Anti-SARS-CoV-2 Antibody Products

Last Updated: April 21, 2021

Summary Recommendations

Anti-SARS-CoV-2 Monoclonal Antibodies

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody combinations (listed in alphabetical order) to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the Emergency Use Authorization (EUA) criteria for the products:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa)**; *or*
  - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa)**.
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset.
- There are no comparative data to determine whether there are differences in clinical efficacy or safety between bamlanivimab plus etesevimab and casirivimab plus imdevimab.
  - There are SARS-CoV-2 variants, particularly those that contain the mutation E484K, that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
  - In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial **(AIIa)**. However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

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.
- 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 are insufficient data 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 are insufficient data 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.

Anti-SARS-CoV-2 Specific Immunoglobulin

- There are insufficient data for the Panel to recommend either for or against the use of anti-SARS-CoV-2 specific immunoglobin 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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Background

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 S 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 resulting in virus-host cell membrane fusion and viral entry.[1]

Many individuals with COVID-19 produce neutralizing antibodies to SARS-CoV-2 about 10 days after disease onset, with higher antibody levels observed in those with severe disease.[2] The neutralizing activity of COVID-19 patients' plasma was correlated with the magnitude of antibody responses to SARS-CoV-2 S and N proteins. Monoclonal antibodies targeting the S protein have the potential to prevent SARS-CoV-2 infection and to alleviate symptoms and limit progression to severe disease in patients with mild to moderate COVID-19, particularly in those who have not yet developed an endogenous antibody response.[3]

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

Bamlanivimab (also known as LY-CoV555 and LY3819253) is a neutralizing monoclonal antibody that targets the RBD of the S protein of SARS-CoV-2. Etesevimab (also known as LY-CoV016 and LY3832479) is another neutralizing monoclonal antibody that binds to a different but overlapping epitope in the RBD of the SARS-CoV-2 S protein. Casirivimab (previously REGN10933) and imdevimab (previously REGN10987) are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the S protein RBD of SARS-CoV-2.

Two combination products, bamlanivimab plus etesevimab and casirivimab plus imdevimab, are available through Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) 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. Because of an increasing number of reports of SARS-CoV-2 variants that are resistant to bamlanivimab alone, FDA has recently revoked the EUA for bamlanivimab, and the product will no longer be distributed in the United States.[4]

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using one of the following anti-SARS-CoV-2 monoclonal antibody combinations (listed in alphabetical order) to treat outpatients with mild to moderate COVID-19 who are at high risk of clinical progression, as defined by the EUA criteria:
  - **Bamlanivimab 700 mg plus etesevimab 1,400 mg (AIIa)**; *or*
  - **Casirivimab 1,200 mg plus imdevimab 1,200 mg (AIIa)**.
- Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset.

- There are SARS-CoV-2 variants, particularly those that contain the mutation E484K (see below), that reduce the virus' susceptibility to bamlanivimab and, to a lesser extent, casirivimab and etesevimab in vitro; however, the clinical impact of these mutations is not known.
- In regions where SARS-CoV-2 variants with reduced in vitro susceptibility to bamlanivimab plus etesevimab are common, some Panel members would preferentially use casirivimab plus imdevimab while acknowledging that it is not known whether in vitro susceptibility data correlate with clinical outcomes.
- The Panel **recommends against** the use of **anti-SARS-CoV-2 monoclonal antibodies** for patients who are hospitalized because of COVID-19, except in a clinical trial **(AIIa)**. However, their use should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

For additional information on the rationale for the Panel's recommendations regarding anti-SARS-CoV-2 monoclonal antibodies for nonhospitalized patients with mild to moderate COVID-19, see Therapeutic Management of Patients with COVID-19.

SARS-CoV-2 Variants of Concern or Interest and Their Susceptibility to Anti-SARS-CoV-2 Monoclonal Antibodies

In laboratory studies, some SARS-CoV-2 variants of concern or interest that harbor certain mutations have markedly reduced susceptibility to bamlanivimab and may have lower sensitivity to etesevimab and casirivimab.[5] However, the impact of these mutations on the clinical response to anti-SARS-CoV-2 monoclonal antibody combinations is uncertain, and the prevalence of these variants in different regions may vary. Of note:

