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Treatments for COVID-19

Hayden S. Andrews,[1] Jonathan D. Herman,[2,3] and Rajesh T. Gandhi[1]

[1] Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; email: hsandrews@mgh.harvard.edu, rgandhi@mgh.harvard.edu

[2] Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; email: jdherman@partners.org

[3] Ragon Institute of Mass General, MIT, and Harvard, Cambridge, Massachusetts, USA

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Abstract

The treatment for COVID-19 has evolved rapidly since the start of the pandemic and now consists mainly of antiviral and immunomodulatory agents. Antivirals, such as remdesivir and nirmatrelvir-ritonavir, have proved to be most useful earlier in illness (e.g., as outpatient therapy) and for less severe disease. Immunomodulatory therapies, such as dexamethasone and interleukin-6 or Janus kinase inhibitors, are most useful in severe disease or critical illness. The role of anti-SARS-CoV-2 monoclonal antibodies has diminished because of the emergence of viral variants that are not anticipated to be susceptible to these treatments, and there still is not a consensus on the use of convalescent plasma. COVID-19 has been associated with increased rates of venous thromboembolism, but the role of antithrombotic therapy is limited. Multiple investigational agents continue to be studied, which will alter current treatment paradigms as new data are released.

INTRODUCTION

Since the first cases of coronavirus disease 2019 (COVID-19) were identified, over 700 million people had been infected and 6 million deaths worldwide reported by May 2023 (1). The causative virus, SARS-CoV-2, is an RNA virus belonging to the coronavirus family that can cause a range of human illness from asymptomatic carriage to an upper respiratory illness to fulminant respiratory failure (2). The postinfectious, longer-term effects remain an active area of research (3).

Given the novel nature of SARS-CoV-2, there were no known efficacious treatments at the start of the pandemic. However, within weeks, many clinical trials were scaled-up to test a variety of agents. This review covers the general scope of current therapeutics broken down by class of agent: antivirals, immunomodulators, neutralizing antibodies and convalescent plasma, and antithrombotic therapy. Treatments have been evaluated in patients with different severities of disease: mild to moderate COVID-19 in nonhospitalized patients; severe COVID-19, in which patients were hospitalized and required supplemental oxygen; and critical illness, in which patients needed noninvasive or mechanical ventilation. This review focuses on randomized trials that have most informed the current treatment paradigms and areas for future research. Multiple clinical treatment guidelines are available from professional societies and governmental health agencies to inform clinical practice. This review references the National Institutes of Health (NIH) COVID-19 Treatment Guidelines after each therapeutic's section to provide perspective on its recommended use (4).

TREATMENT ACROSS THE COVID-19 SPECTRUM

Soon after infection, when people have mild or moderate disease, SARS-CoV-2 levels in the upper respiratory tract are high (see **Figure 1**). In this phase of infection, antiviral therapy is most likely to be effective. If the infection progresses to severe disease, when people are usually hospitalized,

