

EVIDENCE-BASED STRATEGIES FOR THE MANAGEMENT OF PATIENTS HOSPITALIZED WITH COVID-19

Based on a Medscape Education Online Activity

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CME/ABIM MOC:

Release Date: 09/01/22

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Target Audience: This activity is intended for hospitalists, infectious disease specialists, critical care specialists, pulmonologists, and emergency medicine physicians practicing in the United States.

Goal Statement: The goal of this activity is that learners are up to date on the latest data and recommendations for immunomodulators in the treatment of patients hospitalized with severe COVID-19 and understand how to appropriately incorporate therapies into patient care.

Learning Objectives:

Upon completion of this activity, participants will:

- Have increased knowledge regarding the key clinical data on immunomodulators for the treatment of patients hospitalized with COVID-19
- Demonstrate greater confidence in their ability to treat patients hospitalized with COVID-19

Disclosures

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Medscape had the pleasure of speaking with Raymund R. Razonable, MD, professor of medicine and vice chair of the Division of Public Health, Infectious Diseases and Occupational Medicine at the Mayo Clinic in Rochester, Minnesota. We discussed the treatment of patients with COVID-19 in the hospital setting with regard to recognizing the phases of COVID-19, recognizing patients at risk for progression to severe disease, and implementing appropriate treatment and management strategies with a focus on when to use recommended immunomodulators.

Medscape: Which patients with COVID-19 are at the highest risk for progression to severe disease?

Dr Razonable: The presence of certain clinical characteristics and comorbidities predicts whether a patient is at risk for progression to severe disease. The number 1 factor is age; people ≥ 65 years of age have a higher risk of progression, and the risk directly increases with increasing age. Comorbidities and medical conditions that increase the risk of severe disease include diabetes mellitus, obesity, hypertension, chronic cardiac and pulmonary diseases, and chronic kidney disease. In addition, patients who are immunocompromised, either because of an underlying condition or because of the use of medications that suppress the immune system, are also at increased risk of disease progression. Other conditions such as pregnancy and dependency on medical devices (eg, tracheostomy and gastrostomy tubes) also put patients at increased risk of progression.

Vaccination may prevent severe disease progression, but it is not 100% protective, so other factors are at play and must be considered. The Mayo Clinic has developed a weighted comorbidity score called the Monoclonal Antibody Screening Score or MASS, which is used to identify patients who are at high risk of progression; the higher the score, the higher the risk of progression to severe COVID-19 disease.¹

Medscape: Are the variants of SARS-CoV-2 clinically relevant for determining the risk for disease progression?

Dr Razonable: Not really. In a clinical setting, knowledge of the viral variant causing a particular infection is not determined in real time because sequencing is not routinely performed in practice. Instead, we rely and depend on public health data from the US Department of Health and Human Services to gather and understand the general trends in terms of current progression rates of each variant.

Medscape: In your experience, what is the typical clinical presentation of patients with COVID-19?

Dr Razonable: There is no single, typical, or unique clinical presentation of patients with COVID-19. The presentation can range from asymptomatic illness to one of 4 symptomatic categories. Asymptomatic patients are often diagnosed with COVID-19 through screening since they do not show symptoms, and they typically do not require COVID-19 directed treatment. These

patients are usually in the community or are admitted to the hospital for another indication, and they are diagnosed when they are screened for COVID-19 at hospital entry. Then, there are patients that develop upper respiratory symptoms and get tested for COVID-19. These patients are generally categorized into one of 4 levels: 1, mild (have upper respiratory symptoms); 2, moderate (have cough and shortness of breath, but oxygen saturation $> 94\%$); 3, severe (have oxygen saturation $< 94\%$ that requires supplemental oxygen); or 4, critical (require admission to an intensive care unit, invasive mechanical ventilation, or extracorporeal membrane oxygenation and have evidence of multi-organ dysfunction).

