

4. Clinical Management Summary

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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 appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19.

The clinical spectrum of SARS-CoV-2 infection includes asymptomatic or presymptomatic infection and mild, moderate, severe, and critical illness. Figure 1 provides guidance for clinicians on the therapeutic management of nonhospitalized adult patients. This includes patients who do not require hospitalization or supplemental oxygen and those who have been discharged from an emergency department or a hospital. Figure 2 provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements. Figure 3 provides guidance on the therapeutic management of pediatric patients with multisystem inflammatory syndrome in children (MIS-C).

Figure 1. Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	<p>All patients should be offered symptomatic management (AIII).</p> <p>For patients who are at high risk of progressing to severe COVID-19,^a use 1 of the following treatment options:</p> <p>Preferred Therapies <i>Listed in order of preference:</i></p> <ul style="list-style-type: none"> • Ritonavir-boosted nirmatrelvir (Paxlovid)^{b,c} (AIIa) • Remdesivir^{c,d} (BIIa) <p>Alternative Therapies <i>For use <u>ONLY</u> when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:</i></p> <ul style="list-style-type: none"> • Bebtelovimab^e (CIII) • Molnupiravir^{c,f} (CIIa) <p>The Panel recommends against the use of dexamethasone^g or other systemic corticosteroids in the absence of another indication (AIII).</p>
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	<p>The Panel recommends against continuing the use of remdesivir (AIIa), dexamethasone^g (AIIa), or baricitinib (AIIa) after hospital discharge.</p>
<p>Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen</p> <p><i>For those who are stable enough for discharge but who still require oxygen^h</i></p>	<p>There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.</p>
<p>Discharged From ED Despite New or Increasing Need for Supplemental Oxygen</p> <p><i>When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensuredⁱ</i></p>	<p>The Panel recommends using dexamethasone 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use should not exceed 10 days) with careful monitoring for AEs (BIII).</p> <p>Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized,^j clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.</p>
<p>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</p>	

^a For a list of risk factors, see the CDC webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](#) and the Patient Prioritization for Treatment section in [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

^b Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions.

^c If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.

^d Administration of remdesivir requires 3 consecutive days of IV infusion.

^e Bebtelovimab is active in vitro against all circulating Omicron subvariants, but there are no clinical efficacy data from placebo-controlled trials that evaluated the use of bebtelovimab in patients who are at high risk of progressing to severe COVID-19. Therefore, bebtelovimab should be used only when the preferred treatment options are not available, feasible to use, or clinically appropriate.

^f Molnupiravir has lower efficacy than the preferred treatment options. Therefore, it should be used only when the preferred options are not available, feasible to use, or clinically appropriate.

^g There is currently a lack of safety and efficacy data on the use of this agent in outpatients with COVID-19; using systemic glucocorticoids in this setting may cause harm.

^h These individuals should receive oximetry monitoring and close follow-up through telehealth, visiting nurse services, or in-person visits.

ⁱ Provide an advanced level of home care, including supplemental oxygen (whether patients are receiving oxygen for the first time or are increasing their baseline oxygen requirements), pulse oximetry, laboratory monitoring, and close follow-up through telehealth, visiting nurse services, or in-person visits.

^j See [Therapeutic Management of Hospitalized Adults With COVID-19](#).

Key: AE = adverse event; CDC = Centers for Disease Control and Prevention; ED = emergency department; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally

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	<p>The Panel recommends against the use of dexamethasone (AIIa) or other corticosteroids (AIII).^a</p> <p>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.</p>	<p>For patients without evidence of VTE:</p> <ul style="list-style-type: none"> • Prophylactic dose of heparin, unless contraindicated (AI)
Hospitalized and Requires Supplemental Oxygen	<p>Use 1 of the following options:</p> <ul style="list-style-type: none"> • Remdesivir^{b,c} (e.g., for patients who require minimal supplemental oxygen) (BIIa) • Dexamethasone plus remdesivir^{b,c} (BIIb) • Dexamethasone (BI) <p>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).</p>	<p>For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk:^f</p> <ul style="list-style-type: none"> • Therapeutic dose of heparin^g (CIIa) <p>For other patients:</p> <ul style="list-style-type: none"> • Prophylactic dose of heparin,^g unless contraindicated (AI)
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	<p>Use 1 of the following options:</p> <ul style="list-style-type: none"> • Dexamethasone (AI) • Dexamethasone plus remdesivir^b (BIIb) <p>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}</p>	<p>For patients without evidence of VTE:</p> <ul style="list-style-type: none"> • Prophylactic dose of heparin,^g unless contraindicated (AI)
Hospitalized and Requires MV or ECMO	<p>Dexamethasoneⁱ (AI)</p> <p>For patients who are within 24 hours of admission to the ICU:</p> <ul style="list-style-type: none"> • Dexamethasone plus IV tocilizumab (BIIa) <p>If IV tocilizumab is not available or not feasible to use, IV sarilumab can be used (BIIa).</p>	<p>For patients without evidence of VTE:</p> <ul style="list-style-type: none"> • Prophylactic dose of heparin,^g unless contraindicated (AI) <p>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).</p>

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).
- ^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 10⁹/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

Figure 3. Therapeutic Management of Hospitalized Pediatric Patients With MIS-C

PANEL'S RECOMMENDATIONS

MIS-C

Initial treatment for MIS-C includes both immunomodulatory and antithrombotic therapy.

Initial Immunomodulatory Therapy:

- **IVIG** 2 g/kg IBW/dose (up to a maximum total dose of 100 g)^a IV **plus** low-to-moderate dose **methylprednisolone** (1–2 mg/kg/day) IV^a or another glucocorticoid at an equivalent dose^a (**AIIb**).
- The Panel recommends against the routine use of IVIG monotherapy for the treatment of MIS-C unless glucocorticoid use is contraindicated (**AIIb**).

Intensification Immunomodulatory Therapy:

- For children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy, start 1 of the following (listed in alphabetical order) (**AIII**):
 - High-dose **anakinra** 5–10 mg/kg IV or SUBQ daily (**BIIb**), *or*
 - **Higher-dose glucocorticoid** (e.g., **methylprednisolone** 10–30 mg/kg/day IV or equivalent glucocorticoid) (**BIIb**),^b *or*
 - **Infliximab**^c 5–10 mg/kg IV for 1 dose (**BIIb**).

Antithrombotic Treatment:

- Low-dose **aspirin** (3–5 mg/kg/day, up to maximum daily dose of 81 mg) PO for all patients without risk factors for bleeding (**AIII**), **AND**
- Anticoagulation for patients who fall under 1 of the following clinical scenarios:
 - **Therapeutic anticoagulation** for patients with large CAAs according to the American Heart Association guidelines for Kawasaki disease (**AIII**).
 - **Therapeutic anticoagulation** for patients with moderate to severe LV dysfunction who have no risk factors for bleeding (**AIII**).
 - For patients with MIS-C who do not have large CAAs or moderate to severe LV dysfunction, consider **prophylactic or therapeutic anticoagulation** on an individual basis, taking into consideration risk factors for thrombosis. See below for additional information.

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 Duration of therapy may vary. For more information, see [Therapeutic Management of Hospitalized Pediatric Patients With Multisystem Inflammatory Syndrome in Children \(MIS-C\) \(With Discussion on Multisystem Inflammatory Syndrome in Adults \[MIS-A\]\)](#).

^b In certain patients with severe illness, intensification therapy may include dual therapy with higher-dose glucocorticoids and infliximab or anakinra. Anakinra and infliximab **should not be given** in combination.

^c Infliximab **should not be used** in patients with macrophage activation syndrome.

Key: CAA = coronary artery aneurysm; IBW = ideal body weight; IV = intravenous; IVIG = intravenous immunoglobulin; LV = left ventricular; MIS-C = multisystem inflammatory syndrome in children; PO = oral; SUBQ = subcutaneously