

Therapeutic Management of Hospitalized Adults With COVID-19

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Table 2c. Therapeutic Management of Hospitalized Adults With COVID-19

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19 ^a	See Therapeutic Management of Nonhospitalized Adults With COVID-19 . ^b	For patients without an indication for therapeutic anticoagulation: <ul style="list-style-type: none"> • Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Supplemental Oxygen	All patients	The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19. ^c	
	Patients who are at high risk of progressing to severe COVID-19 ^a	Remdesivir^d (BIIb) for patients who are immunocompromised; (BIII) for other high-risk patients	
Hospitalized and Requires Conventional Oxygen^e	Patients who require minimal conventional oxygen	Remdesivir^{d,f} (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: <ul style="list-style-type: none"> • Therapeutic dose of heparin^h (CIIa)
	Most patients	Use dexamethasone plus remdesivirⁱ (BIIa) . If remdesivir cannot be obtained, use dexamethasone (BI) .	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add 1 of the following immunomodulators: ^g <i>Preferred</i> <ul style="list-style-type: none"> • PO baricitinib (BIIa) • IV tocilizumab (BIIa) <i>Alternatives (Listed in Alphabetical Order)</i> <ul style="list-style-type: none"> • IV abatacept (CIIa) • IV infliximab (CIIa) 	For other patients: <ul style="list-style-type: none"> • Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	<p>Dexamethasone should be administered to all patients (AI). If not already initiated, promptly add 1 of the following immunomodulators:^{g,i}</p> <p><i>Preferred</i></p> <ul style="list-style-type: none"> • PO baricitinib (AI) <p><i>Preferred Alternative</i></p> <ul style="list-style-type: none"> • IV tocilizumab (BIIa) <p><i>Additional Alternatives (Listed in Alphabetical Order)</i></p> <ul style="list-style-type: none"> • IV abatacept (CIIa) • IV infliximab (CIIa) <p>Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).^j</p>	<p>For patients without an indication for therapeutic anticoagulation:</p> <ul style="list-style-type: none"> • Prophylactic dose of heparin, unless contraindicated (AI); (BIII) for pregnant patients <p>For patients who start on a therapeutic dose of heparin in a non-ICU setting and then transfer to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BIII).</p>
	All patients	<p>Dexamethasone should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order):^{i,k}</p> <ul style="list-style-type: none"> • PO baricitinib^l (BIIa) • IV tocilizumab^l (BIIa) <p>See footnote k for a discussion on the use of remdesivir.</p>	

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See [Guidelines Development](#) for more information.

^a For a list of risk factors, see the CDC webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](#).

^b If the patient is hospitalized for reasons other than COVID-19, the treatment duration for remdesivir is 3 days.

^c Corticosteroids that are prescribed for an underlying condition should be continued.

^d Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 (e.g., within 10 days of symptom onset).

^e Conventional oxygen refers to oxygen supplementation that is not HFNC oxygen, NIV, MV, or ECMO.

^f If these patients progress to requiring HFNC oxygen, NIV, MV, or ECMO, the full course of remdesivir should still be completed.

^g If none of the preferred or alternative options are available or feasible to use, the JAK inhibitor **PO tofacitinib (CIIa)** or the IL-6 inhibitor **IV sarilumab (CIIa)** can be used in combination with dexamethasone. Sarilumab is only commercially available as a SUBQ injection; see [Table 5e](#) for information regarding the preparation of an IV infusion using the SUBQ product.

^h Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a PLT <50,000 cells/μL, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the past 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder.

ⁱ Dexamethasone should be initiated immediately, without waiting until the second immunomodulator can be acquired. If other immunomodulators cannot be obtained or are contraindicated, use dexamethasone alone **(AI)**.

^j Examples of patients who may benefit most from remdesivir include patients who are immunocompromised **(BIIb)**; patients with evidence of ongoing viral replication

(e.g., those with a low Ct value, as measured by an RT-PCR result or with a positive rapid antigen test result) **(BIII)**; or patients who are within 10 days of symptom onset **(CIIa)**. For more information on using remdesivir in people with immunocompromising conditions, see [Special Considerations in People Who Are Immunocompromised](#).

^k There is insufficient evidence for the Panel to recommend either for or against the use of remdesivir in hospitalized patients with COVID-19 who require MV or ECMO. Some Panel members would add remdesivir to immunomodulator therapy in patients who have recently been placed on MV or ECMO, who are immunocompromised, who have evidence of ongoing viral replication, or who are within 10 days of symptom onset. See text for more information.

^l If PO baricitinib and IV tocilizumab are not available or feasible to use, **PO tofacitinib** can be used instead of PO baricitinib **(CIIa)**, and **IV sarilumab** can be used instead of IV tocilizumab **(CIIa)**.

Key: CDC = Centers for Disease Control and Prevention; Ct = cycle threshold; ECMO = extracorporeal membrane oxygenation; ED = emergency department; HFNC = high-flow nasal cannula; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PLT = platelet count; PO = oral; RT-PCR = reverse transcription polymerase chain reaction; SUBQ = subcutaneous; ULN = upper limit of normal

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease is driven by a dysregulated immune/inflammatory response to SARS-CoV-2 infection that may lead to further tissue damage and thrombosis. Based on this understanding, therapies that directly target SARS-CoV-2 are anticipated to have the greatest effect early in the course of the disease, whereas immunosuppressive, anti-inflammatory, and antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia, endothelial dysfunction, and immunothrombosis.

