

# Intravenous Immunoglobulin

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## Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **intravenous immunoglobulin (IVIG)** for the treatment of acute COVID-19 in adults and children, except in a clinical trial (**AIII**). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of underlying conditions or complications that arise during the course of COVID-19.
- For the Panel’s recommendations on the use of IVIG in people with multisystem inflammatory syndrome in children (MIS-C) or multisystem inflammatory syndrome in adults (MIS-A) and a discussion of the clinical data that support those recommendations, see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

## Rationale

It is unknown whether IVIG products derived from pooled donor plasma contain high titers of antibodies that neutralize SARS-CoV-2. Information on SARS-CoV-2 antibody titer was not reported in the clinical trials that evaluated the use of IVIG for the treatment of COVID-19. The levels of SARS-CoV-2 antibodies in IVIG products likely vary depending on which SARS-CoV-2 variant was dominant when the plasma products were collected, and different lots of IVIG may have different titers of antibodies. Although IVIG preparations may have general immunomodulatory effects, these theoretical effects do not appear to benefit patients with COVID-19.<sup>1</sup>

## Considerations in Pregnant People

IVIG is commonly used during pregnancy for indications such as alloimmune thrombocytopenia.<sup>2</sup> However, because there is no clear evidence that IVIG is an effective treatment for acute COVID-19 in nonpregnant adults, the Panel **recommends against** the use of **IVIG** for the treatment of acute COVID-19 in pregnant individuals, except in a clinical trial (**AIII**). This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of underlying conditions or complications that arise during the course of COVID-19.

## Considerations in Children

No comparative studies have evaluated the use of IVIG in pediatric patients with acute COVID-19. IVIG is used in combination with glucocorticoids to treat MIS-C in pediatric patients.<sup>3-6</sup> However, because there is no clear evidence that IVIG is an effective treatment for acute COVID-19 in adults, the Panel **recommends against** the use of **IVIG** for the treatment of acute COVID-19 in children, except in a clinical trial (**AIII**). This recommendation should not preclude the use of IVIG when it is otherwise indicated.

For the Panel’s recommendations for children with MIS-C, see [Therapeutic Management of Hospitalized Children With MIS-C, Plus a Discussion on MIS-A](#).

## Clinical Data

In a meta-analysis of 6 randomized controlled trials that enrolled hospitalized patients with COVID-19, the use of non-SARS-CoV-2–specific IVIG was not associated with a survival benefit.<sup>1</sup> All of the

included trials were conducted in 2020, when the presence of SARS-CoV-2 antibodies in blood donors was likely uncommon. None of the studies measured the titers of anti-SARS-CoV-2 antibodies. Blood supplies collected since that time likely have a higher level of these antibodies, and the IVIG derived from those supplies could be expected to have a higher level of SARS-specific antibodies. A British study performed in 2022 evaluated serum anti-SARS-CoV-2 spike antibody titers before and after IVIG infusion in 35 patients with primary immunodeficiencies who were receiving regular immunoglobulin replacement therapy.<sup>7</sup> The study found that anti-SARS-CoV-2 spike antibody titers and the neutralization capacity of serum increased after IVIG infusion in most patients.

Different brands of commercially available IVIG products exhibit different levels of neutralizing activity against SARS-CoV-2 variants (e.g., BA.1, BA.4, BA.5, BQ.1.1, XBB). A study compared the anti-SARS-CoV-2 antibody levels in U.S. IVIG products that had expiration dates from 2020 to 2025.<sup>8</sup> The study found that products with expiration dates in 2023 and 2024 were more likely to have higher levels of anti-SARS-CoV-2 antibodies than those with earlier expiration dates. In addition, the study reported an association between later expiration dates and increased inhibition of angiotensin-converting enzyme 2 binding activity. Preparations that were intended for intravenous administration had higher titers than those intended for subcutaneous administration. However, the neutralizing activity against the Omicron variant was lower than the activity against prior variants, and the efficacy of using IVIG for the treatment of COVID-19 remains uncertain.

These data do not provide clear evidence for a clinical benefit of administering IVIG to people with COVID-19. Randomized controlled trials are needed to further define the role of IVIG in the treatment of COVID-19. The use of non-SARS-CoV-2–specific IVIG for the treatment of COVID-19 should be limited to clinical trials.

Concentrated antibody preparations derived from pooled plasma collected from individuals who have recovered from COVID-19 can be manufactured as SARS-CoV-2 hyperimmunoglobulin (hIVIG). Treatment with SARS-CoV-2 hIVIG did not alter patient outcomes in a large randomized controlled trial of hospitalized patients with COVID-19, and hIVIG is not currently available for clinical use in the United States.<sup>9</sup>

## References

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