- The B.1.1.7 variant of concern, which is increasing in frequency in the United States, retains in vitro susceptibility to the anti-SARS-CoV-2 monoclonal antibodies that are currently available through EUAs.[6,7]
- The B.1.351 variant of concern has been infrequently detected among SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.[8,9] In vitro studies suggest that bamlanivimab plus etesevimab has markedly reduced activity against the B.1.351 variant.[6] In vitro studies also suggest that the K417N mutation, which is present in the B.1.351 variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[7]
- The P.1 variant of concern has been infrequently detected among SARS-CoV-2 samples sequenced in the United States to date. This variant includes the E484K mutation, which results in a marked reduction in in vitro susceptibility to bamlanivimab.[6,10] In vitro studies suggest that bamlanivimab plus etesevimab also has markedly reduced activity against the P.1 variant.[6,8,10] In vitro studies also suggest that the K417T mutation, which is present in the P.1 variant along with the E484K mutation, reduces casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[7]
- The B.1.429/B.1.427 variants of concern (also called 20C/CAL.20C) that are circulating in parts of the United States, including California, Arizona, and Nevada, have the L452R mutation. This mutation is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to be a modest in vitro decrease in susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.[6]
- The B.1.526 variant of interest is circulating in parts of the United States, such as New York.

It commonly has the E484K mutation, which is associated with a marked reduction in in vitro susceptibility to bamlanivimab. There appears to also be reduced in vitro susceptibility to the combination of bamlanivimab and etesevimab, although the clinical implications of this finding are not known.[6] In vitro studies suggest that the E484K mutation may reduce casirivimab activity, although the combination of casirivimab and imdevimab appears to retain activity.[7]

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

Use of 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 monoclonal antibodies for patients who are hospitalized for COVID-19 or for the following patients:

- 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, because of COVID-19, require an increase in oxygen flow rate from baseline.

The FDA EUAs do permit the use of these monoclonal antibodies for patients who are hospitalized for an indication other than COVID-19 provided they have mild to moderate COVID-19 and are at high risk for progressing to severe disease and/or hospitalization.[11,12]

Anti-SARS-CoV-2 monoclonal antibodies 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 antibodies provide clinical benefits in people with B-cell immunodeficiency or other immunodeficiencies.

Anti-SARS-CoV-2 monoclonal antibodies have not been shown to be beneficial in hospitalized patients with severe COVID-19.[7,12] A substudy of A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19 (ACTIV-3) randomized patients hospitalized with COVID-19 to receive bamlanivimab 7,000 mg or placebo, each in addition to remdesivir. On October 26, 2020, following a prespecified interim futility analysis, enrollment into this study was stopped due to lack of clinical benefit.[13] Among 314 hospitalized adults (163 in the bamlanivimab arm and 151 in the placebo arm), pulmonary outcomes were similar at Day 5 (OR of being in a more favorable category in the bamlanivimab arm than in the placebo arm 0.85; 95% CI, 0.56–1.29; $P = 0.45$). The time to hospital discharge was also similar in the two arms (rate ratio 0.97; 95% CI, 0.78–1.20).[14]

Clinical Trial Data

See Table 3a for information on the clinical trials evaluating the safety and efficacy of anti-SARS-CoV-2 monoclonal antibodies.

Monitoring

- These anti-SARS-CoV-2 monoclonal antibodies are to be given as intravenous infusions and should only be administered in health care settings by qualified health care providers who have immediate access to medications to treat severe infusion reactions and to emergency medical services.

- Patients should be monitored during the infusion and for at least 1 hour after the infusion is completed.
- No dosage adjustments are required for body weight, renal impairment, or mild hepatic impairment.

Adverse Effects

- In the Phase 2 Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) trial, the most common adverse events associated with bamlanivimab were nausea, diarrhea, dizziness, headache, pruritis, and vomiting. The safety profile of bamlanivimab at all three doses was reportedly like that of the placebo.
- According to the EUA fact sheet for bamlanivimab plus etesevimab, the following adverse events were reported: nausea, dizziness, rash, pruritis, and pyrexia. In the Phase 3 BLAZE-1 study, 1% of the participants experienced hypersensitivity events, including infusion-related reactions, rash, and pruritis. All events resolved.
- Hypersensitivity, including anaphylaxis and infusion reactions, may occur. According to the EUA for bamlanivimab, among >850 participants in ongoing trials who have received bamlanivimab, one anaphylactic reaction and one serious infusion-related reaction occurred, and both required treatment, which in one case included epinephrine.
- According to the EUA fact sheet for casirivimab plus imdevimab, among the 533 participants who received casirivimab plus imdevimab in the R10933-10987-COV-2067 trial, one participant had an anaphylaxis reaction that required treatment with epinephrine, and four participants who received casirivimab 4,000 mg plus imdevimab 4,000 mg had an infusion reaction of grade 2 severity or higher, which, in two cases, resulted in permanent discontinuation of the infusion.

