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Pharmacologic Treatment and Management of Coronavirus Disease 2019

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KEYWORDS

• COVID-19 • SARS CoV-2 • Monoclonal antibodies • Corticosteroids • Tocilizumab • Baricitinib • Antivirals

KEY POINTS

- Most patients with mild or moderate COVID-19 recover without treatments, but patients with high risk of progression or patients with severe or critical COVID-19 can benefit from pharmacotherapy.
- Treatments like glucocorticoids, interleukin (IL)-6 inhibitors, and Janus kinase (JAK) inhibitors have shown a mortality benefit in severe or critical COVID-19.
- Treatments like anti-SARS CoV-2 antibodies and direct-acting antivirals have been shown to decrease the need for medically attended visits, hospitalizations or length of hospital stay.
- Assessing severity of COVID-19 and duration of illness is necessary to identify patients who will benefit most from specific therapies.

INTRODUCTION

At the outset of the pandemic, efficacy data for potential treatments were sparse and of low quality. Despite the dynamic demands of the pandemic, it is remarkable how much our understanding of the efficacy and harms of coronavirus disease 2019 (COVID-19) treatment options has evolved in less than 2 years. During these months, pivotal adaptive COVID-19 treatment trials like SOLIDARITY[1] and RECOVERY[2,3] were successfully completed and have been instrumental in guiding treatment recommendations for the management of patients with COVID-19.

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The Infectious Disease Society of America (IDSA) and the National Institutes of Health have produced comprehensive guidelines for the treatment and management of patients with COVID-19.[4,5] The IDSA Guideline has used the GRADE Methodology[58] in the development of their treatment guideline. GRADE (Grading of Recommendations Assessment, Development and Evaluation) provides a framework that allows for frontline clinicians to appreciate the confidence in an estimate of treatment effect in a given patient population and for a particular outcome. The IDSA guidelines use 4 categories of ratings for the quality of evidence: high, moderate, low, and very low; these ratings are based on the certainty of the treatment effect, as well as any methodological concerns or risk of bias within the supporting evidence base. The word "recommend" in the IDSA COVID guideline indicates a strong recommendation, and the word "suggest" indicates a conditional recommendation.

Treatment recommendations are developed around PICO (population, intervention, comparator, outcome) questions. For example, "in hospitalized patients with COVID-19 (population), should hydroxychloroquine (intervention) versus no hydroxychloroquine (comparator) be used"? This question can be applied for various outcomes of COVID-19, like mortality, hospitalization, progression to mechanical ventilation, and serious adverse events.

As a clinician applying treatment recommendations to patients with COVID-19, it is vital to classify the patient's current disease severity (population) because subtle differences in the known benefits and harms (outcomes) of various treatments exist (interventions/comparators). **Fig. 1** displays the spectrum of disease for patients with COVID-19, and certain types of treatments may be more advantageous or harmful at a particular stage of disease. From a mechanistic perspective, early in the infection, when viral burden is high and the host's adaptive immune system has not mounted an

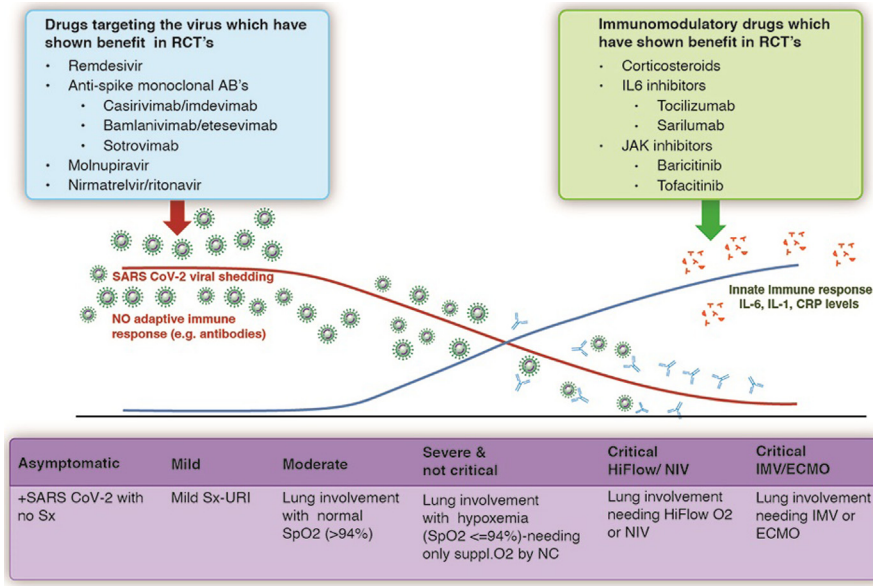

Fig. 1. Plausible mechanisms of action of COVID-19 therapies by disease severity. RCTs, randomized controlled trials; ABs, antibodies; Sx, symptoms; URI, upper respiratory infection; Spo_2, oxygen saturation as measured by pulse oximetry; NC, nasal cannula; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

