

# Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group

## Therapeutic Management of Adult Patients with COVID-19



Recommendations apply to patients >18 years of age. Recommendations are based on the best available data and may change as additional data becomes available. Science Briefs can be found on the [Ontario COVID-19 Science Advisory Table](https://www.ontario.ca/page/ontario-covid-19-science-advisory-table) website.

### SEVERITY OF ILLNESS

### RECOMMENDATIONS

#### Critically Ill Patients

Patients requiring ventilatory and/or circulatory support, including high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO

- **Dexamethasone** 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended**.
- **Tocilizumab** **is recommended** for patients who are on recommended doses of dexamethasone therapy (or a dose-equivalent corticosteroid) AND are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if the infection was nosocomially acquired).

#### RECOMMENDATIONS FOR DRUG SHORTAGE SITUATIONS

- In **drug shortage** situations, a single dose of **tocilizumab 400 mg IV** or **sarilumab 400 mg IV** should be used for all eligible patients. A second dose of tocilizumab or sarilumab should not be given to any patient.
- **Baricitinib** 4 mg PO/NG daily for 14 days (or until discharge if sooner) **is recommended** in patients who are on recommended doses of dexamethasone therapy (or a dose-equivalent corticosteroid) or who have a contraindication to corticosteroid treatment. The panel does not recommend combined use of baricitinib and IL-6 inhibitors due to absence of safety and efficacy evidence.
- ▲ **Dexamethasone** 12 mg PO/IV daily for 10 days (or until discharge if sooner) **may be considered** in patients who are unable to receive IL-6 inhibitors (tocilizumab, sarilumab) or baricitinib. This recommendation is based on very low certainty evidence of reduction in days alive without life support, and the need for inpatient treatment options with a reasonable safety profile during the anticipated spike in COVID-19 cases due to the Omicron variant and widespread shortages of IL-6 inhibitors and baricitinib.

- **Prophylactic dose low molecular weight or unfractionated heparin** **is recommended**.
  - These patients **should not receive therapeutic dose anticoagulation** unless they have a separate indication for this treatment.
  - **Remdesivir** **is not recommended** for patients receiving mechanical ventilation.
  - ▲ **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 4 days **may be considered** in patients requiring high-flow oxygen (i.e., oxygen by mask, oxygen by high-flow nasal cannula, or non-invasive mechanical ventilation).
  - **SARS-CoV-2 neutralizing antibodies** **are not recommended** for critically ill patients. For symptomatic inpatients with nosocomial infection, see mildly ill recommendations for sotrovimab on page 2.
  - **Nirmatrelvir/ritonavir (Paxlovid)** **is not recommended** for critically ill patients.
- Bacterial infection is uncommon in COVID-19 pneumonia at presentation. **Do not use empiric antibiotics for bacterial pneumonia** unless bacterial infection is strongly suspected. Continue empiric antibiotics for no more than 5 days, and discontinue on the basis of microbiology results and clinical judgment.

#### Moderately Ill Patients

Patients newly requiring low-flow supplemental oxygen

- **Dexamethasone** 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended**.
- ▲ If patients are discharged with home-based oxygen therapy, **dexamethasone** 6 mg PO daily until oxygen no longer required (for a maximum of 10 days) **may be considered**.
- **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 4 days **is recommended**.
- ▲ **Therapeutic dose anticoagulation** **may be considered** over prophylactic dose anticoagulation in patients who are felt to be at low risk of bleeding.
- **All other patients should receive prophylactic dose anticoagulation.**
- **SARS-CoV-2 neutralizing antibodies** **are not recommended** for moderately ill patients. For symptomatic inpatients with nosocomial infection, see mildly ill recommendations for sotrovimab on page 2.
- **Nirmatrelvir/ritonavir (Paxlovid)** **is not recommended** for moderately ill patients.

- **Tocilizumab** **is recommended** for patients who have evidence of systemic inflammation, defined as a serum CRP of 75 mg/L or higher, AND have evidence of disease progression (i.e., increasing oxygen or ventilatory requirements) despite 24-48 hours of recommended doses of dexamethasone therapy (or a dose-equivalent corticosteroid), AND are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if the infection was nosocomially acquired).

#### RECOMMENDATIONS FOR DRUG SHORTAGE SITUATIONS

- In **drug shortage** situations, a single dose of **tocilizumab 400 mg IV** or **sarilumab 400 mg IV** should be used for all eligible patients. A second dose of tocilizumab or sarilumab should not be given to any patient.
- **Baricitinib** 4 mg PO/NG daily for 14 days (or until discharge if sooner) **is recommended** in patients who are on recommended doses of dexamethasone therapy (or a dose-equivalent corticosteroid) or who have a contraindication to corticosteroid treatment. The panel does not recommend combined use of baricitinib and IL-6 inhibitors due to absence of safety and efficacy evidence.

