discharge. Available at https://www.cms.gov/files/document/qso-20-13-hospitalspdf.pdf-2. March 4, 2020; Accessed: March 4, 2020.
390. Puopolo KM, Hudak ML, Kimberlin DW, Cummings J. Management of Infants Born to Mothers with COVID-19. American Academy of Pediatrics. Available at https://downloads.aap.org/AAP/PDF/COVID%2019%20Initial%20Newborn%20Guidance.pdf. April 2, 2020; Accessed: April 3, 2020.
391. [Guideline] AAP. FAQs: Management of Infants Born to Mothers with Suspected or Confirmed COVID-19. American Academy of Pediatrics. Available at https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/faqs-management-of-infants-born-to-covid-19-mothers/. May 21, 2020; Accessed: May 27, 2020.
392. [Guideline] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. 2021 Mar 05; Accessed: March 12, 2021.
393. [Guideline] Moores LK, Tritschler T, Brosnahan S, Carrier M, Collen JF, Doerschug K, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. Chest. 2020 Jun 2. [Medline]. [Full Text].
394. [Guideline] Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020 May. 18 (5):1023-1026. [Medline]. [Full Text].
395. [Guideline] COVID-19 Treatment Guidelines Panel. Antithrombotic Therapy in Patients with COVID-19. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/. 2021 Feb 11; Accessed: June 28, 2021.
396. Mouffak S, Shubbar Q, Saleh E, El-Awady R. Recent advances in management of COVID-19: A review. Biomed Pharmacother. 2021 Nov. 143:112107. [Medline].