COVID-19 Therapeutics: Making Sense of It All

Lolade S. Bakare, PharmD
John M. Allen, PharmD, BCPS, BCCCP

Coronavirus disease 2019 (COVID-19) is a global pandemic with over 9.1 million laboratory-confirmed cases and more than 473 000 deaths reported worldwide since first being identified in China in December 2019.[1] In the United States, current projections indicate that the death toll will exceed 180 000 by October 2020.[2] COVID-19 is caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although most patients with COVID-19 recover without complications, a unique subset of patients develop severe disease. Recent data suggest that patients with severe COVID-19 account for only 6% to 15% of all cases but make up approximately 60% of all intensive care unit (ICU) admissions for the disease.[3,4] Complications of COVID-19 include acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure. As of June 2020, there were no US Food and Drug Administration (FDA)–approved drugs for the treatment of COVID-19. Clinical practice guidelines for the management of COVID-19 are available and include critical care–specific guidance yet are limited by the lack of robust research.[5-7] Given the unique and nearly unparalleled impact of COVID-19, particularly in the ICU, the rapid search for therapeutic agents has involved reinvigorated research efforts related to investigational drugs considered in previous viral epidemics such as Ebola and SARS and the repurposing of currently FDA-approved drugs for other indications. In this column, we review selected drug therapies currently used in the treatment of COVID-19, discuss the rationale for their use, and provide recommendations on their potential application in clinical practice. A summary of drugs commonly used in COVID-19 treatment is presented in Table 1, and current clinical practice guideline recommendations are outlined in Table 2.

Investigational Drugs: Remdesivir

Remdesivir is an investigational antiviral agent that acts as a nucleoside RNA polymerase inhibitor, ultimately decreasing viral replication. Remdesivir was initially evaluated as an antiviral for the treatment of Ebola virus.[8-10] Remdesivir has demonstrated in vitro activity against SARS-CoV-2. When they were published in March 2020, the Surviving Sepsis Campaign guidelines on the management of critically ill patients with COVID-19 indicated that there was insufficient evidence to make recommendations for remdesivir use in critically ill patients with COVID-19.[7] However, since the publication of those guidelines, multiple remdesivir studies have been reported. In the first randomized, placebo-controlled trial evaluating remdesivir in hospitalized adult patients with severe COVID-19, Wang and colleagues[11] examined 237 patients at 10 hospitals in

Lolade S. Bakare is PGY-1 Pharmacy Resident, Cleveland Clinic Martin Health, Stuart, Florida.

John M. Allen is Clinical Assistant Professor, Department of Pharmacotherapy and Translational Research, College of Pharmacy, University of Florida, 6550 Sanger Rd, Ste 420G, Orlando, FL 32827 (john.allen @cop.ufl.edu).

Table 1: Drugs Commonly Used for Treating COVID-19

Drug	Proposed COVID-19 Mechanism	Proposed COVID-19 Dosing	Adverse Drug Events	Comments
Remdesivir	Decreased SARS-CoV-2 replication	200 mg IV on day 1, then 100 mg IV daily for up to 10 d	Elevated liver enzymes, infusion-related reactions	Avoid use if baseline ALT concentrations ≥5x normal. Discontinue use if ALT concentrations ≥5x normal OR signs/symptoms of liver dysfunction during treatment.
Dexamethasone	Reduced cytokine and acute phase reactant inflammatory processes in cytokine storm	6 mg/d daily IV or orally for up to 10 d	Hyperglycemia, secondary bacterial infection, nausea, vomiting, increased appetite	Use is only recommended in patients with severe COVID-19 requiring supplemental oxygen; use is not recommended in patients with mild to moderate disease.
Tocilizumab	Reduced cytokine and acute phase reactant inflammatory processes in cytokine storm	8 mg/kg, generally 400 mg IV, maximum dose 800 mg IV	Boxed warning for serious active TB and opportunistic infections, elevated hepatic enzymes (ALT, AST); increased cholesterol, lipids, and triglycerides; neutropenia; infusion and injection site reactions	Infuse over 1 h. Monitor liver function tests and lipids. Screen patients for TB before initiation.
Lopinavir/ritonavir	Decrease viral replication via reduced viral protein production	Lopinavir 400 mg and ritonavir 100 mg orally twice daily for 10-14 d	Skin rash, lipid abnormalities, GI issues (nausea, vomiting, abdominal pain, diarrhea, dysgeusia), upper and lower respiratory tract and skin infections	Consider avoiding in patients with HIV because of potential resistance. Monitor lipids.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; GI, gastrointestinal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TB, tuberculosis.