Currently, most people in the United States have some degree of immunity to SARS-CoV-2 due to COVID-19 vaccination or SARS-CoV-2 infection. The increase in population immunity and the change in variants have led to a decrease in the rate of severe disease caused by COVID-19. Because other co-existing diseases can cause hypoxemia in patients who test positive for SARS-CoV-2 infection, clinicians should perform the appropriate evaluations to rule out alternative diagnoses. However, the ongoing evolution of SARS-CoV-2 can lead to immune escape, allowing the virus to continue circulating in the community. Thus, COVID-19 remains a concern for public health.

Many of the patients who are hospitalized for COVID-19 are immunocompromised to some degree. For most hospitalized patients with severe or critical COVID-19 who are immunocompromised, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using antiviral drugs and immunomodulatory therapies at the doses and durations recommended for the general population **(AIII)**. Some patients who are immunocompromised have prolonged COVID-19 symptoms and evidence of ongoing SARS-CoV-2 replication. See [Special Considerations in People Who Are Immunocompromised](#) for additional guidance on managing these patients.

Below is a summary of the rationale for the Panel's recommendations on the therapeutic management of hospitalized patients with COVID-19. For dosing information for each of the recommended drugs, see Table 2d below. For more information about these therapies and the evidence that supports the Panel's recommendations, please refer to the specific drug pages and clinical data tables.

Patients Who Are Hospitalized for Reasons Other Than COVID-19 and Who Do Not Require Supplemental Oxygen

Hospitalized patients with COVID-19 who do not require supplemental oxygen are a heterogeneous population. Some patients may be hospitalized for reasons other than COVID-19 but may also have mild to moderate COVID-19 (see [Clinical Spectrum of SARS-CoV-2 Infection](#)). In these cases, patients who

are at high risk of progressing to severe COVID-19 may benefit from receiving antiviral therapy.

Remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adults who:

- Are hospitalized; *or*
- Are not hospitalized, have mild to moderate COVID-19, and are at high risk of progressing to severe COVID-19.

If the patient is hospitalized for reasons other than COVID-19, the treatment duration for remdesivir is 3 days.

Ritonavir-boosted nirmatrelvir (Paxlovid) is approved by the FDA and molnupiravir has an Emergency Use Authorization from the FDA for use in patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease. These therapies can be used in hospitalized patients who qualify for therapy if they were admitted to the hospital for a diagnosis other than COVID-19. The Panel's recommendations for these patients are the same as those for nonhospitalized patients (see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#)).

Patients Who Are Hospitalized for COVID-19 and Who Do Not Require Supplemental Oxygen

Recommendations

- The Panel recommends using **remdesivir** for the treatment of COVID-19 in hospitalized patients who do not require supplemental oxygen and who are immunocompromised (**BI Ib**) and for other patients who are at high risk of progressing to severe disease (**BIII**).
- Remdesivir should be administered for 5 days or until hospital discharge, whichever comes first.

The rationale for using remdesivir in high-risk patients is based on several lines of evidence. In a trial conducted predominantly among hospitalized patients with COVID-19 who were not receiving supplemental oxygen at enrollment, a 5-day course of remdesivir was associated with greater clinical improvement when compared with standard of care.¹ Evidence from the PINETREE trial also suggests that early therapy reduces the risk of progression, although that study was performed in high-risk, unvaccinated, nonhospitalized patients with ≤ 7 days of symptoms who received a 3-day course of remdesivir.²

Other studies have not shown a clinical benefit of remdesivir in this group of patients. In the ACTT-1 trial, remdesivir showed no significant benefit in hospitalized patients with mild to moderate COVID-19; however, only 13% of the study population did not require supplemental oxygen.³ In the large Solidarity trial, the use of remdesivir was not associated with a survival benefit among the subset of hospitalized patients who did not require supplemental oxygen.⁴ See [Table 4a](#) for more information.

The aggregate data on using remdesivir to treat all high-risk patients with COVID-19 show a faster time to recovery in patients who received remdesivir but no clear evidence of a survival benefit. Therefore, the Panel recommends using **remdesivir** in hospitalized patients with COVID-19 who do not require supplemental oxygen and who are at high risk of progressing to severe disease (**BIII**).

In a large, retrospective cohort study of hospitalized patients with COVID-19 who were immunocompromised ($n = 28,338$), patients who received remdesivir had a lower risk of mortality than those who did not receive remdesivir.⁵ Forty percent of patients in this cohort were not receiving supplemental oxygen at baseline; mortality was reduced in this subset of patients. Therefore, the Panel recommends using **remdesivir** in hospitalized patients with COVID-19 who do not require supplemental oxygen and who are immunocompromised (**BI Ib**).

For information on medical conditions that confer high risk, see the Centers for Disease Control and Prevention webpage [People With Certain Medical Conditions](#).

Recommendation

- The Panel **recommends against** the use of **dexamethasone (AIIa)** or other systemic corticosteroids (**AIII**) for the treatment of COVID-19 in patients who do not require supplemental oxygen.

