Therapeutic Management of Hospitalized Adults With COVID-19

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Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Dosing regimens for the drugs recommended in this figure are listed in Table A below.

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., **baricitinib**[e] or **tocilizumab**[e]) **(CIIa)**.	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:[f] • **Therapeutic dose** of heparin[g] **(CIIa)** For other patients: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the options above.[d,h]	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone**[i] **(AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa)**.	For patients without evidence of VTE: • **Prophylactic dose** of heparin,[g] unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] Corticosteroids that are prescribed for an underlying condition should be continued.

[b] If the patient progresses to requiring high-flow oxygen, NIV, MV, or ECMO, complete the full course of remdesivir (refer to Table A).

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[c] 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). Clinical trials have not demonstrated a mortality benefit for remdesivir, but a large, placebo-controlled trial showed that the use of remdesivir reduced time to clinical recovery in hospitalized patients. See Rationale for the Use of Remdesivir below.

[d] Drugs are listed alphabetically. There are no studies that directly compare the use of baricitinib and tocilizumab, and there is insufficient evidence to recommend a drug or class of drug (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

[e] If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.

[f] Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include platelet count <50 x 10^9/L, Hgb <8 g/dL, the need for dual antiplatelet therapy, bleeding within the last 30 days that required an ED visit or hospitalization, a history of a bleeding disorder, or an inherited or active acquired bleeding disorder. This list is based on the exclusion criteria from clinical trials; patients with these conditions have an increased risk of bleeding.

[g] Either LMWH or UFH heparin can be used. In general, LMWH is preferred.

[h] The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

[i] The combination of **dexamethasone plus remdesivir** may be considered for patients who have recently been intubated **(CIII)**. The Panel **recommends against** the use of **remdesivir** monotherapy in these patients **(AIIa)**.

Key: ECMO = extracorporeal membrane oxygenation; ED = emergency department; Hgb = hemoglobin; ICU = intensive care unit; IL = interleukin; IV = intravenous; JAK = Janus kinase; LMWH = low-molecular-weight heparin; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; UFH = unfractionated heparin; ULN = upper limit of normal; VTE = venous thromboembolism

Table A. Dosing Regimens for the Drugs Recommended in Figure 2

Drug Name	Dosing Regimen	Comments
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge	• 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.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge	• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.
Baricitinib	Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.	• eGFR ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: Baricitinib **is not recommended**.
Heparin	Therapeutic dose of SUBQ LMWH or IV UFH	• Administer for 14 days or until hospital discharge, 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.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge	• Use as an alternative immunomodulatory drug if baricitinib is not available or not feasible to use **(BIIa)**. • eGFR <60 mL/min/1.73 m^2: Tofacitinib 5 mg PO twice daily

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Drug Name	Dosing Regimen	Comments
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.
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.	• Use as an alternative immunomodulatory drug if tocilizumab is not available or not feasible to use **(BIIa)**. • 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.
Key: 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		

Introduction

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. Subsequently, the disease appears to be also driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to 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/antithrombotic therapies are likely to be more beneficial after COVID-19 has progressed to stages characterized by hypoxemia.

Patients Who Do Not Require Supplemental Oxygen

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19. Patients with COVID-19 who are receiving dexamethasone or another corticosteroid for an underlying condition should continue this therapy as directed by their health care provider.
- There is insufficient evidence to recommend either for or against the routine use of remdesivir for the treatment of patients who are hospitalized for COVID-19 who do not require supplemental oxygen. However, the use of remdesivir may be appropriate in patients who are at high risk of disease progression.

Rationale for Recommending Against the Use of Dexamethasone or Other Corticosteroids

In the RECOVERY trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive dexamethasone plus standard of care or standard of care alone (control arm).[1] No survival benefit for dexamethasone was observed among the patients who did not require supplemental oxygen at enrollment: 17.8% of patients in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). See Table 4a for additional information.

Based on these data, the Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)** for the treatment of COVID-19 in hospitalized patients who do not require supplemental oxygen, unless the patient has another indication for corticosteroid therapy.

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Rationale for Determining That There Is Insufficient Evidence to Recommend Either for or Against the Use of Remdesivir

ACTT-1 was a multinational randomized controlled trial that compared intravenous (IV) remdesivir to placebo in hospitalized patients with COVID-19. Remdesivir showed no significant benefit in patients with mild to moderate disease, which was defined as oxygen saturation >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen (rate ratio for recovery 1.29; 95% CI, 0.91–1.83); however, there were only 138 patients in this subgroup.[2]

In a manufacturer-sponsored, open-label randomized trial that included 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of a better clinical status on Day 11 (based on a 7-point ordinal scale) than those who received standard of care (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$).[3]

The Solidarity trial was a large, multinational, open-label randomized controlled trial that compared a 10-day course of remdesivir to standard of care. About 25% of hospitalized patients in both arms did not require supplemental oxygen at study entry. The primary endpoint of in-hospital mortality occurred in 11 of 661 patients (2%) in the remdesivir arm and 13 of 664 patients (2.1%) in the control arm (rate ratio 0.90; 99% CI, 0.31–2.58).[4] Please see Table 2a for more information.

