7: Anti-SARS-CoV-2 Antibody Products

Last Updated: October 19, 2021

Summary Recommendations

Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody (mAb) products (listed alphabetically and not in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by criteria in the Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the products:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low (see the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions); *or*
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion or as subcutaneous (SQ) injections; *or*
  - **Sotrovimab 500 mg** administered as an IV infusion
- When using casirivimab plus imdevimab, the Panel recommends:
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion **(AIIa)**
  - If an IV infusion is not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** can be administered as four SQ injections (2.5 mL per injection) **(BIII)**.
- The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at risk for progression to severe COVID-19 and/or hospitalization (see Anti-SARS-CoV-2 Monoclonal Antibodies). The ratings for the recommendations for using anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for:
  - High-risk conditions that were represented in patients in clinical trials **(AIIa)**, *and*
  - Other medical conditions and factors that had limited representation in patients in clinical trials **(BIII)**; however, for immunocompromising conditions or receipt of immunosuppressive therapy, the rating is **AIII**.
- When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- The availability of bamlanivimab plus etesevimab was previously restricted in areas with an elevated combined frequency of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). See the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions for updates on the distribution of bamlanivimab plus etesevimab.
- The use of anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who either have not developed an antibody response or are not expected to mount an effective immune response to SARS-CoV-2 infection.

Anti-SARS-CoV-2 Monoclonal Antibodies as Post-Exposure Prophylaxis for SARS-CoV-2 Infection

- The Panel recommends using one of the following anti-SARS-CoV-2 mAb combinations as post-exposure prophylaxis (PEP) for people who are at high risk for progression to severe COVID-19 if infected with SARS-CoV-2 **AND** who have the vaccination status **AND** exposure history as outlined in the Prevention of SARS-CoV-2 Infection section:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an IV infusion; *or*
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as SQ injections **(AI)** or as an IV infusion **(BIII)**.

COVID-19 Convalescent Plasma

- The Panel **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**. Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

Summary Recommendations, continued

- For hospitalized patients with COVID-19 who do not have impaired immunity:
  - The Panel **recommends against** the use of **COVID-19 convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
  - The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.
- For hospitalized patients with COVID-19 who have impaired immunity:
  - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
- For nonhospitalized patients with COVID-19:
  - There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.

Anti-SARS-CoV-2 Specific Immunoglobulins

- There is insufficient evidence for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobulins for the treatment of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

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

Anti-SARS-CoV-2 Monoclonal Antibodies

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The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into two subunits, S1 and S2, that mediate host cell attachment and invasion. Through its receptor-binding domain (RBD), S1 attaches to angiotensin-converting enzyme 2 (ACE2) on the host cell; this initiates a conformational change in S2 that results in virus-host cell membrane fusion and viral entry.[1] Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have a clinical benefit in treating SARS-CoV-2 infection (as discussed below). Some anti-SARS-CoV-2 mAbs have been found to be effective in preventing SARS-CoV-2 infection in household contacts of infected patients[2] and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities.[3]

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations From the Food and Drug Administration

Currently, three anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization. The issuance of an EUA does not constitute FDA approval. These products are:

- *Bamlanivimab plus etesevimab:* These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
  - The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.[4] However, distribution of the agents has been reinstated in states with low rates of these and other variants that have reduced susceptibility to bamlanivimab and etesevimab. Please refer to the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions for the latest information on bamlanivimab plus etesevimab distribution.
- *Casirivimab plus imdevimab:* These are recombinant human mAbs that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
- *Sotrovimab:* This mAb was originally identified in 2003 from a SARS-CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

The FDA has expanded the EUAs for bamlanivimab plus etesevimab and casirivimab plus imdevimab to authorize their use as post-exposure prophylaxis (PEP) for certain individuals who are at high risk of acquiring SARS-CoV-2 infection and, if infected, are at high risk of progressing to serious illness. See Prevention of SARS-CoV-2 Infection and the FDA EUA fact sheets for bamlanivimab plus etesevimab and casirivimab plus imdevimab for more information.

Anti-SARS-CoV-2 Monoclonal Antibodies for the Treatment of COVID-19

The recommendations and discussion below pertain only to the use of the authorized anti-SARS-CoV-2 mAb products for the treatment of COVID-19. For recommendations and discussion regarding the use of mAb products as PEP, see Prevention of SARS-CoV-2 Infection.

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 mAb products (listed alphabetically and **not** in order of preference) to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression (see the EUA criteria for use of the products and the related discussion below):
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg** administered as an intravenous (IV) infusion in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low (see the FDA webpage Bamlanivimab and Etesevimab Authorized States, Territories, and U.S. Jurisdictions; *or*
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion or as subcutaneous (SQ) injections; *or*
  - **Sotrovimab 500 mg** administered as an IV infusion.
- When using casirivimab plus imdevimab, the Panel recommends:
  - **Casirivimab 600 mg plus imdevimab 600 mg** administered as an IV infusion **(AIIa)**
  - If an IV infusion is not feasible or would cause a delay in treatment, **casirivimab 600 mg plus imdevimab 600 mg** can be administered as four SQ injections (2.5 mL per injection) **(BIII)**.
- When using anti-SARS-CoV-2 mAbs, treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen test or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.
- The use of anti-SARS-CoV-2 mAbs should be considered for patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 if they otherwise meet the EUA criteria for outpatient treatment.
- Anti-SARS-CoV-2 mAbs are not currently authorized for use in patients who are hospitalized with severe COVID-19; however, they may be available through expanded access programs for patients who either have not developed an antibody response to SARS-CoV-2 infection or are not expected to mount an effective immune response to infection.
- For guidance on prioritizing the use of anti-SARS-CoV-2 mAbs for the treatment or prevention of SARS-CoV-2 infection when logistical or supply constraints limit their availability, see The Panel's Updated Statement on the Prioritization of Anti-SARS-CoV-2 Monoclonal Antibodies.

Rationale

In randomized, placebo-controlled trials in nonhospitalized patients who had mild to moderate COVID-19 symptoms and certain risk factors for disease progression, the use of anti-SARS-CoV-2 mAb products reduced the risk of hospitalization and death (see Table 3a).[5-7] It is worth noting that these studies were conducted before the widespread circulation of variants of concern (VOC). The potential impact of these variants and their susceptibility to different anti-SARS-CoV-2 mAbs is discussed below.

Bamlanivimab Plus Etesevimab

This anti-SARS-CoV-2 mAb combination has demonstrated a clinical benefit in people with mild to moderate COVID-19 who are at high risk for progression to severe disease and/or hospitalization (see Table 3a). The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.[4] However, distribution of the product has been reinstated across the United States because the combined frequency of the Gamma and Beta variants is <5%. Casirivimab plus imdevimab and sotrovimab are expected to remain active against the Gamma and Beta variants.

The FDA provides a list of states, territories, and U.S. jurisdictions in which bamlanivimab plus etesevimab is currently authorized. The Centers for Disease Control and Prevention (CDC) COVID-19 Data Tracker website has the latest information on variant frequencies by region in the United States.

Casirivimab Plus Imdevimab

On June 3, 2021, the FDA updated the EUA for casirivimab plus imdevimab to reduce the authorized dosage for a single IV infusion from casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg.[6] The update also authorized SQ injection of these lower doses of casirivimab and imdevimab if an IV infusion is not feasible or would delay treatment. SQ administration requires four injections (2.5 mL per injection) at four different sites (see the FDA EUA for details).

The recommendation for using the lower dose of casirivimab 600 mg plus imdevimab 600 mg IV is based on the Phase 3 results from the R10933-10987-COV-2067 study (ClinicalTrials.gov Identifier NCT04425629). This double-blind, placebo-controlled randomized trial in outpatients with mild to moderate COVID-19 evaluated different doses of casirivimab plus imdevimab. The modified full analysis set included participants aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had one or more risk factors for progression to severe COVID-19. The results demonstrated a 2.2% absolute reduction and a 70% relative reduction in hospitalization or death with receipt of casirivimab 600 mg plus imdevimab 600 mg. These results are comparable to the those observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg, which demonstrated a 3.3% absolute reduction and a 71% relative reduction in hospitalization or death among patients who received this higher dose of casirivimab plus imdevimab.[8] See Table 3a for additional details from the trial.