adequate response, treatments targeting viral replication can be more effective. Examples would be antiviral therapies like remdesivir, molnupiravir, nirmatrelvir/ritonavir, and neutralizing antibody therapies. Like influenza, the earlier the antiviral therapies are administered the more efficacious they likely would be. There may be subsets of patients like immunocompromised patients or patients who have not had an adaptive immune response, with high viral burden even later in the disease process, who may still benefit from antiviral treatments. Treatments like glucocorticoids may also be harmful early in mild or moderate disease.

OTHER CLINICAL CONSIDERATIONS WHEN CHOOSING CORONAVIRUS DISEASE 2019 PHARMACOTHERAPIES

As a treating clinician it is also important to appreciate the contraindications and relative contraindications for COVID-19 treatments as well as the specific criteria in the US Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs). For example, many trials of immunomodulatory agents such as interleukin (IL)-6 or Janus kinase (JAK) inhibitors for autoimmune or hematologic processes excluded patients with active infections, but these are not absolute contraindications to their use except in certain types of infections. Patients with a hypercoagulable state or a history of clots were often excluded from the studies of JAK inhibitors due to the risk of clots; however, many patients with COVID-19 who are severely or critically ill are on prophylactic anticoagulation. It is also important to identify if the patients have other acute diseases that either mimic COVID-19 or present concomitantly with COVID-19. Patients can have a positive result of severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) polymerase chain reaction (PCR) from a nasopharyngeal sample, and present with pulmonary diseases caused by a bacterial pneumonia or pulmonary edema. Patients with COVID-19 can also have pulmonary embolism contributing to their symptoms and hypoxemia. It is important to avoid anchoring bias to COVID-19 and consider other causes. Many of the COVID-19 therapies have an EUA from the US FDA, rather than a full approval, so it is necessary to follow the scope of the authorization for these agents.

Here we provide a review of treatment options by class based on a patient's current clinical stage of disease with a focus on agents that have efficacy demonstrated through well-designed randomized controlled trials (RCTs). In this review, we focus on a few important therapeutic options for the management of patients with COVID-19, and pooled estimates of treatment effect are derived from the IDSA guidelines. **Table 1** is a summary table of treatments available in the United States. Preexposure and postexposure prophylaxis, as well as anticoagulation, are outside the scope of this review and are discussed. Because the evidence behind the guidelines and the guidelines themselves are rapidly being updated, we encourage readers to refer to the continuously updated IDSA and National Institutes of Health guidelines.

MANAGEMENT OF AMBULATORY PATIENTS WITH MILD OR MODERATE CORONAVIRUS DISEASE 2019 WHO ARE AT RISK FOR SEVERE DISEASE

The disease severity for ambulatory patients with COVID-19 can range from asymptomatic to severe disease. Recommendations for ambulatory patients who are asymptomatic or have mild to moderate disease and have risk factors for severe disease should be promptly identified and treated. Mild COVID-19 is when there are clinical features suggestive of upper respiratory tract involvement without features of lung or other end organ involvement. Moderate COVID-19 includes pulmonary involvement without hypoxia. Most patients improve with supportive care at this stage, but patients

Table 1
Currently available coronavirus disease 2019 therapies by disease severity and care location

