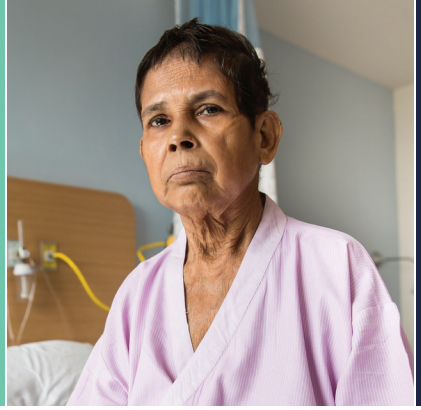

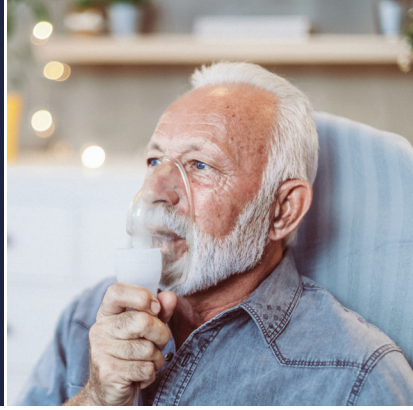

Society of Hospital Medicine

COVID-19 Inpatient Treatment Guide

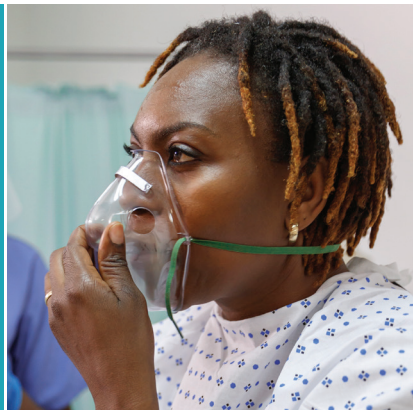

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Table of Contents

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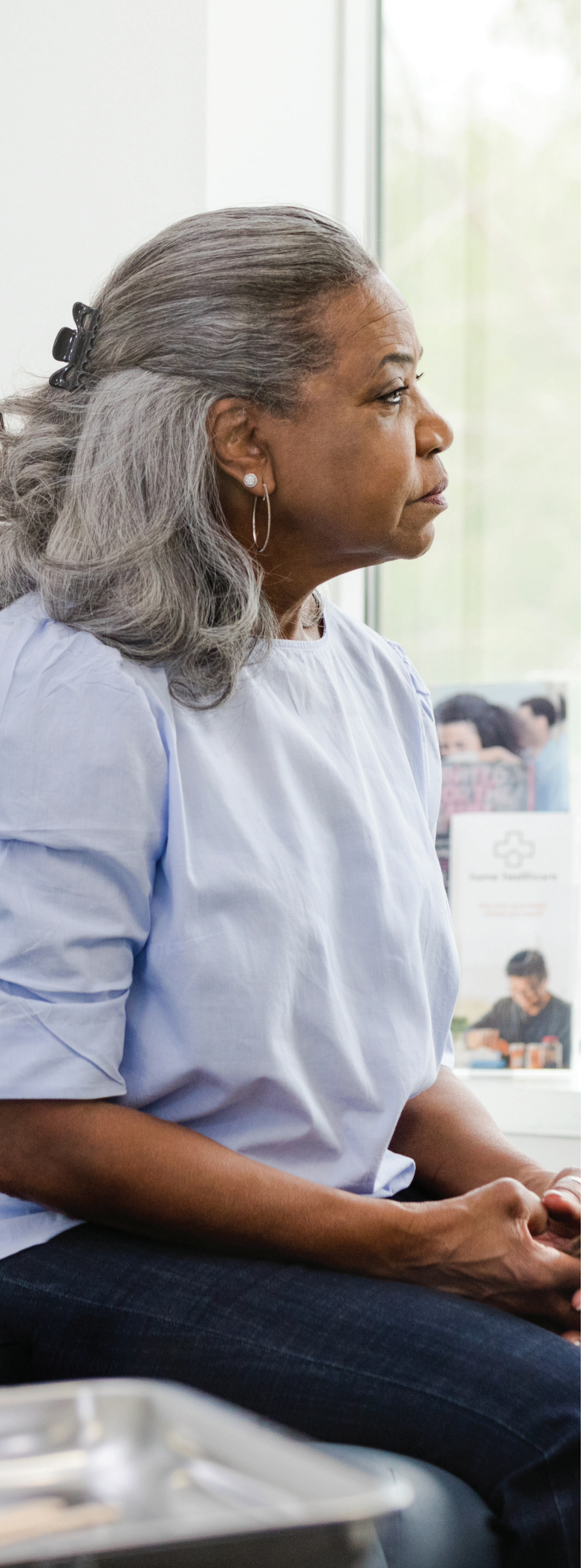


Introduction

Since SARS-CoV-2 (COVID-19) virus was first identified in December 2019, there have been more than 750 million confirmed infections, with over 7 million deaths worldwide, making COVID-19 one of the deadliest viruses in history[1]. During the early stages of the pandemic in 2020, the global fatality rate was greater than 20%. In the following 2.5 years it decreased to less than 0.3%, largely due to vaccination and prior infection, which both confer some degree of immunity[2]. In addition to rising immunity among the population, changes in COVID-19 strains led to reduced rates of severe disease. Although the World Health Organization (WHO) determined that the COVID-19 pandemic was no longer a public health emergency in May 2023, infections continue to cause serious complications among patients.

