Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Framework

1. COVID-19 Specific Management
2. Non-COVID Viral Pathogen Management
3. Supportive ICU Care

1. COVID-19 Specific Management

Disclaimer:
The Ottawa Hospital [TOH] P&T Committee can only endorse COVID-19 infection specific treatment(s) from appraisal of the minimally-biased evidence available. The information provided below is a guideline to facilitate the *safe use* of specific treatment(s) for COVID-19 infection after due consideration by the MRP or most responsible medical team and the patient or their SDM(s). It does NOT mandate any treatment(s)

- We advocate for patient participation in clinical trials, if there are no contraindications and patient or their SDM(s) provide consent
- **These recommendations will be reviewed and updated as necessary according to;**
  - Accrual of evolving minimally-biased evidence
  - TOH's allocated medication supply
  - TOH participation in clinical therapy trials

N.B.

- The MRP or most responsible medical team should consider consultation with an Infectious Disease physician regarding initiation and management of anti-COVID therapies in patients who are not eligible for treatment in the context of a clinical trial.

M. McGuinty M.D., R. Zvonar BSc.Pharm, C Nott M.D., A Buchan M.D., A Kuo BSc. Pharm., R Patel M.D. Pharm.D. & TOH Drug Information Pharmacists, on behalf of Pharmacy & Therapeutics Committee, The Ottawa Hospital

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Clinical Presentations (*hospitalized populations*):

The spectrum of illness due to COVID-19 for hospitalized patients includes but is not limited to:

Symptoms/Signs:

- Fever (89.1 - 98%)
- Cough (76%), productive cough (28 - 32.2%)
- Dyspnea (55%)
- Difficulty breathing (6.9% overall, 32.6% in severe cases)
- Fatigue/Myalgias (42.5 - 44%)
- ARDS (14.8%)
- Headache (6.5 - 8.7%),
- Diarrhea (3 - 7.4%)
- Rhinitis (3.4%)
- Nausea/Vomiting (1.3%)
- Disordered sense of taste or smell (15-71%)

Imaging Features:

- Bilateral infiltrate on chest CT or X-ray (80-96%)

Risk Factors for Severe Disease and Increased Mortality risk:

- Age > 60, especially >80
- Cardiovascular disease
- Respiratory disease
- Diabetes
- Hypertension
- Obesity
- Transplant
- Malignancy

Timing of treatment initiation:

Initiation of anti-COVID infection therapies, particularly Dexamethasone, should be considered for hospitalized patients after laboratory testing confirms diagnosis of COVID-19 infection or it remains highly suspected despite a negative test result.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Severity of COVID-19 illness for applying interventions (adapted from Ontario COVID-19 Clinical Practice Guideline)

- Severely Ill patients (*hospitalized and either Step-u/down Unit or ICU-based*)
  - Patients usually managed in an intensive care unit or step-down/step-up unit (e.g. AMA), requiring invasive mechanical ventilation [*IMV*] and/or hemodynamic support, including extracorporeal membrane oxygenation (*ECMO*).
  - Patients requiring oxygen by high-flow nasal cannula (*HFNC*), non-invasive ventilation (*NIV*), or higher concentrations of oxygen by mask (e.g. >50%)

- Moderately Ill patients (*hospitalized, ward-based*)
  - Patients usually managed on a hospital medical/general ward. This may include patients receiving low-flow supplemental oxygen (e.g. 1-6L/min via nasal prongs), HFNC or NIV.

- Mildly Ill patients (*ambulatory, outpatient*)
  - Patients usually managed outside of hospital, and do not require supplemental oxygen, intravenous fluids, or other physiologic support. Patients hospitalized for reasons other than medical/nursing support are included in this category.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

COVID-19 specific therapies for hospitalized patients with laboratory test confirmed infection or where it remains highly suspected despite a negative test result**:**

Consider patient enrolment in interventional trials of COVID-19 therapies (*contact the 'ICU Research Nurse Coordinator' via locating*).

Dexamethasone[1]:

Dexamethasone 6mg PO (or IV, **IF** po dosing is contraindicated) daily for up to 10 days [or hospital discharge if sooner] is **recommended for** patients who are moderately or severely ill with COVID-19 (receiving oxygen support of any type, inclusive of MV)

Note: Other corticosteroids at equivalent dose (e.g. *hydrocortisone 160mg/day or prednisone 40mg/day*) are acceptable as alternatives to Dexamethasone for COVID-19, particularly if they are otherwise indicated or already in use.

1 – When prescribing Dexamethasone or other steroids at moderate or high dose, consider screening for latent infection with Hepatitis B and *Strongyloides*, and consider the risk of secondary infection with *Aspergillus.* Refer to **Appendix C** for more details.

Remdesivir:

The Remdesivir arm of the CATCO/SOLIDARITY trial has closed.

Remdesivir **is recommended** for patients who are **moderately ill** with COVID-19 *(inpatients requiring low-flow O2 – see definition above)* for a total duration of 5 days.

Remdesivir **can be considered** for patients who are **severely ill** with COVID-19 *(inpatients requiring HFNC or NIV)* for a total duration of 5 days.