Data from the PINETREE trial showed a clinical benefit for early treatment with remdesivir in nonhospitalized patients with COVID-19 who had a high risk of clinical progression. Patients were randomized to receive 3 days of IV remdesivir or placebo. The median duration of symptoms was 5 days at treatment initiation. By Day 28, there was a significant decrease in the proportion of patients who were hospitalized and/or died in the remdesivir arm: this primary endpoint occurred in 0.7% of remdesivir recipients and in 5.3% of placebo recipients (HR 0.13; 95% CI, 0.03–0.59; $P = 0.008$).[5]

Because these trials produced conflicting results regarding the benefits of remdesivir, the Panel finds the available evidence insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes that clinicians may decide that remdesivir is appropriate for certain hospitalized patients with moderate disease (e.g., those who have a particularly high risk for clinical progression).

Patients Who Require Supplemental Oxygen

Patients who require supplemental oxygen, but not high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation are a heterogeneous group. Some of these patients will have mild disease that will improve after a short period with or without treatment with remdesivir, dexamethasone, or both; others will develop progressive disease despite treatment and require a more intensive level of care. There is no consensus on which clinical or laboratory parameters allow for reliable risk-stratification to guide therapy and/or identify which subsets of patients will experience progressive lung injury and hypoxemia.

Some studies have tried to define this group according to traditional risk factors for COVID-19 progression and/or by the presence of elevated inflammatory markers like C-reactive protein (CRP), but evidence to support a specific identifying biomarker or clinical threshold is lacking.

Recommendations

- The Panel recommends using 1 of the following options for hospitalized patients who require supplemental oxygen:
  - **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)**
  - **Dexamethasone plus remdesivir (BIIb)**

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- **Dexamethasone (BI)**; for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug (e.g., **tocilizumab** or **baricitinib**) **(CIIa)**

- If dexamethasone is not available, an alternative corticosteroid (e.g., **prednisone**, **methylprednisolone**, or **hydrocortisone**) can be used **(BIII)**. See Corticosteroids for dosing recommendations.
- For nonpregnant patients, the Panel recommends using a **therapeutic dose** of heparin for patients who have D-dimer levels above the upper limit of normal (ULN), require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin.

Rationale for the Use of Remdesivir

In the ACTT-1 trial, remdesivir was associated with improved time to recovery in the 435 patients who required oxygen supplementation but not high-flow oxygen, NIV, or mechanical ventilation (7 days for remdesivir vs. 9 days for placebo; recovery rate ratio 1.45; 95% CI, 1.18–1.79). Fewer patients in the remdesivir arm than in the placebo arm progressed to requiring high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) (17% vs. 24%). In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit in this subgroup (HR for death 0.30; 95% CI, 0.14–0.64).[2]

The Solidarity trial reported no difference in the rate of in-hospital deaths between patients who received remdesivir and those who received standard of care (rate ratio for death in the overall study population 0.95; 95% CI, 0.81–1.11; rate ratio for death in patients who did not require mechanical ventilation at entry 0.86; 99% CI, 0.67–1.11). There was no difference between patients who received remdesivir and those who received standard of care in the percentage of those who progressed to mechanical ventilation (11.9% vs. 11.5%) or in length of hospital stay.[4] However, an open-label trial like Solidarity is less well-suited to assess time to recovery than a placebo-controlled trial. In the Solidarity trial, because both clinicians and patients knew that remdesivir was being administered, it is possible that hospital discharge was delayed in order to complete the 10-day course of therapy.

DisCoVeRy was a multinational, open-label randomized controlled trial that compared up to 10 days of remdesivir plus standard of care to standard of care alone in hospitalized patients with moderate or severe COVID-19. There was no significant difference in the odds of improved clinical status by Day 15 between the patients in the remdesivir arm and the standard of care arm (OR 0.98; 95% CI, 0.77–1.25). At Day 28, there were also no differences between the arms in either mortality (8% in remdesivir arm vs. 9% in standard of care arm) or clinical status. The DisCoVeRy trial shared with the Solidarity trial the major limitation of open-label design. Additionally, 440 of the 832 participants in the DisCoVeRy trial (219 in the remdesivir arm and 221 in the standard of care arm) were also Solidarity trial participants.[6]

Although the open-label Solidarity and DisCoVeRy trials demonstrated no mortality benefit for remdesivir, in ACTT-1, a large randomized placebo-controlled trial, remdesivir significantly reduced time to clinical recovery. In a post hoc analysis, this clinical benefit of remdesivir was most evident in those who had symptoms for ≤10 days. The evidence from the ACTT-1 and PINETREE trials suggests that remdesivir will have its greatest impact when administered early in the clinical course, which is also the case for antiviral agents used to treat other viral infections.[5] The Panel recommends **remdesivir** (without dexamethasone) as a treatment option for certain patients with COVID-19 who require minimal supplemental oxygen and are in the early course of the disease **(BIIa)**. In these individuals, the hyperinflammatory state where corticosteroids might be most beneficial may not yet be present or fully developed.