Care Location and COVID-19 Severity	Pharmacologic Treatments Available in the United States
Ambulatory mild to moderate disease (not hypoxic)	• Casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab, or bebtelovimabfor high-risk patients. • Systemic glucocorticoids have no demonstrated benefit and may harm. • No clear benefit for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.
Hospitalized for mild to moderate COVID-19 (not hypoxic)	• Systemic glucocorticoids have no demonstrated benefit and may harm. • Casirivimab/imdevimab, bamlanivimab/etesevimab, sotrovimab, bebtelovimab: no FDA approval or emergency use authorization for inpatient use. • No clear benefit for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.
Hospitalized for severe, but not critical, COVID-19 (hypoxic needing low-flow supplemental oxygen)	• Glucocorticoids (dexamethasone 6 mg daily for 10 days or until discharge or an equivalent dose of hydrocortisone). • May consider remdesivir. • Tocilizumab or sarilumab in progressive disease & elevated inflammatory makers. • Baricitinib or tofacitinib in patients with elevated inflammatory markers. • No clear benefit for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.
Hospitalized for critically ill COVID-19, needing noninvasive ventilation or high-flow oxygen	• Glucocorticoids (dexamethasone 6 mg daily for 10 days or until discharge or an equivalent dose of hydrocortisone). • Tocilizumab or sarilumab in progressive disease & elevated inflammatory makers. • Baricitinib or tofacitinib in patients with elevated inflammatory markers • No clear benefit for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.
Hospitalized for critically ill COVID-19, needing invasive mechanical ventilation or ECMO	• Glucocorticoids (dexamethasone6 mg daily for 10 days or until discharge or an equivalent dose of hydrocortisone. • Tocilizumab or sarilumab in progressive disease & elevated inflammatory makers. • Baricitinib or tofacitinib in patients with elevated inflammatory markers. • No clear benefit for hydroxychloroquine, azithromycin, Lopinavir/ritonavir and remdesivir. • No clear benefit for convalescent plasma, hydroxychloroquine, azithromycin, lopinavir/ritonavir, or ivermectin.

Abbreviation: ECMO, extracorporeal membrane oxygenation.

with risk factors can progress to more severe or critical disease or death and may benefit from pharmacotherapies. There are no universally accepted clinical prediction rules or risk calculators, but the US FDA EUAs mention a few of these risk factors to consider for treatment with anti-SARS CoV-2 antibodies. More research is needed to identify precise prediction instruments and determinants that both increase and decrease the risk of severe disease and how potentially protective factors like prior infection or vaccination influence risk stratification. Other potential benefits include use of antiviral and antibody therapies in early disease to reduce symptom duration, period of infectivity, and the risk of postacute sequelae of COVID-19, although impact on these outcomes has not been established and is an area of active inquiry.

Certain interventions may provide more benefit and less harm, depending on the patient's severity of disease.

NEUTRALIZING MONOCLONAL ANTIBODY TREATMENTS

These agents interact with the receptor-binding domain of the spike glycoprotein of SARS CoV-2. Neutralizing antibodies directed at SARS-CoV-2 have been derived from convalescent plasma, recombinant approaches using humanized mice, or a combination of the approaches. Modifications to various portions of the antibody can provide advantages that can alter the pharmacokinetics of the various compounds and may be more or less active against potential variants. Bamlanivimab was the first available neutralizing antibody, and it was given FDA EUA status as monotherapy for COVID-19 treatment of those at high risk for severe disease in November 2020. Issuance of the EUA was based on data from the phase 2 BLAZE-1 trial in which bamlanivimab was compared with placebo.[6] Owing to the emergence of viral variants and availability of combination neutralizing antibodies, the US FDA revoked the EUA for bamlanivimab monotherapy on April 16, 2021.

Combining 2 antibodies such as bamlanivimab/etesevimab or casirivimab/imdevimab or developing antibodies that target the highly conserved regions of SARS CoV-2 may help to overcome any decrease in activity due to circulating variants.[7] Similarly, neutralizing antibodies like sotrovimab, which target the highly conserved region of the spike receptor-binding domain, may offer an advantage against circulating variants. Sotrovimab has been shown to neutralize SARS CoV-2 in vitro, including variants of concern.[8]

In ambulatory patients with mild to moderate COVID-19 who are at high risk for progression to severe disease, early intervention with neutralizing monoclonal antibody treatments has been shown to reduce mortality,[9] progression to hospitalization,[9–11] and severe disease.[11] Three neutralizing monoclonal antibody treatments, bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab have been granted EUA for the treatment of COVID-19 in those patients who are at high risk for severe disease. The IDSA treatment guidelines suggest using these agents rather than no neutralizing monoclonal antibody treatment in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease[4]; however, it is important to ensure that the neutralizing antibodies are active against the locally circulating variants. **Fig. 2** lists the risk factors for the progression to severe COVID-19 or hospitalization per US FDA EUA.

Neutralizing monoclonal antibody treatments are well tolerated; however, these agents require an intravenous infusion or other parenteral route of injection, and monitoring for 1 hour postadministration. The Centers for Disease Control and Prevention recommends that those receiving neutralizing monoclonal antibodies should wait to receive a COVID vaccine for at least 90 days after administration.[12]

The following medical conditions or other factors may place adults and pediatric patients (age 12–17 y and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥65 y of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12–17, have BMI ≥85th percentile for their age and gender based on CDC growth charts
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19])

Fig. 2. Risk factors and conditions placing adults and pediatric patients at higher risk for progression to severe COVID-19 per FDA EUA.