Patients with mild to moderate disease are best managed in the outpatient setting. Patients who progress from moderate to severe disease or beyond should be hospitalized because they will need supplemental oxygen and close monitoring in the hospital setting. When a patient develops organ dysfunction or requires invasive mechanical ventilation, they are classified as having a critical COVID-19 illness. Only a minority of patients progress to critical disease and, unfortunately, some will eventually die from COVID-19.

Medscape: What are the different stages of the COVID-19 disease course, and what stages do you see most often in the hospital?

Dr Razonable: The clinical presentations that I just described overlap with the 3 stages of disease (Figure 1)²: stage 1 is the early/viral phase, stage 2 is the pulmonary phase, and stage 3 is the proinflammatory or hyperinflammation phase.² Symptoms are superimposed with the disease stages across a spectrum. Stage 1 coincides with mild to moderate symptoms such as fever and cough. Stage 2 typically coincides with moderate to severe symptoms such as shortness of breath, chest radiography findings of ground glass opacities that are indicative of pneumonia, and hypoxia. Patients usually come into the hospital during stage 2 or when their disease is progressing from stage 2 to stage 3. Stage 3 is the proinflammatory response phase manifested by hypoxia requiring supplemental oxygen and elevation of C-reactive protein (CRP), interleukin-6 (IL-6), and other inflammatory markers, and patients typically experience severe or critical signs and symptoms such as hypotension and respiratory failure. Notably, in all stages, patients have lymphopenia.