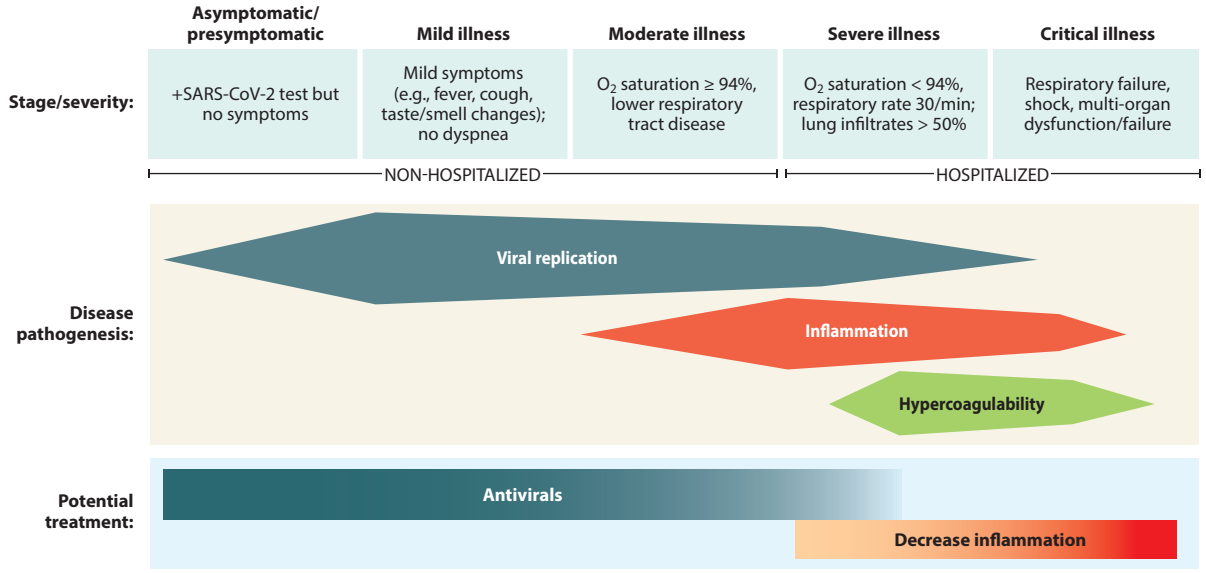

Figure 1

Treatment across the COVID-19 spectrum (5). From *N. Engl. J. Med.* Mild or moderate Covid-19. Gandhi RT, Lynch JB, Del Rio C. 383(18):1757–66. Copyright © (2020) Massachusetts Medical Society. Reprinted with permission. **https://www.nejm.org/doi/full/10.1056/nejmcp2009249**.

Table 1 A summary of the main antiviral agents used in the treatment of COVID-19

Antiviral agent	Important trials	Summary of data	NIH COVID-19 Treatment Guidelines recommendation (3)
Remdesivir	ACTT-1 (6), CATCO (7), SOLIDARITY (8), PINETREE (9)	Earlier time to recovery for hospitalized patients requiring oxygen therapy Decreased progression to severe disease for high-risk, nonhospitalized patients	First-line for hospitalized patients requiring oxygen therapy Second-line for nonhospitalized, high-risk patients
Nirmatrelvir-ritonavir	EPIC-HR (10), EPIC-SR (11), Ganatra et al. 2023 (14)	Reduction in rate of hospitalization and death for high-risk, nonhospitalized patients (both vaccinated and unvaccinated)	First-line for nonhospitalized, high-risk patients
Molnupiravir	MOVe-OUT (17), PANORAMIC (18)	Reduction in rate of hospitalization and death for high-risk, nonhospitalized patients (only seen in unvaccinated patients)	Third-line for nonhospitalized, high-risk patients

excess inflammation seems to drive many of the clinical features, including hypoxemia requiring oxygen supplementation, thrombosis, and, at times, multi-organ failure, necessitating ventilatory and circulatory support. In the phase of severe or critical illness, immunomodulators are the mainstay of pharmacologic treatment (along with critical care in those with respiratory failure). In hospitalized patients, prophylactic anticoagulation is usually indicated; there is a narrow window during which therapeutic anticoagulation may also be helpful (see below).

ANTIVIRALS

Table 1 summarizes the main antiviral agents used in the treatment of COVID-19.

Remdesivir

Remdesivir, a viral RNA-dependent RNA polymerase inhibitor, was one of the first identified agents to show efficacy in a randomized controlled trial (RCT) during the early months of the pandemic. That sentinel trial was the multinational Adaptive COVID-19 Treatment Trial-1 (ACTT-1), which enrolled 1,062 unvaccinated, hospitalized patients requiring supplemental oxygen (6). The study showed a time to recovery of 10 days in the remdesivir group versus 15 days in the placebo group (6), with the benefit of remdesivir most evident in those requiring conventional oxygen supplementation and those within 10 days of symptom onset. Follow-up studies in the dexamethasone era (see the section titled Immunomodulatory Therapy below) sought to clarify if there was a mortality benefit to the drug. The Canadian Treatments for COVID-19 (CATCO) trial, an open-label RCT performed in Canada, showed no decrease in mortality compared to standard of care, but did show decreased rate of progression to mechanical ventilation (7). Similarly, the Solidarity trial, a multinational study consortium, showed no decrease in mortality for patients mechanically ventilated at enrollment; however, a modest mortality benefit (14.6% versus 16.3%, $p = 0.03$) was seen for patients requiring supplemental oxygen but not mechanical ventilation (8).