Drug-Drug Interactions

- Drug-drug interactions are unlikely between bamlanivimab plus etesevimab or casirivimab plus imdevimab and medications that are renally excreted or that are cytochrome P450 substrates, inhibitors, or inducers.
- Please see Table 3c for more information.

Vaccination

- SARS-CoV-2 vaccination should be deferred for ≥90 days in people who have received anti-SARS-CoV-2 monoclonal antibodies. This is a precautionary measure, as the antibody treatment may interfere with vaccine-induced immune responses.[15]
- For people who develop COVID-19 after receiving SARS-CoV-2 vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment with monoclonal antibodies.[15]

Considerations in Pregnancy

- As immunoglobulin (Ig) G monoclonal antibodies, bamlanivimab plus etesevimab, casirivimab plus imdevimab, and bamlanivimab alone would be expected to cross the placenta. There are no available data on the use of these anti-SARS-CoV-2 monoclonal antibodies during pregnancy; however, IgG products are generally not withheld because of pregnancy when their use is indicated.
- Anti-SARS-CoV-2 monoclonal antibodies should not be withheld from a pregnant individual with

COVID-19 who has a condition that poses a high risk of progression to severe COVID-19, and the patient and provider determine that the potential benefit of the drug outweighs the potential risk (see the EUA criteria for the use of these products below).

- Inclusion of pregnant people in clinical trials should be encouraged to inform decisions on whether to use anti-SARS-CoV-2 monoclonal antibody therapy in this population.

Considerations in Children

- There are insufficient pediatric data to recommend either for or against the use of anti-SARS-CoV-2 monoclonal antibody products for children with COVID-19 who are not hospitalized but who have risk factors for severe disease. Based on adult studies, bamlanivimab plus etesevimab or casirivimab plus imdevimab may be considered for nonhospitalized children who meet EUA criteria, especially those who meet more than one criterion or are aged ≥16 years, on a case-by-case basis in consultation with a pediatric infectious disease specialist. Additional guidance on the use of anti-SARS-CoV-2 monoclonal antibodies for the treatment of COVID-19 in children is provided in a recent publication endorsed by the Pediatric Infectious Diseases Society.[16]
- Most children with mild or moderate COVID-19, even those with risk factors specified in the EUAs for bamlanivimab plus etesevimab or casirivimab plus imdevimab, will not progress to more severe illness and will recover without specific therapy.
- Risk factors for hospitalization have not been as clearly defined in children with COVID-19 as in adults with the disease, making it difficult to identify those children at the highest risk of hospitalization and those who would be likely to benefit from monoclonal antibody therapy.
- Additional data on clinical outcomes in children who receive monoclonal antibodies for the treatment of COVID-19, including in those with specific risk factors, are needed.
- Please see Special Considerations in Children for more information.

Clinical Trials

- Health care providers are encouraged to discuss participation in anti-SARS-CoV-2 monoclonal antibody clinical trials with patients who have mild to moderate COVID-19.

Drug Availability

- Bamlanivimab plus etesevimab and casirivimab plus imdevimab are available through FDA EUAs.[17]
- Given the possibility of a limited supply of bamlanivimab plus etesevimab and casirivimab plus imdevimab, as well as challenges of distributing and administering the drugs, patients who are at highest risk for COVID-19 progression based on the EUA criteria should have priority access to the drugs.[18,19]
- Efforts should be made to ensure that communities most affected by COVID-19 have equitable access to these monoclonal antibodies.

High-Risk Criteria in the Emergency Use Authorizations for Anti-SARS-CoV-2 Monoclonal Antibodies

The FDA EUAs for all available anti-SARS-CoV-2 monoclonal antibodies and combinations have the same criteria for use: they allow for the use of the monoclonal antibodies for the treatment of COVID-19 in nonhospitalized adults and children aged ≥12 years and weighing ≥40 kg who are at high risk for progressing to severe COVID-19 and/or hospitalization.