### Mildly Ill Patients

▶ Go to [page 2](#) for recommendations in mildly ill patients

### CURRENTLY NOT RECOMMENDED\*

There is insufficient evidence to support the use of the following therapies in the treatment of COVID-19 outside of clinical trials or where other indications would justify its use:

- ◆ [Colchicine](#)
- ◆ [Interferon](#) (with or without lopinavir-ritonavir and ribavirin)
- ◆ [Vitamin D](#)

### RECOMMENDED AGAINST\*

The following therapies are not recommended for treatment of COVID-19 due to lack of benefit, potential harm, and system implications of overuse:

- **Antibiotics** ([azithromycin](#))
- [Casirivimab-imdevimab](#) due to lack of neutralizing activity against the Omicron variant
- [Hydroxychloroquine](#) or [chloroquine](#)
- [Ivermectin](#)
- [Lopinavir/ritonavir](#)

\* Applies to patients with any severity of illness

This guidance applies to mildly ill patients in any setting, including the community, hospital (including nosocomial cases), and congregate care settings.

It is recommended that eligibility for outpatient therapies include patients who test positive for SARS-CoV-2 on either PCR or a healthcare-professional administered RAT or ID Now.

Mildly Ill Patients

Patients who do not require new or additional supplemental oxygen from their baseline status

Tier 1

Immunocompromised individuals<sup>1</sup> not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status; OR Unvaccinated<sup>2</sup> individuals at highest risk of severe disease (only if also age ≥70 years, Indigenous and age ≥60 years, or age ≥60 years with one or more risk factors<sup>3</sup>). Older immunocompromised individuals are at higher risk, and should be prioritized for treatment in this tier.<sup>4</sup>

Tier 2

Unvaccinated<sup>2</sup> individuals at risk of severe disease (only if also age ≥60 years, Indigenous and age ≥50 years, or ≥50 years with one or more risk factors<sup>3</sup>).<sup>4</sup>

Tier 3

Vaccinated individuals at highest risk of severe disease (only if also age ≥70 years, Indigenous and age ≥60 years, or age ≥60 years with one or more risk factors<sup>3</sup>). Vaccinated individuals who are >6 months from their last dose of vaccine are at higher risk, and should be prioritized for treatment in this tier.<sup>4</sup>

Tier 4

Vaccinated individuals at risk of severe disease (only if also age ≥60 years, Indigenous and age ≥50 years, or ≥50 years with one or more risk factors<sup>3</sup>). Vaccinated individuals who are >6 months from their last dose of vaccine are at higher risk, and should be prioritized for treatment in this tier.<sup>4</sup>