In addition to its role in hospitalized patients, early use of remdesivir also prevents progression in high-risk, nonhospitalized patients with mild or moderate COVID-19. The PINETREE study enrolled unvaccinated outpatients who were at high risk for progression based on age

or comorbidities and who were within 7 days of symptom onset (9). The study showed that, compared to placebo, a 3-day course of remdesivir significantly reduced hospitalization and all-cause mortality (0.7% versus 5.3%, $p = 0.008$) (9). The data for vaccinated patients are much more limited across all phases of care.

In clinical practice, the NIH COVID-19 Treatment Guidelines recommend remdesivir as a first-line therapy in patients hospitalized for COVID-19 (in conjunction with immunomodulators if the patient is requiring oxygen) and as a second-line therapy (after nirmatrelvir-ritonavir) for high-risk outpatients (4).

Nirmatrelvir-Ritonavir

Nirmatrelvir is an oral medication that targets the SARS-CoV-2 protease and is paired with ritonavir, a pharmacologic booster. The sentinel trial that evaluated this agent was EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients), which enrolled high-risk, unvaccinated outpatients and showed an 89% risk reduction in hospitalization or death when compared to placebo (10). The EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) study evaluated the drug's efficacy in standard-risk patients (those with risks but who had been vaccinated or those who did not have conditions that conferred excess risk of progression). In this trial, there was no effect of the medication on sustained alleviation of symptoms, and the rates of hospitalization were low for participants in both arms (11).

As the pandemic shifted into the postvaccination era, there was some question if this agent would have similarly dramatic efficacy data for high-risk, vaccinated patients. Several observational studies have suggested a benefit of nirmatrelvir-ritonavir in vaccinated individuals (12, 13). For example, a retrospective cohort study in high-risk, vaccinated outpatients showed a 45% relative risk reduction in the composite outcome of emergency department visit, hospitalization, or death in the nirmatrelvir-ritonavir group compared to placebo (7.87% versus 14.4%, $p < 0.005$), confirming its ongoing relevance for clinical practice (14).

As millions of patients worldwide have been treated with the drug, there has been concern raised about viral "rebound" or resurgence of COVID-19 symptoms after completing the treatment course. The primary EPIC-HR and EPIC-SR trial data, however, did not show a significant difference in the rate of rebound between the treatment and placebo arms at day 10 or 14 (15). Moreover, viral and symptom rebound may occur even in people who are not treated for COVID-19 (16). A notable limitation of the medication is the significant drug–drug interactions secondary to the ritonavir booster, which in some patients can be treatment prohibitive. The NIH COVID-19 Treatment Guidelines recommend the use of oral nirmatrelvir-ritonavir as first-line for high-risk, nonhospitalized patients (4). Because most of the data on nirmatrelvir-ritonavir have been in immunocompetent individuals, an important area of ongoing research is the role of extended courses of therapy in immunocompromised patients, who may sometimes have persistent SARS-CoV-2 replication.

Molnupiravir

Molnupiravir is a prodrug of the small molecule N-hydroxycytidine, which causes accumulation of mutations in SARS-CoV-2 and loss of viral viability. The RCT that led to its authorization was MOVe-OUT, which evaluated 1,433 high-risk, unvaccinated outpatients (17). The 30-day rate of hospitalization or all-cause mortality was significantly lower in the molnupiravir group compared to placebo (7.3% versus 14.1%, $p = 0.001$), a 31% relative risk reduction (17). However, a follow-up open-label study (PANORAMIC) in high-risk outpatients, most of whom had been vaccinated, did not show a decrease in the rate of hospitalization or death with molnupiravir

(18). The group that received the drug had a substantially shorter time to self-reported recovery; however, this result is less definitive because the study was open-label, which may have affected reporting of symptoms by study participants. The NIH COVID-19 Treatment Guidelines currently recommend molnupiravir only when nirmatrelvir-ritonavir and remdesivir cannot be given (4).