In the RECOVERY trial, no survival benefit was observed for dexamethasone among the subset of patients with COVID-19 who did not require supplemental oxygen at enrollment.⁶ In an observational cohort study of U.S. veterans, the use of dexamethasone was associated with higher mortality in hospitalized patients with COVID-19 who did not require supplemental oxygen.⁷

There are insufficient data to inform the use of other systemic corticosteroids in hospitalized patients with COVID-19 who do not require supplemental oxygen. See [Table 5a](#) for more information about the clinical trials that have evaluated the use of these drugs in patients with COVID-19. Patients who are receiving corticosteroid treatment for an underlying condition should continue to receive corticosteroids.

Patients Who Require Conventional Oxygen

Patients with COVID-19 who require conventional oxygen (i.e., those who do not require high-flow nasal cannula [HFNC] oxygen, noninvasive ventilation [NIV], or mechanical ventilation) are a heterogeneous population. Although all patients who require oxygen are considered to have severe disease, some of these patients will improve after a short period with or without treatment; others will develop progressive disease. There is no consensus on which clinical or laboratory parameters should be used to determine a patient's risk of progression and guide therapy.

Recommendation

- For patients with COVID-19 who only require minimal conventional oxygen, the Panel recommends using **remdesivir** without dexamethasone (**BIIa**).

In a subgroup analysis during the ACTT-1 trial, remdesivir significantly reduced the time to clinical recovery and significantly reduced mortality among the subset of patients who were receiving conventional oxygen at enrollment.³ Evidence from ACTT-1 and a pooled analysis of individual data from 9 randomized controlled trials⁸ suggest that remdesivir will have its greatest benefit when administered early in the clinical course of COVID-19 (e.g., within 10 days of symptom onset). See [Table 4a](#) for more information.

Recommendations

- For most patients with COVID-19 who require conventional oxygen, the Panel recommends using **dexamethasone plus remdesivir (BIIa)**.
- If dexamethasone is not available, an equivalent dose of another corticosteroid (e.g., **prednisone**, **methylprednisolone**, **hydrocortisone**) may be used (**BIII**).

The results of several studies suggest that the use of remdesivir plus dexamethasone improves clinical outcomes among hospitalized patients with COVID-19. In the CATCO trial, in which 87% of patients received corticosteroids and 54% were on conventional oxygen, remdesivir significantly reduced the need for mechanical ventilation among the subset of patients who did not require mechanical ventilation at enrollment when compared with standard of care.⁹ In the Solidarity trial, in which approximately two-thirds of the patients received corticosteroids, remdesivir significantly reduced mortality among the large subset of patients (n > 7,000) who were receiving conventional or HFNC oxygen at enrollment.⁴ See [Table 4a](#) for more information.

An individual patient–level meta-analysis of 8 clinical trials examined the efficacy of using remdesivir in hospitalized patients with COVID-19.⁸ This meta-analysis found that remdesivir significantly reduced the number of patients who required mechanical ventilation or who died by Day 28 in the combined subgroups of patients who did not require oxygen or who were receiving conventional oxygen at baseline. However, the effect of remdesivir was not evaluated separately in the subgroup of patients who were receiving conventional oxygen at enrollment.

Recommendation

- If remdesivir is not available, the Panel recommends using **dexamethasone alone** in patients with COVID-19 who require conventional oxygen (**BI**).

In the RECOVERY trial, the use of dexamethasone 6 mg once daily for 10 days or until hospital discharge significantly reduced mortality among the subset of patients who were receiving oxygen (defined as receiving oxygen supplementation but not mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) at enrollment.⁶ Remdesivir was administered to <1% of the study participants. Results for patients who were only receiving conventional oxygen at enrollment were not available. See [Table 5a](#) for more information.

Recommendations

- For patients with COVID-19 who have rapidly increasing oxygen needs and systemic inflammation, the Panel recommends adding 1 of the following immunomodulators to dexamethasone:
 - *Preferred Second Immunomodulators*
 - **Oral (PO) baricitinib (BIIa)**
 - **Intravenous (IV) tocilizumab (BIIa)**
 - *Alternative Second Immunomodulators (Listed in Alphabetical Order)*
 - **IV abatacept (CIIa)**
 - **IV infliximab (CIIa)**

If none of these options are available or feasible to use, the Janus kinase (JAK) inhibitor **PO tofacitinib (CIIa)** or the interleukin (IL)-6 inhibitor **IV sarilumab (CIIa)** can be used in combination with dexamethasone. Sarilumab is only commercially available as a subcutaneous (SUBQ) injection; see [Table 5e](#) for information regarding the preparation of an IV infusion using the SUBQ product.

Several large randomized controlled trials have evaluated the use of dexamethasone in combination with a second immunomodulator, including:

- Abatacept, a cytotoxic T-lymphocyte–associated antigen 4 agonist¹⁰
- Baricitinib, a JAK inhibitor¹¹⁻¹³
- Infliximab, a tumor necrosis factor–alpha inhibitor¹⁰
- Tocilizumab, an IL-6 inhibitor¹⁴⁻¹⁶

These studies included patients who required conventional oxygen only, as well as those with increasing oxygen needs and/or elevated levels of inflammatory markers. Subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from adding a second immunomodulator to corticosteroid therapy. The study endpoints for these trials included progression to more severe disease, the need for mechanical ventilation, and death. Nonetheless, some trials suggest that adding a second immunomodulator provides benefits to patients who require conventional oxygen,

especially those with rapidly increasing oxygen requirements and systemic inflammation.