The recommendation for using SQ injections to administer casirivimab plus imdevimab is based on safety data from the Phase 1 R10933-10987-HV-2093 study (ClinicalTrials.gov Identifier NCT04519437). This double-blind, placebo-controlled randomized trial compared casirivimab plus imdevimab administered by SQ injection to placebo in healthy volunteers who did not have SARS-CoV-2 infection. Injection site reactions were observed in 12% of the 729 casirivimab plus imdevimab recipients and in 4% of the 240 placebo recipients. According to the FDA EUA, in a separate trial that evaluated casirivimab plus imdevimab in symptomatic participants, there were similar reductions in viral load in the participants in the IV and SQ arms of the trial.[6] However, because the safety and efficacy data for **casirivimab plus imdevimab** administered by SQ injection are limited, this route of administration should only be used when IV infusion is not feasible or would lead to a delay in treatment **(BIII)**.

Sotrovimab

The data that support the EUA for sotrovimab are from the Phase 3 COMET-ICE trial (ClinicalTrials.gov Identifier NCT04545060). The COMET-ICE trial included outpatients with mild to moderate COVID-19 who were at high risk for progression to severe disease and/or hospitalization. A total of 583 participants were randomized to receive sotrovimab 500 mg IV (n = 291) or placebo (n = 292). The primary endpoint was the proportion of participants who were hospitalized for ≥24 hours or who died from any cause by Day 29. Endpoint events occurred in 3 of 291 participants (1%) in the sotrovimab arm and 21 of 292 participants (7%) in the placebo arm ($P = 0.002$), resulting in a 6% absolute reduction and an 85% relative reduction in hospitalizations or death associated with sotrovimab.[7]

Criteria for Using Anti-SARS-CoV-2 Monoclonal Antibodies Under the Emergency Use Authorizations

The FDA EUAs for the anti-SARS-CoV-2 mAbs include a list of specific conditions that place patients at high risk for clinical progression. On May 14, 2021, the FDA revised the EUAs to broaden these

criteria.[5,6] Notable changes included lowering the body mass index (BMI) cutoff from ≥35 to >25 and adding other conditions and factors (e.g., pregnancy, race or ethnicity). Other than being aged ≥12 years, there are no longer any age criteria restricting the use of these agents in patients with the following conditions: sickle cell disease, neurodevelopmental disorders, medical-related technological dependence, asthma, cardiovascular disease, hypertension, and chronic lung disease.

Recommendations

The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. The ratings for the recommendations for the use of anti-SARS-CoV-2 mAbs as treatment are based on the FDA EUA criteria for the following.

Medical Conditions or Other Factors That Were Represented in Patients in Clinical Trials That Evaluated Anti-SARS-CoV-2 Monoclonal Antibodies

- Aged ≥65 years **(AIIa)**
- Obesity (BMI >30) **(AIIa)**
- Diabetes **(AIIa)**
- Cardiovascular disease (including congenital heart disease) or hypertension **(AIIa)**
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) **(AIIa)**

Other Conditions or Factors That Had Limited Representation in Patients in Clinical Trials but Are Considered Risk Factors for Progression to Severe COVID-19 by the Centers for Disease Control and Prevention

- An immunocompromising condition or immunosuppressive treatment **(AIII)**. Many experts strongly recommend therapy for patients with these conditions, despite their limited representation in clinical trials.
- Being overweight (BMI 25–30) as the sole risk factor **(BIII)**
- Chronic kidney disease **(BIII)**
- Pregnancy **(BIII)**
- Sickle cell disease **(BIII)**
- Neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies) **(BIII)**
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19) **(BIII)**

It is important to note that the likelihood of developing severe COVID-19 increases when a person has multiple high-risk conditions or comorbidities.[9-12] Medical conditions or other factors (e.g., race or ethnicity) not listed in the EUAs may also be associated with high risk for progression to severe COVID-19. The current EUAs state that the use of anti-SARS-CoV-2 mAbs may be considered for patients with high-risk conditions and factors that are not listed in the EUAs. For additional information on medical conditions and other factors that are associated with increased risk for progression to severe COVID-19, see the CDC webpage People With Certain Medical Conditions. The decision to use anti-SARS-CoV-2 mAbs for a patient should be based on an individualized assessment of risks and benefits.[7]

Some of the Panel's recommendations for using anti-SARS-CoV-2 mAbs according to the updated EUA criteria are based on preliminary results from the clinical trials that have evaluated these products. The

details on the study designs, methods, and follow-up periods for these trials are currently limited. When peer-reviewed data from the Phase 3 trials become publicly available, the Panel will review the results and update the recommendations for using anti-SARS-CoV-2 mAbs if necessary.

Using Anti-SARS-CoV-2 Monoclonal Antibodies in Patients Hospitalized for COVID-19

The FDA EUAs do not authorize the use of anti-SARS-CoV-2 mAbs for the following patients:

- Those hospitalized for COVID-19; *or*
- Those who require oxygen therapy due to COVID-19; *or*
- Those who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and who require an increase in oxygen flow rate from baseline because of COVID-19.

The FDA EUAs do permit the use of these agents in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19 and are at high risk for progressing to severe disease.[13-15]

Anti-SARS-CoV-2 mAbs have been evaluated in hospitalized patients with severe COVID-19. A substudy of the ACTIV-3 trial randomized patients who were hospitalized for COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, study enrollment was halted after a prespecified interim futility analysis indicated a lack of clinical benefit for bamlanivimab.[16,17]

There are now data that support the use of casirivimab 4,000 mg plus imdevimab 4,000 mg in hospitalized patients with COVID-19 who are seronegative for the anti-spike protein antibody. In the RECOVERY study, hospitalized patients with COVID-19 were randomized to receive standard of care with casirivimab 4,000 mg plus imdevimab 4,000 mg IV or standard of care alone. There was no difference in 28-day all-cause mortality between the casirivimab plus imdevimab arm and the standard of care arm; 944 of 4,839 patients (20%) in the casirivimab plus imdevimab arm died versus 1,026 of 4,946 patients (21%) in the standard of care arm (rate ratio 0.94; 95% CI, 0.86–1.03; $P = 0.17$). However, in the subgroup of patients who were seronegative for the anti-spike protein antibody, there was a significant reduction in 28-day all-cause mortality in the casirivimab plus imdevimab arm (396 of 1,633 casirivimab plus imdevimab recipients [24%] died vs. 451 of 1,520 standard of care recipients [30%]; rate ratio 0.80; 95% CI, 0.70–0.91; $P = 0.001$).[18] This higher dose of casirivimab plus imdevimab is not available through the current EUA, and currently, casirivimab plus imdevimab is only authorized for use in nonhospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals in real time is currently not widely available.

Anti-SARS-CoV-2 mAbs may be available through expanded access programs for the treatment of immunocompromised patients who are hospitalized because of COVID-19. It is not yet known whether these mAb products provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

SARS-CoV-2 Variants and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants that harbor certain mutations have markedly reduced susceptibility to a number of the authorized anti-SARS-CoV-2 mAbs.[19] The clinical relevance of reduced in vitro susceptibility of select variants to anti-SARS-CoV-2 mAbs is under investigation.

Some of the key SARS-CoV-2 variants that have been identified are:

- *Alpha (B.1.1.7):* This variant retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through EUAs.[5,6]
- *Beta (B.1.351):* This variant includes the E484K and K417N mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[5] In vitro studies also suggest that the Beta (B.1.351) variant has markedly reduced susceptibility to casirivimab, although the combination of casirivimab and imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the variant.[6,7]
- *Gamma (P.1):* This variant includes the E484K and K417T mutations, which results in markedly reduced in vitro susceptibility to bamlanivimab and etesevimab.[5,20,21] The Gamma (P.1) variant also has reduced susceptibility to casirivimab; however, the combination of casirivimab plus imdevimab appears to retain activity against the variant. Sotrovimab also appears to retain activity against the Gamma (P.1) variant.[6,7]
- *Delta (B.1.617.2, non-AY.1/AY.2):* This is the predominant VOC circulating in the United States. This VOC retains in vitro susceptibility to all the anti-SARS-CoV-2 mAbs that are currently available through FDA EUAs.[5,6]

Table A. SARS-CoV-2 Variants and Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

WHO Label	Pango Lineage	CDC Variant Class	Notable Mutations	Bamlanivimab Plus Etesevimab		Casirivimab Plus Imdevimab		Sotrovimab	
				In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]	In Vitro Susceptibility[a]	Activity[b]
Alpha	B.1.1.7	VBM	N501Y	No change	Active	No change	Active	No change	Active
Beta	B.1.351	VBM	K417N, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	Active	No change	Active
Gamma	P.1	VBM	K417T, E484K, N501Y	Marked change	Unlikely to be active	No change[c]	Active	No change	Active
Delta	B.1.617.2, non-AY.1/ AY.2	VOC	L452R, T478K	No change	Active	No change	Active	No change	Active

[a] Based on the fold reduction in susceptibility reported in the FDA EUAs.[5-7]

[b] Anticipated clinical activity against the variant, based on in vitro studies.