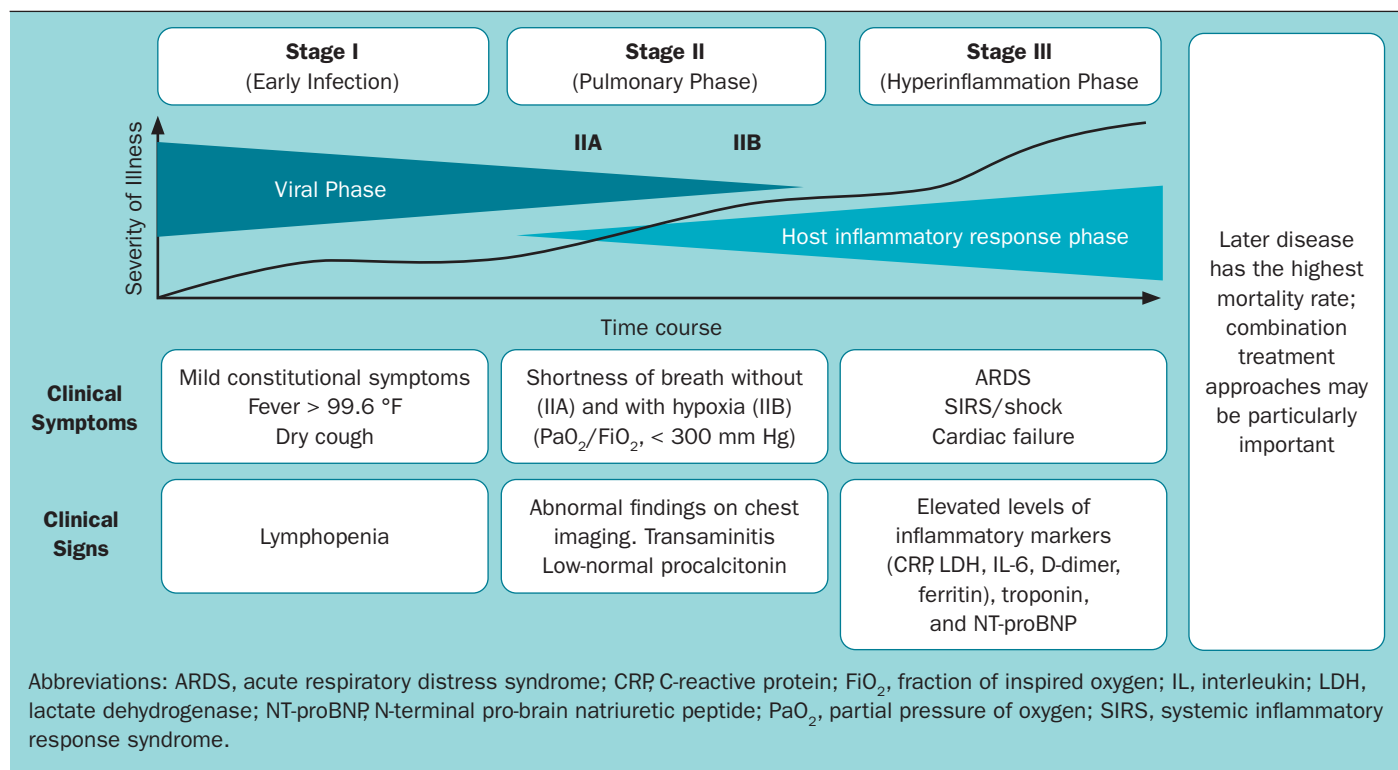


Figure 1. The Spectrum of COVID-19 Disease Stages, Symptom Presentation, and Corresponding Management²

In addition to those presenting with stage 2 or 3 disease, patients who are admitted to the hospital for other indications may also be incidentally diagnosed with COVID-19 from screening and should be considered for treatment. During this period of the pandemic, it is actually common for patients to be diagnosed with COVID-19 unexpectedly or incidentally at the time of hospital admission for another indication. If these patients have mild symptoms and possess risk factors for progression to severe disease (eg, older age > 65 years, medical comorbidities, and immunocompromised status), they may qualify for treatment with an intravenous (IV) remdesivir daily for 3 days, oral nirmatrelvir/ritonavir twice daily for 5 days, oral molnupiravir twice daily for 5 days, or an antispikes monoclonal antibody (mAb) as 1-time infusion (bebtelovimab).

Medscape: Why is it important for providers to know the patient's stage of COVID-19?

Dr Razonable: It is important because the treatment is different depending on the stage and severity of disease. For patients who have stage 1 or mild to moderate disease and are managed in the outpatient setting, the treatments are supportive care, antiviral therapy (IV remdesivir for 3 days, oral nirmatrelvir/ritonavir, or oral molnupiravir), or an antispikes mAb (bebtelovimab). At this stage, treatment should focus on reducing viral replication and symptoms. The use of immunosuppressive or immunomodulator therapy is not approved at this stage. For patients who have stage 2 disease or are progressing to stage

3 or severe/critical disease and are admitted to hospital, treatments that target inflammation can be used, in addition to standard antiviral drug IV remdesivir for 5 days (vs 3 days in outpatient). Immunomodulators that are intended to reduce inflammation include dexamethasone or other corticosteroids, IL-6 inhibitors, and Janus kinase (JAK) inhibitors. These may be used to prevent further inflammation and disease progression and to reduce mortality in selected patients.

Medscape: What is the initial management of a hospitalized patient with COVID-19?

Dr Razonable: Initial management approaches include supportive care to stabilize vital signs and providing oxygen when needed. IV remdesivir is generally started with a plan to complete 5 days of treatment. If there are signs of respiratory compromise such as increasing oxygen requirement, then there is an option to add dexamethasone to the treatment regimen. The decision to add an additional immunomodulator such as an IL-6 inhibitor or a JAK inhibitor depends on the clinical response to dexamethasone treatment. It is also important for the provider to assess any potential contraindications to the immunomodulator therapies, such as active bacterial or fungal infections. COVID-19 predisposes patients to venous thrombosis and efforts to reduce this risk should be implemented. For patients with thrombosis, the use of the immunomodulator baricitinib is contraindicated. Monitoring oxygenation status is important as supplementation is provided based on patient needs.