The Panel recommends either baricitinib or tocilizumab as the preferred second immunomodulator because both are approved by the FDA for the treatment of COVID-19, and data from multiple clinical trials have demonstrated that these agents provide a clinical benefit in patients with COVID-19 who require conventional oxygen.^{6,11-16} There is also more clinical experience with the use of these 2 agents in this setting than other potential treatment options.

The ACTIV-1 immunomodulator trial was a double-blind, multi-arm, randomized trial in moderately to severely ill adults who were hospitalized with COVID-19.¹⁰ The trial separately evaluated treatment with abatacept, cenicriviroc, and infliximab versus placebo. All arms received standard care, and the separate analyses included data from a shared placebo arm. The primary endpoint was time to recovery by Day 28. Key secondary endpoints included clinical status at Day 14 and mortality through Days 28 and 60. The majority of patients received corticosteroids (>89%) and remdesivir (>93%).

None of the study drugs had a significant effect on the time to recovery. Mortality by Day 28 was lower among patients in the abatacept and infliximab arms than among those in the shared placebo arm. Based on the results of this trial, abatacept or infliximab may be considered alternatives to baricitinib or tocilizumab. There are no studies that directly compare the use of abatacept or infliximab to the use of baricitinib or tocilizumab in people with COVID-19.

When baricitinib, tocilizumab, abatacept, or infliximab are not available or feasible to use, the JAK inhibitor tofacitinib or the IL-6 inhibitor sarilumab may be used as alternative agents. Tofacitinib decreased the risk for respiratory failure or death among hospitalized patients with COVID-19 in the STOP-COVID trial,¹⁷ and sarilumab reduced mortality and the duration of organ support to the same degree as tocilizumab in the REMAP-CAP trial.^{14,15}

Use of Anticoagulants

- The Panel recommends using a **therapeutic dose of heparin** for nonpregnant patients with D-dimer levels above the upper limit of normal who require conventional oxygen and who do not have an increased bleeding risk (**CIIa**).
- The Panel recommends the use of a **prophylactic dose of heparin** for patients who do not meet the criteria for receiving therapeutic heparin or are not receiving a therapeutic dose of heparin for other reasons, unless a contraindication exists (**AI**).
- The Panel recommends the use of a prophylactic dose of anticoagulation for pregnant patients who are hospitalized for manifestations of COVID-19, unless a contraindication exists (**BIII**).

The Panel's recommendations for the use of heparin are based on data from 3 open-label randomized controlled trials that compared the use of therapeutic doses of heparin to prophylactic or intermediate doses of heparin in hospitalized patients who did not require intensive care unit (ICU)-level care. Pooled data from the ATTACC/ACTIV-4a/REMAP-CAP trials reported more organ support-free days (i.e., days alive and free of ICU-based organ support) for patients in the therapeutic heparin arm than for those in the usual care arm, but there was no difference between the arms in in-hospital mortality or length of hospitalization.¹⁸ The RAPID trial compared a therapeutic dose of heparin to a prophylactic dose in hospitalized patients with moderate COVID-19. There was no statistically significant difference between the arms in the occurrence of the primary endpoint (which was a composite of ICU admission, NIV or mechanical ventilation, or death by Day 28), but the therapeutic dose of heparin reduced the risk of all-cause death.¹⁹ In the HEP-COVID trial, venous thromboembolism (VTE), arterial thromboembolism, and death by Day 32 occurred significantly less frequently in patients who received a therapeutic dose of heparin than in those who received a prophylactic dose of heparin, but there was no difference in mortality

by Day 32 between the arms.²⁰

Patients Who Require High-Flow Nasal Cannula Oxygen or Noninvasive Ventilation

In these patients, systemic inflammation contributes to hypoxemia, and thus these patients may benefit from receiving a second immunomodulator in addition to dexamethasone. There is no consensus on which clinical or laboratory parameters reliably predict the risk of progression to mechanical ventilation or death.

The available evidence suggests that the benefits of adding baricitinib or tocilizumab to dexamethasone treatment outweigh the potential risks in patients with COVID-19 who require HFNC oxygen or NIV. Although the combination of dexamethasone and secondary immunomodulating medications may increase the risk of opportunistic infections or the risk of reactivating latent infections, there are insufficient data to make recommendations about initiating prophylaxis against these infections.

Recommendations

- **Dexamethasone** should be administered to all patients with COVID-19 who require HFNC oxygen or NIV (AI).
- If not already initiated, promptly add 1 of the following immunomodulators to dexamethasone:
 - *Preferred Second Immunomodulator*
 - **PO baricitinib (AI)**
 - *Preferred Alternative Second Immunomodulator*
 - **IV tocilizumab (BIIa)**
 - *Additional Alternative Second Immunomodulators (Listed in Alphabetical Order)*
 - **IV abatacept (CIIa)**
 - **IV infliximab (CIIa)**

If none of these options are available or feasible to use, **PO tofacitinib (CIIa)** or **IV sarilumab (CIIa)** can be used in combination with dexamethasone. Sarilumab is only commercially available as a SUBQ injection; see [Table 5e](#) for information regarding the preparation of an IV infusion using the SUBQ product.

