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 2c 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 COVID-19

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>Panel’s Recommendations</th>
</tr>
</thead>
</table>
| Does Not Require Hospitalization or Supplemental Oxygen | For All Patients  
  • All patients should be offered symptomatic management (AIII).  
  • The Panel recommends against the use of dexamethasone\(^a\) or other systemic corticosteroids in the absence of another indication (AIIb).  

For Patients Who Are at High Risk of Progressing to Severe COVID-19\(^b\)  
Preferred therapies. Listed in order of preference:  
• Ritonavir-boosted nirmatrelvir (Paxlovid)\(^c,d\) (AIIa)  
• Remdesivir\(^e\) (BIII)  

Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:  
• Bebtelovimab\(^f\) (CIII)  
• Molnupiravir\(^d,g,h\) (CIIa)  

Discharged From Hospital Inpatient Setting in Stable Condition, Even if Receiving Supplemental Oxygen | The Panel recommends against continuing the use of remdesivir (AIIa), dexamethasone\(^a\) (AIIa), or baricitinib (AIIa) after hospital discharge.  

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\(^a\) 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 Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment (including an anti-SARS-CoV-2 mAb) 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 (i.e., >4–6 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 the risk factors affects the level of risk.  
\(^c\) Ritonavir-boosted nirmatrelvir has significant drug-drug interactions. Clinicians should carefully review a patient's concomitant medications and evaluate potential drug-drug interactions. See Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Medications for more information.  
\(^d\) If a patient requires hospitalization after starting treatment, the full treatment course can be completed at the health care provider's discretion.  
\(^e\) Administration of remdesivir requires 3 consecutive days of IV infusion.  
\(^f\) 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.  
\(^g\) Molnupiravir appears to have 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.  
\(^h\) The Panel 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 (AIII).  

Key: CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel
<table>
<thead>
<tr>
<th>Disease Severity</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</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 Oxygen Supplementation | All patients | The Panel recommends against the use of dexamethasone (Ala) or other systemic corticosteroids (AIII) for the treatment of COVID-19.<sup>b</sup> | For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk:  
- **Therapeutic dose of heparin** (CIIa)  
For other patients:  
- **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients |
| Hospitalized and Requires Conventional Oxygen<sup>a</sup> | Patients who require minimal conventional oxygen | Remdesivir<sup>c</sup> (BIIa) |  |
| Hospitalized and Requires Conventional Oxygen<sup>a</sup> | Most patients | Use dexamethasone plus remdesivir<sup>c</sup> (BIIa). If remdesivir cannot be obtained, use dexamethasone (BII). |  |
| Hospitalized and Requires Conventional Oxygen<sup>a</sup> | Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation | Add PO baricitinib<sup>f</sup> or IV tocilizumab<sup>f</sup> to 1 of the options above (BIIa). |  |
| Hospitalized and Requires HFNC Oxygen or NIV | Most patients | Promptly start 1 of the following, if not already initiated:  
- Dexamethasone plus PO baricitinib<sup>f</sup> (AI)  
- Dexamethasone plus IV tocilizumab<sup>f</sup> (BIIa)  
If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained:  
- Dexamethasone<sup>e</sup> (AI)  
Add remdesivir to 1 of the options above in certain patients (CIIa).<sup>i</sup> | For patients without an indication for therapeutic anticoagulation:  
- **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients  
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 | Most patients | Promptly start 1 of the following, if not already initiated:  
- Dexamethasone plus PO baricitinib<sup>f</sup> (BIIa)  
- Dexamethasone plus IV tocilizumab<sup>f</sup> (BIIa)  
If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained:  
- Dexamethasone<sup>e</sup> (AI) |  |

Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See [Guidelines Development](https://www.covid19treatmentguidelines.nih.gov/) for more information.

<sup>a</sup> For a list of risk factors, see the CDC webpage [Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-foods-precautions/patients-risk-factors.html).

<sup>b</sup> Corticosteroids that are prescribed for an underlying condition should be continued.
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).

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

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

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

Contraindications for the use of therapeutic anticoagulation in patients with COVID-19 include a platelet count <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.

If a JAK inhibitor or an anti-IL-6 receptor mAb is not readily available, start dexamethasone while waiting for the additional immunomodulator to be acquired. If neither of the other immunomodulators can be obtained, use dexamethasone alone.

Clinicians may consider adding remdesivir to 1 of the recommended immunomodulator combinations in patients who require HFNC oxygen or NIV, including immunocompromised patients. The Panel recommends against the use of remdesivir without immunomodulators in these patients (AIIa).

Key: CDC = Centers for Disease Control and Prevention; 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; mAb = monoclonal antibody; MV = mechanical ventilation; NIV = noninvasive ventilation; the Panel = the COVID-19 Treatment Guidelines Panel; PO = oral; ULN = upper limit of normal