What’s New in the Guidelines

Last Updated: January 5, 2022

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:

January 5, 2022

The COVID-19 Treatment Guidelines Panel’s Statement on Tixagevimab Plus Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis for SARS-CoV-2 Infection

On December 8, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibodies (mAbs) tixagevimab plus cilgavimab (Evusheld). The EUA allows this combination to be used as pre-exposure prophylaxis (PrEP) in certain individuals who, if infected, are at high risk of progressing to severe COVID-19.

The Panel recommends using tixagevimab plus cilgavimab as SARS-CoV-2 PrEP for adults and adolescents (aged ≥12 years and weighing ≥40 kg) who do not have SARS-CoV-2 infection, who have not been recently exposed to an individual with SARS-CoV-2 infection, AND who:

- Are moderately to severely immunocompromised and may have an inadequate immune response to COVID-19 vaccination (BIIa); or
- Are not able to be fully vaccinated with any available COVID-19 vaccines due to a documented history of severe reactions to a COVID-19 vaccine or any of its components (AIIa).

The statement includes a list of moderately or severely immunocompromising conditions that will qualify an individual to receive tixagevimab plus cilgavimab as SARS-CoV-2 PrEP under the EUA. It also includes a detailed discussion of the clinical data that support the recommendations.

The COVID-19 Treatment Guidelines Panel’s Statement on Anticoagulation in Hospitalized Patients With COVID-19

Several randomized controlled trials have evaluated the role of therapeutic doses of heparin in reducing venous thromboembolism or mortality in patients hospitalized for COVID-19. This statement includes the Panel’s recommendations on the use of anticoagulation therapy in hospitalized, nonpregnant adults with COVID-19 who are receiving supplemental oxygen. These recommendations are presented according to whether the patient is receiving intensive care unit level of care.

The statement includes additional recommendations on the use of anticoagulation therapy in pregnant adults with COVID-19 and discusses the clinical data supporting the Panel’s recommendations.
The COVID-19 Treatment Guidelines Panel’s Statement on Therapies for High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19

The FDA recently issued EUAs that allow 2 oral antiviral agents to be used as treatments for COVID-19 in nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to serious disease: ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir. This statement contains the Panel’s recommendations for treating these nonhospitalized patients using the currently available therapies.

The Panel’s recommendations take into account the efficacies of these drugs and the high prevalence of the B.1.1.529 (Omicron) variant of concern (VOC). When resources are limited, therapy should be prioritized for patients who are at the highest risk of progressing to severe COVID-19 (see the Panel’s statement on patient prioritization for outpatient therapies).

The Panel’s current outpatient treatment recommendations are as follows (in order of preference):

- Paxlovid (nirmatrelvir 300 mg plus ritonavir 100 mg) orally twice daily for 5 days
- Sotrovimab 500 mg administered as a single intravenous (IV) infusion
- Remdesivir 200 mg IV on Day 1 followed by remdesivir 100 mg IV on Days 2 and 3
- Molnupiravir 800 mg orally twice daily for 5 days

The statement includes additional considerations for using these treatments and a detailed discussion of the clinical data that support the recommendations.

The COVID-19 Treatment Guidelines Panel’s Statement on Potential Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications

On December 22, 2021, the FDA issued an EUA for ritonavir-boosted nirmatrelvir (Paxlovid) for the treatment of patients with mild to moderate COVID-19. The dose in patients with normal renal function is nirmatrelvir 300 mg (two 150 mg tablets) plus ritonavir 100 mg (one 100 mg tablet) orally twice daily for 5 days. Boosting with ritonavir, a strong cytochrome P450 3A4 inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2.

This statement highlights the critical importance of evaluating a patient’s medication regimens for potentially serious drug-drug interactions before prescribing ritonavir-boosted nirmatrelvir (Paxlovid). The statement provides suggested resources (i.e., an EUA fact sheet and the Liverpool COVID-19 Drug Interactions website) to identify potential drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications and outlines potential strategies to manage any interactions. The statement includes a table that lists drugs that are contraindicated or should not be coadministered with ritonavir-boosted nirmatrelvir (Paxlovid).

The COVID-19 Treatment Guidelines Panel’s Statement on the Use of Anti-SARS-CoV-2 Monoclonal Antibodies or Remdesivir for the Treatment of COVID-19 in Nonhospitalized Patients When Omicron Is the Predominant Circulating Variant

The Omicron VOC has become the dominant variant in many parts of the United States. Omicron has markedly reduced susceptibility to the anti-SARS-CoV-2 mAbs bamlanivimab plus etesevimab and casirivimab plus imdevimab. However, sotrovimab, another mAb, is expected to retain activity against the variant. Intravenous remdesivir is approved by the FDA for the treatment of COVID-19 in...
hospitalized patients. A 3-day regimen of remdesivir has been studied in nonhospitalized patients and resulted in a significant reduction in hospitalizations and deaths compared to placebo. Remdesivir is expected to retain activity against the Omicron VOC.

With the rapid rise in the prevalence of the Omicron VOC, it is anticipated there will be a limited supply of therapeutic agents that are active against the variant (e.g., sotrovimab and small molecule antiviral agents, once they become available) for patients who are at high risk of progression to severe COVID-19 and who might benefit from these therapies.