Future Directions for Antiviral Therapy in COVID-19

Interferon lambda induces antiviral immunity and has activity against multiple viruses. In the TOGETHER trial, approximately 2,000 high-risk, nonhospitalized patients (83% of whom had received at least one dose of a COVID-19 vaccine) were randomized to receive either a single subcutaneous dose of pegylated interferon lambda or placebo (19). The primary outcome of emergency department visits or hospitalization for COVID-19 was significantly lower in the pegylated interferon lambda group compared to the placebo group (2.7% versus 5.6%, with a relative risk reduction of 51%) (19). However, this drug is not currently available in the United States.

Multiple additional antiviral agents are in various stages of clinical trials, notably ensitrelvir and oral remdesivir analogues. Ensitrelvir is a SARS-CoV-2 protease inhibitor that does not require pharmacologic boosting, in contrast to nirmatrelvir-ritonavir. There are, however, many drug–drug interactions with this agent. A phase III trial in nonhospitalized adults (inclusive of vaccinated/unvaccinated patients and all levels of risk for progression to severe disease) reported a significant reduction in time to resolution of COVID-19 symptoms (167.9 versus 192.2 h, $p = 0.0407$) (20). Interestingly, at the 2023 Conference on Retroviruses and Opportunistic Infections, the study team presented exploratory data (not a primary or secondary endpoint) that showed the ensitrelvir group had a lower rate of persistent COVID-19 or neurologic symptoms—known as long COVID or post-acute sequelae of COVID-19 (PASC)—when compared to placebo (20). This finding was a first for an RCT and warrants further study in future trials.

VV116 is a modified version of remdesivir that can be given orally. In an RCT that compared VV116 to nirmatrelvir-ritonavir in high-risk outpatients, VV116 was noninferior to nirmatrelvir-ritonavir with respect to time to clinical recovery and notably had fewer adverse events (21). Another oral form of remdesivir, called obeldesivir, is being evaluated in clinical trials (NCT05603143).

IMMUNOMODULATORY THERAPY

Table 2 summarizes the main immunomodulatory agents used in the treatment of COVID-19.

Corticosteroids

Arguably the most important trial that changed the early trajectory of the pandemic was the RECOVERY study of dexamethasone. It was an open-label trial in 6,425 unvaccinated hospitalized patients comparing a 10-day course of dexamethasone to usual care alone. The results showed a dramatic reduction in 28-day mortality for patients requiring mechanical ventilation (29.3% versus 41.4%) and for patients receiving supplemental oxygen (23.3% versus 26.2%) when compared to usual care alone (22). No difference was seen for patients not requiring supplemental oxygen, and there was a trend toward harm with dexamethasone in this group (22). The results rapidly changed the standard of care to include dexamethasone for hospitalized patients requiring supplemental oxygen, and most future studies included patients on dexamethasone (4).

The RECOVERY study used 6 mg of dexamethasone per day (standard dose), and there was some question if higher doses might offer even greater benefit. However, when 20 mg of dexamethasone was compared to the standard dose in patients requiring conventional oxygen support, the high-dose group had a higher rate of death (23). Trials of high-dose dexamethasone are still

Table 2 A summary of the main immunomodulatory agents used in the treatment of COVID-19

Immunomodulatory agent	Important trials	Summary of data	NIH COVID-19 Treatment Guidelines recommendation (3)
Corticosteroids	RECOVERY (22)	Decreased mortality for hospitalized patients requiring oxygen therapy Trend toward harm in patients not requiring oxygen therapy	First-line for hospitalized patients requiring oxygen therapy
IL-6 inhibitors	RECOVERY (26), REMAP-CAP (27)	Decreased mortality for critically ill patients requiring oxygen and receiving dexamethasone	First-line for critically ill patients in conjunction with dexamethasone
JAK inhibitors	COV-BARRIER (28), RECOVERY (29)	Decreased mortality for critically ill patients requiring oxygen and receiving dexamethasone	First-line for critically ill patients in conjunction with dexamethasone

Abbreviations: IL, interleukin; JAK, Janus kinase.

ongoing in critically ill patients but, for now, the data indicate that standard-dose dexamethasone should be used in clinical practice (4). No trial has shown benefit for dexamethasone in nonhospitalized patients (4), and it is likely to be harmful in this setting.