Drug	Dosing	Usage
Antiviral		
Remdesivir	Dose for Adults and Children Weighing ≥ 40 kg: <ul style="list-style-type: none"> • 200 mg IV on day 1, then 100 mg IV once daily from day 2 Total Treatment Duration: <ul style="list-style-type: none"> • Hospitalized patients with severe disease: 5 days or until hospital discharge • Nonhospitalized patients with mild disease: 3 days 	Remdesivir is approved by the FDA for the treatment of COVID-19 in individuals aged ≥ 28 days and weighing ≥ 3 kg.
Corticosteroids		
Dexamethasone	Dose for COVID-19: <ul style="list-style-type: none"> • 6 mg IV or PO once daily Duration of Therapy: <ul style="list-style-type: none"> • Up to 10 days or until hospital discharge 	Dexamethasone is not approved by the FDA for COVID-19 but is recommended by the NIH panel in certain patients hospitalized for COVID-19.
IL-6 Inhibitors		
Tocilizumab	FDA EUA Doses for COVID-19 for Hospitalized Patients Aged ≥ 2 Years, Based on Body Weight: <ul style="list-style-type: none"> • < 30 kg: 12 mg/kg (maximum 800 mg) by IV infusion over 1 hour • ≥ 30 kg: 8 mg/kg (maximum 800 mg) by IV infusion over 1 hour • Per the EUA, if clinical signs or symptoms worsen or do not improve following the first infusion, 1 additional dose may be administered ≥ 8 hours after the first dose. 	IV tocilizumab, which has been approved for non-COVID-19 indications, is available commercially and through an FDA EUA for the treatment of COVID-19 in hospitalized adults and pediatric patients aged ≥ 2 years who are receiving systemic corticosteroids and require supplemental oxygen, NIV, MV, or ECMO.
Sarilumab	Dose for COVID-19 in Clinical Trials: <ul style="list-style-type: none"> • Single dose of 400 mg IV 	The IV formulation of sarilumab is not approved by the FDA, but is recommended by the NIH panel when tocilizumab is not available.
JAK Inhibitor		
Baricitinib	FDA-Approved Doses for COVID-19 for Adults Aged ≥ 18 Years, Based on eGFR: <ul style="list-style-type: none"> • ≥ 60 mL/min/1.73 m²: 4 mg PO once daily • 30 to < 60 mL/min/1.73 m²: 2 mg PO once daily • 15 to < 30 mL/min/1.73 m²: 1 mg PO once daily • eGFR < 15 mL/min/1.73 m²: not recommended Duration of Therapy: <ul style="list-style-type: none"> • For up to 14 days or until hospital discharge 	Baricitinib is approved by the FDA for the treatment of COVID-19 in hospitalized adults aged ≥ 18 years requiring supplemental oxygen, NIV, MV, or ECMO and is available through an FDA EUA for children aged 2-17 years who require supplemental oxygen, NIV, MV, or ECMO.
Abbreviations: ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; IV, intravenous; kg, kilogram; mg, milligram; min, minute; mL, milliliter; MV, mechanical ventilation; NIH, National Institutes of Health; NIV, noninvasive ventilation; PO, by mouth		

Table 1 . Characteristics of Antiviral and Immunomodulator Therapies Used for Patients Hospitalized for COVID-19^{3,4}

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy
Hospitalized but Does Not Require Supplemental Oxygen	<p>The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII)^a. There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.</p>
Hospitalized and Requires Supplemental Oxygen	<p>Use 1 of the following options: Remdesivir^{b,c} (eg, for patients who require minimal supplemental oxygen) (BIIa) Dexamethasone plus remdesivir^{b,c} (BIIb) Dexamethasone (BI) For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug^d (eg, baricitinib^e or tocilizumab^e) (CIIa).</p>
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	<p>Use 1 of the following options: Dexamethasone (AI) Dexamethasone plus remdesivir (BIIb) For patients with rapidly increasing oxygen needs and systemic inflammation, add either baricitinib^e (BIIa) or IV tocilizumab^e (BIIa) to 1 of the options above.^{d,h}</p>
Hospitalized and Requires MV or ECMO	<p>Dexamethasoneⁱ (AI) For patients who are within 24 hours of admission to the ICU: Dexamethasone plus IV tocilizumab (BIIa) If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (BIIa). In May 2022, the FDA approved baricitinib for treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or ECMO with a recommended dose of 4-mg once daily for 14 days or until hospital discharge, whichever comes first. An alternative administration may be used for patients unable to swallow tablets.</p>