RISK LEVEL	RECOMMENDATIONS
HIGHER RISK OF SEVERE DISEASE	<p><b>INFUSION THERAPIES</b></p> <ul style="list-style-type: none"> <li><b>Sotrovimab</b> 500 mg IV x 1 dose is recommended for these patients if they present within 7 days of symptom onset.                     <ul style="list-style-type: none"> <li>Previous SARS-CoV-2 infection and vaccination status do not need to be considered. Serologic testing is not recommended.</li> <li>These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.</li> <li>It is recommended that monoclonal antibody therapy be administered to non-hospitalized individuals across Ontario using a hybrid network that includes, but is not limited to, mobile integrated healthcare services, community paramedicine, and outpatient infusion clinics.</li> </ul> </li> <li><b>Remdesivir</b> is currently not recommended for mildly ill patients. This recommendation is based on current shortages of remdesivir. Remdesivir should be preferentially used in moderately ill patients and may be considered in severely ill patients requiring high-flow oxygen, as it has a relatively greater benefit in these populations than in mildly ill patients.</li> </ul> <p><b>ORAL THERAPIES may be considered if infusion therapies are unavailable or contraindicated</b></p> <ul style="list-style-type: none"> <li><b>Nirmatrelvir/ritonavir (Paxlovid)</b> at a dose of 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together orally twice daily for 5 days, may be considered for these patients if they present within 5 days of symptom onset.                     <ul style="list-style-type: none"> <li>In patients with moderate renal impairment (eGFR ≥30 to &lt;60 mL/min), the dose should be reduced to 150 mg nirmatrelvir (one 150 mg tablet) and 100 mg ritonavir (one 100 mg tablet) taken together twice daily for 5 days. Paxlovid is not recommended in patients with severe renal impairment (eGFR &lt;30 mL/min).</li> <li>Specialized pharmacist consultation is important to mitigate any significant drug-drug interactions with other drugs.</li> <li>Paxlovid should be preferentially deployed in regions and to populations where administration is a barrier to intravenous medication. It is recommended that oral antiviral therapy be administered to non-hospitalized individuals across Ontario using a hybrid network that includes services such as mobile integrated healthcare services, community paramedicine, virtual/remote assessment, and outpatient clinics.</li> <li>The panel felt the strength of Paxlovid's potential benefit in reducing hospitalizations is low based on available data. However, the evidence supporting this benefit in high priority populations (e.g., older unvaccinated and vaccinated immunocompromised patients) has very low certainty, is not accounted for in submissions to regulatory agencies, and full data have not been presented as a publicly available preprint or peer-reviewed publication. The panel also noted the marginal benefit in individuals at low risk of hospitalization, and the high certainty of harm with Paxlovid if known drug-drug interactions are not mitigated. There are significant operational considerations in the use of this drug that are barriers to its implementability. For this reason, an additional recommendation for the use of this drug in highest risk eligible patients has been made. This recommendation will be reassessed when a full data set is available for public review.</li> <li>Paxlovid is not recommended for pregnant patients.</li> </ul> </li> <li><b>If Paxlovid is unavailable or contraindicated:</b> <ul style="list-style-type: none"> <li><b>Fluvoxamine</b> 50 mg PO daily titrated up to 100 mg PO twice daily for a total of 15 days may be considered for patients with mild COVID-19 illness presenting within 7 days of symptom onset. The recommended starting dose is 50 mg PO daily, titrated up to 100 mg PO twice daily for a total of 15 days. Pharmacist consultation and outpatient provider follow-up is important to avoid any significant adverse drug interactions with fluvoxamine. This recommendation is based on very low certainty evidence of benefit for preventing hospitalization with the need for management options for mild illness with a reasonable safety profile during an anticipated spike in COVID-19 cases due to the Omicron variant.</li> <li><b>Budesonide</b> 800 mcg inhaled twice daily for 14 days may be considered for these patients. This recommendation is based on very low certainty evidence of reduction in duration of symptoms, and the need for outpatient treatment options with a reasonable safety profile during an anticipated spike in COVID-19 cases due to the Omicron variant. Budesonide may have a role as an additional therapy in patients already on other therapies who have respiratory symptoms.</li> </ul> </li> </ul>
MODERATE RISK	<ul style="list-style-type: none"> <li><b>Fluvoxamine</b> 50 mg PO daily titrated up to 100 mg PO twice daily for a total of 15 days may be considered for these patients if they present within 7 days of symptom onset. See fluvoxamine recommendation statement for higher risk mildly ill patients.</li> <li><b>Budesonide</b> 800 mcg inhaled twice daily for 14 days may be considered for these patients. See budesonide recommendation statement for higher risk mildly ill patients.</li> <li>The following therapies are not recommended for these patients: <b>sotrovimab</b><sup>5</sup>, <b>remdesivir</b><sup>5</sup>, and <b>nirmatrelvir/ritonavir (Paxlovid)</b>.</li> </ul>
LOW RISK	<ul style="list-style-type: none"> <li><b>Reassurance and information for self-monitoring</b> of symptoms (including self-monitoring of oxygen saturation) are recommended.</li> <li>The following therapies are not recommended for these patients: <b>sotrovimab</b><sup>5</sup>, <b>remdesivir</b><sup>5</sup>, <b>nirmatrelvir/ritonavir (Paxlovid)</b>, <b>fluvoxamine</b>, and <b>budesonide</b>.</li> </ul>

There is currently insufficient evidence to make a recommendation around aspirin or anticoagulation for mildly ill patients.

The following therapies are not recommended for mildly ill patients: dexamethasone, tocilizumab, sarilumab, and baricitinib.

1. Examples of immunocompromised or immunosuppressed individuals include individuals with active treatment for solid tumor and hematologic malignancies, receipt of solid-organ transplant and taking immunosuppressive therapy, receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy), moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good's syndrome, hyper IgE syndrome), advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory. For individuals who are immunosuppressed or receiving immunosuppressants, their condition is considered both an underlying risk factor AND a marker of insufficient ability to mount an immune response to SARS-CoV-2. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.

2. Unvaccinated is defined as individuals who have received one or zero doses of a COVID-19 vaccine.

3. Risk factors include obesity (BMI ≥30), dialysis or stage 5 kidney disease (eGFR <15 mL/min), diabetes, cerebral palsy, intellectual disability of any severity, sickle cell disease, receiving active cancer treatment, solid organ or stem cell transplant recipients. If patients have, in the opinion of a physician, other important risk factors for disease progression beyond this list that merit the use of specific drugs or therapeutics, these should be clearly documented at the time of administration.

4. Although pregnancy is a risk factor for severe COVID-19, the absolute risk for this population remains low due to the young age and lack of comorbidities of most pregnant individuals. Considerations for the use of specific COVID-19 therapeutics should therefore be made on a case-by-case basis.

5. This recommendation is based on current limited supply, and prioritizing its administration in patients at greatest risk of progressing to severe disease.