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, therapies that directly target SARS-CoV-2 are anticipated to 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. Table 2a 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. Table 2b provides guidance on the therapeutic management of hospitalized adult patients according to their disease severity and oxygen requirements.
Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Panel’s Recommendations</th>
</tr>
</thead>
</table>
| All Patients                             | • Symptom management should be initiated for all patients \(\text{(AIII)}\).  
• The Panel \textit{recommends against} the use of dexamethasone\(^a\) or other systemic corticosteroids in the absence of another indication \(\text{(AIIb)}\). |
| Patients Who Are at High Risk of Progressing to Severe COVID-19\(^{b,c}\) | \textit{Preferred therapies. Listed in order of preference:}  
• Ritonavir-boosted nirmatrelvir \(\text{(Paxlovid)}\)^{d} \(\text{(AIIa)}\); see footnote on drug interactions\(^e\)  
• Remdesivir\(^{\text{f,l}}\) \(\text{(BIIa)}\)  
\textit{Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:}  
• Molnupiravir\(^{\text{d,g,h}}\) \(\text{(CIIa)}\) |

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 \textit{Guidelines Development} for more information.

\(^a\) There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

\(^b\) For a list of risk factors, see the CDC webpage \textit{Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19}. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.

\(^c\) For a discussion of potential treatment options for patients who are immunocompromised and have prolonged COVID-19 symptoms and evidence of ongoing viral replication, see below and \textit{Special Considerations in People Who Are Immunocompromised}.

\(^d\) If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider’s discretion.

\(^e\) Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient’s concomitant medications and evaluate potential drug-drug interactions. See \textit{Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications} for more information.

\(^f\) Administration of remdesivir requires an IV infusion once daily for 3 days.

\(^g\) Molnupiravir appears to have lower efficacy than the other options recommended by the Panel. Therefore, it should be considered when the other options are not available, feasible to use, or clinically appropriate.

\(^h\) The Panel \textit{recommends against} the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated \(\text{(AII)}\).

\textbf{Key:} CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel
### Table 2b. Therapeutic Management of Hospitalized Adults With COVID-19

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Clinical Scenario</th>
<th>Recommendations for Antiviral or Immunomodulator Therapy</th>
<th>Recommendations for Anticoagulant Therapy</th>
</tr>
</thead>
</table>
| 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<sup>a,b</sup> | See [Therapeutic Management of Nonhospitalized Adults With COVID-19](https://www.covid19treatmentguidelines.nih.gov/) | For patients without an indication for therapeutic anticoagulation:  
  - **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.  
  - **Remdesivir** (BIIb) for patients who are immunocompromised; (BII) for other high-risk patients | For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk:  
  - **Therapeutic dose of heparin**<sup>c</sup> (CIIa) |
| Hospitalized and Requires Conventional Oxygen<sup>d</sup> | Patients who require minimal conventional oxygen                                 | **Remdesivir**<sup>d</sup> (BIIa)                                                                                      | For other patients:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients |
|                                                        | Most patients                                                                    | Use dexamethasone plus remdesivir<sup>d</sup> (BIIa). If remdesivir cannot be obtained, use dexamethasone (BII). | For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BIII). |
|                                                        | Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation | Add 1 of the following immunomodulators:<sup>g</sup>  
  - **Preferred**  
    • PO baricitinib (BIIa)  
    • IV tocilizumab (BIIa)  
  - **Alternatives**  
    • IV abatacept (CIIa)  
    • IV infliximab (CIIa) | For patients without an indication for therapeutic anticoagulation:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients |
| Hospitalized and Requires HFNC Oxygen or NIV         | All patients                                                                     | **Dexamethasone** should be administered to all patients (AI). If not already initiated, promptly add 1 of the following immunomodulators:  
  - **Preferred**  
    • PO baricitinib<sup>n</sup> (AI)  
  - **Preferred Alternative**  
    • IV tocilizumab<sup>n</sup> (BIIa)  
  - **Additional Alternatives (Listed in Alphabetical Order)**  
    • IV abatacept<sup>n</sup> (CIIa)  
    • IV infliximab<sup>n</sup> (CIIa)  
  - Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).<sup>j</sup> | For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BIII). |
| Hospitalized and Requires MV or ECMO                 | All patients                                                                     | **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):  
  - PO baricitinib<sup>k</sup> (BIIa)  
  - IV tocilizumab<sup>k</sup> (BIIa) | For patients without an indication for therapeutic anticoagulation:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients |

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<sup>A</sup> AI: Antidote; BIIa: Level of evidence BII; CIIa: Level of evidence CII; ULN: Upper limit of normal; AI: Anti-infective; BM: Body mass; C: Clinical; CI: Cardiovascular; CII: Level of evidence CII; D-dimer: D-dimer assay; ECMO: Extracorporeal membrane oxygenation; HFNC: High-flow nasal cannula; I: Insult; ICU: Intensive care unit; IV: Intravenous; NIV: Noninvasive ventilation; MV: Mechanical ventilation; PO: By mouth; RR: Respiratory rate; SpO<sub>2</sub>: Percentage of arterial oxygen saturation; T: Temperature; WBC: White blood cell count.  
<sup>a</sup> The Panel recommends against the use of dexamethasone (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19.  
<sup>b</sup> For patients without an indication for therapeutic anticoagulation:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients  
  - For patients who do not have an increased bleeding risk:  
    - **Therapeutic dose of heparin** (CIIa)  
<sup>c</sup> For other patients:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients  
<sup>d</sup> For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk:  
  - **Therapeutic dose of heparin** (CIIa)  
<sup>e</sup> For other patients:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients  
<sup>f</sup> For patients who are immunocompromised; (BIII) for other high-risk patients  
<sup>g</sup> For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk:  
  - **Therapeutic dose of heparin** (CIIa)  
<sup>h</sup> For other patients:  
  - **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients  
<sup>i</sup> Use dexamethasone plus remdesivir (BIIa). If remdesivir cannot be obtained, use dexamethasone (BII).  
<sup>j</sup> Add remdesivir to 1 of the options above in certain patients (for examples, see footnote).  
<sup>k</sup> For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a prophylactic dose of heparin, unless there is another indication for therapeutic anticoagulation (BIII).
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 Ritonavir-boosted nirmatrelvir (Paxlovid) has not been studied in hospitalized patients. The FDA product label for ritonavir-boosted nirmatrelvir allows for its use in hospitalized patients with mild to moderate COVID-19 (i.e., those who do not require supplemental oxygen) who are at high risk of progressing to severe COVID-19 and who are within 5 days of symptom onset.

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 x 10^9/L, 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 adding 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) (BII), or patients who are ≤10 days from symptom onset (CIIa). For more information on immunocompromising conditions, see Special Considerations in People Who Are Immunocompromised.

k 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; FDA = Food and Drug Administration; 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.