What’s New in the Guidelines

Last Updated: February 23, 2021

The Coronavirus Disease 2019 (COVID-19) Treatment Guidelines is published in an electronic format that can be updated in step with the rapid pace and growing volume of information regarding the treatment of COVID-19.

The COVID-19 Treatment Guidelines Panel (the Panel) is committed to updating this document to ensure that health care providers, patients, and policy experts have the most recent information regarding the optimal management of COVID-19 (see the Panel Roster for a list of Panel members).

New Guidelines sections and recommendations and updates to existing Guidelines sections are developed by working groups of Panel members. All recommendations included in the Guidelines are endorsed by a majority of Panel members (see the Introduction for additional details on the Guidelines development process).

Major revisions to the Guidelines within the last month are as follows:

February 23, 2021


On February 9, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) to make the anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies bamlanivimab 700 mg and etesevimab 1,400 mg available for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. After reviewing the available evidence, the Panel has determined the following:

• The Panel recommends the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria (BIIa). Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset.

• It is important to note that the authorized dose of bamlanivimab 700 mg plus etesevimab 1,400 mg is lower than the dose given to participants in the Phase 3 study that provides clinical data in support of this therapy. The authorized dose was extrapolated from data demonstrating its antiviral activity, as well as from in vitro studies and pharmacokinetic/pharmacodynamic modeling.

• The Panel recommends against the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for patients who are hospitalized because of COVID-19, except in a clinical trial. However, the combination should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

• Given the possibility of a limited supply of bamlanivimab plus etesevimab, as well as challenges of distributing and administering the drugs, priority should be given to patients who are at highest risk for COVID-19 progression based on the EUA criteria.

• Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to bamlanivimab plus etesevimab.

• Bamlanivimab plus etesevimab should not be withheld from a pregnant individual who has a
condition that poses a high risk of progression to severe COVID-19 if the clinician thinks that the potential benefit of the combination outweighs the potential risk.

- There are insufficient pediatric data to recommend either for or against the use of bamlanivimab plus etesevimab or other monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab may be considered on a case-by-case basis for children who meet EUA criteria, especially those who meet more than one criterion or who are aged ≥16 years. In such cases, consultation with a pediatric infectious disease specialist is recommended.

February 11, 2021

Key Updates to the Guidelines

Introduction

Each recommendation in the Guidelines is assigned a rating for the strength of the recommendation statement and the quality of the evidence that supports the recommendation. The rating scheme for the quality of evidence has been revised to better define the type of scientific evidence used to support the Panel’s recommendations. The new ratings are as follows:

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
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<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials without major limitations</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</td>
<td>IIa: Other randomized trials or subgroup analyses of randomized trials</td>
</tr>
<tr>
<td>C: Optional recommendation for the statement</td>
<td>IIb: Nonrandomized trials or observational cohort studies</td>
</tr>
<tr>
<td></td>
<td>III: Expert opinion</td>
</tr>
</tbody>
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Prevention and Prophylaxis of SARS-CoV-2 Infection

A brief discussion of the SARS-CoV-2 mRNA vaccines that are currently available through EUAs from the FDA has been added to this section. This section also includes updated clinical trial data on the use of hydroxychloroquine for post-exposure prophylaxis (PEP).

Therapeutic Management of Patients With COVID-19

This section has been updated to add rationale to support the recommendations presented in Figure 1. Minor clarifying updates have also been made to the text in Figure 1.

Ivermectin

This section now incorporates the new information and recommendations from the Panel’s statement on ivermectin that was released on January 14, 2021. A new table summarizes the results from several randomized clinical trials and retrospective cohort studies of ivermectin use in patients with COVID-19 that have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review.

Anti-SARS-CoV-2 Monoclonal Antibodies

Bamlanivimab and the combination of casirivimab and imdevimab are available through FDA EUAs for the treatment of outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. This new section of the Guidelines expands on the bamlanivimab statement that was released on November 18, 2020, and the casirivimab plus imdevimab statement that was released on December 2, 2020. This section also includes considerations for using these anti-SARS-CoV-2 monoclonal antibodies in pregnant people and children. A separate table has been created to
summarize the clinical trial data that led to the issuance of the EUAs.

On February 9, 2021, the FDA issued an [EUA for bamlanivimab plus etesevimab](https://www.covid19treatmentguidelines.nih.gov/) for the treatment of mild to moderate COVID-19 in outpatients who have received positive results on a nucleic acid amplification test or an antigen test for SARS-CoV-2 and who are at high risk for clinical progression. The Panel will issue recommendations on the use of bamlanivimab plus etesevimab shortly.

**Kinase Inhibitors: Baricitinib and Other Janus Kinase Inhibitors, and Bruton’s Tyrosine Kinase Inhibitors**

The information and recommendations from the Panel’s December 14, 2020, statement on the use of baricitinib have been added to this section. The section also includes a more detailed description of the clinical data from the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) study that led to the FDA issuing an EUA for the use of baricitinib and remdesivir for the treatment of certain hospitalized patients with COVID-19.

**Other Updates to the Guidelines**

The following sections received minor updates during this revision:

- General Considerations
- Testing for SARS-CoV-2 Infection
- Antithrombotic Therapy in Patients With COVID-19
- Zinc Supplementation and COVID-19

**February 3, 2021**

*The COVID-19 Treatment Guidelines Panel’s Statement on the Use of Tocilizumab (and Other Interleukin-6 Inhibitors) for the Treatment of COVID-19*

Results from several randomized controlled trials of tocilizumab have been published since the last revision of the [Interleukin-6 Inhibitors](https://www.covid19treatmentguidelines.nih.gov/) section of the Guidelines. In addition, preliminary results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) have been released in a non-peer reviewed report. REMAP-CAP is the largest trial to date that has investigated the use of interleukin (IL)-6 inhibitors in patients with COVID-19. After reviewing the collective evidence from REMAP-CAP and other trials, the Panel has revised the recommendations on the use of tocilizumab and sarilumab in patients with COVID-19:

- For patients who are within 24 hours of admission to the intensive care unit (ICU) and require invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO₂/30 L/min oxygen flow), there are insufficient data to recommend either for or against the use of tocilizumab or sarilumab for the treatment of COVID-19.
- Although many trials of tocilizumab for the treatment of COVID-19 have included patients who meet the above criteria, the collective data available to date preclude a definitive recommendation for or against the use of the drug.
- In view of the results from the REMAP-CAP trial, some Panel members would administer a single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) in addition to dexamethasone to patients who meet the above criteria and who are also exhibiting rapid progression of respiratory failure.
- Too few patients in REMAP-CAP received sarilumab for the Panel to assess its efficacy in the treatment of patients who met the above criteria.
• For patients who do not require ICU-level care or are admitted to the ICU but do not meet the above criteria, the Panel **recommends against** the use of **tocilizumab** or **sarilumab** for the treatment of COVID-19, except in a clinical trial (BIIa).

Additional results of randomized controlled trials of tocilizumab and sarilumab will further understanding of the role these IL-6 inhibitors play in the treatment of COVID-19. Future updates to the Interleukin-6 Inhibitors section will include discussion of these studies.