Wuhan, Hubei, China. Patients were treated for 10 days and randomized to receive remdesivir 200 mg on day 1, followed by 100 mg on days 2 through 10, or placebo. Eligible patients had laboratory-confirmed SARS-CoV-2 infection, pneumonia confirmed by chest imaging, an oxygen saturation (SpO_2) of 94% or lower while breathing room air or a ratio of Pao_2 to fraction of inspired oxygen (FiO_2) of 300 or less, and a symptom onset of within 12 days. Concomitant COVID-19 treatments were allowed. Notable exclusion criteria were need for renal replacement therapy and liver cirrhosis. Among all enrolled patients, the median time from symptom onset to starting study treatment was 10 days. The primary study outcome, time to clinical improvement, was not significantly different in the remdesivir

Table 2: Clinical Practice Guideline Recommendations for the Use of Various Drugs in the Management of COVID-19

Topic	US NIH[5]	SSC[7]	IDSA[6]
Intended patient population	All patients with COVID-19; includes critical care–specific recommendations	Critically ill adult patients with COVID-19	All patients with COVID-19; includes critical care–specific recommendations
Remdesivir	**Severe COVID-19** Recommended in patients hospitalized with severe COVID-19[a] **Mild to moderate COVID-19** Insufficient data to recommend for or against remdesivir	Insufficient evidence to provide recommendations	**Patients with severe COVID-19[a] on supplemental oxygen** Treatment for 5 d **Patients with severe COVID-19[a] on mechanical ventilation or ECMO** Treatment for 10 d
HCQ/CQ with or without azithromycin	**HCQ/CQ** Recommends against the use of CQ or HCQ, except in a clinical trial **HCQ plus azithromycin** Recommends against the use, except in the context of a clinical trial	Insufficient evidence to provide recommendations	**HCQ/CQ** Recommended only in the context of a clinical trial **HCQ/CQ with azithromycin** Suggests against use outside of the context of a clinical trial
Lopinavir/ritonavir	Routine use not recommended, except in the context of a clinical trial	Routine use not recommended	Recommended only in the context of a clinical trial
Tocilizumab	Insufficient data to recommend either for or against use	Insufficient evidence to provide recommendation	Recommended only in the context of a clinical trial
Antithrombotics	**VTE prophylaxis** Routine use is recommended per the standard of care for other hospitalized adults **Increased VTE prophylaxis dosing** Insufficient data to recommend for or against use outside the setting of a clinical trial **tPA** Insufficient data to recommend for or against use outside the setting of a clinical trial	No recommendations provided	No recommendations provided
Corticosteroids	**Patients on mechanical ventilation or requiring supplemental oxygen** Dexamethasone (6 mg/d for up to 10 d) **Patients not requiring supplemental oxygen** Dexamethasone is not recommended	**Respiratory failure without ARDS** Routine use not recommended **Respiratory failure with ARDS** Systemic corticosteroids recommended **Refractory shock** Low-dose corticosteroid therapy recommended	**Respiratory failure without ARDS** Routine use not recommended **Respiratory failure with ARDS** Recommended only in the context of a clinical trial **Refractory shock** No recommendation provided

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CQ, chloroquine; ECMO, extracorporeal membrane oxygenation; HCQ, hydroxychloroquine; IDSA, Infectious Diseases Society of America; NIH, National Institutes of Health; SSC, Surviving Sepsis Campaign; tPA, tissue plasminogen activator; VTE, venous thromboembolism.
[a] Severe COVID-19 was defined as oxygen saturation of 94% or less, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.

group compared with the placebo group (21 vs 23 days; hazard ratio [HR], 1.23; 95% CI, 0.87-1.75).[11] Day 28 mortality was also similar between the treatment groups (14% vs 13%; difference, 1.1 percentage point [95% CI, –8.1 to 10.3]). The rate of adverse events was also similar in the remdesivir and placebo groups (66% vs 64%, *P* value not reported). Of these, most adverse events were minor in severity and did not require drug discontinuation. Commonly reported adverse events in the remdesivir group were constipation (14%), hypoalbuminemia (13%), hypokalemia (12%), and increased aspartate aminotransferase (5%). The results reported by Wang and colleagues[11] suggest that remdesivir use was not associated with reduced time to clinical improvement and gave clinicians pause when considering the potential role of remdesivir.

