PURPOSE

The purpose of this document is to provide guidance for the medication management of adult patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. For management of pediatric patients, please see St. Louis Children’s Hospital Guidance for the Management of Acute COVID-19 in Children.

Additional information can be found at the following resources:

- NIH COVID-19 Treatment Guidelines[1]
- IDSA Guidelines on the Treatment and Management of Patients with COVID-19[2]
- BJC COVID-19 Resources
- BJC Outpatient Treatment Options for Mild to Moderate COVID-19

MANAGEMENT

Consultation with clinical experts in the treatment of COVID-19 should be considered for management of critically ill patients, pediatric patients, pregnant/breastfeeding patients, and/or patients with risk factors for progression to severe COVID-19 illness (See Table 1).[3, 4] [5]

Table 1. Risk Factors for Severe Illness (CDC) [3]

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tr>
<td>Increasing age, especially over 50 years of age</td>
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<tr>
<td>Younger than one year old</td>
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<tr>
<td>Part of a group with long-standing systemic health and social inequities, including racial and ethnic minorities and people with disabilities</td>
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Adults of any age with the following conditions are at increased risk for severe illness (listed in alphabetical order and not in order of risk):

- Cancer
- Chronic kidney disease
- Chronic liver disease
- Chronic lung diseases, including COPD, asthma (moderate to severe), bronchiectasis, bronchopulmonary dysplasia, interstitial lung disease, cystic fibrosis, pulmonary embolism, pulmonary hypertension
- Dementia or other neurological conditions
- Diabetes (type 1 or type 2)
- Disabilities including people who need help with self-care, ADHD, cerebral palsy, birth defects, spinal cord injuries, Down Syndrome
- Heart conditions (such as heart failure, coronary artery disease, cardiomyopathies, or hypertension)
- HIV infection
- Immunocompromised state
- Mental health conditions including depression, and schizophrenia spectrum disorders
- Overweight (body mass index [BMI] ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²)
- Physical inactivity
- Pregnancy
- Sickle cell disease or thalassemia
- Smoking, current or former
- Solid organ or blood stem cell transplant
- Stroke or cerebrovascular disease
- Substance use disorders
- Tuberculosis
Currently, there are no authorized or approved agents for pre-exposure prophylaxis. Individuals should keep up to date with COVID-19 vaccination and boosters, take precautions to avoid infection, and be tested for SARS-CoV-2 if they experience signs and symptoms consistent with COVID-19 and, if infected, promptly seek medical attention.

The agents below are not authorized for patients hospitalized due to COVID-19, requiring oxygen, or an increase in baseline oxygen due to COVID-19.

Dexamethasone or other systemic glucocorticoids should not be used for mild to moderate COVID-19 in the absence of another indication.

Oral antiviral approved through an EUA for high-risk patients ≥ 12y:
- Initiate within 5 days of symptom onset
- Contraindicated with strong CYP3A inducers or CYP3A substrates for which elevated drug concentrations are associated with serious and/or life-threatening reactions

IV antiviral FDA-approved for high-risk patients > 3 kg AND > 28 days old:
- Initiate within 7 days of symptom onset
- Room air or baseline oxygen
- ONLY available for high risk patients who are unable to receive Paxlovid. Many Paxlovid drug interactions can be safely managed.

Oral antiviral approved through an EUA for high-risk patients ≥ 18y if no other FDA-authorized treatments are clinically appropriate or accessible:
- Initiate within 5 days of symptom onset
- Not recommended in pregnancy. Contraception required for females of childbearing age during therapy and 4 days following last dose. Contraception required for males with partners of childbearing age during therapy and 3 months following last dose.

During times of supply or logistical constraints, patients will be prioritized by highest risk of clinical progression based on age, vaccination status, immune status, and risk factors according to NIH prioritization.