[c] Marked change for CAS and no change for IMD. The combination of CAS plus IMD appears to retain activity against the variant.

Key: CAS = casirivimab; CDC = Centers for Disease Control and Prevention; IMD = imdevimab; VOC = variant of concern; VBM = variant being monitored; WHO = World Health Organization

Ongoing population-based genomic surveillance of the types and proportions of circulating SARS-CoV-2 variants, as well as studies on the susceptibility of different variants to available anti-SARS-CoV-2 mAbs, will be important in defining the utility of specific mAbs in the future.

Clinical Trials

See Table 3a for information on the clinical trials that are evaluating the safety and efficacy of anti-SARS-CoV-2 mAbs in patients with COVID-19.

SARS-CoV-2 Vaccination

The CDC recommends that SARS-CoV-2 vaccination for people who have received anti-SARS-CoV-2 mAbs be deferred until ≥90 days after the therapy is completed. This is a precautionary measure, as the mAb treatment may interfere with vaccine-induced immune responses.[22]

For people who develop COVID-19 after SARS-CoV-2 vaccination, if there are no logistical or supply constraints limiting the availability of the authorized mAbs, prior vaccination should not affect decisions regarding the use and timing of mAb treatment.[22] For guidance on the use of anti-SARS-CoV-2 mAbs when there are logistical or supply constraints, see the Panel's updated statement on the prioritization of anti-SARS-CoV-2 mAbs.

Monitoring

The authorized anti-SARS-CoV-2 mAbs should be administered by IV infusion or SQ injections and should **only be administered in health care settings** by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion-related reactions.

Patients should be monitored during the IV infusion or SQ injections and for at least 1 hour after the infusion or injections are completed.

Adverse Effects

Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, dizziness, and pruritis have also been reported.[6,7,14] Injection site reactions, including ecchymosis and erythema, were reported in clinical trial participants who received casirivimab plus imdevimab by SQ administration.[6]

Drug-Drug Interactions

Drug-drug interactions are unlikely between the authorized anti-SARS-CoV-2 mAbs and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers (see Table 3c).

Considerations in Pregnancy

The use of anti-SARS-CoV-2 mAbs can be considered for pregnant people with COVID-19, especially those who have additional risk factors for severe disease (see the EUA criteria for the use of these products above).

As immunoglobulin (Ig) G mAbs, the authorized anti-SARS-CoV-2 mAbs would be expected to cross the placenta. There are no pregnancy-specific data on the use of these mAbs; however, other IgG products have been safely used in pregnant people when their use is indicated. Therefore, authorized anti-SARS-CoV-2 mAbs should not be withheld in the setting of pregnancy. When possible, pregnant and lactating people should be included in clinical trials that are evaluating the use of anti-SARS-CoV-2 mAbs for the treatment and/or prevention of COVID-19.

Considerations in Children

Please see Special Considerations in Children for therapeutic recommendations for children.

Drug Availability

Bamlanivimab plus etesevimab, casirivimab plus imdevimab, and sotrovimab are available through FDA EUAs. The availability of bamlanivimab plus etesevimab was previously restricted in areas

with an elevated combined frequency of variants that have markedly reduced in vitro susceptibility to these agents (e.g., the Gamma and Beta variants). The FDA provides updated information on the distribution of bamlanivimab plus etesevimab in the United States. Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these mAbs.

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Table 3a. Anti-SARS-CoV-2 Monoclonal Antibodies: Selected Clinical Data

Last Updated: October 19, 2021

This table describes only clinical trials that have evaluated anti-SARS-CoV-2 mAbs for the treatment of COVID-19. Please refer to the Prevention of SARS-CoV-2 Infection section for a discussion of clinical trials that have evaluated anti-SARS-CoV-2 mAbs for PEP of SARS-CoV-2 infection.

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[1]		

Key Inclusion Criteria:
• Aged ≥12 years
• At high risk for severe COVID-19 or hospitalization
Interventions:
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg (n = 511)
  • Placebo (n = 258)
Primary Endpoint:
• Proportion of patients with COVID-19-related hospitalization (defined as ≥24 hours of acute care) or all-cause death by Day 29
	Participant Characteristics:
	• Median age 56 years; 30% ≥65 years; 53% female
	• 87% White; 27% Hispanic/Latinx; 8% Black/African American
	• Mean duration of symptoms was 4 days.
	• 76% had mild COVID-19 and 24% had moderate COVID-19.
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (6%) in placebo arm; relative risk difference: 87%; *P* <0.0001.
	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm; *P* = 0.01.
		Key Limitation:
		• Trial results not yet published in peer-reviewed journal
		Interpretation:
		• Compared to placebo, receipt of BAM plus ETE was associated with 5% absolute reduction and 87% relative reduction in COVID-19-related hospitalizations or all-cause deaths.

BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2]		
Key Inclusion Criteria: • Aged ≥12 years • At high risk for severe COVID-19 or hospitalization **Key Exclusion Criteria:** • SpO_2 ≤93% on room air, *or* • Respiratory rate ≥30 breaths/min, *or* • Heart rate ≥125 bpm **Interventions:** • Within 3 days of a positive SARS-CoV-2 test result, single infusion of: • BAM 2,800 mg plus ETE 2,800 mg (n = 518)	**Participant Characteristics:** • Mean age 53.8 years; 31% ≥65 years; 52% female; 48% male • 87% White; 29% Hispanic/Latinx; 8% Black/African American • Median days from symptom onset to infusion was 4 days. • 77% had mild COVID-19. **Primary Outcomes:** • COVID-19-related hospitalizations or all-cause deaths by Day 29: 11 (2.1%) in BAM plus ETE arm vs. 36 (7.0%) in placebo arm; relative risk difference: 70%; *P* < 0.001.	**Interpretation:** • Compared to placebo, receipt of BAM plus ETE was associated with 4.8% absolute reduction and 70% relative reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind, Phase 3 RCT of Bamlanivimab 2,800 mg Plus Etesevimab 2,800 mg in Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
• Placebo (n = 517) **Primary Endpoint:** • Proportion of patients with COVID-19-related hospitalization or all-cause death by Day 29 **Secondary Endpoint:** • Proportion of patients with SARS-CoV-2 VL >5.27 $\log_{10}$ copies/mL at Day 7	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 10 (1.9%) in placebo arm. **Secondary Outcome:** • Proportion of patients with high VL at Day 7: 9.8% in BAM plus ETE arm vs. 29.5% in placebo arm ($P < 0.001$)	
Double-Blind, Phase 3 RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		

Key Inclusion Criteria:
• Aged ≥18 years
• Positive SARS-CoV-2 diagnostic test result
• Symptom onset within 7 days of randomization
• For patients included in the modified full analysis only:
  • ≥1 risk factor for severe COVID-19
  • Positive SARS-CoV-2 RT-PCR result at baseline
Interventions:
• Single IV infusion of:
  • CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)
  • CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)
Primary Endpoint:
• Proportion of patients with COVID-19-related hospitalization or all-cause death through Day 29
	Participant Characteristics:
	• Median age 50 years; 35% Hispanic/Latinx; 5% Black/African American
	• Median duration of symptoms prior to enrollment was 3 days.
	Primary Outcomes:
	• COVID-19-related hospitalizations or all-cause deaths through Day 29:
	  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm ($P = 0.002$).
	  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm ($P < 0.001$).
	• All-cause deaths:
	  • 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm.
	  • 1 (< 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm.
		Interpretation:
		• Compared to placebo, receipt of CAS 600 mg plus IMD 600 mg was associated with 2.2% absolute reduction and 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.
		• Compared to placebo, receipt of CAS 1,200 mg plus IMD 1,200 mg was associated with 3.3% absolute reduction and 71% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths.