In the setting of high-dose steroids, the possibility of secondary infections or reactivation of infection has been reported (e.g., invasive fungal infections, strongyloidiasis, hepatitis B, tuberculosis) and requires consideration when starting therapy (24–26). Dexamethasone remains a cornerstone of COVID-19 therapy for hospitalized patients requiring conventional oxygen, high-flow oxygen, or noninvasive or mechanical ventilation, and it is recommended as first-line therapy by the NIH COVID-19 Treatment Guidelines for these groups of patients (4).

Interleukin-6 Inhibitors

Interleukin-6 (IL-6) is a proinflammatory cytokine, and monoclonal antibodies (mAbs) that inhibit it have previously been approved by the US Food and Drug Administration (FDA) for the treatment of autoimmune conditions (e.g., rheumatoid arthritis) and of cytokine release syndrome associated with chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab is a recombinant, humanized anti-IL-6 receptor mAb that blocks the downstream IL-6 cytokine signaling pathway (27). Given the observed high levels of acute phase reactants [e.g., C-reactive protein (CRP), ferritin] in many patients with severe COVID-19, there was interest in its potential use early during the pandemic.

In an arm of the RECOVERY platform trial from the United Kingdom, hospitalized patients with hypoxemia and elevated CRP over 75 mg/L were randomized to tocilizumab versus standard of care alone. The tocilizumab group had a significant reduction in mortality compared to standard of care (31% versus 35%, $p = 0.0028$) (27). The REMAP-CAP (Randomized Embedded Multifactorial Platform for Community-acquired Pneumonia) trial randomized patients within 24-hours of intensive care unit admission with severe COVID-19 to tocilizumab with dexamethasone, sarilumab (another human anti-IL-6 receptor mAb) with dexamethasone, or standard care of dexamethasone alone. Both the tocilizumab and sarilumab groups had reduced 28-day all-cause mortality and shorter duration of organ support (28).

Given these results, the NIH COVID-19 Treatment Guidelines recommend the addition of tocilizumab to dexamethasone for patients requiring high-flow nasal cannula, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO), or patients on conventional oxygen with rapidly increasing oxygen needs and evidence of systemic inflammation

(e.g., elevated CRP) (4). Sarilumab is recommended as an alternative if tocilizumab is unavailable (4). Tocilizumab is FDA approved for treatment of COVID-19 in hospitalized adults who are receiving a systemic corticosteroid and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO.

Janus Kinase Inhibitors

Baricitinib is a Janus kinase (JAK) inhibitor that blocks activation of the signal transducers and activators of transcription (STAT) pathway, which leads to the production of cytokines including IL-6. Baricitinib is FDA approved for the treatment of rheumatologic diseases such as rheumatoid arthritis. In the COV-BARRIER study, hospitalized patients who were randomized to baricitinib in addition to standard of care (which included dexamethasone) had lower mortality than those who received placebo (29). In a second study, an arm of the RECOVERY open-label platform trial, patients hospitalized for COVID-19 receiving baricitinib versus standard of care alone had decreased 28-day all-cause mortality (12% versus 14%, $p = 0.028$) (30). The NIH COVID-19 Treatment Guidelines recommend the addition of baricitinib to dexamethasone for patients requiring high-flow nasal cannula, noninvasive ventilation, mechanical ventilation, or ECMO, or patients on conventional oxygen with rapidly increasing oxygen needs and evidence of systemic inflammation (e.g., elevated CRP) (4). Baricitinib is FDA approved for treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO.

Future Directions for Immunomodulatory Therapy in COVID-19

Many other immunomodulators have been studied for treatment of COVID-19, including anakinra (an IL-1 receptor antagonist FDA authorized for COVID-19); vilobelimab (an anti-C5a mAb, FDA authorized for COVID-19); infliximab (a tumor necrosis factor inhibitor, FDA approved for other indications), and abatacept (a T cell costimulation modulator, FDA approved for other indications). However, the role of these agents in people with severe or critical COVID-19, and how they should be used, if at all, in combination with or in lieu of other immunomodulators is not yet certain.

NEUTRALIZING ANTIBODIES AND CONVALESCENT PLASMA

Monoclonal and Polyclonal Antibody Therapies

For the first few years of the pandemic, antibody therapy was a powerful way to prevent and treat COVID-19. The two types of antibody products used were mAbs targeting the S1 domain of the SARS-CoV-2 spike protein or convalescent plasma (CP) from recovered COVID-19 patients.