ANTIVIRAL AGENTS FOR AMBULATORY PATIENTS WITH MILD OR MODERATE CORONAVIRUS DISEASE 2019

In late 2021, several oral antiviral agents were authorized by the US FDA. Logistical challenges associated with infusion of neutralizing antibody treatments may be lessened with the availability of easier-to-administer oral antiviral agents.

Molnupiravir

Molnupiravir is an oral antiviral that targets the genetic machinery that is responsible for SARS COV-2 viral replication. Molnupiravir is an oral prodrug that is converted to its active form and acts as a substrate for RNA-dependent RNA polymerase. After it is incorporated into the viral RNA, serial mutations develop, resulting in a virus that is less fit for ongoing viral replication.[13] In the MOVe-OUT trial, patients at risk for severe COVID-19 were randomized to molnupiravir or placebo. In an interim analysis, patients receiving molnupiravir had a lower risk of hospitalization or death through day 29, compared with placebo (relative risk, 0.52; 95% confidence interval [CI], 0.33, 0.80)[14]; however, in the final results, the benefits of molnupiravir were diminished. Mortality was lower in patients receiving molnupiravir (RR, 0.11; 95% CI, 0.01, 0.86); however, mortality events were sparse.[15] Molnupiravir was granted US FDA EUA on December 23, 2021, for the treatment of patients with mild to moderate COVID-19 who are at high risk for progression to severe disease when there are no other alternative COVID-19 treatments available.[16] Molnupiravir should not be used in pregnant individuals due to evidence of fetal harm in animal studies.[17] Molnupiravir must be initiated within 5 days of symptom onset.

Nirmatrelvir/Ritonavir

Nirmatrelvir/ritonavir (Paxlovid), a combination of a novel SARS CoV-2 protease inhibitor, nirmatrelvir, and low dose of the human immunodeficiency virus protease

ritonavir, used as a pharmacokinetic booster, was granted US FDA EUA on December 22, 2021.[18] Data for authorization are based on results from the EPIC-HR study, which was a randomized trial of nirmatrelvir/ritonavir compared with placebo in nonhospitalized adult patients with COVID-19 at high risk for severe disease. Nirmatrelvir/ritonavir reduced COVID-19-related hospitalization compared with placebo (RR, 0.12; 95% CI, 0.06, 0.26). Similarly, there were no deaths in those who received nirmatrelvir/ritonavir, whereas there were 12 deaths in the placebo group.[19] Given the use of ritonavir as a boosting agent, there are significant drug interactions even with short-course therapy that need careful management, specifically with drugs that are metabolized by CYP3A4. Nirmatrelvir also requires renal dose adjustment in those with moderate renal impairment and is not recommended in those with severe renal impairment.

Remdesivir

Remdesivir may be considered in ambulatory patients with mild to moderate COVID-19 who are at risk for progression to severe disease or death, but it should be initiated within 7 days of symptom onset. In the PINETREE trial, treatment with remdesivir for 3 days, compared with placebo in ambulatory patients showed a reduction in hospitalizations (hazard ratio [HR], 0.28; 95% CI, 0.1, 0.75) and COVID-19-related medically attended visits though day 28 (HR, 0.19; 95% CI, 0.07, 0.56).[20] Administering 3 consecutive days of infusions has significant resource and access challenges but should be considered for high-risk populations if more accessible alternatives are not available.

REPURPOSED TREATMENTS

Fluvoxamine

Selective serotonin reuptake inhibitors (SSRIs) may play a role in systemic inflammation given their affinity for the sigma-1 receptor. Fluvoxamine has been shown to have the highest affinity for these receptors compared with other SSRIs,[21] and inhibition of sigma-1 receptors by fluvoxamine resulted in cytokine release in preclinical models of bacterial infection.[22] SSRIs also have been shown to decrease platelet aggregation and neutrophil activation,[23,24] which may mitigate inflammatory and thrombotic events related to COVID-19. In vitro models suggest that fluvoxamine has also demonstrated enhanced viral endocytosis of the SARS CoV-2 spike protein.[25]