High-risk individuals as specified in the EUA are those who meet at least one of the following criteria:

- Body mass index (BMI) ≥35
- Chronic kidney disease
- Diabetes mellitus
- Immunocompromising condition
- Currently receiving immunosuppressive treatment
- Aged ≥65 years
- Aged ≥55 years and have:
  - Cardiovascular disease, *or*
  - Hypertension, *or*
  - Chronic obstructive pulmonary disease or another chronic respiratory disease.
- Aged 12 to 17 years and have:
  - BMI ≥85th percentile for their age and gender based on the Centers for Disease Control and Prevention growth charts; *or*
  - Sickle cell disease; *or*
  - Congenital or acquired heart disease; *or*
  - Neurodevelopmental disorders (e.g., cerebral palsy); *or*
  - A medical-related technological dependence that is not related to COVID-19 (e.g., tracheostomy, gastrostomy, positive pressure ventilation); *or*
  - Asthma or a reactive airway or other chronic respiratory disease that requires daily medication for control.

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

Last Updated: April 21, 2021

Study Design	Methods	Results	Limitations and Interpretation
Bamlanivimab Plus Etesevimab Versus Placebo in Outpatients With COVID-19 (BLAZE-1)[1,2]			

Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19 and/or hospitalization as defined in the BAM plus ETE EUA (n = 1,035)
 	
Note: These data are from the FDA EUA for BAM plus ETE and from a conference abstract presentation.
	Key Inclusion Criteria:
	• Aged ≥12 years
	• Not currently hospitalized
	• ≥1 mild or moderate COVID-19 symptom
	• At high risk for progressing to severe COVID-19 and/or hospitalization
	
	Key Exclusion Criteria:
	• SpO_2 ≤93% on room air, *or*
	• Respiratory rate ≥30 breaths/min, *or*
	• Heart rate ≥125 bpm
	
	Interventions:
	• Single IV infusion of:
	  • BAM 2,800 mg plus ETE 2,800 mg, *or*
	  • Placebo
	• Administered within 3 days after receiving a positive result on a SARS-CoV-2 virologic test
	
	Primary Endpoint:
	• Proportion of participants with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29
	
	Secondary Endpoints:
	• Proportion of participants with persistently high VL (defined as SARS-CoV-2 level >5.27 $\log_{10}$ copies/mL) at Day 7
	• Mean change in VL from baseline to Days 3, 5, and 7
		Number of Participants:
		• BAM plus ETE (n = 518) and placebo (n = 517)
		
		Participant Characteristics:
		• Median age was 56 years; 31% of the participants were aged ≥65 years.
		• 48% of the participants were men.
		• 87% of the participants were White; 8% were Black or African American; and 29% were Hispanic/Latinx.
		• Mean duration of symptoms was 4 days.
		• 77% of the participants had mild COVID-19.
		
		Primary Outcomes:
		• Proportion of participants with COVID-19 related hospitalization or death by any cause by Day 29:
		  • 11 of 518 participants (2.1%) in the BAM plus ETE arm vs. 36 of 517 (7.0%) in the placebo arm ($P = 0.0004$)
		  • Relative reduction: 70%
		• Proportion of participants who had died from any cause by Day 29:
		  • 0 of 518 participants (0%) in the BAM plus ETE arm vs. 10 of 517 (1.9%) in the placebo arm ($P < 0.001$).
		
		Secondary Outcome:
		• The proportion of participants with persistently high VLs at Day 7 was 10% in the BAM plus ETE arm vs. 29% in the placebo arm ($P < 0.000001$).
			Limitation:
			• Trial data have not yet been peer reviewed and published.
			
			Interpretation:
			• There was a 5% absolute reduction and a 70% relative reduction in COVID-19-related hospitalizations or deaths from any cause among the participants who received BAM plus ETE compared to those who received placebo.
			• Data are for a BAM plus ETE dose which is not the dose authorized in the EUA.

<table>
<tr><th>Study Design</th><th>Methods</th><th>Results</th><th>Limitations and Interpretation</th></tr>
<tr><td colspan="4">REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients with COVID-19 (Modified Full Analysis of R10933-10987-COV-2067 Trial)[3]</td></tr>
<tr>
<td>Double-blind, Phase 3 RCT in outpatients with mild to moderate COVID-19 (n = 4,180 for modified full analysis subset of the Phase 3 trial)

