

2025 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Treatment and Management of COVID-19: Vilobelimab

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This article provides a focused update to the clinical practice guideline on the treatment and management of patients with coronavirus disease 2019 (COVID-19), developed by the Infectious Diseases Society of America. The guideline panel presents a recommendation on the use of vilobelimab in hospitalized adults with critical COVID-19. The recommendation is based on evidence derived from a systematic literature review and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

Keywords. COVID-19; SARS-CoV-2; vilobelimab; monoclonal antibody; guideline.

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In adults hospitalized with critical COVID-19, should vilobelimab compared to no vilobelimab be added to standard care?

Recommendation: In hospitalized adults with critical coronavirus disease 2019 (COVID-19) requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), the IDSA guideline panel recommends vilobelimab only in the context of a clinical trial (*knowledge gap*).

BACKGROUND

Vilobelimab is a monoclonal antibody that targets C5a, a component of the complement system, which is known to play a key role in the excessive inflammation seen in critical coronavirus disease 2019 (COVID-19) cases [1]. C5a has been found to be elevated in patients with critical COVID-19, contributing to acute respiratory distress syndrome and end-organ failure [2]. A study in mice demonstrated that an anti-C5a monoclonal antibody can reduce immune system activation and inhibit lung injury [3]. Vilobelimab specifically binds to C5a and blocks its interaction with the C5a receptor, thereby inhibiting its pro-inflammatory effects. By targeting this pathway,

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vilobelimab reduces the inflammatory response without compromising the rest of the immune system.

On 4 April 2023, the Food and Drug Administration issued an Emergency Use Authorization for the use of vilobelimab to treat COVID-19 in hospitalized adults, specifically when administered within 48 hours of mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [4]. This authorization was based on results of the PANAMO trial [5].

In this focused update to the 2023 guideline [6], a recommendation is provided for vilobelimab. The primary audience for this recommendation is clinicians treating hospitalized adults with critical COVID-19.

METHODS

The panel's recommendation is based upon a systematic review of available evidence and adheres to a standardized methodology for rating the certainty of evidence and strength of recommendation according to the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach (Supplementary Figure 1) [7]. The recommendation has been endorsed by the Society of Infectious Diseases Pharmacists, the Society for Healthcare Epidemiology of America, and the Society of Critical Care Medicine.

Strong recommendations are made when the recommended course of action would apply to most people with few exceptions. Conditional recommendations are made when the suggested course of action would apply to the majority of people with many exceptions and shared decision making is important.

Literature searches (up to November 2024) were conducted as part of a systematic review. Key eligibility criteria at the clinical question level guided the selection of studies for inclusion. For this clinical question, only hospitalized adults were included. The primary comparison of interest was vilobelimab versus no vilobelimab.

A critical appraisal of the evidence according to the GRADE approach, along with an assessment of the benefits and harms of care options, informed the recommendation [7, 8]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

The search identified 2 randomized controlled trials that reported on adults aged 18 years and older with critical COVID-19 who were randomized to treatment with vilobelimab (800 mg intravenously [IV]) or placebo/best supportive care (Supplementary Table 1) [5, 9]. One phase 2 open-label, multicenter trial (n = 30) treated patients in the vilobelimab arm with a maximum of 7 doses of 800 mg IV. In the subsequent blinded, placebo-controlled, phase 3 trial, PANAMO (n = 369) patients were treated with a maximum of 6 doses of vilobelimab 800 mg IV. Of participants in the PANAMO trial,

Table 1. GRADE Evidence Profile: In adults hospitalized with critical COVID-19, should vilobelimab be added to standard care?