Remdesivir is **not recommended** for patients who are mildly ill with COVID-19 (*outpatients, or inpatients not requiring supplemental O2*).

Remdesivir is **not recommended** for patients with COVID-19 who are invasively ventilated. Treatment initiated before intubation should be continued for the 5day course.

IL-6 Inhibitors (Tocilizumab):

Tocilizumab is **not recommended** for patients admitted to hospital with **Mild** illness due to COVID-19 (*not requiring supplemental O2*).

Tocilizumab **should be considered** for hospitalized patients with confirmed COVID infection with **Moderate,** or **Severe** illness (*requiring any level of O2 support*) meeting the following current criteria:

- Inclusion
  - Receiving invasive or non-invasive mechanical ventilation for ≤ 48 hours **OR**

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

- Receiving high-flow nasal cannula if flow rate >30L/min and FiO2 >0.4 for ≤ 48 hours
- CRP ≥75mg/L
- Receiving dexamethasone 6mg po/IV daily for COVID infection

- Exclusion
  - High concern for, or presence of, tuberculosis, systemic bacterial or fungal co-infection
  - ALT or AST > 5x ULN
  - Treatment with anakinra, tocilizumab, or sarilumab in past 30 days
  - Known hypersensitivity to tocilizumab
  - Death is deemed to be imminent and inevitable within 24 hours
  - More than 14 days have elapsed since admitted to hospital with symptoms of an acute illness due to suspected or laboratory test proven COVID-19
  - Pregnancy – consult with MFM prior to use of Tocilizumab

N.B.

1. Tocilizumab should be administered ***in addition to*** dexamethasone
2. Accessibility of Tocilizumab for COVID patients is subject to TOH allocation

Lopinavir/Ritonavir (Kaletra):

Lopinavir/Ritonavir (Kaletra) is **not recommended** for treatment of COVID-19

Chloroquine or Hydroxychloroquine:

Chloroquine or Hydroxychloroquine are **not recommended** for treatment of COVID-19

Azithromycin:

Azithromycin is **not recommended** for treatment of COVID-19

Colchicine:

Colchicine is **not recommended** for treatment of COVID-19 in hospitalized patients

Ivermectin:

Ivermectin is **not recommended** for treatment of COVID-19

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

2. Other Viral pathogens

For Influenza A&B, Parainfluenza, RSV, Human metapneumovirus, adenovirus:

- No change to current supportive ICU care

Empiric therapies for hospitalized patients with undifferentiated viral pneumonia:

Oseltamivir:

Initiation of Oseltamivir x 5 days is recommended if Influenza is diagnosed or clinically suspected.
Discontinuation of Oseltamivir is recommended if Influenza is ruled out, or alternate diagnosis is established.

3. Usual Critical Care

Many patients with severe COVID-19 develop acute respiratory distress syndrome (ARDS). Evidence-based guidelines for ARDS in the context of COVID-19 include treatments include:

a) Conservative intravenous fluid strategies
b) Consideration for invasive ventilation
c) Lung-protective ventilation strategies
d) Periodic prone positioning during non-invasive or invasive ventilation
e) Consideration of ECMO

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Antiviral and COVID-19 therapy dosing guide:

Medication	Normal renal function (CrCl > 50 mL/min)	Impaired renal function	Renal Replacement Therapies	Hepatic Dose Adjustments
Oseltamivir (*active vs Influenza virus only*)	75 mg PO BID for 5 days	CrCl 31-50 mL/min: 30mg PO q12h for 5 days CrCl 10-30 mL/min: 30mg PO once daily, for 5 days CrCl < 10 mL/min and NOT on dialysis: 75 mg PO x 1 dose only	Hemodialysis: 75 mg PO now, then 75 mg after each hemodialysis session, for 5 days Peritoneal dialysis: 30 mg PO x 1 dose only SLED or CRRT: 30 mg PO once daily, for 5 days	No dose adjustment required
Remdesivir	200mg IV x1 loading dose, then 100mg IV daily x 4d	CrCl 30-50 mL/min: 200mg IV x1 loading dose, then 100mg IV daily x 4d CrCl <30 mL/min: Assess risks vs benefits of use in this setting	Assess risks vs benefits of use in this setting.	Should not be initiated in patients with ALT ≥5 times the ULN
Dexamethasone	6mg PO or IV daily for up to 10 days	No dose adjustment required	No dose adjustment required	No data for dosage adjustment
Tocilizumab	Single dose based on weight: >90kg: 800 mg >65 and ≤90 kg: 600 mg; >40 and ≤65 kg:400 mg ≤40 kg: 8mg/kg No second dose permitted due to allocation limitation	No dose adjustment required	No dose adjustment required	No dose adjustment required; Should not be initiated in patients with ALT ≥5 times the ULN

Refer to **Appendix A** for recommendations for drug administration tips.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Treatment duration:

Treatment duration for certain medications used to manage COVID-19 infection (antivirals, Il-6 inhibitors) remains uncertain. For patients receiving treatment(s) outside of clinical trials, consider treatment(s) discontinuation if:

1. An alternate diagnosis is established
   -OR-
2. After 5 days of therapy AND Resolution of fever AND respiratory symptoms AND Absence of supplemental O2 requirements (or return to baseline home oxygen need)
   -OR-
3. Fitness for discharge home (*no need to continue therapy at home*)

Refer to **Appendix B** for a summary of antiviral adverse effects, contra-indications and drug interactions in addition to those highlighted below.

