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 website.

SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO



| 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 an 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 co-infection is uncommon in COVID-19 pneumonia at presentation. **Do not administer empiric antibiotics 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.

## 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 is no longer required (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*

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## Mildly Ill Patients

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

**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.

### STEP 1 ▶ Determine the risk of disease progression.

- **Higher risk** individuals are those who have a ≥5% risk of hospitalization if they develop COVID-19. **Standard risk** individuals are those who have a <5% of hospitalization.
- Indigenous people, Black people, and members of other racialized communities may be at increased risk of disease progression due to disparate rates of comorbidity, increased barriers to vaccination, and social determinants of health. They should be considered **priority populations** for access to COVID-19 drugs and therapeutics.

| AGE (years) | NUMBER OF VACCINE DOSES | | | RISK FACTORS |
|---|---|---|---|---|
| | 0 doses | 1 or 2 doses | 3 doses | |
| <20[1] | **Higher risk** if ≥3 risk factors[1] | Standard risk[1] | Standard risk[1] | • Obesity (BMI ≥30 kg/m²)<br>• Diabetes<br>• Heart disease, hypertension, congestive heart failure<br>• Chronic respiratory disease, including cystic fibrosis<br>• Cerebral palsy<br>• Intellectual disability<br>• Sickle cell disease<br>• Moderate or severe kidney disease (eGFR <60 mL/min)<br>• Moderate or severe liver disease (e.g., Child Pugh Class B or C cirrhosis) |
| 20 to 39 | **Higher risk** if ≥3 risk factors | **Higher risk** if ≥3 risk factors | Standard risk | |
| 40 to 69 | **Higher risk** if ≥1 risk factors | **Higher risk** if ≥3 risk factors | Standard risk | |
| ≥70 | **Higher risk** | **Higher risk** if ≥1 risk factors | **Higher risk** if ≥3 risk factors | |
| **Immunocompromised[2] individuals of any age** | **Higher risk**: Therapeutics should always be recommended for immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying immune status, regardless of age or vaccine status.[1,2] | | | |
| **Pregnancy** | **Higher risk**[3] | Standard risk | Standard risk | |

1. Evidence for the safety and efficacy of sotrovimab and nirmatrelvir/ritonavir (Paxlovid) in children <18 years of age is limited. While early evidence on risk factors for moderate and severe COVID-19 in children is emerging, the ability to reliably predict disease progression in children remains very limited, and the frequency of progression is rare. While not routinely recommended in children <18 years of age, the use of these agents may be considered in exceptional circumstances (e.g., severe immunocompromise and/or multiple risk factors, clinical progression) on a case-by-case basis. Multidisciplinary consultation with Infectious Diseases (or Pediatric Infectious Diseases) and the team primarily responsible for the child's care is recommended to review the individual consideration of these indications.
2. Examples of immunocompromised or immunosuppressed individuals include receipt of treatment for solid tumors and hematologic malignancies (including individuals with lymphoid malignancies who are being monitored without active treatment), 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 immunosuppressive 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. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.
3. Therapeutics should always be recommended for pregnant individuals who have received zero vaccine doses.

### STEP 2 ▶ Based on the risk level, refer to the corresponding recommendation statements below.

| RISK LEVEL | RECOMMENDATIONS |
|---|---|
| **HIGHER RISK OF SEVERE DISEASE**<br>*Individuals who have ≥5% risk of hospitalization or are immunocompromised* | ▶ *It is recommended that higher risk patients receive one of nirmatrelvir/ritonavir (Paxlovid), sotrovimab, or remdesivir. The choice of drug depends on availability, contraindications, and ease of administration. These individuals should have a reasonable expectation for 1-year survival prior to SARS-CoV-2 infection.*<br>● **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, **is recommended** for these patients if they present within 5 days of symptom onset.<br>• In 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).<br>• Specialized pharmacist consultation is important to mitigate any significant drug-drug interactions with other drugs.<br>• Paxlovid should be preferentially deployed in regions and to populations where administration is a barrier to intravenous medication.<br>● **Sotrovimab** 500 mg IV x 1 dose **is recommended** for these patients if they present within 7 days of symptom onset.<br>• Individuals' SARS-CoV-2 infection and vaccination status do not need to be considered. Serologic testing is not recommended.<br>● **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 2 days **is recommended** for these patients if they present within 7 days of symptom onset.<br>▶ *If the above drugs are unavailable or contraindicated:*<br>▲ **Fluvoxamine 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 balances the very low certainty evidence of benefit for preventing hospitalization with the need for management options for mild illness with a reasonable safety profile during a surge in COVID-19 cases due to the Omicron variant.<br>▲ **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. |
| **STANDARD RISK**<br>*Individuals with <5% risk of hospitalization* | ● **Reassurance and information for self-monitoring of symptoms** (including self-monitoring of oxygen saturation) **are recommended**.<br>▲ **Fluvoxamine** 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.<br>▲ **Budesonide** 800 mcg inhaled twice daily for 14 days **may be considered** for these patients. See budesonide recommendation statement for higher risk mildly ill patients.<br>■ The following therapies are **not recommended** for these patients: **sotrovimab**, **nirmatrelvir/ritonavir (Paxlovid)**, and **remdesivir**. |

◆ 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**.