Severe outcomes from COVID-19, defined by hospitalization, admission to the intensive care unit (ICU), intubation or mechanical ventilation, or death, are higher among certain patient populations. Patients with existing comorbidities such as cardiovascular disease, chronic obstructive pulmonary disease, diabetes, hypertension, cancer, chronic kidney disease, chronic liver disease, and obesity[3,4] are at increased risk of poor outcomes. Older individuals are at especially at higher risk; a meta-analysis evaluating the risk factors for patients with COVID-19 found that age >65 years compared to under age 65 had a significantly higher mortality [RR 3.59, 95% CI (1.87-6.90), $p<0.001$][4]. Other relatively common comorbidities such as diabetes showed two times higher risk of mortality compared to patients without[4]. In a study evaluating patients with solid organ transplantation hospitalized with COVID-19 vs. non-COVID-19 admissions, there was a higher odds of ICU admission, mechanical ventilation, and in-hospital death[5]. These factors are important to consider in caring for the hospitalized patient with COVID-19.

The Role of The Hospitalist In Caring For The Patient With COVID-19

Hospitalists provide direct care for most of the patients who are hospitalized with COVID-19. This includes care initiated in the emergency room and continued on the inpatient unit. Some hospitalists manage patients with COVID-19 in critical care settings, including the "ICU" and the step-down unit. Additionally, hospitalists oversee care in observation units, hospital at home, and post-acute care facilities. Telemedicine may also factor into some facet of care since the pandemic. Because of the vast areas of oversight, it is imperative that hospitalists are well versed in the management of the entire spectrum of COVID-19 disease management in the acute care setting. In particular, the transition of care from one setting to the next requires close oversight and individualized care.

We developed this case-based, educational guide for hospitalists caring for patients with COVID-19. More specifically, the resource will provide guidance specific to the National Institutes of Health (NIH) COVID-19 Treatment Guidelines.

Treatment

Because of the high rate of morbidity and mortality during early stages of the COVID-19 pandemic, substantial resources were mobilized to rapidly develop treatments to reduce the severity of infections[6]. In the early phase of infection, viral replication is key to disease progression. Therefore, antiviral agents are most efficacious in the early stage of infection. In the later stage of COVID-19, the host's inflammatory and immune responses to the virus cause further disease manifestations, characterized by endothelial dysfunction, thrombosis, and hypoxia. Thus, anti-inflammatory, immunosuppressive, and antithrombotic agents have the highest impact in the later stage of COVID-19.

Treatments commonly used to treat COVID-19 are summarized for reference in the following table:

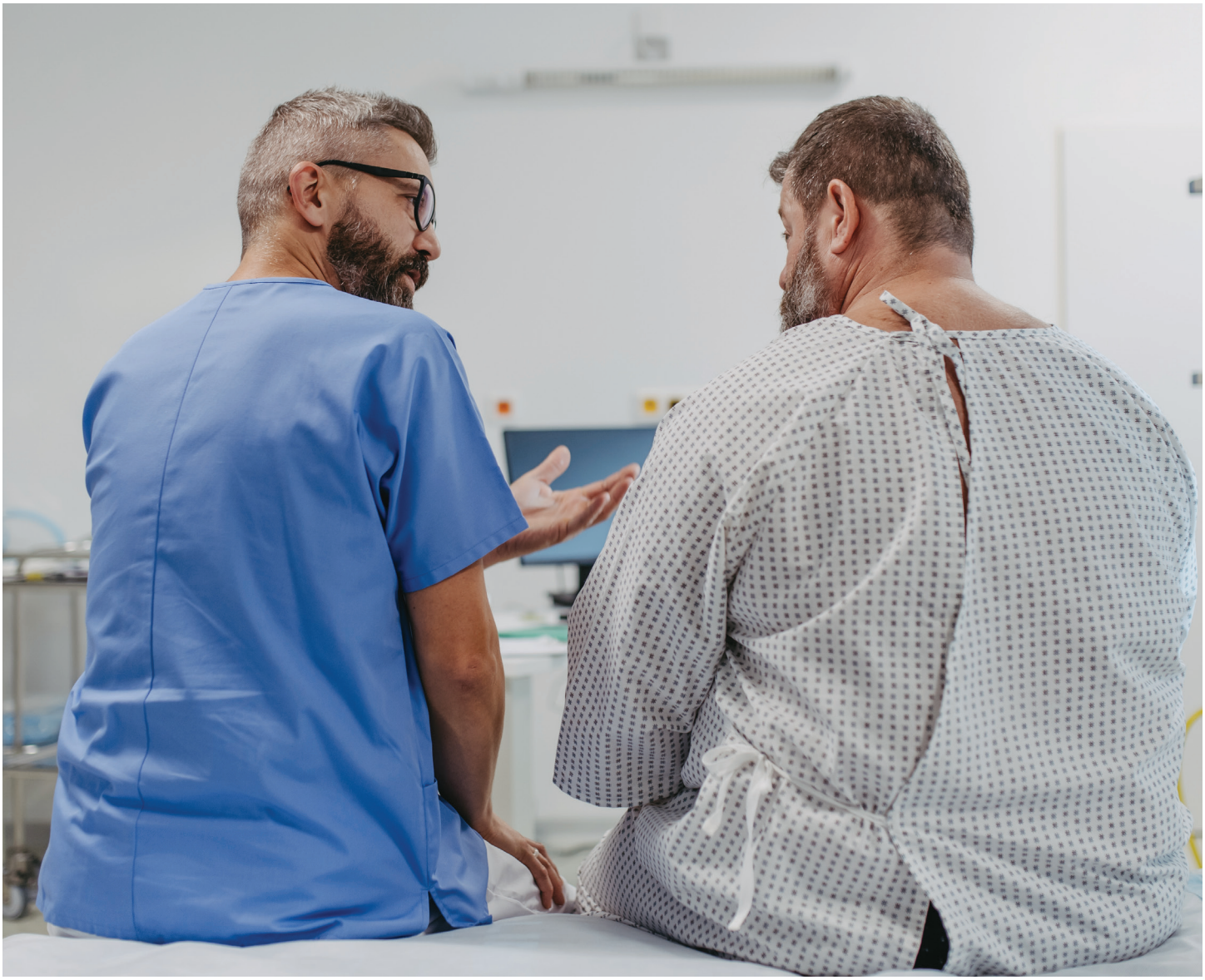
Medication	Mechanism	Dose	Comments
Abatacept (Orencia)[7]	Cytotoxic T-lymphocyte associated (CTLA) antigen-4-immunoglobulin CTLA-4-Ig prevents the T cell proliferation and stimulation that are important for progression of COVID-19.	10 mg/kg (up to a maximum of 1,000 mg) IV x1 dose	No dose adjustment needed for renal function. Monitor for new infections, since abatacept has immunosuppressive effects.
Baricitinib (Olumiant)[8-10]	Janus kinase (JAK) inhibitor JAK inhibitors block phosphorylation of important proteins that are required for the signal transduction that precedes inflammation.	Depends on renal function (eGFR in mL/min/1.73 m2). For eGFR >=60: 4 mg PO once daily; 30 - <60: 2 mg PO once daily; 15 - <30: 1 mg PO once daily; <15: not recommended To be used for up to 14 days or until discharged from the hospital, whichever occurs first.	Monitor for new infections, since baricitinib has immunosuppressive effects.
Dexamethasone (Decadron)[11]	Corticosteroid Corticosteroids most likely act by diminishing the systemic inflammation caused by COVID-19.	6 mg IV or PO once daily To be given for up to 10 days or until discharged from the hospital, whichever occurs first.	Need to monitor for adverse effects such as opportunistic infections, hyperglycemia, and neuropsychiatric effects (including acute psychosis, mania, and mood lability).
Infliximab (Remicade)[7]	Tumor necrosis factor (TNF) alpha inhibitor TNF-alpha is a cytokine that promotes inflammation. Reducing levels of this cytokine by administering a TNF alpha inhibitor should favorably impact COVID-19 manifestations.	5 mg/kg IV x 1 dose	No dose adjustment needed for renal function. Monitor for new infections since infliximab has immunosuppressive effects.

