**Therapeutic Management of Adult Patients with COVID-19**

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

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 website.

## SEVERITY OF ILLNESS

<table>
<thead>
<tr>
<th>Critically Ill Patients</th>
<th>Moderately Ill Patients</th>
<th>Mildly Ill Patients</th>
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<tbody>
<tr>
<td>Patients requiring ventilatory and/or circulatory support, including high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO</td>
<td>Patients newly requiring low-flow supplemental oxygen</td>
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</tbody>
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### RECOMMENDATIONS

- **Desmethylone**: 6 mg PO/I.V. daily for 10 days (or until discharge if sooner) is recommended.
- **Tocilizumab**: is recommended for patients who are on recommended doses of desmethylone 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).
- **Propylactic dose low molecular weight or unfractoned 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.

### 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/N.D. 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/I.V. 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 an anticipated spike in COVID-19 cases due to the Omicron variant and widespread shortages of IL-6 inhibitors and baricitinib.

- **Dexamethasone**: 6 mg PO/I.V. daily for 10 days (or until discharge if sooner) is recommended.
- **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).
- **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.

- **Ivermectin**: is not recommended for bacterial pneumonia unless bacterial infection is strongly suspected. Continue empiric antibiotics for no more than 5 days, and de-escalate on the basis of microbiology results and clinical judgment.

### CURRENTLY NOT RECOMMENDED

- **Colchicine**
- **Interferon (with or without 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 (antimicrobics)**
- **Casirivimab-idevirmab**: 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.

### RISK LEVEL

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<th>RECOMMENDATIONS</th>
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#### HIGHER RISK OF SEVERE DISEASE

**Tier 1**
- Immuno compromised individuals 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 individuals at highest risk of severe disease (only if also age ≥70 years, Indigenous and age ≥50 years, or age ≥60 years with one or more risk factors)1. Older immuno compromised individuals are at higher risk, and should be prioritized for treatment in this tier.

**Tier 2**
- Unvaccinated individuals at risk of severe disease (only if also age ≥60 years, Indigenous and age ≥50 years, or age ≥50 years with one or more risk factors)1.

**Tier 3**
- Vaccinated individuals at highest risk of severe disease (only if also age ≥70 years, Indigenous and age ≥50 years, or age ≥60 years with one or more risk factors)2.

**Tier 4**
- Vaccinated individuals at risk of severe disease (only if also age ≥60 years, Indigenous and age ≥50 years, or age ≥50 years with one or more risk factors)3.

### INFUSION THERAPIES

**Tier 1**
- Sotrovimab 500 mg IV x 1 dose is recommended for these patients if they present within 7 days of symptom onset. Previous SARS-CoV-2 infection and vaccination status do not need to be considered. Serologic testing is not recommended. 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.

**Tier 2**
- Remdesivir is currently not recommended for these patients. This recommendation is based on current shortages of this drug. 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.

### ORAL THERAPIES may be considered if infusion therapies are unavailable or contraindicated

**Tier 1**
- Nirmatrelvir/ritonavir (Paxlovid) 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 7 days of symptom onset.

**Tier 2**
- If patients with moderate renal impairment (eGFR 30 to <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 <30 mL/min).

**Tier 3**
- Specialized pharmacist consultation is important to mitigate any significant drug-drug interactions with other drugs.

**Tier 4**
- Paxlovid should be preferentially deployed in regions and to populations where administration is a barrier to intravenous medicines. 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.

- The panel felt the strength of Paxlovid’s potential benefit in reducing hospitalizations is high based on available data. However, the evidence supporting this benefit in high priority populations (e.g., older unvaccinated and vaccinated immuno compromised 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 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 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 interim conditional recommendation for the use of this drug in high risk eligible patients has been made. This recommendation will be reassessed when a full data set is available for public review.

### MODERATE RISK

**Tier 3**
- Fluvoxamine 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 balances the very low certainty evidence of benefit for preventing hospitalization with the need for management options for mildly ill with a reasonable safety profile during a surge in COVID-19 cases due to the Omicron variant.

**Tier 4**
- Budesonide 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.

### LOWER RISK

**Any individual not included in tiers 1 to 4**
- There is currently insufficient evidence to make a recommendation around aspirin or anticoagulation for mildly ill patients.

- The following therapies are not recommended for these patients: sotrovimab1, remdesivir1, and nirmatrelvir/ritonavir (Paxlovid).

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1. Examples of immuno compromised or immuno suppressed 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., Severe combined immunodeficiency, Wiskott-Aldrich syndrome, common variable immunodeficiency, Good’s syndrome, hyper-IgM syndrome, advanced or untreated HIV infection, active treatment with high-dose corticosteroids (i.e., >30 mg prednisone or equivalent per day when administered for 2 weeks), alkylating agents, antimetabolites, transplant related immunosuppressive drugs, cancer chemotherapy 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 immunosuppressant therapies, there is a higher risk, and should be prioritized for treatment in this tier.

2. Vaccinated 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, or (severe) 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 low risk of severe disease in any given pregnancy, and lack of completeness 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.