The anti-SARS-CoV-2 mAb combination tixagevimab and cilgavimab (Evusheld™) was FDA authorized for pre-exposure prophylaxis for immunocompromised patients (31). Several anti-SARS-CoV-2 mAbs were authorized for treatment, including bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, and bebtelovimab (32–35). In vitro viral and pseudoviral neutralization activities of the mAbs were used to predict clinical efficacy as different variants of concern (VOCs) rose in prevalence. As VOCs became the predominant strains in 2020, many mAbs retained neutralizing activity against B.1.1.7 (Alpha) (36). However, with the fixation of Omicron (B.1.1.529) at the end of 2021, only bebtelovimab and sotrovimab remained active, and with further evolution of Omicron subvariants in 2022, none of the authorized mAbs maintained cross-neutralizing activity (37). As a result, the anti-SARS-CoV-2 mAbs are no longer used for prophylaxis, pre-exposure prophylaxis, or treatment of COVID-19 (4).

CP, a therapy with a historical foundation of use and safety (38), was an immediately available treatment for COVID-19 early in the pandemic. Many studies have evaluated the efficacy of CP for COVID-19. Large studies of CP in hospitalized patients did not demonstrate efficacy (39, 40), perhaps because by the time most patients are hospitalized, it is too late for the antiviral effect of CP to improve clinical outcomes. However, trials have found that using high-titer CP early in disease in nonhospitalized patients may decrease disease severity (41, 42), and a meta-analysis also supported this finding (43). Now in the era of COVID-19 VOCs, the lack of CP that is matched to the circulating variants has limited its routine use in treating COVID-19 (4). Rather, CP has been used on a case-by-case basis when an immunocompromised individual has not responded to other therapies for COVID-19 and has evidence of active viral replication.

How COVID-19 Antibody Therapies Work

Antibodies have two major components: the Fab, which directs an antibody to its target, and the Fc, or the fragment crystallizable region, which binds to a variety of antibody receptors to direct how an antibody interacts with the innate immune system (44). Antibody neutralization of the virus, driven by Fab binding activity, has been established as a correlate of protection in animal models and human studies of natural SARS-CoV-2 infection and vaccination (45–48). However, Fc function is also important. Enhancing the Fc effector function of antispike receptor binding domain (RBD) mAbs leads to improved protection in multiple models of disease (49), and effector functions were essential for protection when anti-RBD mAbs were given as a therapy after the onset of infection (50, 51). Together, these animal model studies suggest the importance of Fc-effector function in anti-RBD mAb activity.

The anti-SARS-CoV-2 RBD mAbs that were used clinically were designed primarily for neutralizing antibody function. In fact, AstraZeneca mAbs tixagevimab and cilgavimab and Eli Lilly's etesevimab were engineered to minimize Fc activity to avoid a hypothetical concern for antibody-dependent enhancement of infection (52). On the other hand, polyclonal antibody therapies, like CP, are a mixture of antibodies targeting the RBD of spike protein and many other epitopes within the SARS-CoV-2 proteome. Both neutralizing antibody (53) and the Fc-effector function of CP (54, 55) have been proposed to be important for its effect in patients with COVID-19.

Future Directions for Antibody Therapies in COVID-19

Since all mAb treatments that had received FDA emergency use authorization have lost activity against the most recent VOCs, new approaches have been proposed to avoid the strong evolutionary selection at the RBD of spike protein. The first approach has been to target the S2 domain of spike, a more conserved region among beta-coronaviruses responsible for viral and host cell membrane fusion (56). Multiple groups have made combinations with S1 and S2-targeting mAbs that have shown promise for prophylaxis and treatment in animal models with multiple VOCs (57, 58).

A second approach is to develop mAbs targeting the SARS-CoV-2 nucleocapsid protein. Emerging work has shown that nucleocapsid, previously thought to be only an internal viral protein, is exposed on the surface of SARS-CoV-2 infected cells (59) and activates the mannose-binding lectin complement pathway (60). Research on the mechanisms of CP has demonstrated the importance of antinucleocapsid antibodies and found an association between antinucleocapsid antibody-dependent cell-mediated cytotoxicity and better COVID-19 outcomes (54, 61). Following these new developments, experiments in animal models have shown that antinucleocapsid antibodies can improve SARS-CoV-2 outcomes (62). Though much work has to be done to

characterize the potential mechanism of protection in animal models and then translate these studies into human trials, an antinucleocapsid mAb has the potential to remain active despite the continued evolution of VOCs.