Methods	Results	Limitations and Interpretation
COMET-ICE: Double-Blind, Phase 3 RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19 Interim Analysis[4]		
Key Inclusion Criteria: • Aged ≥18 years with ≥1 comorbidity or aged ≥55 years regardless of comorbidities • Laboratory-confirmed COVID-19 • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria:** • Hospitalized or requiring supplemental oxygen • Severely immunocompromised **Interventions:** • SOT 500 mg IV (n = 291) • Placebo (n = 292) **Primary Endpoint:** • Proportion of patients with all-cause hospitalization or death by Day 29	**Participant Characteristics:** • Median age 53 years; 22% ≥65 years • 63% Hispanic/Latinx; 7% Black/African American **Primary Outcome:** • All-cause hospitalizations or deaths by Day 29: 3 (1%) in SOT arm vs. 21 (7%) in placebo arm (P = 0.002).	**Key Limitation:** • Trial results not yet published in peer-reviewed journal **Interpretation:** • Compared to placebo, receipt of SOT was associated with 6% absolute reduction and 85% relative risk reduction in all-cause hospitalizations or deaths.

Key: BAM = bamlanivimab; CAS = casirivimab; ETE = etesevimab; IMD = imdevimab; IV = intravenous; mAbs = anti-SARS-CoV-2 monoclonal antibodies; PEP = post-exposure prophylaxis; RCT = randomized controlled trial; RT-PCR = reverse transcription polymerase chain reaction; SOT = sotrovimab; SpO_2 = oxygen saturation; VL = viral load

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Convalescent Plasma

Last Updated: April 21, 2021

Plasma from donors who have recovered from COVID-19 may contain antibodies to SARS-CoV-2 that may help suppress the virus and modify the inflammatory response.[1] The Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for convalescent plasma for the treatment of certain hospitalized patients with COVID-19.

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **low-titer COVID-19 convalescent plasma** for the treatment of COVID-19 **(AIIb)**.
  - Low-titer COVID-19 convalescent plasma is no longer authorized through the convalescent plasma EUA.

For Hospitalized Patients With COVID-19 Who Do Not Have Impaired Immunity

- The Panel **recommends against** the use of COVID-19 **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated patients **(AI)**.
- The Panel **recommends against** the use of **high-titer COVID-19 convalescent plasma** for the treatment of COVID-19 in hospitalized patients who do not require mechanical ventilation, except in a clinical trial **(AI)**.

For Hospitalized Patients With COVID-19 Who Have Impaired Immunity

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19.
  - Observational data including data from case reports, case series, and a retrospective case control study suggest a benefit of COVID-19 convalescent plasma in patients with various primary and secondary humoral immunodeficiencies.[2-16]
  - Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with COVID-19 convalescent plasma.[17-19]
  - High-titer convalescent plasma is authorized under the EUA for the treatment of hospitalized patients with COVID-19 and impaired immunity.

For Nonhospitalized Patients With COVID-19

- There is insufficient evidence for the Panel to recommend either for or against the use of high-titer COVID-19 convalescent plasma for the treatment of COVID-19 in patients who are not hospitalized, except in a clinical trial.
  - Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.
  - Results from additional adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of COVID-19 convalescent plasma in the treatment of nonhospitalized patients with COVID-19.

Rationale for Recommendation

On August 23, 2020, the FDA issued an EUA for convalescent plasma for the treatment of hospitalized patients with COVID-19 based on retrospective, indirect evaluations of efficacy generated from a large Expanded Access Program (EAP). The EAP allowed for the use of convalescent plasma regardless of titer. The Panel reviewed the EAP analyses and determined that the data were not sufficient to establish the efficacy or safety of COVID-19 convalescent plasma due to potential confounding, the lack of randomization, and the lack of an untreated control group.

On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma and only for the treatment of hospitalized patients with COVID-19 early in the disease course or hospitalized patients who have impaired humoral immunity.

Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Without Impaired Humoral Immunity

An updated retrospective analysis of data collected through the EAP indicated that patients who received high-titer plasma had a lower relative risk of death within 30 days after transfusion than patients who received low-titer plasma (relative risk 0.82; 95% CI, 0.67–1.00).[20]

- Among the patients who were on mechanical ventilation before transfusion, no effect of high-titer plasma versus low-titer plasma was observed (relative risk 1.02; 95% CI, 0.78–1.32).
- Among the patients who were not on mechanical ventilation before transfusion, mortality was lower among patients who received high-titer plasma than among those who received low-titer plasma (relative risk 0.66; 95% CI, 0.48–0.91).[20]

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is an open-label, randomized controlled platform trial evaluating potential treatments for COVID-19. In the convalescent plasma portion of the trial, 11,558 patients were randomized to receive either convalescent plasma (n = 5,795) or usual care (n = 5,763) before enrollment was stopped due to futility.[21]

The trial results demonstrated no significant differences in the primary endpoint of 28-day mortality between the convalescent plasma arm (24%) and the usual care arm (24%; risk ratio 1.00; 95% CI, 0.93–1.07). Additionally, the trial did not meet its two secondary endpoints: time to hospital discharge and, for those not on mechanical ventilation at randomization, receipt of invasive mechanical ventilation or death. The proportion of patients discharged within 28 days was similar in the convalescent plasma arm and the usual care arm (66% vs. 67%; rate ratio 0.98; 95% CI, 0.94–1.03). Among those not requiring invasive mechanical ventilation at baseline, the proportion of those progressing to invasive mechanical ventilation or death was also similar in the convalescent plasma arm and the usual care arm (28% vs. 29%; risk ratio 0.99; 95% CI, 0.93–1.05). The 28-day mortality rate ratio was similar in all prespecified patient subgroups, including in those patients without detectable SARS-CoV-2 antibodies at randomization (32% in the convalescent plasma arm vs. 34% in the usual care arm; rate ratio 0.94; 95% CI, 0.84–1.06). Subgroup analyses suggested a slight trend towards benefit of convalescent plasma in certain subgroups (e.g., those with symptom onset ≤7 days, no requirement for supplemental oxygen at baseline, no concomitant use of corticosteroids). See Table 3b for additional details.

Data from several other randomized clinical trials, all of which were underpowered, have not demonstrated the efficacy of convalescent plasma for the treatment of hospitalized patients with COVID-19.[22-29] See Table 3b for details.

Additionally, two large, randomized trials evaluating convalescent plasma in hospitalized patients have been paused or have limited enrollment due to futility.

- The CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1) trial, which evaluated convalescent plasma versus usual care, was stopped after an interim analysis of 614 patients met the predefined threshold for futility.[30]
- The Randomised, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), which evaluated convalescent plasma in hospitalized patients, paused enrollment for patients in intensive care units after a preliminary analysis that included 912 participants indicated that convalescent plasma was unlikely to benefit this patient group.[31] REMAP-CAP continues to recruit hospitalized patients who do not require intensive care support into the trial's convalescent plasma evaluation domain.

Results from adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of hospitalized patients with COVID-19 who do not have impaired humoral immunity.

Use of Convalescent Plasma in Hospitalized Patients With COVID-19 and Impaired Humoral Immunity

Data from case reports, case series, and a retrospective case-control study suggest a benefit of convalescent plasma in patients with primary and secondary humoral immunodeficiencies, including patients with hematologic malignancy, common variable immune deficiency, and agammaglobulinemia, and those who have received a transplanted solid organ.[2-13,15,16] Several case reports indicate that patients with impaired humoral immunity may experience persistent SARS-CoV-2 viral replication and, therefore, may be at risk for developing viral resistance to SARS-CoV-2 antibodies after treatment with convalescent plasma.

Results from adequately powered, well-designed, and well-conducted randomized clinical trials are needed to provide more specific, evidence-based guidance on the role of convalescent plasma in the treatment of patients with COVID-19 who have impaired humoral immunity.[17-19]

Use of Convalescent Plasma in Nonhospitalized Patients With COVID-19

Current data are insufficient to establish the safety or efficacy of convalescent plasma in outpatients with COVID-19.