These study results, however, were in stark contrast to those of an ongoing US National Institutes of Health Adaptive COVID-19 Treatment Trial (ACTT).[12] This study is an adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents, including remdesivir, in hospitalized adults diagnosed with COVID-19. The ACTT used similar remdesivir dosing as Wang and colleagues,[11] allowing remdesivir to be used for up to 10 days.[12] In this study, 1059 patients were randomized to receive remdesivir or placebo. Remdesivir was associated with an improved median time to recovery as compared with placebo (11 vs 15 days, *P* < .001). These positive results appear to be driven by those with moderate severity of illness (ie, requiring supplement oxygen), as there was no difference observed in patients with a lower (ie, not receiving oxygen), or higher severity of illness (ie, requiring mechanical ventilation). These results provide a framework to identify specific COVID-19 patients who are most likely to benefit from remdesivir. The 14-day mortality rate did not differ significantly between the 2 treatment groups (HR, 0.70; 95% CI, 0.47-1.04).[13] These developments suggest a potential role for remdesivir to reduce the time to clinical improvement, which may be considered a clinically relevant end point, as a shorter time to clinical improvement may be a surrogate for a reduced burden on the health care system. On the basis of the results from the ACTT, on May 1, 2020, the FDA granted an Emergency Use Authorization (EUA) to remdesivir for the treatment of suspected or laboratory-confirmed severe COVID-19. Severe COVID-19 was defined as an SpO_2 of 94% or less while breathing room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. Details including specific hospitals and quantity of remdesivir will be controlled by the state health departments, and the drug will be distributed only by authorized wholesalers.[14] Further studies are underway investigating the potential benefit of using remdesivir in combination with other COVID-19 treatments.

Remdesivir is not recommended for patients with liver enzyme levels greater than 5 times the upper limit of normal or signs and symptoms of liver failure owing to potential drug-induced hepatotoxicity. Remdesivir is also not recommended for patients with a creatinine clearance less than 30 mL/min owing to the potential for accumulation of the excipient sulfobutylether-β-cyclodextrin in patients with renal dysfunction. Clinical practice guidelines from the National Institutes of Health recommend remdesivir only for patients with severe COVID-19.[5] At present, remdesivir represents the first drug for which robust research methods have demonstrated possible clinical benefits such as faster time to clinical recovery in patients with severe COVID-19. It remains to be elucidated if remdesivir is useful in patients with less severe disease, what the optimal timing of its initiation is, and whether shorter courses of therapy are beneficial.

Repurposed Drugs
Chloroquine or Hydroxychloroquine +/– Azithromycin

Initial reports of drugs with therapeutic benefit in COVID-19 centered on a potential role for the antimalarial agents chloroquine and hydroxychloroquine. These 2 agents have similar mechanisms of action with in vitro activity against SARS-CoV-2[15] and are generally well tolerated, with frequent adverse effects being gastrointestinal in nature. However, hydroxychloroquine is associated with fewer severe adverse effects, such as permanent retinopathy and cardiomyopathy, at high doses and with long-term use. Consequently, hydroxychloroquine has become the central antimalarial agent studied in COVID-19. The proposed mechanism in SARS-CoV-2 has not been established, but some theories include preventing the virus from entering human cells and replicating intracellularly and reducing cytokine

release.[15] Azithromycin is a macrolide antibiotic with activity against a variety of gram-positive, gram-negative, and atypical pathogens. It has reported in vitro activity against viruses, including influenza A (hemagglutinin type 1 and neuraminidase type 1 [H1N1]) and Zika, although its activity against SARS-CoV-2 has not yet been established. A secondary benefit of azithromycin is its adjunctive antibacterial coverage for underlying bacterial coinfections.

Earlier trials evaluating hydroxychloroquine in COVID-19 were predominantly observational, with design flaws such as small sample size, mild disease severity, and limited follow-up, minimizing its applicability in patients with severe disease. In one of the first studies to show a potential role for hydroxychloroquine in COVID-19, Chen and colleagues[16] evaluated hydroxychloroquine versus placebo in 62 adults hospitalized with mild COVID-19 in Wuhan, China. Notably, although the study was published online as a preprint study, it was not peer reviewed. Eligible patients had laboratory-confirmed SARS-CoV-2, pneumonia confirmed by chest computed tomography, an arterial oxygen saturation (SaO_2) to SpO_2 ratio greater than 0.93, or a Pao_2/FiO_2 ratio greater than 300. Notable exclusion criteria included severe or critical illness, retinopathy, arrhythmias, and severe liver or renal dysfunction. Patients were randomized to receive oral hydroxychloroquine 200 mg twice a day for 5 days or placebo. The primary end point of time to clinical recovery was shorter in the hydroxychloroquine group by approximately 1 day (time to body temperature recovery: 2.2 vs 3.2 days, $P < .001$; time to cough remission: 2.0 vs 3.1 days, $P = .002$). No deaths were observed during the trial, and 2 mild adverse reactions were observed, both in the hydroxychloroquine group.

