Supplementary Material for the 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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METHODS

Panel formation and conflicts of interest

The chair and vice chair of the guideline panel were selected by the leadership of IDSA. Twenty-four additional panelists comprised the full panel. The panel included clinicians with expertise in infectious diseases, pediatric infectious diseases, critical care medicine, pulmonology, maternal fetal medicine, and pharmacology, as well as biostatistics. Guideline methodologists oversaw all methodological aspects of the guideline development, including the identification and summarization of scientific evidence for each clinical question. IDSA staff oversaw all administrative and logistic issues related to the guideline panel.

All members of the expert panel complied with the IDSA policy on conflict of interest (COI), which requires disclosure of any financial, intellectual, or other interest that might be construed as constituting an actual, potential, or apparent conflict. Evaluation of such relationships as potential conflicts of interest was determined by a review process which included assessment by the Standards and Practice Guidelines Subcommittee (SPGS) Chair, and if necessary, the Conflict of Interests Ethics Committee. This

assessment of disclosed relationships for possible COI was based on the relative weight of the financial relationship (i.e., monetary amount) and the relevance of the relationship (i.e., the degree to which an independent observer might reasonably interpret an association as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. See the Notes section at the end of the guideline for the disclosures reported to IDSA.

Practice recommendations
Clinical Practice Guidelines are statements that include recommendations intended to optimize patient care by assisting practitioners and patients in making shared decisions about appropriate health care for specific clinical circumstances. These are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options [IOM 2011]. The "IDSA Handbook on Clinical Practice Guideline Development" provides more detailed information on the processes followed throughout the development of this guideline [IDSA CPG Handbook].

Review and approval process
Feedback was obtained from two external individual peer expert reviewers as well as the endorsing organizations. The IDSA Standards and Practice Guidelines Subcommittee (SPGS) and Board of Directors reviewed and approved the guideline prior to publication.

Process for updating
IDSA guidelines are regularly reviewed for currency. The need for updates to the guideline is determined by a scan of current literature and the likelihood that any new data would impact the recommendations. Any changes to the guideline will be submitted for review and approval to the appropriate Committees and Board of IDSA.

Clinical questions
Each clinical question was formatted according to the PICO style: Patient/Population (P), Intervention/Indicator (I), Comparator/Control (C), Outcome (O). For each PICO question, outcomes of interest were identified a priori and rated for their relative importance for decision-making.

Literature search
The U.S. Food and Drug Administration's Emergency Use Authorization for vilobelimab (Gohibic) for treatment of COVID-19 was downloaded from the FDA's website. Additionally, literature searches were conducted in Ovid Medline, Embase, and Cochrane Library. The last literature search was completed in November 2024. Searches were limited to studies published in English.

Search terms: vilobelimab OR vilobelimab (tiab)

Study selection
Inclusion and exclusion criteria were pre-defined. The eligibility criteria below were used.
Inclusion criteria:

- *Patient population*- Patients with critical COVID-19
- *Intervention*- Vilobelimab
- *Comparator*- No vilobelimab
- *Outcomes*- Mortality, serious adverse events
- *Study design*- RCTs

Exclusion criteria:

- *Patient population*- Patients without critical COVID-19
- *Intervention*- N/A
- *Comparator*- N/A
- *Study design***-** Review articles, case reports

Data extraction and analysis

Guideline methodologists, with panelist assistance, extracted the data for each pre-determined patient-important outcome. If a relevant publication was missing raw data for an outcome prioritized by the panel, an attempt was made to contact the author(s) for the missing data.

Evidence to decision

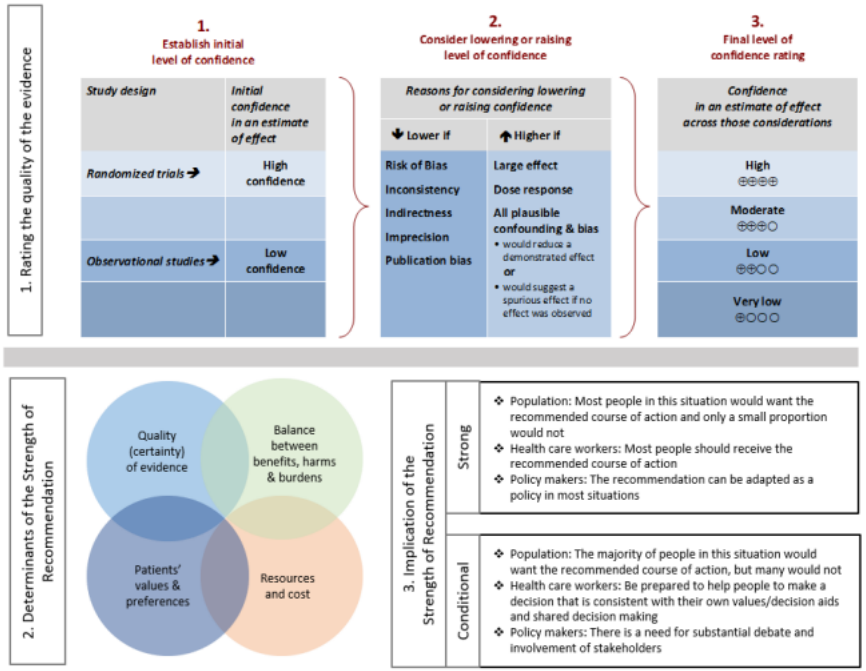
Guideline methodologists prepared the evidence summaries for each question and assessed the risk of bias and the certainty of evidence. Risk of bias was assessed by using the Cochrane Risk of Bias tool for RCTs [Higgins 2011]. The certainty of evidence was determined first for each critical and important outcome and then for each recommendation using the GRADE approach for rating the confidence in the evidence [Guyatt 2008, GRADE Handbook/Schunemann]. Evidence profiles were developed using the GRADEpro Guideline Development Tool [Guyatt 2008] and reviewed by panel members.