These data are publicly available but have not been peer reviewed or published.</td>
<td>Key Inclusion Criteria:
• Onset of COVID-19 symptoms ≤7 days before randomization
• SARS-CoV-2 PCR positive at baseline
• Criteria only for the modified full analysis:
  • Aged ≥18 years
  • ≥1 risk factor for severe COVID-19
Interventions:
• Single IV infusion of:
  • CAS 600 mg plus IMD 600 mg,
  • CAS 1,200 mg plus IMD 1,200 mg, or
  • Placebo
Endpoint:
• Proportion of participants with COVID-19-related hospitalization or all-cause death through Day 29</td>
<td>Number of Participants:
• CAS 600 mg plus IMD 600 mg (n = 736) vs. placebo (n = 748)
• CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) vs. placebo (n = 1,341)
Participant Characteristics:
• Median age was 50 years.
• 35% of the participants were Hispanic/Latinx and 5% were Black or African American.
• Median duration of symptoms prior to enrollment was 3 days (IQR 2–5 days).[4]
Outcomes:
• Percentage of participants with COVID-19-related hospitalization or all-cause death through Day 29 (based on participants in the modified cohort):
  • 7 of 736 (1.0%) in the CAS 600 mg plus IMD 600 mg arm vs. 24 of 748 (3.2%) in the placebo arm ($P = 0.0024$)
  • 18 of 1,355 (1.3%) in the CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 of 1,341 (4.6%) in the placebo arm ($P < 0.0001$)
• Percentage of participants who died (based on all study participants):
  • 1 of 827 (0.1%) in the CAS 600 mg plus IMD 600 mg arm
  • 1 of 1,849 (0.05%) in the CAS 1,200 mg plus IMD 1,200 mg arm
  • 5 of 1,843 (0.3%) in the placebo arm</td>
<td>Limitations:
• The modified full analysis data have not been peer reviewed or published.
• Details of the study design, follow-up, and full methods are limited.
Interpretation:
• There was a 2.2% absolute reduction and a 70% relative risk reduction in COVID-19-related hospitalizations or all-cause deaths in participants who received CAS 600 mg plus IMD 600 mg compared to those who received placebo.
• There was a 3.3% absolute reduction and a 71% relative risk reduction in COVID-19 related hospitalizations and all-cause deaths in participants who received CAS 1,200 mg plus IMD 1,200 mg compared to those who received placebo.</td>
</tr>
</table>

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Trial)[5]			

Double-blind, Phase 1 and 2 RCT in outpatients with mild to moderate COVID-19 (n = 799)
 	
Note: These data are from the FDA EUA for CAS plus IMD.
	Key Inclusion Criteria:
	• Onset of COVID-19 symptoms ≤7 days before randomization
	• SpO2 ≥93% on room air
	
	Key Exclusion Criteria:
	• Hospitalization before or at randomization due to COVID-19
	• Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 CP, IVIG for any indication)
	
	Interventions:
	• Single IV infusion of:
	  • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg),
	  • CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg), *or*
	  • Placebo
	• Administered ≤3 days after receiving a positive result on a SARS-CoV-2 virologic test
	
	Primary Endpoint:
	• TWA change in NP VL from baseline to Day 7
	
	Secondary Endpoints:
	• COVID-19-related medical visits including hospitalization or ED, urgent care, or physician office/telemedicine visit within 28 days of treatment
	• Safety
	• Symptom improvement
		Number of Participants:
		• CAS plus IMD (n = 533):
		  • CAS plus IMD 2,400 mg (n = 266)
		  • CAS plus IMD 8,000 mg (n = 267)
		• Placebo (n = 266)
		
		Participant Characteristics:
		• Median age was 42 years; 7% of the participants were aged ≥65 years.
		• 34% of the participants had risk factors for severe COVID-19.
		• Median duration of symptoms was 3 days.
		
		Primary Outcome:
		• The primary endpoint was evaluated in the modified full analysis set of participants with detectable virus at baseline (n = 665).
		• TWA change in NP VL at Day 7 was greater among the CAS plus IMD-treated participants overall than among the placebo-treated participants (-0.36 $\log_{10}$ copies/mL; $P < 0.0001$).
		