Clinicians should make a significant effort to obtain and administer 1 of the recommended second immunomodulators. However, dexamethasone should be initiated immediately, without waiting until the second immunomodulator can be acquired. Dexamethasone was used as a single-agent immunomodulatory strategy in the RECOVERY trial and demonstrated a survival benefit among patients who required supplemental oxygen.⁶ In this trial, the treatment effect for dexamethasone was not evaluated separately for those who required conventional oxygen and those who required HFNC oxygen or NIV.

Several large randomized controlled trials have demonstrated that patients with COVID-19 who require HFNC oxygen or NIV benefit from combining dexamethasone with an additional immunomodulator, such as a JAK inhibitor or an IL-6 inhibitor. The quality of the evidence and the totality of the data support a stronger recommendation for baricitinib than for tocilizumab.

Two large randomized controlled trials (RECOVERY and COV-BARRIER) both reported a survival benefit among hospitalized patients with COVID-19 who required HFNC oxygen or NIV and who received baricitinib plus dexamethasone.^{12,13} Data from the ACTT-2¹¹ and ACTT-4²¹ trials support the overall safety of using baricitinib in combination with remdesivir and the potential for a clinical benefit of this combination, but neither trial studied baricitinib in combination with dexamethasone as the standard of care. A retrospective analysis of data from 11 U.S. health systems suggests that the use of

baricitinib may be associated with fewer adverse effects than tocilizumab, including fewer secondary infections, thrombotic events, and cases of acute liver injury.²²

The use of tocilizumab in combination with corticosteroids reduced in-hospital mortality in patients with rapid respiratory decompensation who were admitted to the ICU in the REMAP-CAP trial.¹⁴ Similar results were reported during the RECOVERY trial, although patients were only randomized into the tocilizumab arm if they had an oxygen saturation <92% on room air and C-reactive protein levels ≥ 75 mg/L.¹⁶ Both REMAP-CAP and RECOVERY evaluated the efficacy of adding tocilizumab to standard care; in both cases, standard care included dexamethasone therapy. Other randomized trials that have evaluated the use of tocilizumab have demonstrated mixed results, including a lack of benefit when tocilizumab was administered without dexamethasone as part of standard care.²³⁻²⁶

In the ACTIV-1 trial, which evaluated the use of abatacept, cenicriviroc, and infliximab in hospitalized patients with COVID-19, neither abatacept nor infliximab demonstrated a significant effect on the primary endpoint of time to recovery.¹⁰ In the subgroup of patients who received HFNC oxygen or NIV, mortality at Day 28 (a secondary outcome) was lower in both the abatacept and the infliximab arms than in the shared placebo arm.

Combinations of 3 immunomodulators (e.g., dexamethasone plus baricitinib plus tocilizumab) have not been studied in clinical trials. Although some patients in the baricitinib arm of the RECOVERY trial also received tocilizumab, data from the study are insufficient to issue a recommendation.¹³ When both agents are used, there is a potential for greater risk of secondary infections.

The clinical trial data cited above informed the Panel's recommendations for adding a second immunomodulator to dexamethasone in hospitalized patients who require HFNC oxygen or NIV. After reviewing these clinical trial results, the Panel recommends baricitinib over tocilizumab as the second immunomodulator. See [Table 5c](#) and [Table 5d](#) for more information. Because the evidence for the use of either abatacept or infliximab in people with COVID-19 is derived from a single study while multiple trials have demonstrated a beneficial effect of using baricitinib or tocilizumab, the Panel recommends using abatacept or infliximab only when baricitinib and tocilizumab are not available or their use is contraindicated.

Recommendations

- For certain hospitalized patients who require HFNC oxygen or NIV, the Panel recommends adding **remdesivir** to 1 of the recommended immunomodulator combinations. Examples of patients who may benefit most from adding remdesivir include:
 - Patients who are immunocompromised (**BIIB**);
 - Patients with evidence of ongoing viral replication (e.g., those with a low cycle threshold [Ct] value, as measured by a reverse transcription polymerase chain reaction [RT-PCR] result or with a positive rapid antigen test result) (**BIII**); *or*
 - Patients who are within 10 days of symptom onset (**CIIa**).

Clinical trial data have not clearly established that remdesivir reduces the time to recovery or improves survival in patients who require HFNC oxygen or NIV. However, because clinical trials have found that remdesivir prevents clinical progression in patients who are not on mechanical ventilation, some patients receiving HFNC oxygen or NIV might benefit from receiving remdesivir. In the Solidarity trial, remdesivir had a modest but statistically significant effect on reducing the risk of death or progression to ventilation in patients who were receiving oxygen but who were not ventilated at baseline.⁴

However, these effects could not be evaluated separately for patients who required conventional oxygen supplementation and those who required HFNC oxygen or NIV.⁴ In the CATCO trial, among the patients

who were not receiving mechanical ventilation at baseline, 8% of patients who received remdesivir required mechanical ventilation compared to 15% of those who received standard of care (relative risk 0.53; 95% CI, 0.38–0.75).⁹ See [Table 4a](#) for more information.