Two RCTs have evaluated the SSRI fluvoxamine in the management of COVID-19 in ambulatory patients with a diagnostic test positive for SARS CoV-2 infection.[26,27] The 2 trials compared fluvoxamine 100 mg either 2 or 3 times per day with placebo. Both trials reported on mortality by day 28 (IDSA guidelines pooled relative risk [2 studies]; RR, 0.69; 95% CI, 0.38, 1.27; low certainty of evidence) and hospitalization by day 28 (IDSA guidelines pooled relative risk [2 studies]; RR, 0.75; 95% CI. 0.57, 0.99; low certainty of evidence). The primary outcome of the TOGETHER trial was a composite outcome of a prolonged emergency room visit or hospitalization through day 28. In the composite outcome, patients who received fluvoxamine had a lower relative risk of emergency room visit/hospitalization compared with placebo (RR, 0.68; 95% CI, 0.52, 0.88); however, the difference in the composite outcome was largely driven by emergency room visits lasting greater than 6 hours. Given the resource constraints in Brazil during the time of the TOGETHER study, it is unclear if these results would be generalizable to other settings. STOP-COVID 2 was a contactless, randomized trial in outpatients with SARS CoV-2 that compared fluvoxamine with placebo that was stopped prematurely for futility when fluvoxamine was no different from placebo in the outcome of clinical deterioration. In addition, it became difficult to enroll in this study with the widespread availability of vaccines and outpatient monoclonal antibodies.[28]

WHAT NOT TO USE IN AMBULATORY PATIENTS WITH MILD OR MODERATE CORONAVIRUS DISEASE 2019

Hydroxychloroquine, azithromycin, and lopinavir/ritonavir have not shown evidence of benefit in RCTs.[4,29] Although there are several reported studies evaluating ivermectin in ambulatory patients with COVID-19, there does not seem to be any meaningful benefit on mortality or progression to severe disease.[4] There is a need for well-done clinical trials to evaluate ivermectin's utility for the treatment of COVID-19, and some of the early reports showing benefit have since been retracted.[30] Use of systemic glucocorticoids in mild to moderate COVID-19 may be harmful. Although the RECOVERY trial was not done in ambulatory patients, and was conducted in hospitalized patients, it demonstrated a trend to increase mortality when used in patients with mild to moderate COVID-19 (RR, 1.19; 95% CI, 0.92, 1.55).[3]

PHARMACOLOGIC TREATMENT OF PATIENTS HOSPITALIZED FOR MILD OR MODERATE CORONAVIRUS DISEASE 2019

Neutralizing Monoclonal Antibody Treatments

The US FDA has not authorized the neutralizing monoclonal antibody treatments for patients admitted to the hospital for COVID-19. The ACTIV-3 study was an early trial of bamlanivimab for the management of hospitalized patients with COVID-19.[31] In this trial, a single dose of bamlanivimab 7000 mg was compared with placebo in hospitalized patients who were positive for SARS CoV-2 who had a duration of illness less than or equal to 12 days. In this trial, more than 50% of patients in each group were on supplemental oxygen at baseline. Enrollment of this trial was stopped prematurely when the prespecified futility criteria were met and data were censored on October 26, 2020. Patients receiving bamlanivimab had a higher risk of mortality compared with those who did not receive bamlanivimab (HR, 2.00; 95% CI, 0.67, 5.99). The IDSA guideline panel has strongly recommended against the use of bamlanivimab in hospitalized patients based on the lack of clinical benefit demonstrated.[4] To date, EUAs for all neutralizing antibodies have excluded patients who are hospitalized due to COVID-19, who require oxygen therapy, or who require an increase in baseline oxygen flow due to COVID-19.

In the RECOVERY trial, hospitalized patients with COVID-19 were randomized to a single dose of casirivimab/imdevimab or usual care. In the overall population, there was no mortality benefit at 28 days; however, a prespecified analysis done before unblinding tested the hypothesis that casirivimab/imdevimab would be more beneficial in patients who tested negative for SARS CoV-2 antibodies. In this analysis, in seronegative patients, casirivimab/imdevimab conferred a mortality benefit compared with standard of care (RR, 0.80; 95% CI, 0.70, 0.91).[32] Two subsequent arms of the ACTIV-3 study, including sotrovimab or Brii-196 and Brii-198 were also stopped when futility criteria were met, and there was no clear signal toward benefit for patients in either of these arms who tested negative for SARS-CoV-2 antibodies at the time of randomization.[31] At present, no neutralizing monoclonal antibodies have EUA or US FDA approval for patients hospitalized due to COVID or with severe COVID.

Convalescent Plasma

Convalescent plasma has been used as a treatment of COVID-19 since the early days of the pandemic; it works similar to neutralizing antibodies as a passive immunotherapy, where naturally derived antibodies from the convalescent donor infused into an infected patient may inhibit viral entry into cells or assist in viral phagocytosis or antibody-dependent cellular cytotoxicity.