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Although several trials studied a 10-day course of remdesivir,[2,4] a 5-day course has been shown to be comparable to 10 days of therapy in hospitalized patients with moderate to severe COVID-19.[3,7] For more information, please see Table 2a.

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require supplemental oxygen **(BIIb)**, despite important limitations of observational data.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among patients who required supplemental oxygen at enrollment. Fewer patients in the dexamethasone arm than in the standard of care arm died within 28 days of enrollment (23.3% vs. 26.2%; rate ratio 0.82; 95% CI, 0.72–0.94).[1] However, the amount of supplemental oxygen that patients were receiving and the proportions of patients who required oxygen through a high-flow device or NIV were not reported. It is possible that the benefit of dexamethasone was greatest in those who required more respiratory support. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. For more information, see Corticosteroids.

Some experts prefer not to use dexamethasone monotherapy in patients who require supplemental oxygen because of the theoretical concern that corticosteroids might slow viral clearance when administered without an antiviral drug. Corticosteroids have been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.[11-13] Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the results to date are inconclusive.[14-18]

Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Patients Who Require Rapidly Increasing Oxygen Supplementation

Several major randomized trials that evaluated the use of interleukin (IL)-6 inhibitors or Janus Kinase (JAK) inhibitors with or without corticosteroids in patients with COVID-19 have included patients who required only low-flow supplemental oxygen. However, subgroup analyses in these trials have not clearly defined which patients in this heterogeneous group are most likely to benefit from using corticosteroids with another immunomodulator. Direct comparison between trials is not possible because background therapies (e.g., corticosteroids) and inclusion criteria (e.g., the requirement for elevated inflammatory markers) differed between trials. Nonetheless, some trials suggest that adding a second immunomodulator to dexamethasone provides benefits in patients who require low-flow supplemental oxygen.[19-21] The RECOVERY trial showed that in a subgroup of patients that included patients on low-flow oxygen, those who received tocilizumab plus dexamethasone had a lower incidence of 28-day mortality than those who received usual care (which included dexamethasone).[19] Similarly, data on JAK inhibitors are also inconclusive; for example, the COV-BARRIER trial did not find a statistically significant benefit

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for baricitinib in patients on low-flow oxygen,[20] whereas the placebo-controlled STOP-COVID trial demonstrated a reduction in the incidence of respiratory failure or death in the subgroup of patients on low-flow oxygen who received tofacitinib.[21]

Given the uncertainty concerning which patients in this group would benefit from adding a second immunomodulator (e.g., baricitinib, tocilizumab) to dexamethasone treatment, the Panel recommends considering these therapies on a case-by-case basis for individuals with rapidly increasing oxygen requirements and elevated markers of systemic inflammation **(CIIa)**. Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.

Additional Considerations

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab as a second immunomodulatory drug is necessary.
- Because there are no studies that directly compare the use of baricitinib and tocilizumab as treatments for COVID-19, the Panel has insufficient evidence to recommend 1 drug or class of drugs (i.e., JAK inhibitors, anti-IL-6 receptor mAbs) over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
- The Panel **recommends against** the use of **baricitinib** in combination with tocilizumab for the treatment of COVID-19, except in a clinical trial **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.
- Combination immunosuppressive therapy (e.g., dexamethasone with baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[22,23] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

Rationale for Using a Therapeutic Dose of Heparin in Certain Patients

Three open-label randomized controlled trials 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. The entry criteria into these studies varied, but they typically included those who required supplemental oxygen, had elevated D-dimer levels, and were not at risk of major bleeding events.

The largest multiplatform trial (ATTACC/ACTIV-4a/REMAP-CAP) showed an increase in the number of organ support-free days in the therapeutic heparin arm, but no difference in mortality or length of hospitalization.[24] The RAPID trial enrolled patients with elevated D-dimer levels and hypoxemia. The patients were randomized to receive therapeutic or prophylactic doses of heparin. There was no statistically significant difference between the arms in the occurrence of the primary endpoint (a

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composite of ICU admission, receipt of NIV or mechanical ventilation, or death by Day 28), but the use of therapeutic heparin reduced 28-day mortality.[25] The HEP-COVID trial enrolled patients who required supplemental oxygen and who had D-dimer levels that were >4 times the ULN or a sepsis-induced coagulopathy score of ≥4. The primary endpoint (a composite of venous thromboembolism [VTE], arterial thromboembolism, and death by Day 30) occurred significantly less frequently in patients who received therapeutic LMWH than in those who received prophylactic LMWH, but there was no difference in mortality by Day 30 between the arms.[26] The results from smaller randomized trials, single-center trials, and observational studies have also been published.