Supply of all outpatient therapeutic agents is currently sufficient that all eligible patients should receive treatment for COVID-19.
Figure 2. Pharmacologic Management of Hospitalized Adults with COVID-19

See Table 2 for more information and BJC Criteria for Use

**Hospitalized But Does Not Require Supplemental Oxygen**

- Remdesivir - Mild to Moderate (3 days) may be considered for patients at high risk of disease progression (see Table 1)
- Dexamethasone or other systemic glucocorticoids should not be used in the absence of another indication

**Hospitalized and Requires Supplemental Oxygen**

- Use one of the following options:
  - Remdesivir - Severe (5 days) (e.g., for patients who require minimal supplemental oxygen)
  - Dexamethasone + remdesivir (5 days) (e.g., for patients who require increasing amounts of supplemental oxygen)

**Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation**

- Use one of the following options:
  - Dexamethasone
  - Dexamethasone + remdesivir (5 days)
  - Baricitinib OR tocilizumab* may be added to one of the options above for patients with rapidly increasing oxygen needs and systemic inflammation.
  - Convalescent plasma** may be considered for patients who are immunocompromised with significant symptoms of COVID-19 and signs of active replication, or inadequate response to therapy

**Hospitalized and Requires Invasive Mechanical Ventilation or ECMO**

- Use one of the following options:
  - Dexamethasone
  - Dexamethasone + baricitinib
  - Dexamethasone + tocilizumab*
  - A clear benefit of remdesivir has not been demonstrated in this group, but may be considered in patients recently placed on mechanical ventilation (in addition to a regimen above).

*Due to a critical shortage, tocilizumab is currently restricted to any of the following: pregnancy, GFR < 15 mL/min, renal replacement therapy, within 24 hours of ICU admission and rapid progression of respiratory failure, or unable to obtain enteral access.

**COVID-19 convalescent plasma (CCP) supply is extremely variable and recent collection/efficacy against circulating variants cannot be guaranteed
Table 2: Considerations for the management of COVID-19

Recommended as standard of care OR high-quality evidence supporting efficacy and safety [i.e., randomized, controlled trial(s)]

**Supportive Care**
- Appropriate management of respiratory failure, ARDS, sepsis, septic shock
  - NIH Guidelines for Care of Critically Ill Adult Patients with COVID-19
- Unrelenting and high (>39°C) fevers are common in hospitalized COVID-19 patients.
- Antibiotics should only be used for confirmed or strong suspicion of a bacterial infection or sepsis. Antibiotics should be re-evaluated daily and if there is no evidence of bacterial infection, de-escalate or stop antibiotics.

**Nirmatrelvir/ritonavir (Paxlovid™)**

**Outpatient Only**
Inpatient use for treatment of patients hospitalized for reasons other than COVID-19 requires approval from local Incident Command, Chief Medical Officer, or designee. Available through an EUA

Paxlovid Fact Sheet for Healthcare Providers
Paxlovid Fact Sheet for Patients

**Inclusion Criteria (must meet all)**
- Diagnosed with COVID-19
- One or more symptoms consistent with COVID-19
- Able to receive within 5 days of symptom onset
- One or more high-risk conditions in Table 1

**Exclusion criteria (if meets any one)**
- < 12 years old
- < 40 kg
- Asymptomatic
- Hospitalized due to COVID-19
- Requiring oxygen therapy due to COVID-19
- Requiring increase in baseline oxygen due to COVID-19 in those on chronic oxygen therapy
- Severe renal impairment (eGFR < 30 mL/min) or severe hepatic impairment (Child-Pugh Class C)
- Drug Interactions*

*Before prescribing Paxlovid, clinicians should review the patient’s medication list to assess the risk of drug-drug interactions. See Appendix for drug interaction guidance.

**NirmatrelvirAdministration**
- eGFR > 60 mL/min: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days
- eGFR 30 to 59 mL/min: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days
- May be taken with or without food
- Tablets should be swallowed whole and not chewed, broken, or crushed.
- Nirmatrelvir and ritonavir tablets are co-packaged in a carton containing 30 tablets total, divided in 5 daily-dose blister cards
- Nirmatrelvir must be administered with ritonavir
- Not authorized for use for > 5 consecutive days

**Contraindications**
- Nirmatrelvir is a protease inhibitor active against MPRO, a viral protease essential in coronavirus replication. Ritonavir is required to increase nirmatrelvir concentrations to therapeutic ranges.
- EPIC-HR: randomized, double-blind, placebo-controlled trial in patients at high risk for progression to severe disease. All patients were unvaccinated and not previously infected and w/in 5 days of symptom onset. Primary outcome was hospitalization or death due to any cause by Day 28. Primary events occurred in 0.8% (8 of 1,039) of paxlovid patients (8 hospitalizations, 0 deaths), and 6.3% (78 of 1,046) of placebo patients (66 hospitalizations, 12 deaths). Relative risk reduction 88%.
- Pregnancy & Breastfeeding: there is no data in pregnancy or breastfeeding. Consultation with clinical experts is recommended. Paxlovid should be considered 2nd line in pregnancy after monoclonal antibodies.
- Caution should be taken in patients with uncontrolled HIV, as use of Paxlovid may increase risk of developing HIV resistance to protease inhibitors.