- Data from a double-blind, placebo-controlled randomized trial of high-titer convalescent plasma in elderly outpatients with <72 hours of mild COVID-19 symptoms suggested a potential for benefit.[32] However, the trial included relatively few participants, and only a small number of clinical events related to COVID-19 occurred. See Table 3b for details.
- The Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO) evaluated convalescent plasma for the treatment of nonhospitalized patients with ≤7 days of mild or moderate COVID-19 symptoms and at least one risk factor for severe COVID-19. The trial was halted after an interim analysis indicated no benefit of convalescent plasma for this group of patients. The trial enrolled 511 of the planned 900 participants before the study was halted.

Convalescent plasma is not authorized for nonhospitalized patients with COVID-19 under the EUA.

Clinical Data to Date

Table 3b includes a summary of key studies of convalescent plasma for the treatment of COVID-19.

Considerations in Pregnancy

The safety and efficacy of using COVID-19 convalescent plasma during pregnancy have not been evaluated. Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent infection from varicella zoster virus and rabies virus and have been used in clinical trials of congenital cytomegalovirus infection.[33] Some ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.[34]

Considerations in Children

The safety and efficacy of COVID-19 convalescent plasma have not been evaluated in pediatric patients outside of evaluations described in single-center reports. Clinical trials of COVID-19 convalescent plasma in children are ongoing. There is insufficient evidence for the Panel to recommend either for or against the use of convalescent plasma for the treatment of COVID-19 in hospitalized children who do not require mechanical ventilation. The Panel **recommends against** the use of **convalescent plasma** for the treatment of COVID-19 in mechanically ventilated pediatric patients **(AIII)**. In consultation with a pediatric infectious disease specialist, high-titer convalescent plasma may be considered on a case-by-case basis for children with COVID-19 who meet the EUA criteria.

Adverse Effects

Available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications. These risks include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura have also been described.[21,35,36]

Additional risks of COVID-19 convalescent plasma transfusion include a theoretical risk of antibody-dependent enhancement of SARS-CoV-2 infection and a theoretical risk of long-term immunosuppression.

The Panel recommends consulting a transfusion medicine specialist when considering convalescent plasma for patients with a history of severe allergic or anaphylactic transfusion reactions.

Product Availability

On February 4, 2021, the FDA revised the convalescent plasma EUA to limit the authorization to high-titer COVID-19 convalescent plasma.[37]

- The revised EUA Letter of Authorization provides an expanded list of anti-SARS-CoV-2 antibody tests and corresponding qualifying results that may be used to determine the suitability of donated convalescent plasma.
- Please refer to the FDA's Recommendations for Investigational COVID-19 Convalescent Plasma webpage for guidance on the transfusion of investigational convalescent plasma while blood establishments develop the necessary operating procedures to manufacture COVID-19 convalescent plasma in accordance with the Conditions of Authorization described in the EUA.[38]

Clinical Trials

Randomized clinical trials that are evaluating convalescent plasma for the treatment of COVID-19 are underway. Please see ClinicalTrials.gov for the latest information.

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Table 3b. COVID-19 Convalescent Plasma: Selected Clinical Data

Last Updated: April 21, 2021

The clinical trials described in this table do not represent all the trials that the Panel reviewed while developing the recommendations for COVID-19 CP. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Patients With COVID-19 (RECOVERY Trial)[1]			
Open-label, platform RCT evaluating potential treatments, including high-titer CP, in hospitalized patients with COVID-19 in the United Kingdom (n = 11,558) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Clinically suspected or laboratory-confirmed SARS-CoV-2 infection • CP available at study site **Key Exclusion Criteria:** • CP contraindicated (e.g., known allergy to blood components) **Interventions:** • One 275 mL (+/- 75 mL) unit of CP immediately and another unit the next day (≥12 hours after the first unit) • CP was selected by sample to cut-off IgG SARS-CoV-2 spike protein ratio ≥6.0. • Usual care **Primary Endpoint:** • All-cause mortality at Day 28 **Secondary Endpoints:** • Time to hospital discharge • Among patients not receiving IMV at randomization, receipt of IMV or death by Day 28	**Number of Participants:** • ITT analysis: CP (n = 5,795) and usual care (n = 5,763) **Participant Characteristics:** • Mean age was 63.5 years. • 63% of patients in the CP arm and 66% in the usual care arm were men. • 5% of patients in each arm were on IMV. • At baseline, 52% of the patients in the CP arm and 48% in the usual care arm were SARS-CoV-2 antibody seropositive. • 93% of the patients in the CP arm and 92% in the usual care arm received corticosteroids. **Outcomes:** • No difference in 28-day mortality between the CP arm and the usual care arm (24% vs. 24%; rate ratio 1.00; 95% CI, 0.93–1.07). • No difference in the proportion of patients discharged within 28 days (66% in CP arm vs. 67% in usual care arm; rate ratio 0.98; 95% CI, 0.94–1.03; $P = 0.50$). • 28-day mortality rate ratio was consistent across prespecified patient subgroups, including subgroups by SARS-CoV-2 antibody presence at randomization. In particular, among patients without detectable SARS-CoV-2 antibodies, there was no evidence of a mortality difference between those who received CP and those who received usual care (32% vs. 34%; rate ratio 0.94; 95% CI, 0.84–1.06). • Among those not receiving IMV at baseline, the percentage of patients who progressed to IMV or died was similar in the CP arm and the usual care arm (28% vs. 29%; rate ratio 0.99; 95% CI, 0.93–1.05; $P = 0.79$). • Severe allergic reactions were rare (occurred in 16 patients in the CP arm and 2 in the usual care arm).	**Limitations:** • The study was not blinded. • >90% of participants received corticosteroids. There is uncertainty about the effect of CP in hospitalized patients who do not require supplemental oxygen and for whom corticosteroids are not recommended. **Interpretation:** • The trial did not demonstrate a benefit of CP in hospitalized patients with COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Hospitalized Adults With COVID-19 (PLACID Trial)[2]			
Multicenter, open-label, Phase 2 RCT in hospitalized adults with severe COVID-19 in India (n = 464)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • PaO_2/FiO_2 = 200–300 mm Hg or respiratory rate >24 breaths/min with SpO_2 ≤93% on room air **Key Exclusion Criteria:** • Critical illness **Interventions:** • 2 doses of 200 mL CP, transfused 24 hours apart • SOC **Primary Endpoint:** • Composite of progression to severe disease (defined as PaO_2/FiO_2 <100 mm Hg) any time within 28 days of enrollment or all-cause mortality at 28 days	**Number of Participants:** • CP (n = 235) and SOC (n = 229) **Participant Characteristics:** • Median age was 52 years. • 75% of participants in the CP arm and 77% in the SOC arm were men. • Higher prevalence of diabetes in the CP arm (48%) than in SOC arm (38%). **Outcomes:** • No difference between the arms in the primary outcome of progression to severe disease or death (occurred in 18.7% of participants in CP arm and 17.9% in SOC arm). • A post hoc analysis evaluating outcomes among patients without detectable SARS-CoV-2 neutralizing antibody titers at baseline also revealed no benefit of CP.	**Limitations:** • The study was not blinded. • SARS-CoV-2 antibody testing was not used to select donated CP units; therefore, many participants may have received CP units with low titers of SARS-CoV-2 neutralizing antibodies. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)[3]			
Double-blind, placebo-controlled, multicenter RCT in hospitalized adults with severe COVID-19 in Argentina (n = 333)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR • Severe COVID-19 **Key Exclusion Criteria:** • Critical illness **Interventions** *2:1 Randomization:* • Single dose (median volume	**Number of Participants:** • CP (n = 228) and placebo (n = 105) **Participant Characteristics:** • Median age was 62 years. • 67.6% of the participants were men. • 64.9% of the participants had a coexisting condition at trial entry. • Median time from symptom onset to enrollment was 8 days. • Of 215 participants tested, 46% had no detectable SARS-CoV-2 antibodies at baseline. Median SARS-CoV-2 antibody titer in both the CP arm and placebo arm was 1:50.	**Limitations:** • The majority of participants in both arms received concomitant glucocorticoid treatment, potentially masking subtle differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in COVID-19 Severe Pneumonia (PlasmAr Study)[3], continued			
	500 mL) of CP pooled from 2–5 donors. Only plasma units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:800 were transfused. • Placebo **Primary Endpoint:** • Change in clinical status 30 days after intervention measured using a 6-point ordinal scale	**Outcomes:** • No significant differences between the arms in the distribution of outcomes according to the categories on the 6-point ordinal scale (OR 0.83; 95% CI, 0.52–1.35). • 30-day mortality was similar in CP arm (11.0%) and placebo arm (11.4%). • Infusion-related AEs were more frequent in the CP arm than in the placebo arm (occurred in 4.8% vs. 1.9% of participants).	**Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe COVID-19.
Convalescent Plasma in Adults With Severe COVID-19[4]			
Double-blind, Phase 2 RCT in hospitalized adults with severe COVID-19 (n = 223) in the United States (n = 73) and Brazil (n = 150) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • COVID-19 pneumonia • SpO_2 ≤94% on room air or requirement for supplemental oxygen, IMV, or ECMO **Key Exclusion Criteria:** • >5 days on IMV or ECMO • Severe multiorgan failure **Interventions** *2:1 Randomization:* • Single dose of SARS-CoV-2 CP (approximately 250 mL). Only units with a SARS-CoV-2 viral spike-RBD IgG titer ≥1:400 were transfused. • Non-SARS-CoV-2 plasma (normal control plasma)	**Number of Participants:** • CP (n = 150) and normal control plasma (n = 73) • Enrollment initiated in New York City in April 2020 and in Brazil in August 2020 **Participant Characteristics:** • Median age was 61 years. • 66% of the participants were men. • Median duration of symptoms prior to randomization was 9 days. • 57% of the participants required supplemental oxygen at baseline, 25% required high-flow oxygen or noninvasive ventilation, and 13% required IMV or ECMO. • There were some imbalances between the study arms at baseline. The CP arm included more women; the participants were younger and had slightly longer symptom durations. • 81% of the participants received corticosteroids. **Outcomes:** • No difference in clinical status on Day 28 was observed between the CP arm and the control arm (OR 1.5 for being in a better category with CP vs. control plasma; 95% CI, 0.83–2.68; *P* = 0.18).	**Limitations:** • The intervention in the control group arm was blood plasma without SARS-CoV-2 antibodies. This ensured blinded administration; however, because the trial was not placebo controlled; it is not possible to identify potential harm due to plasma infusion. • Low sample size and number of events • There were imbalances in baseline characteristics between the study arms that may have impacted study outcomes. After adjustment for the imbalances, the