Medication	Mechanism	Dose	Comments
Remdesivir (Veklury)[12-14]	Nucleotide prodrug of an adenosine analog This drug attaches to RNA-dependent RNA polymerase and causes early termination of RNA transcription, thus preventing viral replication.	200 mg IV x one dose, then 100 mg IV daily for 4 days or until discharged from the hospital, whichever occurs first. If the patient was not hospitalized for COVID-19, then the duration of treatment is 3 days.	No dose adjustment needed for renal function. May cause nausea, transaminitis, hypersensitivity reactions, bradycardia, and an increased prothrombin time (without change in INR).
Sarilumab (Kevzara)[15]	Anti-interleukin-6 (IL-6) receptor monoclonal antibody COVID-19 is associated with increased release of cytokines (including IL-6), which leads to inflammation. Use of anti-interleukin-6 (IL-6) receptor monoclonal antibodies reduces IL-6 levels.	400 mg IV x 1 dose	Should be cautiously used in patients who belong to groups that have not been sufficiently represented in clinical trials. Need to monitor for development of elevated liver enzymes.
Tocilizumab (Actemra)[16]	Anti-interleukin-6 (IL-6) receptor monoclonal antibody COVID-19 is associated with increased release of cytokines (including IL-6), which leads to inflammation. Use of anti-interleukin-6 (IL-6) receptor monoclonal antibodies reduces IL-6 levels.	8 mg/kg (up to a maximum of 800 mg) IV x1 dose	Only the IV formulation should be used to treat COVID-19. Should be cautiously used in patients who belong to groups that have not been sufficiently represented in clinical trials. Need to monitor for development of elevated liver enzymes.
Tofacitinib (Xeljanz)[17]	Janus kinase (JAK) inhibitor JAK inhibitors block phosphorylation of important proteins that are required for the signal transduction that precedes inflammation.	10 mg PO twice daily for up to 14 days or until discharge from the hospital, whichever occurs first. For eGFR <60: 5 mg PO twice daily.	Monitor for new infections, since tofacitinib has immunosuppressive effects. If tofacitinib is coadministered with a CYP3A4 inhibitor, then dose modification is necessary.

National Institutes of Health COVID-19 Treatment Guidelines

The NIH COVID-19 Treatment Guidelines include clinical recommendations for the treatment of hospitalized patients with COVID-19. The guidelines were last updated on February 29, 2024, at the time of this publication[18]. The panel members who developed the guidelines were appointed based on expertise from various organizations including government agencies, professional societies, academia, and others.