**Drug Interactions:**
- Numerous drug-drug interactions and the potential to cause serious or life-threatening adverse effects.
- Contraindicated with drugs highly dependent on CYP3A
- Contraindicated with strong CYP3A inducers or CYP3A substrates for which elevated drug concentrations are associated with serious and/or life-threatening reactions.
- See Appendix for drug interaction guidance

**Adverse Effects:** dysgeusia, diarrhea, hypertension, myalgia
### Molnupiravir Fact Sheet for Patients

**Outpatient Only** Available through an EUA

#### Inclusion Criteria (must meet all)
- Diagnosed with COVID-19
- One or more symptoms consistent with COVID-19
- Able to receive within 5 days of symptom onset
- One or more high-risk conditions in Table 1
- Other FDA-Approved treatments are not clinically appropriate or accessible

#### Exclusion Criteria (if meets any one)
- < 18 years old due to bone and cartilage toxicity
- Asymptomatic
- Hospitalized due to COVID-19
- Requiring oxygen therapy due to COVID-19
- Requiring increase in baseline oxygen due to COVID-19 in those on chronic oxygen therapy
- Pregnancy

#### Treatment
- 800 mg (four 200 mg capsules) PO every 12 hours for 5 days with or without food
- Not authorized for use > 5 consecutive days

#### Excluded due to risk
- Oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis.
- MOVe-OUT: randomized, placebo-controlled, double-blind trial in non-hospitalized high-risk adults. Primary outcome was hospitalization or death due to any cause at Day 29. Primary events occurred in 6.8% (48 of 709) of molnupiravir patients (47 hospitalizations, 1 death), and 9.7% (68 of 699) of placebo patients (59 hospitalizations, 9 deaths). Relative risk reduction 30%.
- Pediatrics: not recommended in < 18 yrs old due to bone and cartilage toxicity
- Pregnancy: May cause fetal harm. Prior to initiating treatment with molnupiravir, health care providers should assess whether an individual of childbearing potential is pregnant or not. Molnupiravir is authorized to be prescribed to a pregnant individual only after the health care provider has determined that the benefits would outweigh the risks for that individual patient and the known and potential benefits and potential risks of using molnupiravir during pregnancy are communicated to the pregnant individual. Must document that a pregnant individual was made aware of Merck Sharp & Dohme Corp’s pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com.
- Breastfeeding: Not recommended during treatment and for four days after the final dose. Pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir may be considered.
- **Females of Reproductive Potential:** Advised to use an effective method of contraception during treatment and for four days after the last dose.
- **Males of Reproductive Potential:** Sexually active individuals with partners of childbearing potential should use an effective method of contraception during treatment and for at least three months after the last dose of molnupiravir. The risk beyond three months is unknown.
- Adverse Effects: diarrhea, nausea, dizziness

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### Remdesivir (Veklury®)[1, 2, 7-10]

#### Inclusion Criteria:
- Mild to Moderate Illness (3 days)
- Positive SARS-CoV-2 test (rapid antigen or PCR)
- Room air or baseline oxygen
- Within 7 days of symptom onset
- High-risk for progressing to severe illness

#### Treatment for > 28 days AND > 3 kg
- Mild to Moderate
  - 200 mg IV on day 1, then
- Antiviral that inhibits RNA-dependent RNA polymerase in SARS-CoV-2.
- ACTT-1: RCT of 1,059 adults hospitalized with COVID-19. Patients who received remdesivir had significantly faster time to recovery compared to placebo (11 vs. 15 days). Greatest benefit in patients receiving supplemental oxygen
- SOLIDARITY: Multinational study by the World Health Organization included 11,266 adults in 30 countries randomized to local standard of care vs. one of four
**Severe (5 days) (must meet all)**
- Positive SARS-CoV-2 test (rapid antigen or PCR)
- Hospitalized < 14 days
- Oxygen saturation (SpO2) of ≤94% on room air, OR
  - Requiring supplemental oxygen, OR
  - Requiring invasive mechanical ventilation or ECMO*

* A clear benefit of remdesivir has not been demonstrated in patients who require invasive mechanical ventilation or ECMO, but may be considered in patients recently placed on mechanical ventilation in addition to dexamethasone +/- baricitinib or tocilizumab