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma in Adults With Severe COVID-19[4], continued			
	Primary Endpoint: • Clinical status on Day 28, measured using an ordinal scale (initially with 7 categories, but modified to 6). **Secondary Endpoints:** • Time to clinical improvement • In-hospital and 28-day mortality • Time to discontinuation of supplemental oxygen • Time to hospital discharge	• In-hospital mortality was lower in the CP arm (13%) than in the control arm (25%; HR 0.44; 95% CI, 0.22–0.91; $P = 0.034$). The treatment difference was not significant after adjustment for age, sex, and duration of symptoms at baseline. • In both arms, mortality at 28 days was the same as in-hospital mortality. • Time to oxygen discontinuation and time to hospital discharge were similar between the arms. • 25.5% of patients in the CP arm vs. 36.1% in the control arm experienced SAEs.	difference in mortality between the arms was not significant. • The treatment difference in the primary outcome (clinical status on Day 28) was not statistically significant; mortality was a secondary outcome. • There were no subgroup analyses for mortality. **Interpretation:** • Although the difference between the CP arm and the non-SARS-CoV-2 antibody plasma arm for the primary outcome of clinical status on Day 28 was not statistically significant, the lower 28-day mortality in the CP arm suggests a potential benefit of CP in hospitalized patients with severe COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
Early High-Titer Plasma Therapy to Prevent Severe COVID-19 in Older Adults[5]			
Double-blind, placebo-controlled RCT in outpatients with mild COVID-19 in Argentina (n = 160)	**Key Inclusion Criteria:** • Aged >75 years or aged 65–74 years with ≥1 coexisting condition • Outpatient with <72 hours of mild COVID-19 symptoms **Key Exclusion Criteria:** • Severe respiratory disease **Interventions:** • Single 250 mL dose of CP with an IgG titer against SARS-CoV-2 spike protein of >1:1000 • Placebo **Primary Endpoint:** • Severe respiratory disease defined as a respiratory rate ≥30 breaths/min and/or SpO_2 <93% on room air by Day 15	**Number of Participants:** • ITT analysis: CP (n = 80) and placebo (n = 80) **Participant Characteristics:** • Mean age was 77 years. • Most of the patients had comorbidities. **Outcomes:** • 13 of 80 patients (16%) in the CP arm and 25 of 80 (31%) in the placebo arm experienced severe respiratory disease by Day 15 (relative risk 0.52; 95% CI, 0.29–0.94; *P* = 0.026). • 2 participants in the CP arm and 5 in the placebo arm died. • No solicited AEs were reported.	**Limitations:** • The trial was terminated early because cases of COVID-19 at the study site decreased. • The trial included relatively few participants. **Interpretation:** • This trial demonstrated a benefit of CP in elderly outpatients with <72 hours of mild COVID-19 symptoms.
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19[6]			
Multicenter, open-label, randomized trial in hospitalized adults with severe or life-threatening COVID-19 in China (n = 103)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 PCR within 72 hours of randomization • Met study definition of severe or life-threatening COVID-19	**Number of Participants:** • CP (n = 52) and SOC (n = 51) **Participant Characteristics:** • Median age was 70 years. • 58.3% of the participants were men. **Outcomes:** • No significant difference in time to clinical improvement between the CP arm and the control arm (HR 1.40; 95% CI, 0.79–2.49; *P* = 0.26). • No significant difference in mortality between the CP arm (16%) and the control arm (24%; *P* = 0.30).	**Limitations:** • The study was not blinded. • The trial was stopped early because of decreasing numbers of cases of COVID-19 at the study site; therefore, the study lacked sufficient power to detect differences in clinical outcomes.

Study Design	Methods	Results	Limitations and Interpretation
Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-Threatening COVID-19[6], continued			
	Key Exclusion Criteria: • Baseline RBD-specific IgG antibody ≥1:64 • Certain sequalae of severe COVID-19 (e.g., severe septic shock, severe heart failure) **Interventions:** • Single 4–13 mL/kg dose of CP. Only CP units with a SARS-CoV-2 viral spike-RBD-specific IgG titer of ≥1:640 were transfused. • SOC **Primary Endpoint:** • Time to clinical improvement (patient discharge or a reduction of 2 points on a 6-point disease severity scale; 6 points = death, 1 point = hospital discharge) within 28 days.		• Only 103 of 200 planned participants were randomized to receive treatment. • CP was administered late (approximately 1 month) into disease course. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients with severe or life-threatening COVID-19.
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19[7]			
Open-label, single-center, Phase 2 randomized trial in hospitalized adults with COVID-19 in Chile (n = 58)	**Key Inclusion Criteria:** • Aged ≥18 years • ≤7 days of COVID-19 symptoms • High risk of progression to respiratory failure **Key Exclusion Criteria:** • PaO_2/FiO_2 <200 mm Hg • Mechanical ventilation	**Number of Participants:** • Immediate CP (n = 28) and deferred CP (n = 30) **Participant Characteristics:** • Median age was 66 years. • 50% of the participants were men. • Median interval between symptom onset and randomization was 6 days. • 13 of 28 participants (43%) in the deferred CP arm received CP at a median of 3 days after enrollment.	**Limitations:** • The study was not blinded. • Small sample size. **Interpretation:** • This trial did not demonstrate a benefit of immediate vs. deferred administration of CP in hospitalized COVID-19 patients with ≤7 days of COVID-19 symptoms.