Based on the available data, the Panel recommends using a **therapeutic dose** of heparin for patients who have D-dimer levels above the ULN, require low-flow oxygen, and have no increased bleeding risk **(CIIa)**. The rating reflects the fact that, although the 3 randomized controlled trials showed a clinical benefit for therapeutic heparin in hospitalized patients, the inclusion criteria and the beneficial outcomes differed between the trials. In addition, it should be noted that <20% of patients who were screened for these studies were enrolled; therefore, these data may not be generalizable to all hospitalized patients with COVID-19.

Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation

Recommendations

- The Panel recommends using 1 of the following options for hospitalized patients who require oxygen through a high-flow device or NIV:
  - **Dexamethasone (AI)**
  - **Dexamethasone plus remdesivir (BIIb)**
- For patients who have rapidly increasing oxygen needs and have increased markers of inflammation, add either **baricitinib (BIIa)** or **tocilizumab (BIIa)** (drugs are listed alphabetically) to 1 of the options above.
- The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless VTE is confirmed **(BIII)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., enoxaparin 1 mg/kg once daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**.

Additional Considerations

- If dexamethasone is not available, an equivalent dose of another corticosteroid (e.g., **prednisone**, **methylprednisolone**, or **hydrocortisone**) may be used **(BIII)**. See Corticosteroids for more information.
- Immunosuppressive therapy (e.g., dexamethasone with or without baricitinib or tocilizumab) may increase the risk of opportunistic infections or reactivation of latent infections; however, randomized trials to date have not demonstrated an increase in the frequency of infections.
- Cases of severe and disseminated strongyloidiasis have been reported in patients with COVID-19 during treatment with tocilizumab and corticosteroids.[22,23] Many clinicians would initiate empiric treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) with or without

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serologic testing in patients from areas where *Strongyloides* is endemic (i.e., tropical, subtropical, or warm temperate areas).

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among patients who required supplemental oxygen without mechanical ventilation at enrollment: 23.3% of the patients in the dexamethasone arm versus 26.2% in the standard of care arm died within 28 days of enrollment (rate ratio 0.82; 95% CI, 0.72–0.94).[1]

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using a combination of remdesivir and corticosteroids have primarily been evaluated in observational studies. Some of these studies have suggested that there is a clinical benefit of using remdesivir plus dexamethasone.[8-10] Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in a large randomized clinical trial. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to multiple organ dysfunction syndrome. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, the combination of an antiviral agent, such as remdesivir, with an anti-inflammatory agent, such as dexamethasone, may treat the viral infection and dampen the potentially injurious inflammatory response that is a consequence of the infection. Based on the theoretical combined benefit of antiviral and anti-inflammatory therapies, the Panel recommends the combination of **dexamethasone plus remdesivir** as a treatment option for patients who require high-flow oxygen or NIV **(BIIb)**, despite the limitations of observational data.

Rationale for Not Recommending Remdesivir Monotherapy

In the ACTT-1 trial, there was no observed difference in time to recovery between the remdesivir and placebo arms in the subgroup of 193 patients who required high-flow oxygen or NIV at enrollment (recovery rate ratio 1.09; 95% CI, 0.76–1.57). A post hoc analysis did not show a survival benefit for remdesivir at Day 29, but the trial was not powered to detect this difference.[2] The Panel **does not recommend** using **remdesivir monotherapy** in patients who require high-flow oxygen or NIV because there is uncertainty regarding whether remdesivir alone confers a clinical benefit in this subgroup **(AIIa)**. Dexamethasone alone or remdesivir plus dexamethasone are better treatment options for COVID-19 in this group of patients.

Patients who start remdesivir monotherapy and then progress to requiring dexamethasone and oxygen through a high-flow device or NIV should continue to receive remdesivir until the treatment course is completed. Clinical trials that evaluated the use of remdesivir categorized patients based on their severity of illness at the start of treatment with remdesivir; therefore, patients may benefit from remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients

Data from several large clinical trials suggest that adding a second immunomodulatory drug, such as baricitinib or tocilizumab, to dexamethasone provides a clinical benefit in patients who require oxygen supplementation through a high-flow device or NIV.

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, have both reported a mortality benefit for tocilizumab among patients with rapid respiratory decompensation who require oxygen delivery through a high-flow device or NIV.[19,27] Most patients in

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both studies received corticosteroids.

In the REMAP-CAP trial, patients who were admitted to an ICU with severe to critical COVID-19 and rapid respiratory decompensation were randomized to receive open-label tocilizumab or usual care. The use of tocilizumab reduced in-hospital mortality (28% of patients died in the tocilizumab arm vs. 36% in the usual care arm) and, during 21 days of follow-up, increased the median number of days free of respiratory and cardiovascular organ support (10 days in the tocilizumab arm vs. 0 days in the usual care arm; OR 1.64; 95% CI, 1.25–2.14). Enrollment occurred within 24 hours of ICU admission and within a median of 1.2 days of hospitalization (IQR 0.8–2.8 days), suggesting that tocilizumab confers a benefit to patients experiencing rapid respiratory decompensation. The RECOVERY trial also suggested a mortality benefit for tocilizumab plus dexamethasone in a subset of patients that included those who required NIV or high-flow oxygen. In this study, a subset of patients with hypoxemia and CRP ≥75 mg/L were randomized to receive tocilizumab or usual care. Tocilizumab reduced all-cause mortality in these patients; by Day 28, 29% of patients in the tocilizumab arm versus 33% in the usual care arm had died (rate ratio 0.86; 95% CI, 0.77–0.96).