Rating of Recommendations: A, strong; B, moderate; C, weak.
 Rating of Evidence: I, one or more randomized trials without major limitations; IIa, other randomized trials or subgroup analyses of randomized trials; IIb, nonrandomized trials or observational cohort studies; III, expert opinion.
^aCorticosteroids that are prescribed for an underlying condition should be continued.
^bIf a patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir.
^cEvidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (eg, within 10 days of symptom onset). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large, placebo-controlled trial showed that the use of remdesivir reduced time to clinical recovery in hospitalized patients.
^dDrugs are listed alphabetically. There are no studies that directly compare the use of baricitinib and tocilizumab, and there is insufficient evidence to recommend a drug or class of drug (ie, JAK inhibitors and IL-6 inhibitors) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
^eIf baricitinib and IV tocilizumab are not available or not feasible to use, tofacitinib can be used instead of baricitinib (BIIa) and IV sarilumab can be used instead of IV tocilizumab (BIIa).
^fThe COVID-19 Treatment Guidelines Panel recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial (AIII). Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
^gThe combination of dexamethasone plus remdesivir may be considered for patients who have recently been intubated (CIII). The COVID-19 Treatment Guidelines Panel recommends against the use of remdesivir monotherapy in these patients (AIIa).
 Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IL, interleukin; IV, intravenous; JAK, Janus kinase; mAb, monoclonal antibody; MV, mechanical ventilation; NIV, noninvasive ventilation.

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity⁵

Medscape: What are the current therapies used in patients hospitalized for COVID-19?

Dr Razonable: Current therapies for patients who are admitted to the hospital for COVID-19 include antiviral therapy with IV remdesivir for 5 days and immunomodulator therapies including corticosteroid (dexamethasone), IL-6 inhibitors (tocilizumab and sarilumab), and a JAK inhibitor (baricitinib). Characteristics of antiviral and immunomodulator therapies used in patients hospitalized for COVID-19 are listed in Table 1.

Medscape: When should remdesivir and dexamethasone be used or not used in patients hospitalized for COVID-19?

Dr Razonable: Currently, remdesivir and dexamethasone are given to hospitalized patients when supplemental oxygen is required, which means the patient is progressing to severe disease (Figure 2).⁵ Treatment paradigms are continuously evolving based on new clinical data.

The National Institutes of Health (NIH) guidelines currently recommend remdesivir use in hospitalized patients who are on low-flow oxygen and within the first 10 days of the disease course.⁶ This antiviral agent is typically not given to patients hospitalized for COVID-19 who are not on supplemental oxygen, because of lack of data. However, results of the recent PINETREE trial, which evaluated the use of remdesivir vs placebo in the outpatient setting, challenge current recommendations.⁷ Outpatients with mild to moderate COVID-19 with at least 1 risk factor for disease progression had an 87% lower risk of hospitalization and death with a 3-day course of remdesivir treatment compared with placebo.⁷ Thus, the clinical efficacy of remdesivir in patients without supplemental oxygen has been demonstrated in a clinical trial.

Dexamethasone is currently used only in hospitalized patients on supplemental oxygen⁶ based on results of the RECOVERY trial,⁸ but this agent must be used cautiously based on its safety profile and particularly in immunocompromised patients and those at risk for secondary infection. Results of the ACTT-4 study were recently published.⁹ This trial compared dexamethasone plus remdesivir with baricitinib plus remdesivir in hospitalized patients on low-flow and high-flow supplemental oxygen. The primary outcome of mechanical ventilation-free survival at 29 days was similar between the study groups. Baricitinib was associated with a lower incidence of adverse events including severe life-threatening adverse events.⁹ Baricitinib is now approved by the FDA for the treatment of COVID-19 in hospitalized adults requiring oxygen.^{10,11}

Medscape: What are the treatment options for hospitalized patients with increasing oxygen requirements while on dexamethasone and remdesivir?