Clinical Setting	Recommendations
Patients who are hospitalized for reasons other than COVID-19 and do not need supplemental oxygen.	■ All patients should receive symptom management. ■ In order of preference medications that should be utilized are: ▫ ritonavir-boosted nirmatrelvir ▫ remdesivir ▫ molnupiravir
Patients who require hospitalization for COVID-19 and have no requirement for supplemental oxygen.	■ Remdesivir should be utilized for patients at high risk of progressing to severe COVID-19 because they are immunocompromised or have other risk factors. ■ Dexamethasone or other systemic corticosteroids should not be utilized unless it is for another indication.
Patients who require hospitalization for COVID-19 and have a requirement for conventional oxygen.	■ Patients should receive dexamethasone plus remdesivir. ■ For patients with a rapidly increasing oxygen requirement, either intravenous tocilizumab or oral baricitinib should be added. Alternative immunomodulators are either infliximab or abatacept.
Patients who require oxygen delivery via high-flow nasal cannula or noninvasive ventilation.	■ All patients should receive dexamethasone plus a second immunomodulator. ■ The first choice for a second immunomodulator is oral baricitinib, and if this is not available then intravenous tocilizumab should be utilized. ■ Additional options for a second immunomodulator are infliximab or abatacept. ■ Some patients should have remdesivir added to the two immunomodulator drugs. Patients who are expected to receive the most benefit from the addition of remdesivir are those who (a) had symptom onset ≤10 days before their presentation, (b) are immunocompromised, or (c) have ongoing viral replication.
Patients who require mechanical ventilation or extracorporeal membrane oxygenation.	■ Dexamethasone should be given to all patients. ■ Either tocilizumab or baricitinib should be administered as the second immunomodulator. ■ Inadequate evidence is available in regard to use of remdesivir in this group. It may be beneficial to add remdesivir to immunomodulator therapy for patients who (a) had symptom onset ≤10 days before their presentation, (b) are immunocompromised, or (c) have ongoing viral replication.



The recommendations in the NIH COVID-19 Treatment Guidelines were developed from clinical studies and expert opinion. For each recommendation, there are two ratings: a capital letter (A, B, or C) which specifies the recommendation's strength, and also a Roman numeral that may or may not be associated with a lowercase letter (I, IIa, IIb, or III). The table below summarizes how the strength of each recommendation is derived:

Strength of Recommendation For Statement	Strength of Evidence For Recommendation
A. Strong B. Moderate C. Weak	I. High quality (randomized trials or well-constructed subgroup analyses of such trials; meta-analyses with no significant limitations) IIa: Moderate quality (randomized trials or subgroup analyses of such trials that fall short of the standards for a I rating) IIb: Moderate quality (observational studies with no significant limitations; meta-analyses of observational studies) III: Expert opinion

Case Studies: Treating Hospitalized Patients With COVID-19

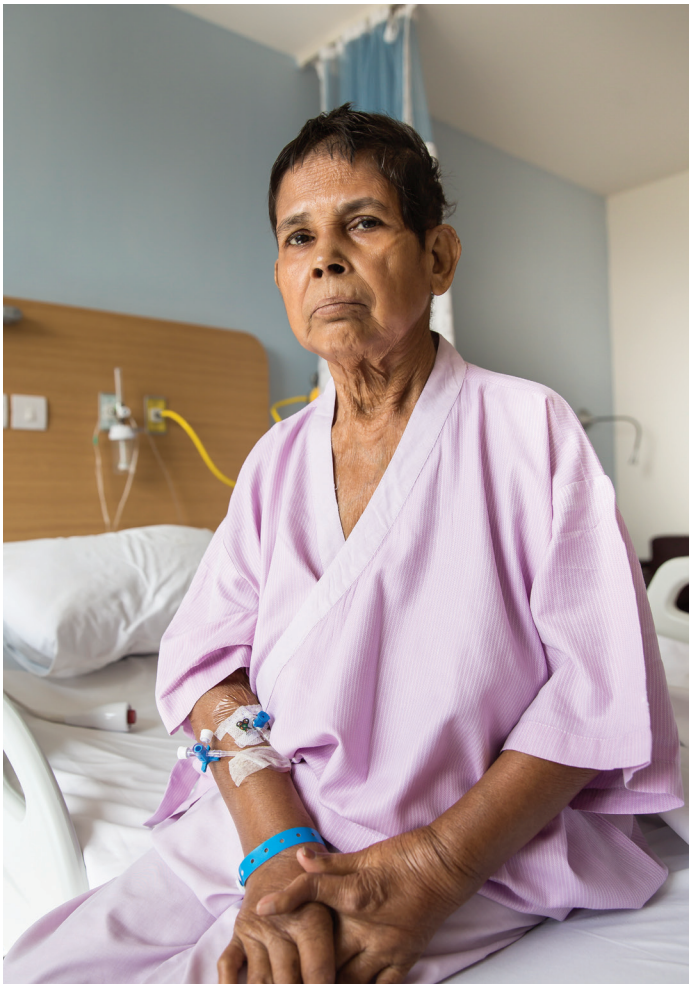
The case studies provided below were developed to assist the clinician learner with identifying appropriate evidence-based treatment solutions for the hospitalized patient diagnosed with COVID-19.

Case Study 1:

Patient Who Requires Hospitalization For COVID-19 And Has No Requirement For Supplemental Oxygen

A 78-year-old woman with a history of type 2 diabetes, coronary artery disease, and heart failure with preserved ejection fraction arrived in the emergency room after a recent trip to visit family during the holidays. She reported progressive fatigue, dyspnea, with fevers and chills for the past 2 days. She also described decreased food and water intake since the symptoms began. Due to increased lethargy, she has been lying in bed for most of the day. She has been taking only acetaminophen for her symptoms, and its effects have been modest. Her initial vital signs included a temperature of 101.5 degrees Fahrenheit, heart rate of 115 beats per minute, respiratory rate of 24 breaths per minute, and oxygen saturation level of 94% on room air. Her physical exam was notable for dry mucous membranes, and crackles in the right lung base. Her COVID-19 PCR test was positive, and her chest radiograph showed consolidation in the right lower lobe consistent with pneumonia. In the emergency room, she was started on intravenous fluids and remdesivir, and she was subsequently admitted to the inpatient medicine unit. In the following days her symptoms improved and her vital signs normalized. She had adequate food intake and was able to ambulate independently. On hospital day 3, she wished to return home, and her physician agreed with discharge from the hospital.