RCTs in hospitalized patients have demonstrated that convalescent plasma has no effect on mortality compared with no treatment (IDSA guidelines pooled relative risk [18 studies]: RR, 0.98; 95% CI, 0.93, 1.03; moderate certainty of evidence). In hospitalized patients who receive convalescent plasma compared with those who do not, data suggest a worrying trend toward an increase in the need for mechanical ventilation ([4 studies]; RR, 1.10; 95% CI, 0.94, 1.29; low certainty of evidence) and an increase in the risk of adverse events ([11 studies], RR, 1.08; 95% CI, 0.94, 1.26).

PHARMACOLOGIC TREATMENT OF SEVERE CORONAVIRUS DISEASE 2019

Patients with severe COVID-19 are those who have pulmonary disease with hypoxia on room air needing treatment with low-flow oxygen. Most existing criteria for trials consider an oxygen saturation as measured by pulse oximetry level less than 94% or 90% and tachypnea (respiratory rate >30) as severe COVID-19. Such criteria help standardize classification in trials, but by no means do they capture the complexity of COVID-19 severity, so clinical judgment should supplement such criteria.

Certain patients develop proinflammatory state characterized by a clinical worsening approximately 7 to 10 days after onset of symptoms. This worsening can be characterized by increasing oxygen requirements and the development of acute respiratory distress syndrome as well as symptoms of hypoperfusion, which may result in progressive organ failure, and complications may involve multiple organ systems (see Winkler and colleagues' article, "Infection Prevention and Control of SARS-CoV-2 In Healthcare Settings," in this issue). Typically, this syndrome is marked by increasing systemic markers of inflammation like C-reactive protein (CRP), D-dimer, ferritin, as well as proinflammatory cytokines.[33,34]

Antivirals

Remdesivir may be considered in patients hospitalized with severe COVID-19, because in the trial ACCT-1 it showed early recovery or time to discharge. However, it did not show a mortality benefit based on a pooled analysis of 3 studies by the IDSA guideline panel (RR, 0.92; 95% CI, 0.77, 1.10).[35–37] Unfortunately, given the varied outcomes of these trials pooling of nonmortal events like clinical improvement was not possible; however, there was a trend toward greater clinical improvement at day 28[37] and reduced need for mechanical ventilation[36] in patients receiving remdesivir.

Remdesivir is solubilized in a vehicle that is renally eliminated, and remdesivir is not recommended for patients with an estimated glomerular filtration rate of less than 30 mL/min. Case series are available to support the use in creatinine clearance less than 30 mL/min[38–40]; however, pharmacovigilance reports provide evidence for adverse renal outcomes,[41,42] so providers must assess the risk versus benefit of remdesivir use and consultation with pharmacy colleagues is recommended. Transaminase elevations may occur with remdesivir, and clinicians should consider discontinuing use if alanine aminotransferase levels increase to greater than 10 times the upper limit of normal.

Glucocorticoids

Glucocorticoids, especially dexamethasone, have demonstrated a mortality benefit, and their use is recommended by the IDSA guidelines for severe or critical illness. In the RECOVERY trial,[3] patients were randomized with dexamethasone 6 mg daily for 10 days or usual care. Patients receiving dexamethasone had a lower

risk of death (RR, 0.83; 95% CI, 0.74, 0.92) and were more likely to be discharged from the hospital through day 28 (RR, 1.11; 95% CI, 1.04, 1.19). Glucocorticoids are generally well tolerated; however, patients may experience significant hyperglycemia.

Interleukin-6 antagonists

Several agents have been studied to attempt to reduce the impact of the inflammatory cascade on disease course. Tocilizumab is the most frequently studied IL-6 antagonist in RCTs. To date there are 8 RCTs evaluating tocilizumab compared with no tocilizumab in the management of COVID-19. Although enrollment criteria for these studies varied, studies included hospitalized patients with evidence of pneumonia or severe disease. In the 8 randomized trials, there is a trend toward reduced mortality at day 28 in those who receive tocilizumab compared with no tocilizumab (IDSA guidelines pooled relative risk [8 studies] RR, 0.91, 95% CI, 0.79, 1.04; moderate certainty of evidence). Two studies that seem to show the largest effect on the reduction of mortality included patients who received tocilizumab around the time of an escalation in their oxygen requirements[43,44]; this may indicate that the timing of tocilizumab therapy is an important factor; however, this needs to be evaluated a priori in clinical trials. After pooling of all the RCTs, patients receiving tocilizumab are less likely to develop clinical deterioration, which was characterized by progression to mechanical ventilation or death in most of the trials (IDSA guidelines pooled relative risk [7 studies]; RR, 0.83, 95% CI, 0.77, 0.89; moderate certainty of evidence).