In the COV-BARRIER trial, 1,525 hospitalized patients with COVID-19 and ≥1 elevated inflammatory biomarker were randomized 1:1 to receive baricitinib 4 mg orally or placebo in addition to the local standard of care for up to 14 days (or until hospital discharge).[20] Overall, there was no difference in the occurrence of the primary endpoint of progression to high-flow oxygen, NIV, mechanical ventilation, or death by Day 28 between the baricitinib arm (27.8% of patients) and the placebo arm (30.5% of patients; OR 0.85; 95% CI, 0.67–1.08; $P = 0.18$). However, all-cause mortality by Day 28 was 8.1% in the baricitinib arm and 13.1% in the placebo arm, resulting in a 38.2% reduction in mortality for patients who received baricitinib (HR 0.57; 95% CI, 0.41–0.78; nominal $P = 0.002$). The difference in mortality was most pronounced in the subgroup of 370 patients receiving high-flow oxygen or NIV at baseline (17.5% in the baricitinib arm vs. 29.4% in the placebo arm; HR 0.52; 95% CI, 0.33–0.80; nominal $P = 0.007$). The occurrence of adverse events, serious adverse events, serious infections, and VTE events in the arms was comparable.

The ACTT-2 trial demonstrated that baricitinib used in combination with remdesivir improved time to recovery in hospitalized patients with COVID-19. The effect was most pronounced in patients who were receiving high-flow oxygen or NIV. However, patients receiving corticosteroids were excluded from the ACTT-2 trial, limiting the generalizability of these findings.

Given the clinical trial data (see Table 4e), the Panel recommends adding **baricitinib** or **tocilizumab** as a second immunomodulatory treatment in combination with dexamethasone for patients who are receiving oxygen supplementation through a high-flow device or NIV **(BIIa)**.

Additional Considerations

- Baricitinib or tocilizumab should only be given in combination with dexamethasone or another corticosteroid. Some clinicians may assess a patient's clinical response to dexamethasone before deciding whether adding baricitinib or tocilizumab is necessary.
- Studies that directly compare baricitinib to tocilizumab as treatments for COVID-19 are not available. Therefore, there is insufficient evidence for the Panel to recommend 1 drug over the other. Treatment decisions should be based on local guidance, drug availability, and patient comorbidities.
- If baricitinib and IV tocilizumab are not available or not feasible to use, **tofacitinib** can be used instead of baricitinib **(BIIa)** and **IV sarilumab** can be used instead of IV tocilizumab **(BIIa)**.
- Although approximately one third of patients in the REMAP-CAP and RECOVERY trials

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received a second dose of tocilizumab at the discretion of their treating physician, data on outcomes based on receipt of 1 or 2 doses is not available. Therefore, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

Rationale for Recommending Against the Use of the Combination of Baricitinib and Tocilizumab

The Panel **recommends against** the use of the combination of **baricitinib** and **tocilizumab** for the treatment of COVID-19 (except in a clinical trial) because there is insufficient evidence for the use of this combination **(AIII)**. Given that both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection.

Rationale for Recommending Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients

In an updated report from the REMAP-CAP trial, the efficacy of tocilizumab and sarilumab in improving survival and reducing the duration of organ support was similar. Compared to noncontemporary control patients who received placebo plus dexamethasone, patients who received sarilumab and dexamethasone demonstrated reduced in-hospital mortality, shorter time to ICU discharge, and more organ support-free days.[28] Administering sarilumab in combination with dexamethasone (n = 483) was noninferior to tocilizumab with dexamethasone (n = 943) with regard to the number of organ support-free days and mortality.

Even though the REMAP-CAP trial reported that sarilumab and tocilizumab have similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends using **sarilumab** only when **tocilizumab** is not available or is not feasible to use **(BIIa)**. The evidence of efficacy for tocilizumab is more extensive than the evidence for sarilumab; in addition, sarilumab is currently only approved for use as a subcutaneous (SUBQ) injection in the United States.

In 1 of the clinical trials, a single dose of sarilumab 400 mg for SUBQ injection was reconstituted in 50 mL or 100 mL of normal saline and administered as an IV infusion over 1 hour.