<table>
<thead>
<tr>
<th>Severe</th>
<th>100mg IV q24h x 2 days, or hospital discharge, whichever comes first</th>
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<tbody>
<tr>
<td>200mg IV on day 1, then 100mg IV q24h x 4 days, or hospital discharge, whichever comes first</td>
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<tr>
<td>different repurposed antivirals, 2750 were randomized to remdesivir. Compared to standard of care, there was no reduction in mortality, initiation of mechanical ventilation, or duration of hospitalization.</td>
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<tr>
<td>No clear benefit demonstrated in patients requiring invasive mechanical ventilation or ECMO. In ACTT-1, remdesivir did not improve recovery or survival in this subgroup.</td>
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<tr>
<td>PINETREE: 562 nonhospitalized patients &gt;18 years with mild-moderate COVID-19 at high risk of severe disease randomized within 7d of symptom onset to 3d of remdesivir vs. placebo. 87% relative reduction in risk of hospitalization or death at day 28 compared to placebo.</td>
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<tr>
<td>Pregnancy &amp; Breastfeeding: remdesivir has been used during pregnancy and no safety concerns have emerged.</td>
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<tr>
<td>Pediatrics: Lyophilized powder should be used instead of the solution due to the higher amount of SBEC in the solution.</td>
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<tr>
<td>Renal Impairment: Although the manufacturer’s labeling recommends against use in patients with eGFR &lt; 30 mL/min, significant toxicity with a 5-day duration is unlikely.</td>
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<td>Monitoring: eGFR, hepatic laboratory testing, prothrombin time</td>
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**Dexamethasone[1, 2, 11-13]**

**Inclusion Criteria:**
- Mechanically ventilated, or
- Requiring supplemental oxygen

**Exclusion Criteria:**
- Patients who do not require supplemental oxygen

| Adults: 6 mg IV/PO daily for up to 10 days or until hospital discharge, whichever comes first. |

**RECOVERY trial**: Multicenter, randomized, open-label trial in hospitalized patients randomized to receive dexamethasone had a lower mortality than those who received standard of care. The benefit was seen in patients who required supplemental oxygen. No benefit was seen in patients who did not require supplemental oxygen.

- A meta-analysis of seven randomized controlled trials found that administration of corticosteroids was associated with a lower 28-day mortality in critically ill patients with COVID-19.
- Alternative steroid regimens have been evaluated with mixed results; however, the most robust clinical evidence remains with dexamethasone 6 mg IV/PO daily for up to 10 days.
- **Adverse Effects**: related to steroid use should be considered including hyperglycemia, electrolyte and fluid-balance abnormalities, secondary infections, psychiatric effects, and critical-illness related myopathy.

**Tocilizumab (Actemra®)[1, 2, 14-20]** DUE TO A CRITICAL SHORTAGE, use for COVID-19 is restricted to the following as well as previously established inclusion and exclusion criteria below:
- Pregnant OR
- GFR < 15 mL/min or renal replacement therapy OR
- Within 24 hours of ICU admission and rapid progression of respiratory failure OR
- Unable to obtain enteral access

| Adults: 8 mg/kg (max 800mg) IV x 1 dose in addition to dexamethasone |

**Tocilizumab**, a monoclonal anti-IL-6 receptor blocking antibody, has been proposed as a therapeutic agent to mitigate hyperinflammation associated with COVID-19. To date, no IL-6 inhibitor is FDA-approved or authorized for the treatment of COVID-19.

- Several trials have failed to demonstrate improvement in clinical status or a reduction of mortality within 1 month of tocilizumab treatment.
- **REMAP-CAP trial** enrolled 803 critically-ill patients requiring respiratory support who were admitted to an ICU. Compared to placebo, the use of tocilizumab reduced in-hospital mortality and increased the number of organ support-free days.
- **RECOVERY trial** enrolled 4116 adults with hypoxia (oxygen saturation < 92% or requiring oxygen therapy) and C-reactive protein ≥ 75 mg/L. Tocilizumab patients demonstrated improved
Inclusion Criteria:
- Receiving systemic corticosteroids AND
  - Requiring high-flow oxygen (>0.4 FiO\textsubscript{2}/30 L/min of oxygen flow), noninvasive, or invasive mechanical ventilation
  - Exhibiting rapid progression of respiratory failure