This case describes a hospitalized patient with moderate COVID-19. She had evidence of lower respiratory tract involvement, but had no need for supplemental oxygen since her room air oxygen saturation level was consistently ≥94%[13]. Other factors such as dehydration, decreased mobility, inability to maintain activities of daily living, and home safety may necessitate hospitalization. Additionally, patients at higher risk of progression to severe disease may require an inpatient stay[19]. Advanced age is a major risk factor for disease progression, as data suggests that patients older than 75 years have over 140 times the risk of severe outcomes compared with those who are 18-29 years old[20]. Comorbidities that increase the risk of progression to severe disease include cerebrovascular disease, chronic kidney disease, chronic lung disease, chronic liver disease, diabetes, heart disease, obesity, primary immunodeficiency, and pregnancy[19]. In this case, the patient had advanced age (78 years), diabetes, and heart disease as risk factors.



Remdesivir is recommended (BIIb for immunocompromised, BIII for other high-risk factors) for hospitalized patients with mild or moderate COVID-19[18]. A randomized, double blind, placebo-

controlled trial demonstrated a shortened recovery time in patients hospitalized with COVID-19 who received remdesivir versus placebo by 5 days (10 days versus 15 days)[21]. Additionally, immunocompromised patients with COVID-19 who were hospitalized and given remdesivir had lower mortality compared to matched non-remdesivir patients at 14 and 28 days[13].

The largest benefit from remdesivir in COVID-19 is seen with early administration, or within 7 to 10 days of symptom onset[18,22]. A 5-day course of remdesivir is recommended; however, if the patient is stable for discharge from the hospital, the course can be stopped early[12]. Evidence from a randomized, double-blind, placebo-controlled trial involving patients with mild COVID-19 and high-risk factors showed an 87% relative reduction in hospitalization or death from a 3-day course of remdesivir compared to placebo, albeit in a non-hospitalized cohort[23]. In the case above, the patient received a 3-day course of remdesivir before she was discharged from the hospital.

The NIH COVID-19 Treatment Guidelines recommend against using dexamethasone (AIIa) or other systemic corticosteroids (AIII) for mild to moderate COVID-19 patients who do not require supplemental oxygen for respiratory support. This excludes patients who require steroids for other medical reasons. This recommendation is supported by evidence from the RECOVERY trial, an open-label, randomized trial comparing dexamethasone to usual care alone[11]. In the subgroup of patients who did not receive supplemental oxygen, dexamethasone did not result in benefit, and the authors noted the possibility of harm. Thus in our case, the patient was appropriately given remdesivir with no steroids.

Side effects of remdesivir include nausea, transaminitis, hypersensitivity reactions. and increased prothrombin time (but no effect on the international normalized ratio), and bradycardia[24]. No dose adjustment of remdesivir is needed for patients who have impaired renal function, including those who are on dialysis. However, sulfobutylether-beta-cyclodextrin (SBECD) sodium, the vehicle in which remdesivir is formulated, is principally removed by the kidneys. For patients who have renal impairment, an increase in the SBECD level may be associated with both hepatotoxicity and nephrotoxicity. Despite this concern, the use of remdesivir in patients with renal impairment has not been associated with an increased frequency of adverse events[25].

The Food and Drug Administration recommends checking the prothrombin time and liver function tests prior to the initiation of remdesivir, and these tests should be repeated as clinically appropriate during the course of treatment. Discontinuation of remdesivir will be necessary if the alanine aminotransferase level rises to more than ten times the upper limit of normal.

Key Takeaways:

- Remdesivir should be given early to patients hospitalized with mild or moderate COVID-19.
- Hospitalization does not need to be prolonged to complete a 5-day course of remdesivir if the patient is stable to be discharged, and a 3-day course is reasonable.
- Dexamethasone should not be given to hospitalized patients with COVID-19 with no supplemental oxygen requirements unless needed for other medical reasons.

Evidence

NEJM 2020 Beigel et al. Remdesivir for the treatment of COVID-19 - Final Report[21]:

- Double-blind, randomized, placebo-controlled trial of intravenous remdesivir.
- Randomly assigned remdesivir 200 mg on day 1, followed by 100 mg daily for up to 10 days vs placebo.
- 1,062 randomized patients: those who received remdesivir had a median recovery of 10 days, compared to 15 days for placebo.
- Remdesivir was superior to placebo in shortening time to recovery in hospitalized patients with COVID-19 with lower respiratory tract infection.

Case Study 2:

Patient Who Requires Hospitalization For COVID-19 And Has A Requirement For Conventional Oxygen

A 75-year-old man with a history of coronary artery disease, hypertension, and renal transplantation (for which he takes mycophenolate mofetil, tacrolimus, and prednisone daily for immunosuppression) was brought to the emergency room by his wife due to a 5-day history of shortness of breath, nonproductive cough, and intermittent fevers. Initial vital signs were as follows: temperature of 102 degrees Fahrenheit, heart rate of 124 beats per minute, blood pressure 115/70 mmHg, respiratory rate of 32 breaths per minute, and oxygen saturation level at 89% on room air. Lab work included white blood cell count 12.6 cells/μL, hemoglobin 10.3 g/dL, and creatinine 2.1 mg/dL. His COVID-19 PCR test result was positive, and his chest x-ray showed ground glass opacities in the right lower lobe. In the emergency room the patient was started on remdesivir and dexamethasone. Supplemental oxygen was initiated at 2 L per minute by nasal cannula and oxygen saturation level increased to 94%. During the next 4 days he was monitored in the inpatient medicine unit, and his respiratory status gradually improved so that he could be weaned off oxygen. On hospital day 5, he was discharged to home.