ANTITHROMBOTIC THERAPY

An increased incidence of venous thromboembolism (VTE) events was seen early in the pandemic in hospitalized COVID-19 patients, most likely related to thromboinflammation (63). The exact rate when compared to historical controls is challenging to elucidate but has been described as up to three times the baseline rate for hospitalized adults (64). Multiple trials have evaluated the role of VTE prophylaxis and empiric anticoagulation to address this increased burden of VTE.

The OVID and ETHIC RCTs studied nonhospitalized patients and compared enoxaparin or standard of care. Both trials were terminated early and neither showed efficacy in reducing hospitalization or mortality (65, 66). With regard to anticoagulation in hospitalized patients, prophylactic-dose heparin is recommended unless there is a contraindication (4). Based on results of RCTs evaluating the use of therapeutic anticoagulation in noncritically ill and critically ill hospitalized patients (67, 68), the NIH COVID-19 Treatment Guidelines recommend (4):

- For adults who require conventional oxygen but not intensive care, therapeutic-dose heparin only if the D-dimer level is elevated and there is no condition that increases the risk of bleeding.
- For adults requiring high-flow oxygen or intensive care, therapeutic-dose heparin should not be used (unless there is another indication, such as known thromboembolic disease); rather, prophylactic-dose heparin should be given (unless there is a contraindication).

CONCLUSION

COVID-19 therapeutics remain an active area of research, including agents that target different aspects of the pathophysiology of disease (antiviral versus immunomodulation) and different stages of illness (outpatient versus hospitalized). As the pandemic evolves with viral variants and increased population immunity, current treatment paradigms will similarly need continual review with data-driven modifications.

SUMMARY POINTS

1. The choice of therapeutic depends on the clinical setting (outpatient versus hospitalized) and the degree of hypoxemia.
2. Antiviral agents have been shown to be most effective earlier during the illness and with noncritical disease.
3. For patients with critical illness, dexamethasone with the addition of a second immunomodulator (e.g., baricitinib or tocilizumab) has shown the greatest benefit.
4. With the evolution of SARS-CoV-2 variants, the use of neutralizing antibodies and CP is more limited.
5. The role of antithrombotic therapy for COVID-19 is generally limited.

FUTURE DIRECTIONS

1. In light of increasing population immunity from SARS-CoV-2 infection and vaccination, which patients are most likely to benefit from antiviral therapy? It is likely there is a gradient of benefit for antiviral therapy, with higher-risk patients (older individuals or younger people with conditions that confer substantial risk) more likely to derive benefit than lower-risk patients.
2. Will treatment with antivirals reduce the time period in which a person is infectious and, therefore, isolation time?
3. In hospitalized patients, high plasma SARS-CoV-2 nucleocapsid antigen levels are associated with worse clinical outcomes (69). Will more potent antivirals improve outcomes in hospitalized individuals with high baseline SARS-CoV-2 antigen levels? Can we use baseline blood SARS-CoV-2 antigen levels to define who will benefit from antivirals?
4. Is there a role for standard or extended courses of antiviral therapy (small molecules, CP, or other polyclonal antibodies) in immunocompromised patients with severe COVID-19 and persistent SARS-CoV-2 replication? Is there a role for combination antiviral therapy to forestall development of resistance?
5. Will early treatment with antiviral therapy ameliorate PASC?
6. For several immunomodulators, the benefit is clearest in patients on high-flow oxygen/noninvasive ventilation or those requiring intensive care. For people on conventional oxygen, when should a second immunomodulator be added to dexamethasone?
7. Given clinical heterogeneity among people hospitalized with COVID-19, are there biomarkers or other traits that can identify who should be treated and with what?
8. Does the benefit seen for immunomodulatory therapies in immunocompetent individuals apply to immunosuppressed patients? Are there harms, such as prolonging SARS-CoV-2 replication?

DISCLOSURE STATEMENT

R.T.G. is a member of the National Institutes of Health and the Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels. The statements in this review are his perspective and not necessarily those of the Panels.

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