Exclusion Criteria (if meets any one criterion)
- > 48 hours of ICU admission at BJC hospital
- > 10 days of invasive mechanical ventilation
- Active systemic bacterial or fungal infection
- AST/ALT 10 x upper limit of normal
- Neutropenia (ANC < 500 cells/mm\textsuperscript{3})
- Thrombocytopenia (<50,000 cells/mm\textsuperscript{3})

*In the trials reporting a benefit, tocilizumab was initiated early (within 3 days of hospitalization or within 24 hours of ICU admission.) Tocilizumab may be more beneficial in patients with early rapidly progressing disease.*

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**Baricitinib (Olumiant\textsuperscript{®})[21, 22]**

**Inclusion Criteria:**
- Receiving systemic corticosteroids AND
  - Requiring high-flow oxygen (>0.4 FiO\textsubscript{2}/30 L/min of oxygen flow), noninvasive, or invasive mechanical ventilation
  - Exhibiting rapid progression of respiratory failure

**Exclusion Criteria (if meets any one)**
- Without enteral access
- > 48 hours of ICU admission at BJC hospital
- > 10 days of invasive mechanical ventilation
- GFR < 15 mL/min or receiving renal replacement therapy or acute kidney injury

**Consider withholding or interruption of therapy for the following:**
- Absolute lymphocyte count < 200 cell/µL
- Absolute neutrophil count < 500 cell/µL
- Suspected drug-induced liver injury

**Adults:**
- GFR > 60 mL/min: 4 mg PO daily
- GFR 30-59: 2 mg PO daily
- GFR: 15-29: 1 mg PO daily
- Duration: 14 days or until hospital discharge, whichever comes first

**Adverse Effects:** secondary infections, gastrointestinal perforation, anemia, hepatitis, infusion reaction, neutropenia

**Pregnancy & Breastfeeding:** there is little safety data in pregnancy or breastfeeding. Consultation with clinical experts is recommended.

**Janus kinase (JAK) inhibitor that may prevent cellular immune activation and inflammation in COVID-19. Approved by FDA for severe rheumatoid arthritis.**

**ACTT-2:** multinational, randomized, placebo-controlled trial in 1,033 hospitalized patients with COVID-19 pneumonia found median time to recovery was shorter in the baricitinib plus remdesivir group (7 days) than in the placebo group plus remdesivir group (8 days) in overall cohort.

**COV-BARRIER:** multinational, randomized, placebo-controlled trial in 1,525 hospitalized patients with pneumonia, and elevation in >1 inflammatory marker found no significant difference in proportion of patients progressing to high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation. 28-day mortality and 60-day all-cause mortality was lower in baricitinib group vs. placebo. (8.4% vs. 13.1% and 10.3% vs. 15.2%, respectively). The most pronounced reduction in mortality was in patients hospitalized requiring non-invasive ventilation or high-flow oxygen (23.0% vs. 33.7%, respectively). Encouraging preliminary data suggests mortality benefit in patients on survival at 28 days and were less likely to progress to mechanical ventilation or death.
mechanical ventilated or ECMO. Frequency of serious adverse events, infections and VTEs were similar between baricitinib and placebo, respectively.

Recommended in the context of a clinical trial OR moderate-quality evidence suggests benefit and has lower potential for harm (i.e., well-designed retrospective, non-randomized studies)

COVID-19 Convalescent Plasma [1, 2, 23-26]

Available through an EUA COVID-19 Convalescent Plasma Fact Sheet for Health Care Providers

CCP may be considered for treatment of immunocompromised patients with:

- significant symptoms of COVID-19 and with signs of active SARS-CoV-2 replication
- inadequate response to therapy

**COVID-19 convalescent plasma (CCP) supply is extremely variable and recent collection/efficacy against circulating variants cannot be guaranteed.**

Inclusion Criteria (must meet all)

- Positive SARS-CoV-2 test (rapid antigen or PCR)
- Immunocompromised* due to a medical condition or receipt of immunosuppressive medication or treatments
- Primary team attending agrees that patient should be given COVID-19 convalescent plasma
- Informed blood transfusion consent provided by the patient or healthcare proxy
- FDA required
  - Convalescent Plasma Fact Sheet for Patients or Parents/Caregivers
  - Plasma will not be released unless the provider attests that fact sheet has been communicated to the patient/caregiver

*CCP should be prioritized for severely immunocompromised patients as below:

- B-cell depleting therapy
- Hematologic malignancy
- Solid organ transplant receiving recent T-cell or B-cell depleting agents
- Primary immunodeficiency
- Untreated HIV with CD4 T lymphocyte cell count < 50 cells/mm³

Exclusion Criteria (if meets any one criterion)

- Immunocompetent
- Any reason for which the provider judges that COVID-19 convalescent plasma is not appropriate

• A meta-analysis of 18 studies of patients with hematologic malignancies (258 patients) found CCP may be associated with improved clinical outcomes including survival rate, viral clearance, and hospital discharge.
• A randomized, double-blind, placebo-controlled trial of convalescent plasma with high antibody titers against SARS-CoV-2 in 160 patients > age 65 years with mild COVID-19 symptoms within 72 hours found 16% of patients receiving convalescent plasma had severe respiratory disease by day 15 compared with 31% of patients receiving placebo (Number Needed to Treat = 7.)
• A randomized, double-blind, placebo-controlled trial in patients with severe COVID-19 pneumonia found no significant difference in clinical status or overall mortality. Median time from onset of symptoms to enrollment was 8 days.
• A randomized controlled trial (PenCCP2) of hospitalized adults compared up to 2 units of CCP plus standard care vs. standard care alone. Primary endpoint was clinical severity score comparison. Clinical severity score median and [interquartile range] was 7 [2.75–12.25] in CCP plus standard care vs. 10 [5.5–30] in standard care alone. 28-day mortality was 5% (2 of 40) in CCP patients vs. 26% (10 of 39) in standard care patients.
• Available data suggest that serious adverse reactions are infrequent and consistent with the risks associated with plasma infusions for other indications.
• Pregnancy & Breastfeeding: Safety and efficacy have not been evaluated.
• Pediatrics: Safety and efficacy have not been evaluated.
See St. Louis Children’s Hospital Guidance for the Management of Acute COVID-19 in Children

Not recommended outside of a clinical trial
Low-quality (i.e., observational) or variable evidence to support use and has higher potential for harm
### Inhaled Prostanoids[27]
- Not routinely recommended
- While there is insufficient data to provide recommendations specific to COVID-19, patients with ARDS may benefit from inhaled prostanoids. Please consult Critical Care for guidance.
- To date, no studies have evaluated use in COVID-19 patients.
- A nationwide shortage of available agents exists
- Data in patients with non-COVID ARDS indicate inhaled prostanoids may reduce mean pulmonary artery pressure and improve oxygenation; however, data demonstrating clinical benefit are lacking.
- Inhaled prostanoids are aerosolized for administration and require filter changes that increase potential exposure of particles within the ventilator circuit to the ambient environment.

### IV Vitamin C[1]
- Not recommended outside of a clinical trial
- Insufficient data to support use in COVID-19
- The 2021 Surviving Sepsis Guidelines recommend against using IV Vitamin C for adults with sepsis or septic shock. [28]

### Other Therapies
- Nitazoxanide
- GM-CSF inhibitors
- Interferons
- IL-1 inhibitors (e.g., anakinra)
- IVIG (non-SARS-CoV-2 specific)
- Leronlimab
- Other IL-6 inhibitors (e.g., sarilumab, siltuximab)
- Other kinase inhibitors (e.g., tofacitinib, ruxolitinib, acalabrutinib, ibrutinib, zanubrutinib)

### Do not use (therapies with evidence of no benefit and/or potential for harm)[1, 2]
- Ivermectin is an antiparasitic drug being investigated as a potential treatment for COVID-19 due to in vitro studies suggesting it may have antiviral and anti-inflammatory properties.
- Although in vitro data suggests ivermectin may inhibit SARS-CoV-2 in cell cultures, pharmacokinetic and pharmacodynamic studies suggest ivermectin doses up to 100-fold higher than those approved for humans would be required to achieve the concentrations necessary to duplicate the drug’s antiviral efficacy in vitro.
- Adequately powered, randomized, placebo-controlled studies have failed to find a clinical benefit from the use of ivermectin for the treatment of COVID-19.
- Many clinical studies have limitations that make them less definitive and informative. Limitations include: incomplete information and significant methodological limitations such as small sample size, various doses and schedules of ivermectin, open-label in which neither participants nor investigators were blinded to treatment arms, various concomitant medications such as corticosteroids, and poorly defined severity and outcome measures.
- The NIH has summarized the data [here](https://www.nih.gov/)