Certainty Assessment			No. of Patients				Effect		Importance			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Vilobelimab	No Vilobelimab		Relative (95% CI)	Absolute (95% CI)	
Mortality (follow-up: 28 days)												
2 [5, 9]	Randomized trials	Not serious	Not serious	Not serious ^a	Very serious ^{b,c}	None	56/192 (29.2%)	81/206 (39.3%)	HR: 0.73 (0.50 to 1.05)	88 fewer per 1000 (from 172 fewer to 15 more)	⊕⊕○○ Low	Critical
Serious adverse events (follow-up: 21 days)												
2 [5, 9]	Randomized trials	Not serious	Not serious	Not serious ^a	Very serious ^d	None	112/190 (58.9%)	127/204 (62.3%)	RR: 0.95 (0.81 to 1.11)	31 fewer per 1000 (from 118 fewer to 68 more)	⊕⊕○○ Low	Critical

Abbreviations: COVID-19, coronavirus disease 2019; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HR, hazard ratio; RR, relative risk.

^aNot rated down for indirectness; however, clinical trials excluded immunocompromised persons and limited administration of study drug to participants receiving invasive mechanical ventilation within 48 hours before vilobelimab infusion.

^bFew events do not meet optimal information size and suggest fragility of the estimate.

^c95% CI includes potential for reduction in mortality, as well as no meaningful difference with a 1% mortality threshold.

^d95% CI crosses multiple thresholds and cannot exclude the possibility of harm.

approximately 17% received treatment with tocilizumab, 6% with remdesivir, and 3% with baricitinib. These trials reported on the outcomes of mortality at 28 days and serious adverse events (Table 1).

Benefits

Among hospitalized patients, vilobelimab showed a trend toward reduced mortality at 28 days compared with no vilobelimab treatment (hazard ratio [HR]: 0.73; 95% CI: 0.50, 1.05) (Supplementary Figure 2).

Harms

Serious adverse events among patients receiving vilobelimab did not differ from those receiving usual care (relative risk [RR]: 0.95; 95% CI: 0.81, 1.11) (Supplementary Figure 3).

Other Considerations

The panel agreed that the overall certainty of evidence was low (Table 1, Supplementary Table 2), given the sparseness in mortality data and because the upper boundary of the 95% CI failed to exclude the risk of possible harms. The panel also expressed concerns regarding the generalizability and indirectness of the results, as both studies excluded immunocompromised populations, had fewer than 33 participants concomitantly receiving tocilizumab or baricitinib, and were conducted during time periods with different circulating variants of COVID-19 than now. Further concerns included the potential toxicity and uncertain efficacy of adding vilobelimab to other immunomodulators (eg, baricitinib or tocilizumab) for which there is greater evidence for benefit. The panel also examined the post hoc subgroup analysis of vilobelimab given with tocilizumab or baricitinib but recognized the need for more information, due to the small number of patients in the subgroup (34 vilobelimab vs 37 placebo) [10]. Additionally, the panel noted the post hoc analysis of vilobelimab's effect by sepsis phenotypes and concluded that future prospective studies are necessary to validate these findings and establish their clinical utility [11]. Because the studies excluded patients younger than 18 years, no statement of benefits versus harms can be made for this age group.

CONCLUSIONS AND RESEARCH NEEDS

The guideline panel recommends vilobelimab only in the context of a clinical trial. Additional data are needed to assess the efficacy and toxicity of vilobelimab when given to patients receiving tocilizumab or baricitinib, immunomodulators for which there is greater evidence of benefit. More information is needed to assess the efficacy and adverse events of vilobelimab in people who are immunocompromised. In addition, more research is needed on the effects of vilobelimab when given after 48 hours of intubation, which may better represent current clinical practice. Further studies should focus on exploring

whether certain subgroups could consistently and reliably benefit more from targeted treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Drs. Adarsh Bhimraj and Rajesh T. Gandhi are chair and vice chair of the panel, respectively. The Hospitalized Patients subgroup, under the leadership of Dr. Nandita Nadig, led the development of the recommendation. The remaining panelists assisted with interpretation of data, as well as drafting, revising, and approving the recommendation and manuscript. Drs. Rebecca Morgan, lead methodologist, and Yngve Falck-Ytter, methodologist, were responsible for designing and performing the data analyses and leading the panel according to the GRADE process. Jennifer Loveless, methodologist, was responsible for project planning and management, including revisions to and final approval of the recommendation and manuscript.

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Additional information. More detailed information on the analysis and development of the recommendation is available in the [Supplementary Material](#).

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