Sarma and colleagues[17] conducted the first meta-analysis comparing hydroxychloroquine +/– azithromycin versus conventional therapy in hospitalized adult and pediatric laboratory-confirmed SARS-CoV-2 infection. Three studies were included in the meta-analysis (n = 128 participants). Among studies that reported virologic cure, there was no difference between the hydroxychloroquine and control groups (odds ratio [OR], 2.37; 95% CI, 0.13-44.53). In addition, no statistically significant difference was observed in the composite end point of death or clinical worsening (OR, 1.37; 95% CI, 0.09-21.97) or occurrence of adverse effects (OR, 2.19; 95% CI, 0.59-8.18). Limitations of this analysis include significant study heterogeneity, with various hydroxychloroquine dosing regimens and no standardized conventional treatment regimen.[17] In later research, Geleris and colleagues[18] completed a single-center, retrospective, observational trial (n = 1376 patients). Patients who were eligible to receive hydroxychloroquine +/– azithromycin had laboratory-confirmed SARS-CoV-2 infection with moderate to severe respiratory illness (resting SaO_2 ≤94% while breathing room air). Notable exclusion criteria included intubation. Standardized hydroxychloroquine and azithromycin dosing were used throughout the study (hydroxychloroquine: 600 mg twice a day on day 1, then 400 mg daily for days 2-5; azithromycin: 500 mg on day 1, then 250 mg daily for days 2-5). Patients were able to use concomitant COVID-19 treatments. There was no significant difference in the primary study outcome, time from study baseline to intubation or death, between hydroxychloroquine alone (HR, 1.04; 95% CI, 0.82-1.32) and hydroxychloroquine +/– azithromycin (HR, 1.03; 95% CI, 0.81-1.31). No adverse events were reported. Limitations included the study's retrospective nature and potential missing data and inaccuracies due to the use of electronic health records.[18]

In March 2020, with limited COVID-19 therapeutic options, the FDA issued an EUA for hydroxychloroquine. However, in April 2020, the FDA published a drug safety communication.[19] The communication warned health care professionals of an increased risk for QT prolongation and fatal ventricular arrhythmias with combinations of QT-prolonging drugs (ie, hydroxychloroquine and azithromycin).[19] This notice cautioned health professionals and the general public that the use of chloroquine or hydroxychloroquine +/– azithromycin should be limited to the context of a clinical trial, tempering initial enthusiasm for their use. This safety warning is supported by a recent case series of critically ill patients with COVID-19 demonstrating that 17 of 40 patients (42.5%) receiving hydroxychloroquine plus azithromycin developed QTc prolongation requiring discontinuation of therapy.[20] Currently, clinical practice guidelines do not recommend the use of hydroxychloroquine plus azithromycin in COVID-19 treatment except in a clinical trial environment. In June 2020, the FDA revoked the EUA for chloroquinine and

hydroxychloroquine. This development was based on a lack of clinical efficacy in emerging and published literature since the EUA was first issued and reports of serious cardiac adverse events and methemoglobinemia in patients with COVID-19 treated with chloroquine and hydroxychloroquine.[21] Despite initial enthusiasm, on the basis of current evidence, hydroxychloroquine +/– azithromycin cannot be recommended for routine use.

Tocilizumab

Significant cytokine elevations described as *cytokine storm* have been associated with severe COVID-19, particularly involving the cytokine interleukin 6 (IL-6). Cytokine storm is an acute inflammatory syndrome that can cause a variety of symptoms ranging in severity from fever to ARDS and multiorgan system failure. The phenomenon of cytokine storm has led to much interest in IL-6 inhibitors for the treatment of COVID-19. The IL-6 inhibitor tocilizumab has garnered the most clinical interest. Tocilizumab is a humanized monoclonal antibody IL-6 receptor antagonist that is used for a variety of proinflammatory conditions, including severe or life-threatening chimeric antigen receptor T-cell therapy–induced cytokine release syndrome, supporting the hypothesis of its potential as an adjunct in COVID-19 therapy. To date, no completed randomized controlled trials demonstrating tocilizumab efficacy in COVID-19 have been reported.

The initial reports of use of tocilizumab in COVID-19 come from 2 small observational studies.[22,23] Luo and colleagues[22] conducted a small, single-center trial in Wuhan, China, in hospitalized adults who were mildly to critically ill with COVID-19. All 15 study patients received tocilizumab. The 15 patients had substantial heterogeneity in the severity of illness, with 2 being moderately, 6 seriously, and 7 critically ill. Most patients received 1 dose of tocilizumab. However, one-third of patients received 2 or more doses. Doses ranged from 80 to 600 mg. After administration of tocilizumab, median C-reactive protein decreased significantly from 126.9 mg/L to 11.2 mg/L ($P < .01$). Ten patients (67%) had a transient initial increase in IL-6 and then a decrease in serum levels. Three deaths were reported. Adverse events were not reported. Xu and colleagues[23] evaluated the