The Panel's rationale for recommending remdesivir for certain patients who require HFNC oxygen or NIV is discussed below. This discussion includes examples of patients who may benefit most from receiving remdesivir. In addition, clinicians may extend the course of remdesivir beyond 5 days in this population based on clinical response.

Patients Who Are Immunocompromised

People who are immunocompromised already have difficulty achieving viral clearance. The use of immunomodulators to treat COVID-19 may further impair this process. Because SARS-CoV-2 replication may be prolonged in these patients, remdesivir may help enhance viral clearance and improve outcomes. In a large, retrospective study of a cohort of patients who were immunocompromised, patients who received remdesivir had a lower risk of mortality than those who did not receive remdesivir; however, only 19% of the patients in the study were receiving HFNC oxygen or NIV.⁵ For more information, see [Special Considerations in People Who Are Immunocompromised](#).

Patients With Evidence of Ongoing Viral Replication

Hospitalized patients who require HFNC oxygen or NIV are routinely treated with 2 immunomodulators to prevent or mitigate inflammation-mediated injury. These treatments may impair the patient's ability to achieve viral clearance; thus, directly treating the virus with remdesivir may theoretically help improve outcomes. Substantial evidence from studies of other viral diseases supports the benefits of reducing the viral burden. Ct values can be obtained from some SARS-CoV-2 RT-PCR assays, and these values may be used as a proxy for the level of ongoing viral replication (low Ct values correspond to higher viral loads). While this information is not available on all RT-PCR platforms, Ct values may be helpful in informing decisions regarding the use of remdesivir. Positive rapid antigen test results are also consistent with higher viral loads.²⁷

Patients Who Are Within 10 Days of Symptom Onset

Active viral replication occurs early in the course of SARS-CoV-2 infection. Evidence from the ACTT-1 and PINETREE trials suggests that remdesivir will have the greatest benefit when administered early in the clinical course of COVID-19.^{2,3} In the ACTT-1 trial, remdesivir demonstrated a greater benefit in patients who were enrolled within 10 days of symptom onset than in those who were enrolled later in the disease course.

Use of Anticoagulants

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists (**AI**); (**BIII**) for pregnant patients.
- The Panel **recommends against** the use of a therapeutic dose of anticoagulation for VTE prophylaxis (**BI**).
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless VTE is confirmed (**BIII**).

The multiplatform randomized controlled trial REMAP-CAP/ACTIV-4a/ATTACC compared the effectiveness of a therapeutic dose of heparin to standard care in critically ill patients with COVID-19.²⁸ The study did not show an increase in the number of organ support-free days or the probability of survival to hospital discharge among patients who received therapeutic doses of anticoagulation. See [Antithrombotic Therapy in Patients With COVID-19](#) for more information.

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- **Dexamethasone** should be administered to all patients with COVID-19 who require mechanical ventilation or ECMO (AI).
- If the patient has not already received a second immunomodulator in addition to dexamethasone, promptly add 1 of the following (listed in alphabetical order):
 - **PO baricitinib (BIIa)**
 - **IV tocilizumab (BIIa)**

Dexamethasone was shown to reduce mortality in critically ill patients with COVID-19 in a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients.²⁹ The largest trial included in the meta-analysis was the RECOVERY trial, which had a subgroup of patients who were receiving mechanical ventilation (see [Systemic Corticosteroids](#) and [Table 5a](#)).⁶ Subsequent studies of immunomodulator therapy suggest that using a second immunomodulator in combination with dexamethasone is more effective than dexamethasone alone in patients with COVID-19 who require mechanical ventilation or ECMO.^{14,16,30}

Clinical trials that have evaluated combining IL-6 inhibitors or JAK inhibitors with corticosteroids for the treatment of patients with COVID-19 provide the most robust evidence for the Panel's recommendations.

Clinical trials of tocilizumab have reported an overall survival benefit in patients with hypoxemia and signs of systemic inflammation (RECOVERY)¹⁶ and in patients who are critically ill and require organ support (REMAP-CAP).¹⁴ Although these studies included patients who were receiving mechanical ventilation at randomization, the studies were not specifically powered to assess the effectiveness of IL-6 inhibitors in these patients. Other studies of tocilizumab in critically ill patients did not find a survival benefit, although the time between initiation of organ support in the ICU and study enrollment differed across the studies (see [Table 5c](#)).^{23,26} The use of corticosteroids also varied across the studies.

An extension of the COV-BARRIER trial compared the efficacy of baricitinib to placebo in 101 critically ill patients with COVID-19.³⁰ The study reported significant reductions in mortality (relative reduction of 46% at 28 days and 44% at 60 days) and no major adverse events among patients who received baricitinib. Systematic reviews of JAK inhibitors confirm the efficacy of using baricitinib in hospitalized patients with COVID-19 who require oxygen support. There is a lower certainty of evidence for patients who were receiving mechanical ventilation or ECMO, and baricitinib may have modestly attenuated efficacy in this group.³¹ Baricitinib or tocilizumab should only be administered in combination with dexamethasone or another corticosteroid.