Unfortunately, there have been shortages of tocilizumab, leading frontline clinicians to look for alternative agents. Sarilumab is another IL-6 inhibitor that is being evaluated for the management of severe COVID-19. The IDSA guidelines suggest the use of sarilumab in those who would otherwise qualify for tocilizumab in addition to standard of care, rather than standard of care alone, when tocilizumab is not available. Data from 3 RCTs and network meta-analysis support this recommendation.[43,45–47]

Janus Kinase Inhibitors

JAK are a group of kinases expressed on many cell surfaces that mediate cytokine signaling. JAK1 and JAK2 inhibitors have been developed and used in inflammatory conditions such as rheumatoid arthritis and ulcerative colitis. The most studied JAK inhibitor in the management of COVID-19 is baricitinib. In the ACTT-2 trial,[48] baricitinib combined with remdesivir was compared with remdesivir with placebo. Notably, study participants were prohibited from receiving glucocorticoids for COVID-19. These data have limited applicability given the widespread use of glucocorticoids in the management of severe COVID-19; however, this study provides guidance into treatment options for those in whom glucocorticoids are contraindicated.

In a large RCT, the COV-BARRIER trial,[49] patients with severe COVID-19 and elevated inflammatory markers were randomized to receive renally dosed baricitinib or no baricitinib. Mortality at day 60 was lower in those receiving baricitinib compared with no baricitinib (HR, 0.62; 95% CI, 0.47–0.83; moderate certainty of evidence). Of note, more than two-thirds of study participants received glucocorticoids.

Tofacitinib has also been evaluated in the STOP-COVID trial in which it was compared with placebo in recently hospitalized patients with PCR-confirmed COVID-19 pneumonia.[50] In this trial, patients receiving tofacitinib had a lower risk of a composite end point of death or respiratory failure at 28 days, compared with participants who did not receive tofacitinib (RR, 0.63; 95% CI, 0.41, 0.97). Owing to the limited number of mortal events, one cannot exclude a beneficial or harmful effect on mortality (RR, 0.49; 95% CI, 0.15, 1.63). Similarly, the study was not able to exclude

a beneficial or harmful effect on progression to mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (RR, 0.25; 95% CI, 0.03, 2.20). Participants receiving tofacitinib experienced numerically more serious adverse events by day 28. Unfortunately, this study excluded patients with an immunosuppressive condition so the results should not be generalized to that population which is at risk for severe COVID-19. In addition, the results from the COV-BARRIER and STOP-COVID trials should not be generalized to other JAK inhibitors, such as ruxolitinib, because currently available data do not suggest a clinical benefit.[51,52]

The US FDA has issued a drug safety communication for tofacitinib after the review of a large, randomized safety trial. Their results indicated an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death when tofacitinib is used for ulcerative colitis or arthritis. Given the shared mechanism of action, the US FDA broadened its warnings to include other agents used for rheumatoid arthritis and include baricitinib and upadacitinib.[53]

Baricitinib requires renal dose adjustment; see **Table 2** for dosing.

PHARMACOLOGIC TREATMENT OF PATIENTS WITH CORONAVIRUS DISEASE 2019 NEEDING NONINVASIVE VENTILATION OR HIGH-FLOW OXYGEN

This severity of critically ill patients requires more ventilator or oxygenation support, with either high-flow oxygen or noninvasive ventilation. High-flow oxygen therapy involves delivery of oxygen via special devices at rates up to 10 to 15 L/min.

We strongly recommend systemic glucocorticoids in critically ill patients with COVID-19 because they have shown the highest 28-day mortality benefit when used in this subpopulation (odds ratio [OR], 0.66; 95% CI, 0.54; 0.82).[54] In critically ill patients, dexamethasone 6 mg daily for 10 days is preferred, but doses up to 20 mg daily can be used if indicated for other reasons. Hydrocortisone 50 mg administered intravenously every 6 hours is an alternative that can also be considered. Safety data in critically ill patients is reassuring.[47]

In addition to glucocorticoids, we recommend using either IL-6 inhibitors (tocilizumab preferred over sarilumab) or JAK inhibitors (baricitinib preferred over tofacitinib) in those patients who have elevated levels of inflammatory markers like CRP. The trials done so far have not identified specific subpopulations of critically ill patients already being treated with corticosteroids that would benefit with additional treatment with IL-6 or JAK inhibitors.