Dr Razonable: If oxygen requirements continue to increase despite treatment with remdesivir and dexamethasone, then other immunomodulators should be considered, such as IL-6 inhibitors or JAK inhibitors. For example, if a patient moves from a nasal canula in the morning to high-flow oxygen in the afternoon

while already receiving remdesivir and dexamethasone, then the addition of tocilizumab or baricitinib should be considered.

Medscape: Where do we stand with data on immunomodulators?

Dr Razonable: Regarding IL-6 agents, the RECOVERY trial showed that tocilizumab significantly reduced mortality in hospitalized patients with COVID-19 whose clinical conditions were deteriorating when used in combination with dexamethasone.¹² The REMAP-CAP trial also evaluated the use of tocilizumab (N = 353) and sarilumab (N = 48) in hospitalized patients whose clinical conditions were deteriorating.¹³ The majority of patients received 1 of the IL-6 inhibitors in combination with a glucocorticoid. Both tocilizumab and sarilumab significantly improved outcomes and mortality compared with placebo this trial. Nine serious adverse events were reported in the tocilizumab group, eleven in the placebo group, and zero in the sarilumab group.¹³ Because tocilizumab has more robust clinical evidence of benefits than sarilumab, and tocilizumab has an FDA EUA in patients hospitalized for COVID-19 who are taking systemic corticosteroids and require supplemental oxygen, NIV, MV, or ECMO,¹⁴ it can be considered the agent of choice within the IL-6 inhibitor class and sarilumab may be reserved for use when tocilizumab is unavailable.⁶

The JAK inhibitor baricitinib in combination with remdesivir was shown in the ACTT-2 trial to significantly benefit hospitalized patients with COVID-19 who were on low-flow and, notably, high-flow supplemental oxygen.¹⁵ Patients on combination remdesivir and baricitinib showed improved time to recovery (particularly those on high-flow supplemental oxygen and noninvasive mechanical ventilation) and 30% higher odds of improvement in clinical status at day 15 vs those on remdesivir alone. Mortality was also improved with baricitinib use. The COV-BARRIER trial compared the addition of baricitinib to standard of care (remdesivir and/or dexamethasone) in hospitalized patients with COVID-19.¹⁶ Although results did not show a significant reduction in disease progression between groups, baricitinib reduced mortality by 38% and had similar safety outcomes compared with placebo.

As previously mentioned, the ACTT-4 trial showed similar outcomes and an improved safety profile with baricitinib compared with dexamethasone in hospitalized patients on low-flow and high-flow oxygen.⁹ On May 10, 2022, the FDA approved baricitinib for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, NIV, MV, or ECMO.^{10,11} This agent remains under EUA status for the treatment of COVID-19 in hospitalized pediatric patients (2 to < 18 years of age) requiring supplemental oxygen, NIV, MV, or ECMO.

Medscape: How do you choose between immunomodulators when patients progress to severe disease while taking remdesivir and dexamethasone?

Dr Razonable: NIH guidelines generally do not recommend one immunomodulator class over another.⁶ Each agent has shown

efficacy and improved outcomes. When choosing between additional immunomodulators, it is important to consider certain characteristics of each therapy and of each patient. Therapy factors to consider include the availability, safety, cost, and ease of administration.⁹ Patient factors to consider include underlying medical conditions/comorbidities, presence of active or latent infections, and baseline level of immunosuppression.

Therapy Factors

Formularies and availability often dictate which agent is used. Tocilizumab may be easy to use because it requires 1 dose with easy monitoring to determine if a second dose is needed.¹⁷ On the other hand, baricitinib has a short half-life¹¹ and may be an appropriate agent to use when there is a risk of secondary infection. Tocilizumab and baricitinib both have efficacy data for use in patients who started or recently received mechanical ventilation.^{16,18} Baricitinib is associated with increased incidence of venous thromboembolism or pulmonary embolism in patients.¹¹

Patient Factors

Considering and testing for concurrent bacterial or viral infections are important. Immunosuppression should be minimized in patients with comorbidities such as chronic hepatitis B or a history of tuberculosis to avoid secondary infection or reactivation of latent infections. In patients who are immunosuppressed at baseline, such as solid organ or stem cell transplant recipients or patients with cancer, it is critical to consider the effects and long-term outcomes of further immunosuppression. Monitoring for potential opportunistic infections has become a crucial consideration as we are now seeing COVID-19-associated pulmonary aspergillosis (CAPA) and other fungal infections, especially when too much immunosuppression is administered. CAPA and other new syndromes have been described as a result of the pandemic, and there is still much to learn regarding their prevention and management.¹⁹

Medscape: What other factors guide treatment choices in patients with severe COVID-19?