The Evidence to Decision framework [GRADEpro] was used to translate the evidence summaries into a practice recommendation. All recommendations are labeled as either “strong” or “conditional” according to the GRADE approach [IDSA CPG Handbook]. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. Supplementary Figure 1 provides the suggested interpretation of strong and conditional recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparator treatment or tests are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention” (either not using a specific treatment or a diagnostic test).

All members of the panel participated in the preparation of the draft guideline and approved the recommendation.

TABLES AND FIGURES

Supplementary Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using GRADE methodology (unrestricted use of figure granted by the U.S. GRADE Network)



Supplementary Table 1. Characteristics of included studies for vilobelimab

Study/year; design	Country/ Hospital	N subjects (intervention/ comparator); % female	Age, mean (SD)/median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Vlaar/2020 Open-label, exploratory randomized trial	Netherlands: Amsterdam UMC location AMC, Amsterdam UMC location VUmc, Maastricht UMC	30 (IFX-1 15/ Control 15) 27% female	IFX-1: 58 (9) Control: 63 (8)	Hospitalized adults with confirmed COVID-19, severe pneumonia, shortness of breath in past 14 days or need for non-invasive or invasive ventilation, PaO_2/FiO_2 ratio of 100–250 mm Hg	800 mg IV (maximum 7 doses) + best supportive care	Best supportive care based on current guidelines (e.g., thrombosis prophylaxis, ECMO)	Hydroxychloroquine (33-47%), anticoagulation (93-100%)	Percentage change in PaO_2/FiO_2 in the supine position between baseline and day 5 Mortality at 28 days Treatment-emergent and serious adverse events	InflaRx
Vlaar/2022 RCT	Netherlands, Germany, France, Belgium, Russia, Brazil, Peru, Mexico, and South Africa/46 hospitals	368 (Vilobelimab 177/ Placebo 191) 31.5% female	Vilobelimab: 56.7 (13.2)/58.0 (47.0-67.0) Placebo: 55.9 (14.5)/57.0 (46.0-68.0)	Hospitalized critically ill adults with severe and confirmed COVID-19 in the past 14 days and receiving invasive mechanical ventilation within 48 hours before the first infusion of study medication,	800 mg IV (maximum 6 doses) + best supportive care	Placebo + standard of care based on current guidelines (e.g., lung protective ventilation, thrombosis prophylaxis, renal replacement therapy)	Corticosteroids, anticoagulants and other medications and extracorporeal membrane oxygenation	All-cause mortality at 28 days and 60 days Proportion of patients with an improvement in the WHO 8-point ordinal scale Acute kidney failure during ICU stay and at day 28 Proportion of patients free from renal replacement therapy at day 28	InflaRx, German federal government

				PaO_2/FiO_2 ratio of 60-200 mm Hg				Treatment-emergent, serious, and special interest adverse events	

Supplementary Table 2. Risk of bias for included randomized controlled trials (vilobelimab vs. no vilobelimab)

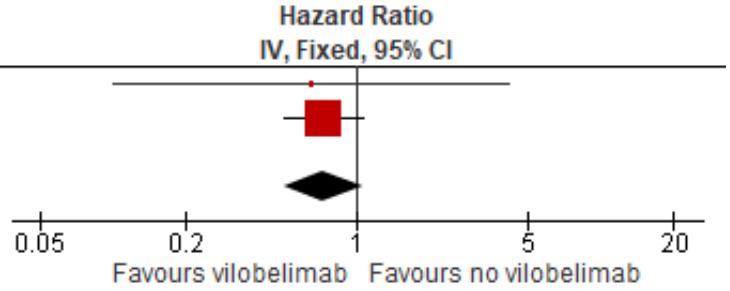
Study	Bias in randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
Vlaar 2020	**Low**	**Some concerns**	**Low**	**Low**	**Low**
Vlaar 2022	**Low**	**Low**	**Low**	**Low**	**Low**

Low	Some Concerns	High

Supplementary Figure 2. Forest plot for the outcome of mortality at 28 days for vilobelimab vs. no vilobelimab

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Vlaar 2020	-0.4308	0.955	3.9%	0.65 [0.10, 4.22]
Vlaar 2022	-0.3147	0.1931	96.1%	0.73 [0.50, 1.07]
Total (95% CI)			**100.0%**	**0.73 [0.50, 1.05]**

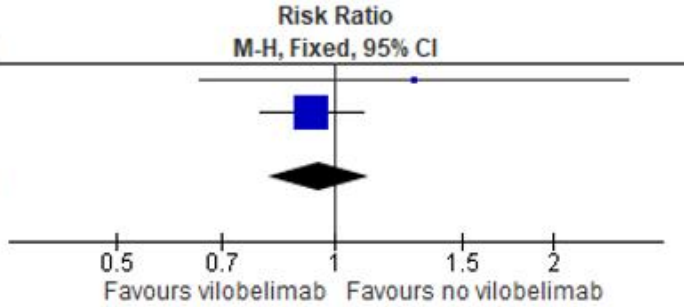
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.69 (P = 0.09)



Supplementary Figure 3. Forest plot for serious adverse events for vilobelimab vs. no vilobelimab

Study or Subgroup	Vilobelimab Events	Vilobelimab Total	No vilobelimab Events	No vilobelimab Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vlaar 2020	9	15	7	15	5.7%	1.29 [0.65, 2.54]
Vlaar 2022	103	175	120	189	94.3%	0.93 [0.79, 1.09]
Total (95% CI)		**190**		**204**	**100.0%**	**0.95 [0.81, 1.11]**
Total events	112		127			

Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)



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