		Secondary Outcomes:
		• The proportion of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the combined CAS plus IMD arms than in the placebo arm:
		  • Combined CAS plus IMD arms: 2.8% of patients
		  • Placebo arm: 6.5% of patients
		• In a post hoc analysis, percentage of participants who were hospitalized or had a medical visit within 28 days of treatment:
		  • All CAS plus IMD doses: 8 of 434 (2%)
		  • CAS plus IMD 2,400 mg: 4 of 215 (2%)
		  • CAS plus IMD 8,000 mg: 4 of 219 (2%)
		  • Placebo: 10 of 231 (4%)
			Limitations:
			• Relatively small number of participants in each arm
			• Low number of hospitalizations or ED visits
			
			Interpretation:
			• Compared to placebo, a single infusion of CAS plus IMD showed a reduction in NP VL at Day 7 among outpatients with mild or moderate COVID-19.
			• The combined hospitalization or ED visit rate was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small.
			• Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD from this study. Additional data from a follow-up trial have been reported but remain unpublished.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 and REGN10987 (Casirivimab Plus Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Trial)[5], continued			
		• In a post hoc analysis, percentage of participants at high-risk for progression to severe COVID-19 and/or hospitalization who required hospitalization or ED visit: • All CAS plus IMD doses: 4 of 151 (3%) • Placebo: 7 of 78 (9%) • Median time to symptom improvement: • Combined CAS plus IMD arms: 5 days • Placebo arm: 6 days • The safety profile of CAS plus IMD was similar to the profile for the placebo. • 4 infusion related reactions of grade 2 severity or higher were reported in the CAS plus IMD 8,000 mg arm resulting in permanent discontinuation of the infusion in 2 participants; 1 participant had an anaphylactic reaction that resolved with treatment.	
REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Interim Analysis)[6] **Note:** The data presented in this published interim analysis represent a subset of participants described in the CAS plus IMD EUA (see study above).			
Double-blind, Phase 1 and 2 RCT in outpatients with mild to moderate COVID-19 (n = 275)	**Key Inclusion Criteria:** • Onset of COVID-19 symptoms ≤7 days before randomization • SpO_2 ≥93% on room air **Key Exclusion Criteria:** • Hospitalization before or at randomization due to COVID-19 • Prior, current, or planned future use of any of the treatments specified in the protocol (e.g., COVID-19 CP, IVIG for any indication) **Interventions:** • Single IV infusion of: • CAS plus IMD 2,400 mg (CAS 1,200 mg and IMD 1,200 mg),	**Number of Participants:** • All CAS plus IMD doses (n = 182): • CAS plus IMD 2,400 mg (n = 92) • CAS plus IMD 8,000 mg (n = 90) • Placebo (n = 93) **Participant Characteristics:** • Median age was 44 years (range 35–52 years). • Median time from symptom onset to randomization was 3 days. • Baseline serum antibody status: • Positive: 45% of participants • Negative: 41% of participants • Unknown: 14% of participants	**Limitations:** • No formal hypothesis testing • Interim analysis • Relatively small number of participants in each arm • These data represent only a subset of participants described in the CAS plus IMD EUA (see the study above). • Low number of medical visits **Interpretation:** • Compared to placebo, a single infusion of CAS plus IMD showed a reduction in VL at Day 7 among outpatients with mild or moderate COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
REGN10933 (Casirivimab) Plus REGN10987 (Imdevimab) Versus Placebo in Outpatients With COVID-19 (R10933-10987-COV-2067 Interim Analysis)[6], continued			

	• CAS plus IMD 8,000 mg (CAS 4,000 mg and IMD 4,000 mg), *or*
	• Placebo
	• Administered ≤3 days after receiving a positive result on a SARS-CoV-2 virologic test
	Primary Endpoint:
	• TWA change in NP VL from baseline to Day 7 in participants with negative serum antibody status at baseline
	Secondary Endpoints:
	• COVID-19-related medical visits, including hospitalization or ED, urgent care, or physician office/telemedicine visit within 28 days of treatment
	• Safety
	• Symptom improvement
		Primary Outcomes:
		• Primary endpoint evaluated in modified full analysis set of participants with detectable virus at baseline (n = 221).
		• TWA change in NP VL at Day 7 was greater among the participants who received CAS plus IMD (-1.74 ± 0.11 $\log_{10}$ copies/mL; 95% CI, -1.95 to -1.53) than among those who received placebo (-1.34 ± 0.13 $\log_{10}$ copies/mL; 95% CI, -1.60 to -1.08).
		• Among the participants with a negative serum antibody status at baseline, TWA change in VL was greater among those who received CAS plus IMD (-1.94 ± 0.13 $\log_{10}$ copies/mL; 95% CI, -2.20 to -1.67) than among those who received placebo (-1.37 ± 0.20 $\log_{10}$ copies/mL; 95% CI, -1.76 to -0.98).
		Secondary Outcomes:
		• The percentage of participants who had COVID-19-related medical visits within 28 days of treatment was lower in the CAS plus IMD arms than in the placebo arm:
		  • All CAS plus IMD doses: 6 of 182 (3%)
		  • Placebo: 6 of 93 (6%)
		• Among participants with negative serum antibody status at baseline, the percentage of those who had COVID-19-related medical visits within 28 days of treatment was lower in the CAS plus IMD arms:
		  • All CAS plus IMD doses: 5 of 80 (6%)
		  • Placebo: 5 of 33 (15%)
		• The safety profile of CAS plus IMD was similar to the profile of the placebo; 2 hypersensitivity or infusion related reactions of grade 2 severity or higher were reported in both the CAS plus IMD 8,000 mg arm and the placebo arm.
		• The mean half-life for both CAS and IMD antibodies ranged from 25–37 days.
			• The percentage of participants with medical visits was lower in the CAS plus IMD arms than in the placebo arm, but the number of events in each arm was small.
			• CAS plus IMD may have a greater effect in patients who are serum antibody negative but further investigation is needed.
			• Because of the small number of clinical events, it is difficult to draw definitive conclusions about the clinical benefit of CAS plus IMD from this study.