This case describes a hospitalized patient with severe COVID-19, indicated by hypoxia (room air oxygen saturation level <94%) and tachypnea (respiratory rate >30 breaths per minute). In the case of this patient requiring conventional oxygen (supplemental oxygen not administered via high-flow nasal cannula, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation), the use of remdesivir plus dexamethasone is recommended (BIIa). A randomized, controlled, open-label trial demonstrated that treatment with dexamethasone is associated with decreased mortality in patients with COVID-19 who require supplemental oxygen[11]. For patients requiring oxygen without invasive mechanical ventilation, the incidence of death within 28 days was 23.3% for those treated with dexamethasone compared to 26.2% (rate ratio, 0.82; 95% CI, 0.72 to 0.94) for those not treated with this steroid. Similarly for patients requiring invasive mechanical ventilation, the incidence of death was 29.3% versus 41.4% (rate ratio, 0.64; 95% CI, 0.51 to 0.81), respectively. Again, this survival benefit was not observed in patients who did not require supplemental oxygen[11]. The patient in this case initially required conventional oxygen and was appropriately treated with remdesivir and dexamethasone. He completed 5-day courses of both medications before he was discharged from the hospital, and his hospitalization did not need to be prolonged to complete a 10-day course of dexamethasone.

The evidence that supports the use of alternative systemic corticosteroids, such as hydrocortisone and methylprednisolone is not as strong as that which exists for dexamethasone[26,27]. However, in the event that dexamethasone is not available, it is acceptable to use an alternative corticosteroid such as methylprednisolone, prednisone, or hydrocortisone (BIII). The NIH COVID-19 Treatment Guidelines recommend that patients with COVID-19 who take steroids chronically for an underlying condition should continue to do so (AIII). The patient in this case received dexamethasone in place of home prednisone during his hospitalization, and his outpatient dose of prednisone was resumed at the time of his hospital discharge.

Adverse effects that may be noted with the use of dexamethasone include steroid-induced hyperglycemia, steroid psychosis, other infections, and avascular necrosis. Since dexamethasone induces cytochrome P450 3A4, it has the potential to reduce levels of medications that are substrates for this enzyme.

Key Takeaways:

- Remdesivir plus dexamethasone should be administered to patients who are hospitalized for COVID-19 and require conventional oxygen.
- Dexamethasone should be given for up to 10 days or until discharged from the hospital, whichever occurs first.

Evidence

NEJM 2021 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19[11]:

- Controlled, randomized, open label trial comparing 2,104 patients receiving 10 days of 6 mg IV dexamethasone versus usual care.
- A lower 28-day mortality was observed with the use of dexamethasone for patients who required mechanical ventilation or supplemental oxygen, but not for those who required no respiratory support.

Case Study 3:

Patient Who Requires Oxygen Via High-Flow Nasal Cannula Or Noninvasive Ventilation

A 56-year-old man with a history of type 2 diabetes mellitus, hypertension, and chronic kidney disease stage 3 was brought to the emergency room by emergency medical services due to a 2-day history of rapidly progressive respiratory distress. At the time of arrival in the emergency room his vital signs were as follows: blood pressure 110/70 mmHg, heart rate 116 beats per minute, respiratory rate 28 breaths per minute, temperature 102.1 degrees Fahrenheit, and oxygen saturation level 88% on oxygen 6 L/minute by nasal cannula. His significant hypoxia prompted the escalation of oxygen delivery to high-flow nasal cannula at a rate of 10 L/minute. Remarkable lab results included white blood cell count 12.3 cells/μL, hemoglobin 10.8 g/dL, and serum sodium 132 mmol/L. His chest x-ray showed ground-glass opacities throughout both lung fields, and his COVID-19 PCR test was positive. He was admitted to the ICU for management of acute hypoxic respiratory failure, and dexamethasone, remdesivir, and baricitinib were administered. His respiratory status gradually improved in the subsequent days and he required only 2 L/minute oxygen via nasal cannula at the end of his hospitalization. He was discharged to a subacute rehabilitation facility on hospital day 16.

This case describes a critically ill patient with COVID-19 requiring high-flow oxygen. All hospitalized patients who require high-flow nasal cannula or non-invasive ventilation should receive dexamethasone (AI), as previously discussed[11]. Additionally, a second immunomodulator should be added, preferably baricitinib (AI), a janus kinase (JAK) inhibitor. A randomized, controlled, open-label platform trial and meta-analysis demonstrated that the addition of baricitinib to usual care in COVID-19 patients was associated with reduced mortality compared to usual care alone (12% versus 14%, respectively, age-adjusted rate ratio 0.87; 95% CI 0.77 - 0.99; p=0.028)[8]. An updated meta-analysis of 9 completed trials demonstrated that use of baricitinib or another JAK inhibitor led to a 20% reduction in mortality (rate ratio 0.80; 95% CI 0.72 - 0.89; p<0.0001)[8].

Patients who receive either baricitinib or tofacitinib (a JAK inhibitor alternative) should be evaluated for the development of new infections since these drugs cause immunosuppression. An increased incidence of stroke, myocardial infarction, and death associated with the long-term use of tofacitinib was noted by the Food and Drug Administration, but thus far these adverse events have not been observed with the short-term use of JAK inhibitors in COVID-19[28,29].

If baricitinib is not available, then the next preferred alternative is the anti-IL-6 receptor monoclonal antibody, tocilizumab (BIIa). In a randomized, controlled, open-label platform trial, lower rates of invasive mechanical ventilation and death were observed in patients who received tocilizumab in addition to steroids[16]. Mortality at 28 days for patients who received tocilizumab in addition to steroids was 31%, in comparison to 35% for patients who received usual care alone (rate ratio 0.85; 95% CI 0.76 - 0.94; p=0.0028). Furthermore, hospital discharge within 28 days was more likely in patients who received tocilizumab compared to control (57% vs 50%; rate ratio 1.22; 1.12 - 1·33; p<0.0001)[16].