Rationale for Recommending the Use of Tofacitinib Plus Dexamethasone in Certain Hospitalized Patients

In the STOP-COVID trial, a double-blind randomized placebo-controlled trial, use of tofacitinib was associated with a decreased risk of respiratory failure and death (risk ratio 0.63; 95% CI, 0.41–0.97). All-cause mortality within 28 days was 2.8% in the tofacitinib arm (n = 144) and 5.5% in the placebo arm (n = 145) (HR 0.49; 95% CI, 0.15–1.63). Approximately 80% of patients in each arm also received corticosteroids.[21]

Data from the STOP-COVID trial supports the idea that tofacitinib plus steroids improves outcomes in hospitalized patients with COVID-19. Both baricitinib and tofacitinib belong to the same class of anti-inflammatory drugs (kinase inhibitors) and have overlapping mechanisms of action. The Panel recommends using **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use because the evidence of efficacy for tofacitinib is less extensive than the evidence for baricitinib **(BIIa)**.

Rationale for the Use of Prophylactic Doses of Heparin

The INSPIRATION trial compared the use of intermediate doses of anticoagulation (enoxaparin 1 mg/kg SUBQ once daily; n = 299) to prophylactic doses of anticoagulation (enoxaparin 40 mg SUBQ once daily; n = 299) in adults who were admitted to the ICU with COVID-19.[29] Among these patients, 34.3%

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received oxygen delivery using high-flow oxygen or NIV. The primary endpoint in this study was a composite of adjudicated VTE, arterial thrombosis, ECMO, or all-cause mortality. The primary endpoint occurred in 45.7% of patients who received the intermediate dose and in 44.1% of patients who received the prophylactic dose (OR 1.06; 95% CI, 0.76–1.48). Overall, there was no significant benefit of using this intermediate dose of anticoagulation in these ICU patients with COVID-19.

The multiplatform randomized controlled trial REMAP-CAP/ACTIV-4a/ATTACC also compared the effectiveness of using a therapeutic dose of heparin or LMWH to standard of care in critically ill patients with COVID-19; 65% of these patients received high-flow oxygen or NIV.[30] The trial was stopped for futility after 536 patients were randomized to receive therapeutic anticoagulation and 564 patients were randomized to receive standard of care. The median number of organ support-free days was 3 days (IQR -1 to 16 days) in patients who received the therapeutic dose of anticoagulation and 4 days (IQR -1 to 16 days) in patients who received standard of care (adjusted OR 0.83; 95% CrI, 0.67–1.03; posterior probability of futility [OR < 1.2] 99.9%). The proportion of patients who survived to hospital discharge did not differ between the arms (62.7% of patients in the therapeutic dose arm vs. 64.5% in the standard of care arm; OR 0.84; 95% CrI, 0.64–1.11). No significant benefit was reported for the use of a therapeutic dose of heparin in patients with COVID-19 who were admitted to the ICU.

Patients Who Require Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

- The Panel recommends using **dexamethasone** for hospitalized patients with COVID-19 who require mechanical ventilation or ECMO **(AI)**.
- The Panel recommends using **dexamethasone plus tocilizumab** for patients with COVID-19 who are within 24 hours of admission to the ICU **(BIIa)**.
- The Panel recommends using a **prophylactic dose** of heparin as VTE prophylaxis, unless a contraindication exists **(AI)**.
- The Panel **recommends against** the use of an **intermediate dose** (e.g., **enoxaparin** 1 mg/kg once daily) or a **therapeutic dose** of anticoagulation for VTE prophylaxis, except in a clinical trial **(BI)**.
- For patients who are started on a therapeutic dose of heparin in a non-ICU setting due to COVID-19 and then transferred to the ICU, the Panel recommends switching from the therapeutic dose to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII)**.

Additional Considerations

- If dexamethasone is not available, an equivalent dose of an alternative corticosteroid (e.g., **prednisone**, **methylprednisolone**, **hydrocortisone**) may be used **(BIII)**.
- For patients who initially received remdesivir monotherapy and progressed to requiring mechanical ventilation or ECMO, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- The Panel **recommends against** the initiation of **remdesivir monotherapy** in patients who require mechanical ventilation or ECMO **(AIIa)**.
- Tocilizumab should be given only in combination with dexamethasone (or another corticosteroid at an equivalent dose).
- Although some patients in the REMAP-CAP and RECOVERY trials received a second dose of tocilizumab at the discretion of their treating physician, there is insufficient evidence to determine which patients, if any, would benefit from an additional dose of the drug.

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- The combination of dexamethasone and tocilizumab may increase the risk of opportunistic infections or reactivation of latent infections. Prophylactic treatment for strongyloidiasis (e.g., with the antiparasitic drug ivermectin) should be considered for patients who are from areas where *Strongyloides* is endemic.

Rationale for the Use of Dexamethasone Monotherapy

As COVID-19 progresses, a systemic inflammatory response may lead to multiple organ dysfunction syndrome. The anti-inflammatory effects of corticosteroids mitigate the inflammatory response, and the use of corticosteroids has been associated with improved outcomes in people with critical COVID-19.