#### Information for Patients
A patient handout can be found on the [BJC intranet](https://www.bjc.net)

*In response to requests for prescriptions and reports of patients taking livestock formulations:*
- Ivermectin is not authorized or approved by the FDA to prevent or treat COVID-19.
- Ivermectin has not been shown to be a safe or effective way to prevent or treat COVID-19 in carefully controlled trials.
- Ivermectin is not an antiviral (a drug for treating viruses.)
- Medications intended for animals should never be used in humans. Preparations for animals are highly concentrated and have ingredients that are not evaluated in humans.
• Taking large doses is dangerous and can cause serious harm.
• Toxicities associated with misuse and overdose include rash, nausea, vomiting, abdominal pain, severe hepatitis, seizures, coma, and death.
• Vaccination remains our safest and most effective tool to prevent COVID-19

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<tr>
<th>Drug</th>
<th>Recommendation</th>
<th>Toxicities/Adverse Reactions</th>
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| Hydroxychloroquine (Plaquenil)[29-33] | Not recommended | Multiple randomized, double-blind, placebo-controlled trials have shown no evidence of benefit for post-exposure prophylaxis, nor treatment across the spectrum of disease severity.  
  • Reports have documented serious dysrhythmias in patients with COVID-19  
  • ADRs: bone marrow suppression, hypoglycemia, retinal toxicity |
| Azithromycin                  | Not recommended | Not recommended with hydroxychloroquine or as monotherapy in hospitalized and in non-hospitalized patients  
  • Associated with QTc prolongation and cardiac adverse events, especially in combination with hydroxychloroquine |
| Colchicine[1, 34]             | Not recommended | • COLCORONA outpatient trial did not reduce hospitalizations or death and had significantly increased adverse events.  
  • RECOVERY trial in hospitalized patients closed due to lack of evidence for efficacy |
| Neuraminidase Inhibitors (oseltamivir, zanamavir, peramivir) | Not recommended | • Neuraminidase inhibitors are NOT recommended for treatment of COVID-19 as coronaviruses have not been shown to utilize neuraminidase for replication.  
  • No data to support use of baloxavir.  
  • Should only be utilized with influenza co-infection. |
| Baloxavir                     | Not recommended | • Studies showing lack of clinical efficacy, or insufficient data to support use. |
| Other therapies               | Not recommended |  
  • Lopinavir/ritonavir (Kaletra)  
  • Vitamin D  
  • Zinc  
  • Oral Ribavirin |

**APPENDIX**

**Management of Drug Interactions**

Ritonavir is a strong CYP3A4 and p-glycoprotein inhibitor, a weak CYP2D6 inhibitor, and a moderate inducer of CYP2B6, CYP2C19, CYP2C9, and CYP1A2 so many drug-drug interactions are possible.

This table is not a comprehensive list of all possible drugs that may interact with Paxlovid. Consultation with an expert (e.g., pharmacist and/or the patient’s specialist provider, if applicable) should be considered. Additional information may also be found at the following:

- Paxlovid Fact Sheet for Healthcare Providers [https://www.fda.gov/media/155050/download](https://www.fda.gov/media/155050/download)
- Lexi-comp® Interactions database
Deviation from this guidance may be appropriate in certain clinical scenarios. Providers should exercise clinical judgement when assessing the risks and benefits of Paxlovid and determine the most appropriate strategy for managing drug interactions.

CYP3A4 inhibition takes place ~day 2 of Paxlovid and resolves approximately 3 days after Paxlovid is discontinued. Unless otherwise stated, interacting medications should be managed (held/dose-reduced/extra monitoring) for 8 days from the first dose of Paxlovid. Very sensitive or narrow therapeutic index CYP3A4 drugs may need to be restarted 10 days after the first dose of Paxlovid.