Study Design	Methods	Results	Limitations and Interpretation
Early Versus Deferred Anti-SARS-CoV-2 Convalescent Plasma in Hospitalized Patients With COVID-19[7], continued			
	Interventions *Immediate CP:* • Two 400 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:400, transfused 24 hours apart *Deferred CP:* • CP transfusion only if PaO_2/FiO_2 <200 mm Hg, or if participant still required hospitalization for COVID-19 symptoms 7 days after enrollment **Primary Endpoint:** • Composite of mechanical ventilation, hospitalization >14 days, or in-hospital death	**Outcomes:** • There was no difference between the arms in the percentage of participants who met the primary composite endpoint of death, mechanical ventilation, or >14 days hospitalization (32% in immediate CP arm vs. 33% in deferred CP arm; OR 0.95; 95% CI, 0.32–2.84). • 18% of participants in the immediate CP arm vs. 7% in the deferred CP arm died within 30 days (OR 3.0; 95% CI, 0.5–17.2; $P = 0.25$).	
Convalescent Plasma for COVID-19 (ConCOVID trial)[8]			
Multicenter, open-label, RCT in hospitalized adults with COVID-19 in the Netherlands (n = 86) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • Clinical disease with positive SARS-CoV-2 RT-PCR within 96 hours of enrollment **Key Exclusion Criteria:** • Mechanical ventilation for >96 hours **Interventions:** • One to two 300 mL doses of CP with anti-SARS-CoV-2 neutralizing antibody titers ≥1:80 • SOC	**Number of Participants:** • CP (n = 43) and SOC (n = 43) **Participant Characteristics:** • Median age was 63 years. • Most of the participants were men. **Outcomes:** • No differences in mortality ($P = 0.95$), length of hospital stay ($P = 0.68$), or disease severity at Day 15 ($P = 0.58$) were observed between the study arms.	**Limitations:** • The study was not blinded. • Trial halted early by the investigators when the baseline SARS-CoV-2 neutralizing antibody titers of participant plasma and CP were found to be comparable, challenging the potential benefit of CP for the study population. Thus, the study lacked sufficient power to detect differences in clinical outcomes between the study arms.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma for COVID-19 (ConCOVID trial)[8], continued			
	Primary Endpoint: • Day-60 mortality		• Only 86 of 426 planned participants were randomized to receive CP or SOC. **Interpretation:** • This trial did not demonstrate a benefit of COVID-19 CP in hospitalized patients.
Convalescent Plasma for COVID-19 (ConPlas-19 Study)[9]			

Multicenter, open-label, RCT in hospitalized adults with COVID-19 in Spain (n = 81)
This is a preliminary report that has not yet been peer reviewed.
	Key Inclusion Criteria:
	• Aged ≥18 years
	Key Exclusion Criteria:
	• Receiving IMV, noninvasive ventilation, or high-flow oxygen
	Interventions:
	• Single dose of 250–300 mL of CP plus SOC.
	  • All administered units had neutralizing antibodies (VMNT-ID50: all titers >1:80, median titer 1:292, IQR 238–451; pseudovirus neutralizing ID50 assay: median titer 1:327; IQR 168–882)
	• SOC alone
	Primary Endpoint:
	• Proportion of patients in ordinal scale categories 5, 6, or 7 at Day 15.
		Number of Participants:
		• CP (n = 38) and SOC (n = 43)
		Participant Characteristics:
		• Mean age was 59 years.
		• At baseline, 49% of the participants were SARS-CoV-2 antibody positive.
		Outcomes:
		• 0 of 38 participants (0%) in the CP arm progressed to ordinal scale categories 5–7 vs. 6 of 43 participants (14.0%) in the SOC arm (P = 0.57, not statistically significant according to the planned analysis; but P = 0.03 using Fisher test as a post hoc sensitivity analysis given small numbers and the by-center heterogenous distribution).
		• 0 of 38 participants (0%) in the CP arm died vs. 4 of 43 (9.3%) in the SOC arm (P = 0.06).
			Limitations:
			• The study was not blinded.
			• The trial was stopped early because of decreasing numbers of COVID-19 cases at the study site and, thus, the study lacked sufficient power to detect differences in clinical outcomes.
			  • Only 81 of planned 278 participants were enrolled.
			Interpretation:
			• Although the results did not reach statistical significance and only a small number of clinical events related to COVID-19 occurred, these results suggest a potential benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Clinical and Immunological Benefits of Convalescent Plasma Therapy in Severe COVID-19[10]			
Single-center, open-label, RCT in hospitalized adults with COVID-19 and ARDS in India (n = 80) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Evidence of ARDS (defined as PaO_2/FiO_2 100–300 mm Hg) • Not on mechanical ventilation **Key Exclusion Criteria:** • Mechanical ventilation **Intervention:** • 2 consecutive doses of ABO-matched 200 mL CP, 1 day apart • SOC alone **Primary Endpoint:** • All-cause mortality at Day 30	**Number of Participants:** • CP (n = 40) and SOC (n = 40) **Participant Characteristics:** • Mean age was 61 years. • 71% of the participants were men. • No difference in mean number of days of hospitalization at enrollment between the CP arm (4.2 days) and the SOC arm (3.9 days). **Outcomes**: • 10 of 40 participants (25%) in the CP arm had died by Day 30 vs. 14 of 40 (35%) in the SOC arm. • Difference in survival between the arms was not statistically significant (HR 0.6731; 95% CI, 0.3010–1.505).	**Limitations**: • The study was not blinded. • The study lacked sufficient power to detect differences in clinical outcomes between the study arms. **Interpretation**: • This trial did not demonstrate a benefit of CP in hospitalized patients with mild to moderate ARDS who are not receiving mechanical ventilation.
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19[11]			
Open-label, RCT in hospitalized adults with COVID-19 in Bahrain (n = 40) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Aged ≥21 years • Radiologic evidence of pneumonia • Requirement for oxygen therapy for COVID-19 **Key Exclusion Criteria:** • Requirement for IMV, noninvasive ventilation, or high-flow oxygen **Interventions:** • Two 200 mL transfusions of CP over 24 hours • SOC alone **Primary Endpoints:** • Requirement for IMV or noninvasive ventilation	**Number of Participants:** • CP (n = 20) and SOC (n = 20) **Participant Characteristics:** • Mean age was 53 years in the CP arm and 51 years in the SOC arm. • Most of the participants were men (75% in the CP arm and 85% in the SOC arm). **Outcomes:** • 6 patients in the SOC arm and 4 patients in the CP arm required mechanical ventilation (risk ratio 0.67; 95% CI, 0.22–2.0; *P* = 0.72). • 2 patients in the SOC arm died vs. 1 in the CP arm.	**Limitations:** • The study was not blinded. • The study lacked sufficient power to detect differences in clinical outcomes between the study arms. **Interpretation:** • This trial did not demonstrate a benefit of CP in hospitalized patients who are not receiving high-flow oxygen, noninvasive ventilation, or invasive ventilation.

Study Design	Methods	Results	Limitations and Interpretation
Convalescent Plasma Therapy Versus Standard Therapy in Patients With Severe COVID-19[11], continued			
	• In patients who require ventilation, duration of ventilation		
Convalescent Plasma Antibody Levels and the Risk of Death from COVID-19[12]			
Retrospective, indirect evaluation of a subset of patients from the Mayo Clinic COVID-19 CP EAP (n = 3,082). More than 100,000 patients hospitalized with COVID-19 in the United States received CP through the Mayo Clinic EAP.	**Key Inclusion Criteria:** • Aged ≥18 years • Severe or life-threatening (critical) COVID-19 • Analysis limited to patients for whom samples were available for retrospective analysis of CP titer. **Intervention:** • CP transfusion (no titer specified in real time; high, medium, and low titer CP determined retrospectively) **Primary Endpoint:** • Mortality 30 days after CP transfusion	**Number of Participants:** • High-titer CP (n = 515), medium-titer CP (n = 2,006), and low-titer CP (n = 561) **Participant Characteristics:** • 61% of the participants were men. • 48% of the participants were White and 37% were Hispanic/Latino. • 61% of the participants required ICU-level care prior to infusion. • 33% of the participants were on mechanical ventilation. • 51% of the participants received corticosteroids; 31% received RDV. **Outcomes:** • The analysis included 3,082 participants who received a single unit of CP. The participants were among 35,322 participants who had received CP through the EAP by July 4, 2020. • Death within 30 days occurred in 115 of 515 patients (22%) in the high-titer group, 549 of 2,006 patients (27%) in the medium-titer group, and 166 of 561 patients (30%) in the low-titer group. • Using a relative-risk regression model that assumed all patients who were discharged were alive at Day 30, patients in the high-titer group had a lower relative risk of death within 30 days than patients in the low-titer group (relative risk 0.82; 95% CI, 0.67–1.00). • Among patients who received mechanical ventilation before transfusion, there was no difference in the risk of death between those who received high-titer CP and those who received low-titer CP (relative risk 1.02; 95% CI, 0.78–1.32). • Mortality was lower among patients who were not receiving mechanical ventilation before transfusion (relative risk 0.66; 95% CI, 0.48–0.91).	**Limitations:** • Lack of untreated control arm limits interpretation of the safety and efficacy data; the possibility that differences in outcomes are attributable to harm from low-titer plasma rather than benefit from high-titer plasma cannot be excluded. • Assays to determine the effective antibody titers remain limited, and the antibody titers of currently available CP from COVID-19 survivors are highly variable. • Efficacy analysis relied on only a subset of EAP patients who represent a fraction of the patients who received CP through the EAP. • Post hoc subgroups were selected by combining several subsetting rules that favored subgroups. This approach tends to overestimate the treatment effect. **Interpretation:** • Given the lack of an untreated control arm and the limitations listed above, this retrospective analysis is not sufficient to establish the efficacy or safety of CP.