Sarilumab, another anti-IL-6 receptor monoclonal antibody, can be used if tocilizumab is not available. Results of an international, multifactorial, adaptive platform trial suggested that tocilizumab and sarilumab are similarly effective in increasing hospital survival rates[30]. For critically ill patients, hospital survival was higher with the use of tocilizumab and sarilumab as compared to controls (median adjusted odds ratio 1.42 (95% CrI 1.05, 1.93) and 1.51 (95% CrI 1.06, 2.20) for tocilizumab and sarilumab, respectively).

The most commonly noted laboratory abnormality associated with tocilizumab and sarilumab is dose-dependent elevation of liver enzymes. Thrombocytopenia or neutropenia is rarely noted[31,32]. Randomized trials did not demonstrate an increase in the development of secondary infections with the use of tocilizumab with corticosteroids, in comparison with control patients[33]. However, the use of tocilizumab was associated with an increased incidence of fungal infections[33].

Other alternative immunomodulators include infliximab (CIIa) and abatacept (CIIa), both of which were shown to reduce mortality in a randomized, double-masked, placebo-controlled clinical trial that investigated the efficacy of these medications in adult patients hospitalized with COVID-19[7]. This study showed that all-cause 28-day mortality was 10.1% for infliximab vs 14.5% for placebo (odds ratio 0.59 [95% CI, 0.39-0.90]) and 11.0% for abatacept vs 15.1% for placebo (odds ratio 0.62 [95% CI, 0.41-0.94]).

Since infliximab and abatacept have immunosuppressive effects, it is necessary to monitor for the development of new infections in patients who receive either of these medications. The single dose of either of these medications that is required for treatment of COVID-19 was not associated with any substantial adverse effects[7].

Finally, the use of remdesivir in addition to dexamethasone plus a second immunomodulator may be beneficial in patients requiring high-flow oxygen or noninvasive ventilation, if any of the following criteria are met: (1) immunocompromised (BIIb), (2) have continuing viral replication (BIII), or (3) developed symptoms ≤10 days before they presented for treatment (CIIa). The most effective strategy for treating patients who have evidence of persistent viral replication (as indicated by a low cycle threshold value) after completion of antiviral therapy is uncertain. Suggested strategies have been discussed in case series, and these include longer courses of antiviral medications or use of combination therapy[34,35].

Key Takeaways:

- A patient who requires high-flow oxygen or noninvasive ventilation should receive dexamethasone plus a second immunomodulator.
- The second immunomodulator can be oral baricitinib (preferred), or intravenous tocilizumab, infliximab, or abatacept.
- Patients with COVID-19 who require high-flow oxygen or noninvasive ventilation may benefit from the addition of remdesivir in addition to dexamethasone plus a second immunomodulator, specifically in those who had symptom onset ≤ 10 days before their presentation, are immunocompromised, or have ongoing viral replication.

Evidence

Lancet 2022 RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19[8]:

- Randomized, controlled, open-label, platform trial that assessed multiple possible treatments for COVID-19.
- 8,156 patients randomly assigned to standard of care alone or standard of care plus baricitinib 4 mg PO daily for 10 days or until discharge if sooner.
- Those who received baricitinib had a reduced mortality rate compared with those who received standard of care alone.