### Do not use Paxlovid. For alternatives visit [https://www.bjc.org/for-physicians/covid](https://www.bjc.org/for-physicians/covid)

<table>
<thead>
<tr>
<th>Abemaciclib</th>
<th>Afinron</th>
<th>Amiodarone</th>
<th>Apalutamide</th>
<th>Bosantan</th>
<th>Bromocriptine</th>
<th>Cabergoline</th>
<th>Carbamezapine</th>
<th>Ceritinib</th>
<th>Clopidogrel(^2)</th>
<th>Clorazepate for seizures</th>
</tr>
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<tbody>
<tr>
<td>Clozapine</td>
<td>Dasatinib</td>
<td>Dihydropyrimidine</td>
<td>Dipyridamole</td>
<td>Dofoxidone</td>
<td>Dofetilide</td>
<td>Dronedarone</td>
<td>Enalatamide</td>
<td>Eplerenone</td>
<td>Ergoloid mesylates</td>
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<td>Ergotamine</td>
<td>Flecainide</td>
<td>Glidaprevir/pibrentasvir</td>
<td>Ibrutinib</td>
<td>Ibradavine</td>
<td>Ivoisidenib</td>
<td>Lomtapide</td>
<td>Lonafarnib</td>
<td>Lumacaftor/ivacaftor</td>
<td>Luvateperone</td>
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<td>Lurasidone</td>
<td>Meperidine</td>
<td>Methylergonovine</td>
<td>Mexiletine</td>
<td>Midazolam - oral</td>
<td>Neratinib</td>
<td>Nilotinib</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
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<td>Pramoxide</td>
<td>Primidone</td>
<td>Propafenone</td>
<td>Quinidine</td>
<td>Rifampin</td>
<td>Rifapentine</td>
<td>Riocigau</td>
<td>Rivaroxaban</td>
<td>Sildenafil for PH</td>
<td>St. John’s wort</td>
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<tr>
<td>Tadalafil</td>
<td>Tadalafil</td>
<td>Triazolam(^2)</td>
<td>Venetoclax</td>
<td>Vardenafil for PH</td>
<td>Vinblastine</td>
<td>Vinclorin</td>
<td>Vicirol</td>
<td>Venlafaxine</td>
<td>Voriconazole</td>
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<td>Triazolam(^2)</td>
<td>Trienza</td>
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</table>

### Temporarily withhold concomitant medication, if clinically appropriate

CYP3A4 inhibition resolves approximately 3 days after Paxlovid is discontinued. Unless otherwise stated, interacting medications should be held for 8 days from the first dose of Paxlovid. For narrow therapeutic index CYP3A4 drugs, additional dosing changes or extra monitoring may be appropriate in certain clinical scenarios. Providers should exercise clinical judgement when assessing the risks and benefits of Paxlovid and determine the most appropriate strategy for managing drug interactions.

### Reduce concomitant medication dose, if clinically appropriate, and monitor for adverse effects

CYP3A4 inhibition resolves approximately 3 days after Paxlovid is discontinued. Unless otherwise stated, interacting medications should be managed (dose-reduced/extra monitoring) for 8 days from the first dose of Paxlovid.

### Select medications that can be co-administered with Paxlovid with caution/monitoring

### Chlordiazepoxide\(^2\) Ciclesonide (inhaled) Cloflazam\(^2\) Clozapam\(^2\) Cobicolistat - regimens monitor for increased Paxlovid or protease inhibitor adverse events

| Codeine | Diazepam\(^2\) | Estrogen-containing contraceptives – back-up non-hormonal method required | Irbesartan | Labelatel | Levotyroxine | Methadone – monitor for withdrawal | Ritonavir – boosted regimens – monitor for increased Paxlovid or protease inhibitor adverse events | Tramadol – monitor for both increased or decreased Tramadol response | Valsartan | Warfarin – monitor INR closely |
|---------|---------------|---------------------------------------------------------------------------|-----------|-----------|-------------|----------------------------------|-------------------------------------------------|----------------------------------|-----------|
| Alprazolam (reduce by 50%) | Amiodipine (reduce by 50%) | Apixaban (reduce by 50%) | Aripiprazole (reduce by 50%) | Brexpiprazole (reduce by 50%) | Buspirone (reduce by 50%) | Cariprazine (reduce by 50%) | Cilostazol (50 mg bid) | Clarithromycin – consult pharmacist | Corticosteroids (standing) (reduce by 50%) – do NOT use for mild/moderate COVID-19 without hypoxia | Cyclosporine |

### Select medications that can be co-administered with Paxlovid. No interaction expected or of minimal significance given short Paxlovid duration

Reduced effectiveness of clopidogrel is likely. Do not administer in patients who are at very high risk of thrombosis (e.g., within 6 weeks of coronary stenting. Consider alternative (i.e., prasugrel) or alternative COVID-19 therapy.

Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate acute withdrawal reactions. The risk is greatest for patients who have been using higher doses of benzodiazepines over an extended period of time.

REFERENCES