Key: ACTIV-3/TICO = A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients With COVID-19; AE = adverse event; BAM = bamlanivimab; BLAZE-1 = Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies; BMI = body mass index; CAS = casirivimab; CP = convalescent plasma; ED = emergency department; ETE = etesevimab; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IMD = imdevimab; IV = intravenous; IVIG = intravenous immunoglobulin; NP = nasopharyngeal; PCR = polymerase chain reaction; RCT = randomized controlled trial; RDV = remdesivir; SpO_2 = saturation of oxygen; TWA = time-weighted average; 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 are insufficient data 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 are insufficient data 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 are insufficient data 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 are insufficient data 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: April 21, 2021

- The information in this table is derived from data on the use of these products in investigational trials in patients with COVID-19. The table includes dose recommendations from the FDA EUAs for patients with COVID-19 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 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 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 for the drugs listed in this table, please refer to the drug-specific sections of the Guidelines and Therapeutic Management of Adults With COVID-19.

Dosing Regimens	Adverse Effects	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: • BAM 700 mg and ETE 1,400 mg IV administered together as a single dose	• Nausea • Dizziness • Rash • Pruritis • Pyrexia • Hypersensitivity, including anaphylaxis and infusion-related reactions • Unexpected SAEs may occur. • These AEs were observed in a trial where the doses of BAM and ETE given (BAM 2,800 mg and ETE 2,800 mg) were higher than the EUA doses.	• Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and for ≥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:** • BAM plus ETE is available through the FDA EUA for high-risk outpatients with mild to moderate COVID-19.[1] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Bamlanivimab plus Etesevimab

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
Casirivimab Plus Imdevimab (Anti-SARS-CoV-2 Monoclonal Antibodies)				
Dose Recommended in EUA: • CAS 1,200 mg and IMD 1,200 mg IV administered together as a single dose	• Hypersensitivity, including anaphylaxis and infusion-related reactions • Unexpected SAEs may occur.	• Only for administration in health care settings by qualified health care providers who have immediate access to medications to treat a severe infusion reaction and emergency medical services. • Monitor patient during the infusion and for ≥1 hour after the infusion is 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 for high-risk outpatients with mild to moderate COVID-19.[2] See Anti-SARS-CoV-2 Monoclonal Antibodies for a list of high-risk conditions. • A list of clinical trials is available: Casirivimab plus Imdevimab
COVID-19 Convalescent Plasma				
Dose Recommended in EUA Authorizing the Use of High-Titer COVID-19 CP for Hospitalized Patients With 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[3] • 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.[4] • Patients with impaired cardiac function and heart failure may require a smaller volume of CP or slower transfusion rate. **Availability:** • High-titer COVID-19 CP is available through the FDA EUA for hospitalized patients with COVID-19.[5] See Anti-SARS-CoV-2 Monoclonal Antibodies. • A list of clinical trials is available: COVID-19 Convalescent Plasma

Dosing Regimens	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Comments and Links to Clinical Trials
SARS-CoV-2-Specific Immunoglobulin				
Dose varies by clinical trial	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • RBC alloimmunization • Transfusion-transmitted infections[3]	• 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; RBC = red blood cell; SAE = serious adverse event; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

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