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

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ABSTRACT. This article provides a focused update to the clinical practice guideline on the treatment and management of patients with COVID-19, developed by the Infectious Diseases Society of America.

The guideline panel presents a recommendation on the use of infliximab in hospitalized adults with severe or 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; infliximab; monoclonal antibody; guideline

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In patients hospitalized with severe or critical COVID-19 receiving systemic glucocorticoids, should infliximab compared to no infliximab be added to standard care?

Recommendation: In hospitalized adults receiving systemic glucocorticoids who are experiencing severe, rapidly progressing COVID-19* or critical COVID-19**, when baricitinib and tocilizumab are not available, the IDSA guideline panel suggests infliximab rather than no infliximab *(conditional recommendation, low certainty of evidence)*.

*Severe, rapidly progressing illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen, who are worsening despite treatment with systemic glucocorticoids.

**Critical illness is defined as patients requiring high-flow nasal cannula oxygen/non-invasive ventilation or invasive mechanical ventilation or ECMO.

BACKGROUND

Infliximab is a chimeric monoclonal antibody that targets tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine mainly generated by activated macrophages, lymphocytes and natural killer

cells. By neutralizing TNF-α, infliximab reduces inflammation and immune system overactivation, making it effective for autoimmune and inflammatory conditions [1]. Infliximab is FDA-approved. Indications include Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis [2,3]. Early in the COVID-19 pandemic, increased levels of interleukin - 6 and TNF-α were identified as independent predictors of disease severity and survival [4]. Further, several cohort studies noted that people receiving TNF-α inhibitors were at lower risk for COVID-19 related hospitalizations and severe disease in comparison to people who were receiving non-TNF- α biologics [5,6]. Although infliximab is not FDA-approved for COVID-19, it has been studied for its potential role in managing severe COVID-19-related inflammation (e.g., cytokine storm), most notably in the ACTIV-1 trial [7].

In this focused update to the 2023 guideline [8], a recommendation is provided for infliximab. The primary audience for this recommendation is clinicians treating hospitalized adults with severe or 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) [9]. The recommendation has been endorsed by the Pediatric Infectious Diseases Society, Society for Healthcare Epidemiology, 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.

A literature search was conducted in August 2024 as part of a systematic review. Key eligibility criteria at both the topic and clinical question levels guided the selection of studies for inclusion. For this

clinical question, only hospitalized adults were included. The primary comparison of interest was infliximab versus no infliximab.

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(s) [9,10]. Details of the systematic review and guideline development processes are available in the Supplementary Material.

SUMMARY OF EVIDENCE

The search identified two randomized controlled trials that reported on adults 18 years or older with severe COVID-19 who were randomized into treatment with infliximab (5 mg/kg) plus standard of care or standard of care alone (Supplementary Table 1) [7,11]. One open-label RCT (N=69), called CATALYST, treated patients 16 years or older with a single IV dose given over 2 hours on day one plus standard of care which consisted of the following: dexamethasone (100%), corticosteroids (94%) remdesivir (29%), tocilizumab (6%) [11]. Patients in the comparison arm received standard of care alone: dexamethasone (100%), corticosteroids (85%), remdesivir (62%), tocilizumab (3%). One blinded and placebo-controlled trial (N=1049), ACTIV-1, treated patients with a single infusion of infliximab plus standard of care compared to standard of care alone [7]. Standard of care across the treatment and control arms included remdesivir (93-94%), corticosteroids (89-93%), tocilizumab (3%), baricitinib (1-3%). Though the primary endpoints of O'Halloran 2023 and Fisher 2022 were time to recovery from COVID-19 pneumonia and improvement in inflammation, respectively, the trials also reported on outcomes of mortality at 28 days, recovery at 28 days (assessed by the first day a hospitalized participant did not require oxygen or on-going care, or patient was not hospitalized with or without limitations on activities, i.e. WHO categories 6, 7 or 8), length of hospitalization, and serious adverse events (Table 1).

Table 1. GRADE Evidence Profile: In patients hospitalized with severe or critical COVID-19 receiving systemic glucocorticoids, should infliximab compared to no infliximab be added to standard care?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	infliximab	no infliximab	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: 28 days)												
2 [7,11]	randomized trials	not serious	not serious	not serious[g]	very serious[a,b]	none	56/552 (10.1%)	80/550 (14.5%)	**RR 0.70** (0.51 to 0.96)	**44 fewer per 1,000** (from 71 fewer to 6 fewer)	⨁⨁◯◯ Low[a,b]	CRITICAL
Recovery (follow-up: 28 days; assessed with: first day a hospitalized participant did not require oxygen or on-going care or patient was not hospitalized with or without limitations on activities)[c]												
1 [7]	randomized trials	not serious	not serious	not serious[g]	serious[b]	none	421/531 (79.3%)	405/530 (76.4%)	**HR 1.12** (0.99 to 1.28)[d]	**38 more per 1,000** (from 3 fewer to 78 more)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Length of hospitalization												
1 [11]	randomized trials	serious[e]	not serious	not serious[g]	very serious[a,f]	none	35	34	-	MD **1 day fewer** (13.27 fewer to 11.27 more)	⨁◯◯◯ Very low[a,e,f]	CRITICAL
SAEs (assessed with: death, life-threatening AE, new/prolonged hospitalization, persistent/significant incapacity/substantial disruption of normal life functions, congenital anomaly/birth defect)												
2 [7,11]	randomized trials	not serious	not serious	not serious[g]	very serious[f]	none	131/552 (23.7%)	135/550 (24.5%)	**RR 0.97** (0.78 to 1.19)	**7 fewer per 1,000** (from 54 fewer to 47 more)	⨁⨁◯◯ Low[f]	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Sample does not meet optimal information size, which suggests fragility with the estimate.
b. 95% CI cannot exclude the potential for no meaningful difference.
c. Equivalent to WHO categories 6, 7 or 8.