use of tocilizumab in a nonrandomized, observational study of 21 adult patients with COVID-19. All patients received lopinavir and methylprednisolone before tocilizumab therapy. Of the 21 patients, 17 (81%) were seriously ill and 4 (19%) were critically ill. Severe illness was defined as the presence of any of the following conditions: (1) respiratory rate of 30 or more breaths/min, (2) SpO_2 of 93% or less while breathing room air, or (3) a Pao_2/FiO_2 ratio of 300 or less. Critical illness was defined as respiratory failure requiring mechanical ventilation, shock, or, in combination with other organ failures, a need to be admitted to the ICU. Reported tocilizumab dosing was 1 to 2 doses at 8 mg/kg intravenously. Among reported clinical outcomes, 15 of 20 patients who initially required oxygen at baseline (75%) had lowered oxygen requirments after receiving tocilizumab.[23] Both studies had major limitations, including small sample size, lack of a comparator group, lack of standard tocilizumab dosing regimen, concomitant use of other anti-inflammatory drugs, and lack of clinical outcomes.

In the most extensive study to date evaluating tocilizumab in hospitalized COVID-19 patients, tocilizumab was compared with placebo in an ongoing phase 2/3 adaptive-designed clinical trial.[24] The randomized phase 2 portion of the trial compared tocilizumab 400 mg (high dose), tocilizumab 200 mg (low dose), and placebo. A total of 457 hospitalized patients with COVID-19 were included in the analysis. In the manufacturer's press release used to report the preliminary results, 28% of patients were categorized as having severe illness, 49% as having critical illness, and 23% as having multiorgan failure. Severely ill patients were defined as those who required oxygen supplementation without mechanical or high-flow oxygenation, and critically ill patients were defined as those who required mechanical ventilation or high-flow oxygenation or treatment in an ICU. In the phase 2 portion of the trial, all 3 study arms showed reduced C-reactive protein, which was the primary end point. On the basis of the exploratory clinical end points from the phase 2 trial, tocilizumab appeared to have the most meaningful results in critically ill patients with COVID-19, with the high-dose tocilizumab group having a lower incidence of the composite end point of death or mechanical ventilation compared with placebo (32% vs

55%) and higher incidences of clinical improvement (59% vs 41%) and discharge from the hospital (53% vs 41%). Statistical analysis was not reported.

Following a review by the independent data monitoring committee of all available phase 2 and phase 3 data, the focus of the phase 3 trial was amended to include only critically ill patients and to reduce the treatment arms to 2 (tocilizumab 400 mg and placebo).[24] Publication of the final results will allow further study evaluation; however, these developments suggest that tocilizumab may have a role in treatment of COVID-19 patients with severe illness. Final results are expected in June 2020.[24] Current COVID-19 guidelines cite insufficient evidence to make a full recommendation on tocilizumab use,[5,6] reserving use to a clinical trial environment.[7] Several safety considerations pertain to use of tocilizumab, including lipid abnormalities, elevated hepatic enzymes, neutropenia, and infusion and injection site reactions. Despite reported dosing variations, the usual practice is to dose at 8 mg/kg, with common reported doses of 400 mg and a maximum dose of 800 mg. Future research is essential to understand the role of tocilizumab in COVID-19 treatment, but the available evidence is promising, particularly in patients with severe illness.

Lopinavir/Ritonavir

Another therapy combination with preliminary promise in the early phases of the pandemic was lopinavir/ritonavir. Lopinavir/ritonavir is a combination antiretroviral used for the treatment of HIV infection. It has demonstrated in vitro activity against SARS-CoV and Middle Eastern respiratory syndrome (MERS)–CoV, in addition to in vitro activity against SARS-CoV-2. The combination is hypothesized to decrease SARS-CoV-2 replication by preventing the production of viral particles. However, the in vitro activity and proposed benefit have not translated to positive clinical results.