Dexamethasone reduces mortality in critically ill patients with COVID-19 according to a meta-analysis that aggregated 7 randomized trials and included data on 1,703 critically ill patients.[31] The largest trial in the meta-analysis was the RECOVERY trial, whose subgroup of mechanically ventilated patients was included.[1] For details about the meta-analysis and the RECOVERY trial, see Corticosteroids and Table 4a. Because the benefits of dexamethasone outweigh the potential harms, the Panel recommends using **dexamethasone** in hospitalized patients with COVID-19 who require mechanical ventilation or ECMO **(AI)**.

Considerations Related to the Use of Dexamethasone Plus Remdesivir Combination Therapy

Dexamethasone plus remdesivir combination therapy has not been evaluated in controlled studies; therefore, there is insufficient information to make a recommendation either for or against the use of this combination therapy. However, there is a theoretical reason to administer dexamethasone plus remdesivir to patients who have recently been intubated. Antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in the setting of other viral infections.[11,12]

Some studies have suggested that corticosteroids slow SARS-CoV-2 clearance, but the studies to date are not definitive. For example, an observational study in patients with nonsevere COVID-19 suggested that viral clearance was delayed in those who received corticosteroids,[32] whereas a more recent study in patients with moderate to severe COVID-19 found no relationship between the use of corticosteroids and the rate of viral clearance.[18] Given the conflicting results from observational studies and the lack of clinical trial data, some Panel members would coadminister **dexamethasone** and **remdesivir** in patients who have recently been placed on mechanical ventilation **(CIII)** until more conclusive evidence becomes available, based on their concerns about delayed viral clearance in patients who received corticosteroids. Other Panel members would not coadminister dexamethasone and remdesivir due to uncertainties about the benefit of using remdesivir in critically ill patients.

Rationale for Recommending the Use of Tocilizumab Plus Dexamethasone in Patients Within 24 Hours of Admission to the Intensive Care Unit

The REMAP-CAP and RECOVERY trials, the 2 largest randomized controlled trials of tocilizumab to date, both reported a mortality benefit for tocilizumab in patients who experienced rapid respiratory decompensation and were recently admitted to the ICU, including those who required mechanical ventilation.[19,27] The REMAP-CAP trial enrolled patients within 24 hours of admission to the ICU. Previous trials that enrolled patients later in the course of ICU care and/or who received oxygen support >24 hours after ICU admission have failed to show consistent clinical benefits for tocilizumab (see Table 4e). Thus, it is unclear whether there is a clinical benefit for tocilizumab in patients who received mechanical ventilation for >24 hours. Findings from the RECOVERY trial suggest a clinical benefit for tocilizumab plus corticosteroids among patients with rapid clinical progression who received mechanical ventilation. Please see the Rationale for Adding a Second Immunomodulatory Drug to Dexamethasone in Certain Hospitalized Patients section above for additional details on the clinical trial data and rationale for using tocilizumab in this situation.

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Rationale for Recommending Against the Use of Remdesivir Monotherapy

A clear benefit of remdesivir monotherapy has not been demonstrated in patients who require mechanical ventilation or ECMO. In the ACTT-1 trial, remdesivir did not improve the recovery rate in this subgroup of patients (recovery rate ratio 0.98; 95% CI, 0.70–1.36), and in a post hoc analysis of deaths by Day 29, remdesivir did not improve survival in this subgroup (HR 1.13; 95% CI, 0.67–1.89).[2] In the Solidarity trial, there was a trend toward increased mortality among patients who received mechanical ventilation and were randomized to receive remdesivir rather than standard of care (rate ratio 1.27; 95% CI, 0.99–1.62).[4] Taken together, these results do not demonstrate a clear benefit of remdesivir in critically ill patients.

For patients who start remdesivir monotherapy and then progress to requiring mechanical ventilation or ECMO, remdesivir should be continued until the treatment course is completed. Clinical trials that evaluated remdesivir categorized patients based on their severity of illness at study enrollment; therefore, patients may benefit from receiving remdesivir even if their clinical course progresses to a severity of illness for which the benefits of remdesivir are less certain.

Rationale for Recommending the Use of Sarilumab and Dexamethasone as an Alternative to Tocilizumab and Dexamethasone in Certain Hospitalized Patients

Please refer to the Patients Who Require Oxygen Through a High-Flow Device or Noninvasive Ventilation section above for the rationale regarding the use of sarilumab and dexamethasone as an alternative to tocilizumab and dexamethasone in certain hospitalized patients.

Rationale for Determining That There is Insufficient Evidence to Recommend the Use of Baricitinib in Addition to Standard of Care in Mechanically Ventilated Individuals

A cohort of critically ill patients was added to the COV-BARRIER trial after the completion of the original study. The results for the cohort were not included in the primary results of the main trial.[33] In this addendum, 101 patients on mechanical ventilation or ECMO were randomized 1:1 to receive baricitinib 4 mg (n = 51) or placebo (n = 50) for up to 14 days in combination with standard of care. Baricitinib significantly reduced 28-day all-cause mortality (39.2% in the baricitinib arm vs. 58.0% in the placebo arm; HR 0.54; 95% CI, 0.31–0.96; $P = 0.030$). However, given the small sample size, the Panel considers the evidence insufficient to issue a recommendation for patients on mechanical ventilation or ECMO.