Dr Razonable: Biomarkers, such as CRP to assess for disease progression and risk of secondary superinfection and D-dimer to assess for risk of thrombosis and the need for anticoagulation, may be used. Although these laboratory values can be theoretically helpful, they all must be interpreted in context of a patient's clinical situation (eg, if a patient is progressing or improving clinically), and thus they are only used adjunctively.

Medscape: Does vaccination status or antibody serostatus influence therapy decision-making?

Dr Razonable: Although vaccination has been associated with reduced risk of disease progression, treatment for COVID-19 does not change based on vaccination status. Breakthrough COVID-19 in fully vaccinated individuals will still need to be treated, especially if the patient is in a high-risk population.

Regarding antibody serostatus, recent data from the RECOVERY study showed that mAb use reduced 28-day mortality in hospi-

talized patients who were seronegative at baseline (eg, those with negative serum antibody test who had not mounted their own humoral immune response) but not in those who were seropositive at baseline.²⁰ However, baseline antibody serostatus is not measured in routine clinical practice because it takes time to obtain the results and by the time the results are available, the patient may already have past the treatment eligibility criteria for the emergency use authorization (EUA) for mAbs. Thus, serology is not used to guide treatment decisions.

Medscape: Is there a role for the use of mAbs in hospitalized patients with COVID-19?

Dr Razonable: The current mAb, bebtelovimab, is authorized for use in the outpatient setting for patients with mild to moderate COVID-19 with risk of progression to severe disease or hospitalization. However, this agent may also be used in high-risk, hospitalized patients who meet the EUA eligibility criteria,^{21,22} have mild to moderate disease, are within 7 days of symptoms onset, and are admitted for non-COVID-19 indications. Typically, these are patients diagnosed from routine screening when they are admitted to the hospital for non-COVID-19 reasons. To be treated with an mAb, patients must:

- Be ≥ 12 years of age
- Have mild to moderate symptoms
- Have increased risk for disease progression
- Not require new or increased supplemental oxygen
- Be within the time frame of symptom onset for the specific mAb (eg, within 7 days of onset of symptoms)

Medscape: Do you have any closing remarks or take-home messages?

Dr Razonable: The importance of vaccination in the prevention of COVID-19 must continue to be emphasized. There is still a minority of patients that progress to severe disease despite the available outpatient treatments, and current data indicate that those that progress despite early treatment are usually unvaccinated. So, prevention of severe disease through COVID-19 vaccination is critical.

In addition to prevention, it is also very important to emphasize the benefits of early diagnosis and early treatment. They are key to preventing hospitalization among patients with COVID-19. There is now easy access to COVID-19 testing without the need to physically go to a laboratory or clinic for testing. There are "Test to Treat" centers²³ across the country, and at-home antigen tests are readily available. Providers can easily prescribe oral nirmatrelvir/ritonavir, as long as they also consider and adjust for potential drug-drug interactions. For patients with contraindications to nirmatrelvir/ritonavir, there remains COVID-19 infusion therapy centers across the country that can administer either IV remdesivir or an mAb to outpatients.

A minority of hospitalized patients with COVID-19 progress to severe or critical disease. These patients will benefit from IV remdesivir with dexamethasone, plus either a baricitinib or a tocilizumab. It is important for providers to recognize the different

disease stages and to know when there is risk of further clinical progression, what treatments are available, and when to use them. As the COVID-19 pandemic evolves, clinical data also continue to evolve and impact treatment paradigms; therefore, staying up to date on the most current recommendations is important to provide the most effective care.

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