In a randomized open-label, placebo-controlled, single-center trial, Cao and colleagues[25] compared lopinavir/ritonavir with placebo in hospitalized patients with severe COVID-19. Eligible patients had laboratory-confirmed SARS-CoV-2 infection, pneumonia confirmed by chest imaging, and resting SaO_2 of 94% or lower while breathing room air or a PaO_2/FiO_2 ratio of 300 or less. Notable exclusion criteria were known HIV infection and known severe liver disease. Patients were randomized to receive either lopinavir/ritonavir 400 mg and 100 mg, respectively, twice a day for 14 days or placebo. All patients were allowed to receive supplemental oxygen, non-invasive and/or invasive ventilation, antibiotics, vasopressors, renal replacement therapy, and extracorporeal membrane oxygenation according to the local standard of care. The primary end point was median time from randomization to clinical improvement. A total of 199 patients were included in the final analysis. The median time between symptom onset and randomization was 13 days. There was no statistically significant difference in the primary end point between lopinavir/ritonavir and placebo groups (16 vs 16 days; HR, 1.31; 95% CI, 0.95-1.80; $P = .09$). Also, there was no statistically significant difference in day 28 mortality (19.2% vs 25.0%; difference, –5.8 percentage points; 95% CI, –17.3 to 5.7). Serious adverse events such as ARDS, shock, and acute heart failure occurred in the lopinavir/ritonavir group (19 patients) compared with the standard care group (32 patients).[25] Limitations of the study include lack of blinding, lack of standardization of concomitant therapies, and delayed time from symptom onset to study enrollment. Despite these discouraging results, lopinavir/ritonavir has continued to be studied in combination with other antivirals and early in the disease course. Hung and colleagues[26] performed an open-label phase 2 randomized controlled trial in adults hospitalized with mild to moderate COVID-19 at 6 hospitals in China. Faster symptom improvement, shorter duration of viral shedding, and shorter hospital stay were observed with the combination of lopinavir/ritonavir, interferon beta-1b, and ribavirin compared with lopinavir/ritonavir alone. Currently, there are insufficient data to support the use of lopinavir/ritonavir in COVID-19 outside the context of a clinical trial. Until more robust study results are available, the role of lopinavir/ritonavir in COVID-19 therapy is limited.

Additional Therapeutic Considerations

COVID-19–Associated Coagulopathy

One clinical feature of patients with severe COVID-19 that warrants further therapeutic consideration is hypercoagulability and subsequent increased risk of

thromboembolism, referred to as COVID-19–associated coagulopathy (CAC). The rate of thrombotic complications in COVID-19 is variable depending on the study quoted, ranging from 3% to 30%.[27-29] In a multicenter, prospective cohort study at 2 French hospitals, Helms and colleagues[27] noted that approximately 17% of patients with COVID-19 had clinically relevant thrombotic complications, which were mostly due to pulmonary embolisms. In a subset of COVID-19 patients with ARDS, thrombotic complications were 5-fold higher compared with patients with non–COVID-19 ARDS (11.7% vs 2.1%; $P<.008$). Some have hypothesized that microvascular thrombosis is associated with hypoxemic respiratory failure in patients with severe COVID-19. Autopsy studies to date have been limited, with some results suggesting microvascular thrombosis and other results showing pulmonary hemorrhage.

Coagulation derangements often noted in CAC include moderate to severe thrombocytopenia (platelet count $<50 \times 10^9/L$), prolonged prothrombin time (PT) and activated partial thromboplastin time, elevated D-dimer, and decreased fibrinogen (<1.0 g/L).[30,31] Han and colleagues[30] compared 94 hospitalized COVID-19 patients with 40 healthy volunteers and found that COVID-19 patients had higher D-dimer levels compared with the control group (10.4 vs 0.26 µg/mL; $P<.001$). Additionally, an elevated D-dimer level may have prognostic implications. Tang and colleagues[32] noted that among hospitalized patients with COVID-19, nonsurvivors had a nearly 3.5-fold increase in baseline D-dimer level and an elevated baseline PT as compared with survivors. Furthermore, a greater proportion of nonsurvivors met the International Society on Thrombosis and Haemostasis criteria for disseminated intravascular coagulation compared with survivors (71% vs 0.6%). Clinical findings of an elevated D-dimer and elevated PT should raise suspicion for disseminated intravascular coagulation and CAC.

Current guidance from the American Society of Hematology recommends that, in the absence of any contraindications (ie, active bleeding and platelet count $<25 \times 10^9/L$), chemical thromboprophylaxis be provided for all patients with COVID-19, with low-molecular-weight heparin such as enoxaparin or the factor Xa inhibitor fondaparinux being the agents of choice.[33] These agents are preferred over

unfractionated heparin because of their less frequent dosing requirements. Specific guidance on prophylactic dosing is unclear. Klok and colleagues[28] investigated the use of chemical thromboprophylaxis using the low-molecular-weight heparin nadroparin in critically ill patients with COVID-19 at 3 Dutch hospitals. Nadroparin dosing was varied and based on institutional preferences, with dosing strategies of 2850 IU daily, 5700 IU daily, and 5700 IU twice a day used. The investigators found that 31% of patients developed a thrombotic complication while receiving chemical thromboprophylaxis. These results suggest that further research is needed to determine whether traditional chemical thromboprophylaxis dosing regimens used in the United States (ie, enoxaparin, fondaparinux) are sufficient or if increased doses are needed in patients with severe COVID-19. Currently available evidence indicates that chemical thromboprophylaxis should be provided to all patients with COVID-19 except those with a contraindication. The choice of specific agent used should be based on institutional and patient-specific factors. Factors that may necessitate higher thromboprophylaxis dosing include obesity, but the potential benefits should be weighed against the increased risk of bleeding.