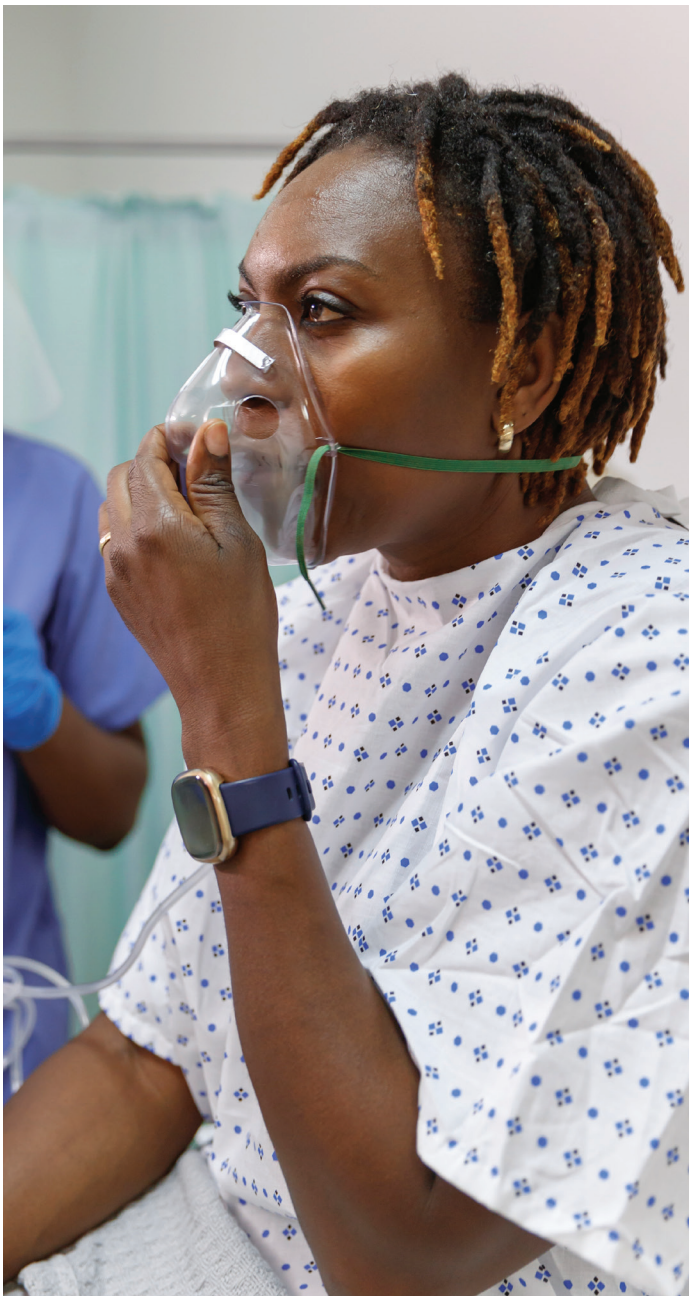
Case Study 4:
Anticoagulation

A 35-year-old woman with a history of hypertension and osteoarthritis was brought to the ED from home due to dyspnea on exertion, a productive cough, and pleuritic chest pain. Her initial vital signs were as follows: temperature 101.0 degrees Fahrenheit, heart rate 110 beats per minute, respiratory rate 22 breaths per minute, and room air oxygen saturation level 88%. Her chest radiograph showed an infiltrate in the left lower lobe, consistent with pneumonia, and her COVID-19 PCR test was positive. Her D-dimer level was elevated. A chest CT angiogram was performed, and it showed no pulmonary embolus. The patient was started on remdesivir, dexamethasone, and a therapeutic dose of heparin, and then she was admitted to the hospitalist service. On hospital day two the patient had worsening vital signs, including an increased oxygen requirement which necessitated intubation and mechanical ventilation. She was transferred to the ICU for further management. Doppler ultrasound of bilateral lower extremities was performed and it was negative for deep venous thrombosis. She was switched to a prophylactic dose of heparin.

The use of antithrombotics changed rapidly during the COVID-19 pandemic. In regards to routine screening for venous thromboembolism (VTE), the NIH COVID-19 Treatment Guidelines concluded that there is insufficient evidence to recommend either for or against this testing, regardless of the status of coagulation markers. For cases with rapid deterioration of pulmonary, cardiac, or neurological function, or sudden loss of peripheral perfusion, they recommend evaluation for VTE (AIII).

In regards to VTE prophylactic versus therapeutic dose of heparin for hospitalized patients, the recommendations are simple for most categories. For patients with no supplemental oxygen requirements, it is recommended to provide prophylactic doses of heparin unless contraindicated (AI, BIII for pregnant patients). The same recommendation for prophylactic dose exists for patients requiring high-flow nasal cannula, noninvasive ventilation, mechanical ventilation or ECMO (AI, BIII for pregnant patients).

Only for patients requiring low-flow supplemental oxygen does the decision for heparin require some nuance. The determination is dependent on D-dimer levels: if the D-dimer level is elevated, then a therapeutic dose of heparin is advised instead of the usual prophylactic dose[36]. The NIH COVID-19 Treatment Guidelines give this recommendation a CIIa rating, and it applies only if no contraindications for therapeutic heparin are present. These contraindications include a platelet count <50 x 10^9/L, hemoglobin <8 g/dL, need for dual antiplatelet therapy, bleeding within the past 30 days that required hospital care, or a history of a bleeding disorder.



For a patient who has an elevated D-dimer level and is initially started on a therapeutic dose of heparin, but is then transferred to ICU, it is advised to switch to a prophylactic dose of heparin, unless another indication for therapeutic dosing exists (BIII). Our patient described above had an elevated D-dimer level and initially required low-flow oxygen, and was administered the appropriate therapeutic dose of heparin. However, after she decompensated and required ICU-level care with mechanical ventilation, she was switched to a prophylactic dose of heparin as per the NIH COVID-19 Treatment Guidelines.

Key Takeaways:

- Prophylactic dose heparin is recommended in most categories of hospitalized patients with COVID-19, unless contraindicated, or therapeutic dose is required for other reasons.
- One exception exists in patients requiring low-flow supplemental oxygen with elevated D-dimer levels, in which a therapeutic dose of anticoagulation is recommended (unless contraindicated) (CIIa).
- If a patient with COVID-19 requires transfer to ICU-level care and was initially started on a therapeutic dose of heparin, then it is recommended to switch to a prophylactic dose of heparin.

Evidence

RAPID trial: Open-label, randomized controlled trial of therapeutic heparin in hospitalized patients with COVID-19[36]:

- Evaluated hospitalized patients with elevated D-dimer level and Sp02 ≤93% on room air.
- Patients received either therapeutic dose heparin (unfractionated heparin or low molecular weight heparin) or prophylactic dose heparin for up to 28 days, until discharge, or death.
- Therapeutic heparin reduced all-cause mortality (secondary endpoint) but no change in primary endpoints of ICU admission, need for noninvasive ventilation or mechanical ventilation, or death up to 28 days.
- There was no difference in VTE or major bleeding events.

Conclusion

While the mortality rate of COVID-19 has decreased considerably since early stages of the pandemic, it continues to be a common cause of hospitalization and morbidity. Patient factors such as advanced age, diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, chronic liver disease, obesity, and immunosuppression, among others place patients with COVID-19 at a higher risk of poor outcomes. The NIH COVID-19 Treatment Guidelines remain the mainstay for guiding hospitalists in treating hospitalized patients and should be the first point of reference for the most updated recommendations. Hospitalists are unique in that they provide direct care for most patients who are hospitalized with COVID-19. From the emergency room to the ICU, from the inpatient setting to home, the oversight of hospitalists remains broad. Thus, it is crucial for hospitalists to understand the entire spectrum of treatment options and the rapid evidence that guide treatment decisions.

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