PHARMACOLOGIC TREATMENT OF PATIENTS WITH CORONAVIRUS DISEASE 2019 NEEDING INVASIVE MECHANICAL VENTILATION OR EXTRACORPOREAL MEMBRANE OXYGENATION

Glucocorticoids

The IDSA guidelines recommend dexamethasone rather than no dexamethasone in critically ill patients with COVID-19. Data supporting this recommendation is based on a systematic review of 7 RCTs that demonstrated a reduction in the odds of mortality in patients treated with glucocorticoids compared with those not treated with glucocorticoids (OR, 0.66; 95% CI, 0.54, 0.82). In addition, patients who received glucocorticoids were more likely to be discharged from the hospital through day 28, compared with those who did not receive glucocorticoids (RR, 1.11; 95% CI: 1.04, 1.19).

Interleukin-6 Inhibitors

To date, there are no randomized trials specifically comparing IL-6 inhibitors with not using IL-6 inhibitors in those on mechanical ventilation and/or ECMO; however,

Table 2
Renal dosing baricitinib

eGFR Range	Adults and Pediatric Patients 9 y and Older	Pediatric Patients 2–9 y
eGFR ≥ 60 mL/	4 mg once daily	2 mg once daily
eGFR 30 to < 60 mL/min	2 mg once daily	1 mg once daily
eGFR 15 to < 30 mL/min	1 mg once daily	Not recommended
eGFR < 15	Not recommended	Not recommended

several trials included patients on mechanical ventilation at baseline[43,44,55,56] and many studies allowed for patients to receive glucocorticoids for COVID-19. The IDSA guidelines suggest the use of tocilizumab in addition to the standard of care, rather than standard of care alone. Systemic inflammatory markers are often elevated in critically ill patients with COVID-19; however, there is no randomized trial data to demonstrate a specific cutoff for CRP that would indicate the appropriate patient for tocilizumab. In RECOVERY, patients were required to have a CRP of 75 mg/L or greater to be included in the IL-6 arm.

Janus Kinase Inhibitors

The role of baricitinib in critically ill patients on invasive mechanical ventilation or ECMO was evaluated in an addendum to the COV-Barrier study.[57] In this small trial with about 50 patients per arm, participants who were on invasive mechanical ventilation or ECMO and at least 1 elevated inflammatory marker were randomized 1:1 to receive baricitinib or standard of care. In this study, there was a reduction in the 60-day mortality rate in those who received baricitinib compared with no baricitinib (RR, 0.56; 95% CI, 0.47, 0.97).

Antivirals

The IDSA guideline does not suggest the use of remdesivir in patients with COVID-19 who are critically ill because the subgroup analysis of ACCT-1 failed to demonstrate a reduction in mortality (RR, 1.23; 95% CI, 0.99, 1.53) in mechanically ventilated patients.[36] Results also failed to demonstrate a beneficial effect of remdesivir on time to clinical recovery (HR, 0.98; 95% CI, 0.70, 1.36).

SUMMARY

It is important for frontline clinicians managing patients with COVID-19 to evaluate the setting as well as the severity of illness for each patient. Agile clinical guidelines are available to inform clinicians about place in therapy for various treatment options. Rigorous guideline methodologies, like GRADE, can be applied in the setting of rapidly emerging and evolving literature to support clinicians and guide decision making.

CLINICS CARE POINTS

- Treating providers must assess each patient's severity of COVID-19 and apply the treatment guidelines based on the clinical severity. Treatments directed at ambulatory patients with COVID-19 are generally recommended for those who are at high risk for progression to severe disease, death, or hospitalization.

- Most patients with mild to moderate disease without risk factors for progression to severe disease will improve without COVID-19 pharmacotherapy.
- The efficacy of neutralizing monoclonal antibodies demonstrated in clinical trials may not be equivalent to the overall effectiveness in real-life settings due to the emergence of circulating variants with reduced susceptibility.
- The ease of use of the oral antivirals may be limited by clinically significant drug interactions with nirmatrelvir/ritonavir and due to reproductive health concerns with molnupiravir.
- Patients with severe COVID-19 appear to benefit from glucocorticoids, baricitinib, interleukin-6 inhibitors, and remdesivir; however additional studies are needed to determine the optimal timing and combination of these agents.

DISCLOSURE

A. H. Shumaker and A. Bhimraj: The authors have nothing to disclose.

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