In the ACTIV-1 trial, the use of abatacept, cenicriviroc, or infliximab did not reduce the time to recovery or mortality in patients with COVID-19 who required mechanical ventilation or ECMO. Therefore, these immunomodulators are not recommended for these patients.

Considerations for the Use of Remdesivir

There is insufficient evidence for the Panel to recommend either for or against the use of remdesivir in hospitalized patients with COVID-19 who require mechanical ventilation or ECMO. For patients who progress to requiring mechanical ventilation or ECMO after they initiate remdesivir, the Panel suggests continuing remdesivir until the treatment course is completed. Remdesivir is most effective against COVID-19 in patients who are earlier in the course of the disease.

In the ACTT-1 trial, there was no difference between the remdesivir and placebo arms in the time to recovery among patients with COVID-19 who were receiving mechanical ventilation or ECMO; however, very few patients received corticosteroids in this trial.³ The Solidarity trial reported no benefit of using remdesivir in hospitalized patients with COVID-19 who were already on mechanical ventilation (mortality rate ratio 1.13; $P = 0.32$).⁴ It is worth noting that only a few patients required mechanical ventilation in these 2 randomized trials, and there was substantial variation in the timing of remdesivir initiation. In contrast, in a propensity score-matched retrospective observational study, the use of remdesivir was associated with a reduction in mortality at 14 and 28 days among patients who required mechanical ventilation or ECMO within 48 hours of hospital admission for COVID-19 pneumonia.³² In this study, over 97% of patients received corticosteroids.

Given the results of the randomized clinical trials and the limitations of observational data, the Panel cannot recommend either for or against the use of remdesivir in this group of patients. However, some Panel members would add remdesivir to immunomodulator therapy in patients with COVID-19 who have recently been placed on mechanical ventilation or ECMO. In this case, the rationale to add remdesivir is based on the observed clinical benefit of remdesivir during earlier stages of infection, the results of the observational study, and the demonstrated safety of remdesivir. In addition, some Panel members would add remdesivir to the regimen for patients with COVID-19 who are immunocompromised, who have evidence for ongoing viral replication, or who are within 10 days of symptom onset.

Use of Anticoagulants

- The Panel recommends using a **prophylactic dose of heparin** as VTE prophylaxis, unless a contraindication exists (**AI**); (**BIII**) for pregnant patients.
- For patients who start on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transfer to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (**BIII**).
- The Panel **recommends against** the use of a therapeutic dose of anticoagulation for VTE prophylaxis (**BI**).

Patients who required mechanical ventilation or ECMO were included in the multiplatform REMAP-CAP/ACTIV-4a/ATTACC trial that studied therapeutic doses of heparin.²⁸ Because these studies reported no benefits of using therapeutic doses of heparin, the recommendations for using prophylactic doses of heparin in hospitalized patients who require mechanical ventilation or ECMO are the same as those for patients who require HFNC oxygen or NIV.

Table 2d. Dosing Regimens for the Drugs Recommended in Table 2c

The drugs in this table are listed in alphabetical order.

Drug Name	Dosing Regimen	Comments
Abatacept	Abatacept 10 mg/kg actual body weight (up to 1,000 mg) administered as a single IV dose	<ul style="list-style-type: none"> • No adjustment based on eGFR
Baricitinib	BAR dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge, whichever comes first.	<ul style="list-style-type: none"> • eGFR ≥ 60 mL/min/1.73 m²: BAR 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m²: BAR 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m²: BAR 1 mg PO once daily • eGFR <15 mL/min/1.73 m²: Not recommended.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge, whichever comes first	<ul style="list-style-type: none"> • If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Systemic Corticosteroids.

Drug Name	Dosing Regimen	Comments
Heparin	Therapeutic dose of SUBQ LMWH or IV UFH	• Administer for 14 days or until hospital discharge (whichever comes first) unless there is a diagnosis of VTE or another indication for therapeutic anticoagulation.
	Prophylactic dose of SUBQ LMWH or SUBQ UFH	• Administer for the duration of the hospital stay.
Infliximab	Infliximab 5 mg/kg actual body weight administered as a single IV dose	• No adjustment based on eGFR
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first	<ul style="list-style-type: none"> • If the patient is hospitalized for reasons other than COVID-19, the treatment duration is 3 days. For more information, see Therapeutic Management of Nonhospitalized Adults With COVID-19. • If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.
Sarilumab	Use the single-dose, prefilled syringe (not the prefilled pen) for SUBQ injection. Reconstitute sarilumab 400 mg in 100 cc 0.9% NaCl and administer as an IV infusion over 1 hour.	• In the United States, the currently approved route of administration for sarilumab is SUBQ injection. In the REMAP-CAP trial, the SUBQ formulation was used to prepare the IV infusion.
Tocilizumab	Tocilizumab 8 mg/kg actual body weight (up to 800 mg) administered as a single IV dose	• In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge, whichever comes first	• eGFR <60 mL/min/1.73 m ² : tofacitinib 5 mg PO twice daily