Another area of debate is the empirical use of therapeutic anticoagulation due to the prothrombotic nature of COVID-19. American Society of Hematology guidance does not recommend therapeutic anticoagulation in patients with COVID-19 unless venous thromboembolism (VTE) or atrial fibrillation is documented.[33] Studies on the benefits of empirical therapeutic anticoagulation in patients with COVID-19 have yielded conflicting results. In a small French study evaluating the incidence of thromboembolic events in patients with severe COVID-19 receiving therapeutic anticoagulation ($n=18$), the rates of VTE (56%) and pulmonary embolism (33%) were high, suggesting that therapeutic anticoagulation at routine doses may be ineffective.[34] Conversely, in an observational trial of 2773 patients hospitalized with COVID-19, longer duration of therapeutic anticoagulation was associated with a reduced risk of mortality (HR, 0.86; 95% CI, 0.82-0.89; $P<.001$).[35] Questions remain whether coagulation parameters (ie, degree of D-dimer elevation) can be used to identify specific patients who may benefit from

empirical therapeutic anticoagulation. On the basis of currently available evidence, routine empirical therapeutic anticoagulation cannot be recommended for patients with COVID-19. Therapeutic anticoagulation should be provided to those with an indication, including VTE or atrial fibrillation. Another therapy that has been discussed as a potential treatment option in patients with severe COVID-19 and rapid clinical deterioration is tissue plasminogen activator (tPA), a thrombolytic agent commonly used in the setting of ischemic stroke. In a small case series (n = 3), Wang and colleagues[36] reported that the use of tPA in patients with COVID-19 requiring mechanical ventilation was associated with a 38% to 100% improvement in the PaO_2/FiO_2 ratio; however, the observed improvements were transient. More research is needed to determine any potential benefits of tPA therapy, define an optimal dosing regimen, determine how long any benefits persist after tPA administration, and determine if and when tPA redosing is needed.

Corticosteroids

The use of corticosteroids for various disease states, including ARDS, has been a source of seemingly endless debate among critical care practitioners. The rationale for corticosteroids is to attenuate the massive cytokine elevations observed in patients with severe COVID-19 pneumonia. However, the use of corticosteroids is not without complications, including hyperglycemia and increased risk of secondary infection. In the only randomized controlled trial published evaluating use of corticosteroids in patients with COVID-19, dexamethasone 6 mg daily for up to 10 days was compared with usual care in patients hospitalized with COVID-19.[37] The study was published in a preprint format and has not undergone formal peer review. Dexamethasone (454 of 2104 patients; 21.6%) was associated with lower 28-day mortality compared with usual care (1065 of 4321 patients; 24.6%; relative risk [RR], 0.83; 95% CI, 0.74-0.92; $P < .001$). In an a priori subgroup analysis according to respiratory support at randomization, dexamethasone reduced 28-day mortality in patients receiving invasive mechanical ventilation (RR, 0.65; 95% CI, 0.51-0.82; $P < .001$) and in patients receiving oxygen without invasive mechanical ventilation (RR, 0.80; 95% CI, 0.70-0.92; $P = .002$). There was no benefit

in patients not requiring oxygen at randomization (RR, 1.22; 95% CI, 0.93-1.61; $P = .14$). Information regarding safety outcomes such as secondary infections and hyperglycemia were not reported. Further evidence for use of corticosteroids in COVID-19 is limited to 1 published but non–peer-reviewed retrospective observational, single-center study.[38] The study indicated that methylprednisolone use was associated with improvement in clinical symptoms (ie, fever, hypoxia) and a shorter disease course compared with patients who did not receive methylprednisolone. Enthusiasm for these results must be tempered by potential confounding bias and small sample size. Until more robust evidence is available, guidance on the use of corticosteroids in COVID-19 should be based on previous literature on use of corticosteroids in critical care and dependent on the specific indication. According to the Surviving Sepsis Campaign COVID-19 guideline, in patients with respiratory failure (without ARDS), corticosteroids are not recommended for routine use, as any potential benefits do not outweigh the risks.[7] However, corticosteroids may be considered in patients with respiratory failure (with ARDS), using lower doses and shorter treatment durations. Furthermore, low-dose corticosteroids are recommended in patients with COVID-19 with shock that is refractory to other interventions.

Conclusion

The COVID-19 global pandemic is an unprecedented event, with new evidence emerging seemingly on a daily basis. Various drugs have been evaluated. However, none are currently approved by the FDA for the treatment of COVID-19. Promising results with remdesivir suggest a prominent role for this agent in the management of severe COVID-19. Other prominent interventions for patients with severe COVID-19 include chemical thromboprophylaxis and the use of corticosteroids. Critical care nurses are essential to optimizing and coordinating therapies for patients with COVID-19, and an understanding of drug therapy is crucial to this process.