In this statement, the Panel issues interim recommendations for the use of anti-SARS-CoV-2 mAbs and remdesivir in nonhospitalized patients with COVID-19. The Panel will update these recommendations as additional options for COVID-19 outpatient treatment become available.

**The COVID-19 Treatment Guidelines Panel’s Interim Statement on Patient Prioritization for Outpatient Anti-SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints**

With the increase in cases of COVID-19 and the emergence of the Omicron VOC, logistical or supply constraints may make it impossible to offer available outpatient therapeutics to all eligible patients. When these constraints limit the availability of anti-SARS-CoV-2 mAbs or small molecule antiviral drugs, the Panel recommends that patients at highest risk of clinical progression should be prioritized to receive these therapies. This statement provides the Panel’s recommendations on patient prioritization based on 4 key patient elements: age, vaccination status, immune status, and clinical risk factors.

**December 16, 2021**

**Key Updates to the Guidelines**

**Therapeutic Management of Hospitalized Adults With COVID-19**

Figure 2 and the text of this section have been updated with changes to the Panel’s recommendations for patients who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, or mechanical ventilation.

Key changes include:

- The Panel has clarified that the recommendation for using remdesivir without dexamethasone applies to patients who are early in their disease course and who require minimal supplemental oxygen.
- The rating for the recommendation on using dexamethasone plus remdesivir has been changed from BIII to BIIb based on data from observational studies.
- A new recommendation has been added to this section:
  - For patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug (e.g., baricitinib, tocilizumab) (CIIa).

**Anti-SARS-CoV-2 Monoclonal Antibodies**

This section has been updated to incorporate information on the newly authorized use of bamlanivimab plus etesevimab as treatment or post-exposure prophylaxis (PEP) for children aged <12 years who are at risk of serious COVID-19.

The text and Table A also now include information on the Omicron variant and its potential impact on the anti-SARS-CoV-2 mAbs that are currently authorized to treat mild to moderate COVID-19 in nonhospitalized patients.
**Convalescent Plasma**

The Panel has simplified the recommendations in this section:

- The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients without impaired humoral immunity (AI).
- There is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in:
  - Nonhospitalized patients without impaired humoral immunity; and
  - Nonhospitalized or hospitalized patients with impaired humoral immunity.

The rationale for the Panel’s recommendations and the clinical data table in this section have been reorganized and updated to incorporate the recently published results of certain trials.

**Interferons**

This section has been moved from the Immunomodulators section to the Antiviral Therapy section based on the proposed antiviral activities of interferons against SARS-CoV-2. The Panel has added new information on the use of interferons, including recently published data from clinical trials. The Panel’s recommendations have been revised, and a new clinical data table (Table 2c) has been added to the Guidelines to summarize the findings from key clinical studies that provide the basis for the Panel’s recommendations.

**Colchicine**

This section has been updated to incorporate results from the PRINCIPLE trial, an open-label, randomized adaptive platform trial that evaluated the use of colchicine in nonhospitalized patients with COVID-19. After reviewing the results of this trial and previous clinical trials, the Panel has revised the recommendation regarding the use of colchicine in nonhospitalized patients with COVID-19; the Panel now **recommends against** the use of **colchicine** in this patient population, except in a clinical trial (BIIa).

**Fluvoxamine**

The Panel has added a discussion on the results of the TOGETHER trial, a placebo-controlled, randomized adaptive platform trial of fluvoxamine in nonhospitalized patients with COVID-19 that was conducted in Brazil. The Panel also noted that STOP COVID 2, a randomized controlled trial of fluvoxamine versus placebo that was conducted in the United States, recently stopped enrollment because of futility. Based on the current evidence, the Panel continues to find that there is insufficient evidence to recommend either for or against the use of fluvoxamine for the treatment of nonhospitalized patients with COVID-19. A new clinical data table (Table 4c) has been added to the Guidelines to summarize the findings from key clinical studies that provide the basis for the Panel’s recommendations.

**Other Updates to the Guidelines**

**Overview of COVID-19**

This section has been updated with information regarding the Omicron variant.

**Remdesivir**

The clinical data table for this section now includes results from the DisCoVeRy trial. In addition, new references that address the use of remdesivir in children and pregnant people have been added to the section, and the information regarding the use of remdesivir in patients with renal impairment has been updated and clarified.
Interleukin-6 Inhibitors
This section has been updated to incorporate results from the REMDACTA trial, a double-blind, placebo-controlled, randomized trial that evaluated the use of tocilizumab in combination with remdesivir in patients who were hospitalized with severe COVID-19 pneumonia.

Kinase Inhibitors: Janus Kinase Inhibitors and Bruton’s Tyrosine Kinase Inhibitors
The results from an additional cohort of critically ill patients that was enrolled into the COV-BARRIER trial have been added to this section. This study evaluated the role of baricitinib in treating hospitalized patients with COVID-19 pneumonia. Due to the small sample size of this additional study cohort, the results did not warrant a change to the Panel’s recommendation.

Minor updates have been made to the following Guidelines sections:

- Prevention of SARS-CoV-2 Infection
- Corticosteroids