Rationale for the Use of Prophylactic Doses of Heparin

Patients who required mechanical ventilation and ECMO were included in the multiplatform REMAP-CAP/ACTIV-4a/ATTACC trial and INSPIRATION trial.[29,30] Based on the results of these trials, the recommendations for using prophylactic doses of heparin in hospitalized, nonpregnant patients who require mechanical ventilation or ECMO are the same as those for patients who require oxygen through a high-flow device or NIV.

References

1. RECOVERY Collaborative Group, Horby P, Lim WS, et al. 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.
2. 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.
3. 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:

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https://www.ncbi.nlm.nih.gov/pubmed/32821939.

4. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for COVID-19—interim WHO Solidarity trial results. *N Engl J Med*. 2021;384(6):497-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33264556.
5. Hill JA, Paredes R, Vaca C, et al. Remdesivir for the treatment of high-risk non-hospitalized individuals with COVID-19: a randomized, double-blind, placebo-controlled trial. Presented at IDWeek. 2021. Virtual.
6. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a Phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis*. 2022;22(2):209-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34534511.
7. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe COVID-19. *N Engl J Med*. 2020;383(19):1827-1837. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459919.
8. Wong CKH, Lau KTK, Au ICH, et al. Optimal timing of remdesivir initiation in hospitalized COVID-19 patients administered with dexamethasone. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34420051.
9. Benfield T, Bodilsen J, Brieghel C, et al. Improved survival among hospitalized patients with coronavirus disease 2019 (COVID-19) treated with remdesivir and dexamethasone. A nationwide population-based cohort study. *Clin Infect Dis*. 2021;73(11):2031-2036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34111274.
10. Mozaffari E, Chandak A, Zhang Z, et al. Remdesivir treatment in hospitalized patients with COVID-19: a comparative analysis of in-hospital all-cause mortality in a large multi-center observational cohort. *Clin Infect Dis*. 2021;Published online ahead of print. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34596223.
11. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29161116.
12. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3(9):e343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16968120.
13. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2016;3:CD010406. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950335.
14. Chen Y, Li L. Influence of corticosteroid dose on viral shedding duration in patients with COVID-19. *Clin Infect Dis*. 2021;72(7):1298-1300. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32588884.
15. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. *Clin Infect Dis*. 2021;72(7):1297-1298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32588877.
16. Ding C, Feng X, Chen Y, et al. Effect of corticosteroid therapy on the duration of SARS-CoV-2 clearance in patients with mild COVID-19: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):943-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32986226.
17. Liu J, Zhang S, Dong X, et al. Corticosteroid treatment in severe COVID-19 patients with acute respiratory distress syndrome. *J Clin Invest*. 2020;130(12):6417-6428. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33141117.
18. Spagnuolo V, Guffanti M, Galli L, et al. Viral clearance after early corticosteroid treatment in patients with moderate or severe COVID-19. *Sci Rep*. 2020;10(1):21291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33277573.
19. 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.
20. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised

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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.

21. Guimaraes 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.
22. Lier AJ, Tuan JJ, Davis MW, et al. Case report: disseminated strongyloidiasis in a patient with COVID-19. *Am J Trop Med Hyg*. 2020;103(4):1590-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32830642.
23. Marchese V, Crosato V, Gulletta M, et al. Strongyloides infection manifested during immunosuppressive therapy for SARS-CoV-2 pneumonia. *Infection*. 2021;49(3):539-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32910321.
24. ATTACC Investigators, ACTIV-4a Investigators, REMAP-CAP Investigators, et al. 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.
25. 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.
26. 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.
27. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. 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.
28. The REMAP-CAP Investigators, Derde LPG. 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.
29. Inspiration Investigators, Sadeghipour P, Talasaz AH, et al. Effect of intermediate-dose vs standard-dose prophylactic anticoagulation on thrombotic events, extracorporeal membrane oxygenation treatment, or mortality among patients with COVID-19 admitted to the intensive care unit: the INSPIRATION randomized clinical trial. *JAMA*. 2021;325(16):1620-1630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33734299.
30. The REMAP-CAP, ACTIV-4a, ATTACC Investigators, Zarychanski R. Therapeutic anticoagulation in critically ill patients with COVID-19—Preliminary Report. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.03.10.21252749v1.
31. WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, Sterne JAC, Murthy S, et al. 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.
32. Li Q, Li W, Jin Y, et al. Efficacy evaluation of early, low-dose, short-term corticosteroids in adults hospitalized with non-severe COVID-19 pneumonia: a retrospective cohort study. *Infect Dis Ther*. 2020;9(4):823-836. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32880102.
33. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus standard of care for hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: results of a randomised, placebo-controlled trial. *medRxiv*. 2021;Preprint. Available at: https://www.medrxiv.org/content/10.1101/2021.10.11.21263897v2.

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