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report 156. Updated June 24, 2020. Accessed June 24, 2020. https://www.who.int/docs/default-source/coronavirus/situation-reports/20200624-covid-19-sitrep-156.pdf?sfvrsn=af42e480_2

2. Institute for Health Metrics and Evaluation, University of Washington. COVID-19 projections. Updated June 24, 2020. Accessed June 24, 2020. https://covid19.healthdata.org/projections

3. World Health Organization. *Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).* World Health Organization; 2020.

4. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(12):343-346.

5. National Institutes of Health, COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Updated June 25, 2020. Accessed June 26, 2020. https://covid19treatment-guidelines.nih.gov

6. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Updated June 22, 2020. Accessed June 24, 2020. http://www.idsociety.org/COVID19guidelines

7. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med.* 2020;48(6):e440-e469. doi:10.1097/CCM.0000000000004363

8. Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res.* 2019;169:104541.

9. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med.* 2017;9(396):eaal3653. doi:10.1126/scitranslmed.aal3653

10. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature.* 2016;531(7594):381-385.

11. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2020;395:1569-1578. doi:10.1016/S0140-6736(20)31022-9

12. Adaptive COVID-19 Treatment Trial (ACTT). ClinicalTrials.gov identifier: NCT04280705. Updated May 7, 2020. Accessed May 14, 2020. https://clinicaltrials.gov/ct2/show/NCT04280705

13. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—preliminary report. *N Engl J Med.* Published online May 22, 2020. doi:10.1056/NEJMoa2007764

14. US Food and Drug Administration. Remdesivir emergency use authorization. US Food and Drug Administration website. Updated May 1, 2020. Accessed May 14, 2020. https://www.fda.gov/media/137564/download

15. Yao X, Ye F, Zhang M, 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.* Published online March 9, 2020. doi:10.1093/cid/ciaa237

16. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Preprint. Posted online April 10, 2020. medRxiv 2020.03.22.20040758. doi:10.1101/2020.03.22.20040758

17. Sarma P, Kaur H, Kumar H, et al. Virological and clinical cure in COVID-19 patients treated with hydroxychloroquine: a systematic review and meta-analysis. *J Med Virol.* Published online April 16, 2020. doi:10.1002/jmv.25898

18. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* Published online May 7, 2020. doi:10.1056/nejmoa2012410

19. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. US Food and Drug Administration. Updated April 24, 2020. Accessed May 14, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or

20. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *JAMA Cardiol.* Published online May 1, 2020. doi:10.1001/jamacardio.2020.1787

21. Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. US Food and Drug Administration. Updated June 15, 2020. Accessed June 25, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and

22. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol.* Published online April 6, 2020. doi:10.1002/jmv.25801

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

24. Sanofi and Regeneron provide update on U.S. phase 2/3 adaptive-designed trial in hospitalized COVID-19 patients. News release. Sanofi; April 27, 2020. Accessed May 14, 2020. https://www.sanofi.com/en/media-room/press-releases/2020/2020-04-27-12-58-00

25. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med.* 2020;382(19):1787-1799.

26. Hung IFN, Lung KC, Tso EYK, 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;395:1695-1704.

27. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med.* Published online May 4, 2020. doi:10.1007/s00134-020-06062-x

28. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147.

29. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of Covid-19 in New York City. *N Engl J Med.* Published online April 17, 2020. doi:10.1056/NEJMc2010419

30. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med.* Published online March 16, 2020. doi:10.1515/cclm-2020-0188

31. COVID-19 and coagulopathy: frequently asked questions. American Society of Hematology. Updated April 14, 2020. Accessed May 16, 2020. https://www.hematology.org/covid-19/covid-19-and-coagulopathy

32. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-847.

33. COVID-19 and VTE/anticoagulation: frequently asked questions. American Society of Hematology. Updated April 17, 2020. Accessed May 12, 2020. https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

34. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost.* Published online April 22, 2020. doi:10.1111/jth.14869

35. Paranjpe I, Fuster V, Lala A, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol.* Published online May 6, 2020. doi:10.1016/j.jacc.2020.05.001

36. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case

series. *J Thromb Haemost.* Published online April 8, 2020. doi:10.1111/jth.14828

37. Horby P Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. Preprint. medRxiv. Posted online June 22, 2020. doi:10.1101/2020.06.22.20137273

38. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. Preprint. Posted online March 12, 2020. medRxiv 2020.03.06.20032342. doi:10.1101/2020.03.06.20032342