d. Recovery rate ratio (RRR) is equivalent to a hazard ratio.
e. Some concerns with lack of allocation concealment and blinding, possibly leading to uneven administration of co-interventions remdesivir and corticosteroids.
f. 95% CI cannot exclude the potential for no meaningful difference or increased hospitalization with infliximab.
g. O'Halloran included patients 18 years or older. Fisher included patients 16 years or older.

BENEFITS

Among hospitalized patients, infliximab reduces mortality at 28 days compared to no infliximab treatment (RR: 0.70; 95% CI: 0.51, 0.96; low certainty of evidence). In addition, patients receiving infliximab trended toward improved recovery as measured by improvement to hospitalization without oxygen requirements or release from the hospital (HR: 1.12; 95% CI: 0.99, 1.28; moderate certainty of evidence). The effect of infliximab treatment on hospitalization is very uncertain (MD: 1 day fewer; 95% CI: 13.27 days fewer, 11.27 days more; very low certainty of evidence).

HARMS

Serious adverse events among patients receiving infliximab did not differ from those receiving usual care (RR: 0.97; 95% CI: 0.78, 1.19; low certainty of evidence). The low certainty of evidence was due to very serious concerns with imprecision, reflecting both the wide confidence interval, which includes appreciable benefits and possible harms, and few reported events.

OTHER CONSIDERATIONS

The panel agreed that the overall certainty of evidence was low (Table 1), given the sparseness in mortality data, risk of bias concerns in the study addressing length of hospitalization (Supplementary Table 2), and because the 95% confidence intervals cannot exclude the potential for no meaningful difference in mortality, recovery, length of hospitalization, and serious adverse events. Regarding the definition of severe, rapidly progressing COVID-19, the panel recognizes that SpO_2 alone may not always correlate with disease severity, and the recommendation should be interpreted in the clinical context of the patient.

There are multiple biosimilars for infliximab, likely impacting the cost of the medication. In pregnant people, there are no randomized controlled trials on infliximab use in pregnancy; however, in available observational data on exposures in pregnancy, infliximab has not been associated with increased risk of miscarriage or birth defects [12]. Use in the third trimester has sometimes been minimized due to the concern of increased risk of infant infection in the first year of life, though registry data has not

suggested this increased risk. Use of infliximab in the setting of COVID-19 is reasonable for pregnant patients if the benefits outweigh potential risks. Additionally, due to the large size of the molecule, minimal infant exposure via breastmilk would be expected [13-16].

CONCLUSIONS AND RESEARCH NEEDS

Head-to-head comparisons of baricitinib, tocilizumab, abatacept, and infliximab in patients with severe, rapidly progressing COVID-19 and critical COVID-19 would be informative. It is also uncertain whether a combination of two or more immunomodulatory agents (i.e., baricitinib, tocilizumab, abatacept, infliximab) offers additional mortality or recovery benefits. In theory, infliximab (a TNF-α inhibitor) targets a different inflammatory pathway than tocilizumab (an IL-6 receptor blocker) or baricitinib (a JAK-STAT pathway inhibitor) and hence, may have a complementary benefit. Additionally, the efficacy of infliximab has not been evaluated in children or adolescents with severe or critical COVID-19. Future studies evaluating infliximab for COVID-19 should consider enrolling children and adolescents, particularly given the extensive pediatric experience with infliximab and available pediatric dosing recommendations for non-COVID-19 indications.

The guideline panel suggests infliximab in hospitalized adults receiving systemic glucocorticoids who are experiencing severe, rapidly progressing COVID-19 or critical COVID-19, when baricitinib and tocilizumab are not available.

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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. Remaining panelists assisted with interpretation of data, as well as drafting, revising, and approving the recommendation and manuscript. Drs. Rebecca L. 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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Possible conflicts of interest. Evaluation of relationships as potential conflicts of interest is determined by a review process. The assessment of disclosed relationships for possible COIs is 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 association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). No panelists had COIs directly related to infliximab. The following panelists have scientific advisory/consultant roles not related to the topic of COVID-19 with indicated companies: R.B. with Merck and Gilead, E.D. with Gilead, D.G. with Merck and Gilead, S. S. with Pfizer (concluded), P.T. with Merck, and R.G. with Merck. The following panelists have scientific advisory/consultant roles related to COVID-19 but not severe/critical COVID-19 with indicated companies: R.B. with Shionogi, K.C. with Pardes Biosciences (concluded), A.K. with Shionogi, S.S. with Adamis and Immunome (concluded), and P.T. with Shionogi. J.P. had a scientific advisory/consultant role (concluded) with InflaRx related to vilobelimab for critical COVID-19. No disclosures were reported for all other authors (the majority of panelists), including chair and vice chair.

Additional Information: More detailed information on the analysis and development of the recommendation is available in the Supplementary Material.

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