Key: BAR = baricitinib; DEX = dexamethasone; eGFR = estimated glomerular filtration rate; IV = intravenous; LMWH = low-molecular-weight heparin; NaCl = sodium chloride; PO = oral; RDV = remdesivir; SUBQ = subcutaneous; UFH = unfractionated heparin; VTE = venous thromboembolism

References

1. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 2020;324(11):1048-1057. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32821939>.
2. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe COVID-19 in outpatients. *N Engl J Med*. 2022;386(4):305-315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34937145>.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19—final report. *N Engl J Med*. 2020;383(19):1813-1826. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32445440>.
4. WHO Solidarity Trial Consortium. Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*. 2022;399(10339):1941-1953. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35512728>.
5. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir reduced mortality in immunocompromised patients hospitalized for COVID-19 across variant waves: findings from routine clinical practice. *Clin Infect Dis*. 2023;77(12):1626-1634. Available at: <https://pubmed.ncbi.nlm.nih.gov/37556727>.
6. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med*. 2021;384(8):693-704. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32678530>.
7. Crothers K, DeFaccio R, Tate J, et al. Dexamethasone in hospitalised COVID-19 patients not on intensive

respiratory support. *Eur Respir J*. 2022;60(1):2102532. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34824060>.

8. Amstutz A, Speich B, Mentré F, et al. Effects of remdesivir in patients hospitalized with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Respir Med*. 2023;11(5):453-464. Available at: <https://pubmed.ncbi.nlm.nih.gov/36828006>.
9. Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;194(7):E242-E251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35045989>.
10. O'Halloran JA, Ko ER, Anstrom KJ, et al. Abatacept, cenicriviroc, or infliximab for treatment of adults hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA*. 2023;330(4):328-339. Available at: <https://pubmed.ncbi.nlm.nih.gov/37428480>.
11. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with COVID-19. *N Engl J Med*. 2021;384(9):795-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33306283>.
12. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled Phase 3 trial. *Lancet Respir Med*. 2021;9(12):1407-1418. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34480861>.
13. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet*. 2022;400(10349):359-368. Available at: <https://pubmed.ncbi.nlm.nih.gov/35908569>.
14. REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Engl J Med*. 2021;384(16):1491-1502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33631065>.
15. REMAP-CAP Investigators. Effectiveness of tocilizumab, sarilumab, and anakinra for critically ill patients with COVID-19: the REMAP-CAP COVID-19 immune modulation therapy domain randomized clinical trial. *medRxiv*. 2021;Preprint. Available at: <https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2>.
16. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637-1645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33933206>.
17. Guimarães PO, Quirk D, Furtado RH, et al. Tofacitinib in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;385(5):406-415. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34133856>.
18. ATTACC, ACTIV-4a, and REMAP-CAP Investigators. Therapeutic anticoagulation with heparin in noncritically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):790-802. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34351721>.
19. Sholzberg M, Tang GH, Rahhal H, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with COVID-19 admitted to hospital: RAPID randomised clinical trial. *BMJ*. 2021;375:n2400. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34649864>.
20. Spyropoulos AC, Goldin M, Giannis D, et al. Efficacy and safety of therapeutic-dose heparin vs standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: the HEP-COVID randomized clinical trial. *JAMA Intern Med*. 2021;181(12):1612-1620. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34617959>.
21. Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022;10(9):888-899. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35617986>.
22. Peterson JH, Paranjape NS, Grundlingh N, Priestley JL. Outcomes and adverse effects of baricitinib versus tocilizumab in the management of severe COVID-19. *Crit Care Med*. 2023;51(3):337-346. Available at: <https://pubmed.ncbi.nlm.nih.gov/36729439>.

23. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe COVID-19 pneumonia. *N Engl J Med*. 2021;384(16):1503-1516. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33631066>.
24. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with COVID-19 pneumonia. *N Engl J Med*. 2021;384(1):20-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33332779>.
25. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with COVID-19. *N Engl J Med*. 2020;383(24):2333-2344. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33085857>.
26. Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34609549>.
27. Regan J, Flynn JP, Choudhary MC, et al. Detection of the Omicron variant virus with the Abbott BinaxNow SARS-CoV-2 rapid antigen assay. *Open Forum Infect Dis*. 2022;9(3):ofac022. Available at: <https://pubmed.ncbi.nlm.nih.gov/35169591>.
28. REMAP-CAP, ACTIV-4a, and ATTACC Investigators. Therapeutic anticoagulation with heparin in critically ill patients with COVID-19. *N Engl J Med*. 2021;385(9):777-789. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34351722>.
29. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330-1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32876694>.
30. Ely EW, Ramanan AV, Kartman CE, et al. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;10(4):327-336. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35123660>.
31. Zhang X, Shang L, Fan G, et al. The efficacy and safety of Janus kinase inhibitors for patients with COVID-19: a living systematic review and meta-analysis. *Front Med (Lausanne)*. 2021;8:800492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35155477>.
32. Mozaffari E, Chandak A, Gottlieb RL, et al. Remdesivir is associated with reduced mortality in COVID-19 patients requiring supplemental oxygen including invasive mechanical ventilation across SARS-CoV-2 variants. *Open Forum Infect Dis*. 2023;10(10):ofad482. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37869410>.