Key: AE = adverse event; ARDS = acute respiratory distress syndrome; ConCOVID Trial = Convalescent-plasma-for-COVID-9; ConPlas-19 Study = Convalescent Plasma for COVID-19; CP = convalescent plasma; EAP = Expanded Access Program; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ID50 = 50% inhibitory dose; IgG = immunoglobulin G; IMV = invasive mechanical ventilation; ITT = intention to treat; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PLACID Trial = Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomized controlled trial; PlasmAr Study = A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia; RBD = receptor binding domain; RCT = randomized controlled trial; RDV = remdesivir; RECOVERY = Randomised Evaluation of COVID-19 Therapy; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SOC = standard of care; SpO_2 = saturation of oxygen; VMNT = virus microneutralization test

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Immunoglobulins: SARS-CoV-2 Specific

Last Updated: July 17, 2020

Recommendation

- There is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against **severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins** for the treatment of COVID-19.

Rationale

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

Proposed Mechanism of Action and Rationale for Use in Patients with COVID-19

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 immunoglobulin, which could potentially suppress the virus and modify the inflammatory response. The use of virus-specific immunoglobulins for other viral infections (e.g., cytomegalovirus [CMV] immunoglobulin for the prevention of post-transplant CMV infection and varicella zoster immunoglobulin for postexposure prophylaxis of varicella in individuals at high-risk) has proven to be safe and effective; however, there are currently no clinical data on the use of such products for COVID-19. Potential risks may include transfusion reactions. Theoretical risks may include antibody-dependent enhancement of infection.

Clinical Data

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Considerations in Pregnancy

Pathogen-specific immunoglobulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmunoglobulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data on their use for other respiratory viruses is limited.

Table 3c. Characteristics of SARS-CoV-2 Antibody-Based Products Under Evaluation for the Treatment of COVID-19

Last Updated: October 19, 2021

- The information in this table is based on data from investigational trials evaluating these products for the treatment or prevention of COVID-19. The table includes dose recommendations from the FDA EUAs for patients who meet specified criteria.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with therapies for the treatment or prevention of COVID-19. When using concomitant medications with similar toxicity profiles, consider performing additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of using combination therapies for the treatment or prevention of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labels and visit the Liverpool COVID-19 Drug Interactions website.
- For the Panel's recommendations on using the drugs listed in this table, please refer to the Anti-SARS-CoV-2 Monoclonal Antibodies, Therapeutic Management of Nonhospitalized Adults With COVID-19, and Prevention of SARS-CoV-2 Infection sections of the Guidelines.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in EUA for Treatment and PEP of COVID-19: • BAM 700 mg plus ETE 1,400 mg administered together as a single IV infusion	• Nausea • Dizziness • Pruritis • Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed in multiple trials in which participants received either the authorized doses of BAM and ETE or higher doses of each drug.	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications to treat severe infusion reactions. • Monitor patient during the IV infusion and for at least 1 hour after the infusion is completed.	• Drug-drug interactions are unlikely between BAM plus ETE and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • The distribution of BAM plus ETE in the United States was paused in June 2021 because the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to BAM and ETE. Distribution of BAM plus ETE was resumed in August 2021. • For updates on the distribution of BAM plus ETE, see this FDA document.

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Bamlanivimab Plus Etesevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
				• BAM plus ETE is available through the FDA EUA as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk patients.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of BAM plus ETE. • A list of clinical trials is available: Bamlanivimab Plus Etesevimab
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in EUA for Treatment of COVID-19: • CAS 600 mg plus IMD 600 mg administered together as a single IV infusion over 1 hour. • IV infusion is the preferred route of administration. However, when IV infusion is not feasible or would delay treatment, CAS 600 mg plus IMD 600 mg can be administered as 4 SQ injections (2.5 mL per injection) at 4 different sites. See the FDA EUA for detailed information. **Dose Recommended in EUA for PEP of COVID-19:** • CAS 600 mg plus IMD 600 mg administered by SQ injections or IV infusion • For individuals with ongoing exposure to SARS-CoV-2, repeat dosing of CAS 300 mg plus IMD	• Hypersensitivity, including anaphylaxis and infusion-related reactions • These AEs were observed over multiple trials where participants received CAS 600 mg plus IMD 600 mg or higher doses. • Injection site reactions, including ecchymosis and erythema, in clinical trial participants who received CAS plus IMD administered by SQ injections.	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions. • Monitor patient during the IV infusion or SQ injections and for at least 1 hour after the infusion or injections are completed.	• Drug-drug interactions are unlikely between CAS plus IMD and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • CAS plus IMD is available through the FDA EUA as treatment for high-risk outpatients with mild to moderate COVID-19 and as PEP for certain high-risk individuals.[2] See Anti-SARS-CoV-2 Monoclonal Antibodies and Prevention of SARS-CoV-2 Infection for a list of high-risk conditions and criteria for use of CAS plus IMD. • A list of clinical trials is available: Casirivimab Plus Imdevimab

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies), continued				
300 mg by SQ injections or IV infusion every 4 weeks for duration of ongoing exposure.				
Sotrovimab (Anti-SARS-CoV-2 Monoclonal Antibody)				
Dose Recommended in EUA for Treatment of COVID-19: • SOT 500 mg administered by IV infusion over 30 minutes	• Rash • Diarrhea • Hypersensitivity, including anaphylaxis and infusion-related reactions	• Only for administration in health care settings by qualified health care providers who have immediate access to emergency medical services and medications that treat severe infusion reactions. • Monitor patient during the IV infusion and for at least 1 hour after the infusion is completed.	• Drug-drug interactions are unlikely between SOT and medications that are renally excreted or that are CYP substrates, inhibitors, or inducers.	**Availability:** • SOT is available through the FDA EUA for the treatment of high-risk outpatients with mild to moderate COVID-19.[3] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Sotrovimab
COVID-19 Convalescent Plasma				
Dose Recommended in EUA for Treatment of COVID-19: • Per the EUA, consider starting clinical dosing with 1 high-titer COVID-19 CP unit (about 200 mL), with administration of additional CP units based on the prescribing provider's medical judgment and the patient's clinical response.	• TRALI • TACO • Allergic reactions • Anaphylactic reactions • Febrile nonhemolytic reactions • Hemolytic reactions • Hypothermia • Metabolic complications • Transfusion-transmitted infections[4] • Thrombotic events • Theoretical risk of antibody-mediated enhancement of infection and suppressed long-term immunity	• Before administering CP to patients with a history of severe allergic or anaphylactic transfusion reactions, the Panel recommends consulting a transfusion medicine specialist who is associated with the hospital blood bank. • Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• The decision to treat patients aged <18 years with COVID-19 CP should be based on an individualized assessment of risk and benefit.[5] • Patients with impaired cardiac function and heart failure may require a smaller volume of CP or a slower transfusion rate. **Availability:** • High-titer COVID-19 CP is available through the FDA EUA for hospitalized patients with COVID-19.[6] See Convalescent Plasma. • A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Events	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin				
Dose in Clinical Trials for Treatment of COVID-19: • Dose varies by clinical trial	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • RBC alloimmunization • Transfusion-transmitted infections[4]	• Monitor for transfusion-related reactions. • Monitor patient's vital signs at baseline and during and after transfusion.	• Drug products **should not be added** to the IV infusion line for the blood product.	• A list of clinical trials is available: SARS-CoV-2 Immunoglobulin

Key: AE = adverse event; BAM = bamlanivimab; CAS = casirivimab; CP = convalescent plasma; CYP = cytochrome P450; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PEP = post-exposure prophylaxis; RBC = red blood cell; SOT = sotrovimab; SQ = subcutaneous; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

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