Drug-Drug Interactions:

Detailed drug-drug interaction information for evolving COVID-19 therapies can be found at https://www.covid19-druginteractions.org/prescribing-resources. Where there is concern about interactions not addressed below, contact Pharmacy regarding advice for dosing and/or co-administration.

1. Remdesivir:
   a. Little information is available on drug-drug interactions of Remdesivir, no important drug-drug interactions have been reported.
   b. Co-administration with Hydroxychloroquine and Chloroquine [*when used for non-COVID infection indications*] may reduce antiviral activity of Remdesivir.
   c. Co-administration with Rifamycins and St. John's Wort is not advised.
2. Dexamethasone:
   a. A Caspofungin maintenance dose of 70 mg daily is suggested when used concomitantly with dexamethasone.
3. Tocilizumab:
   a. Lower concentrations of drugs metabolized by liver cytochrome enzymes (e.g., cyclosporine, warfarin, phenytoin, simvastatin) may be observed in patients with chronic inflammatory conditions treated with tocilizumab. Significance is unknown in patients treated for COVID-19. Monitor levels/therapeutic effects.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Treatment Monitoring:

General Recommendations:

1. CBC with differential, Cr, electrolytes, glucose, liver enzymes q24-48h for the duration of treatment. If abnormal, monitor as clinically needed until return to baseline.
2. For patient receiving steroids/tocilizumab: Hepatitis B serology (sAg, sAb, cAb) recommended, consider Strongyloides serology and/or O&P for high-risk patients.
3. For patients receiving tocilizumab – assess for history of opportunistic infections.

Medication Contra-indications:

1. Remdesivir:
    a. Absolute: hypersensitivity to the drug or its components
    b. Relative: renal failure (CrCl < 30 mmL/min) outside of a clinical trial, ALT ≥5 times the ULN
2. Dexamethasone:
    a. Absolute: hypersensitivity to the drug or its components
    b. Relative: pre-existing psychiatric conditions, increased risk of GI perforation (e.g., diverticulitis, recent intestinal anastomoses, peptic ulcer disease)
3. Tocilizumab
    a. Absolute: hypersensitivity to the drug or its components.
    b. Relative: history of opportunistic infection, latent TB

Medication-Specific Monitoring:

1. Remdesivir:
    a. Daily CBC, electrolytes, Cr, & liver function tests
2. Dexamethasone:
    a. Daily blood glucose
    b. Acute joint pain for avascular necrosis
3. Tocilizumab
    a. Daily CBC with differential, and liver enzyme and function tests
    b. Blood pressure
    c. Monitor for infusion-related reactions up to 24h post dose
    d. Please note that CRP may be depressed for several days after receipt of tocilizumab

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Appendix A: Antiviral Drug Administration Tips

Medication	Oral administration	Swallowing difficulties	Enteral Tube Administration*
Oseltamivir (empiric for influenza)	Capsules may be administered with or without food (food may improve GI tolerance).	Capsule contents may be opened and mixed in applesauce or yogurt or a sugary drink.	Pharmacy will supply a 6 mg/mL suspension for tube administration. If suspension is not available, mix capsule contents with 5-20 mL water.

*General TOH recommendations for administration of drugs via feeding tube can be found here

Appendix B: Antiviral Adverse Effects/Precautions/Drug Interactions

Medication	Usual Side Effects	Potential Serious Side Effects	Contra-indications/ Precautions	Drug Interactions
Oseltamivir (empiric for influenza)	Nausea, vomiting, diarrhea, abdominal pain, headache, dizziness	Hypersensitivity reactions, skin reactions; neuropsychiatric events	History of hypersensitivity reaction to drug	
Remdesivir	Nausea, rash	Hypersensitivity/ anaphylactic reactions, infusion-related reactions, elevations in ALT and AST	Hypersensitivity to the drug or its components; eCrCl < 30ml/min ALT ≥5 times the ULN, pregnancy or planned pregnancy, lactation	Limited data. Co-administration with hydroxychloroquine and chloroquine [*when used for non-COVID infection indications*] may reduce antiviral activity of Remdesivir. Co-administration with Rifamycins and St. John's Wort is not advised
Dexameth-asone	Hyperglycemia; insomnia, psychosis, euphoria, mood swings; nausea, vomiting, anorexia, gastric irritation	Avascular necrosis	Absolute: hypersensitivity to the drug or its components Relative: pre-existing psychiatric conditions, increased risk of GI perforation (e.g., diverticulitis, recent intestinal anastomoses, peptic ulcer disease); systemic fungal infections	A Caspofungin maintenance dose of 70 mg daily is suggested and it may interact with certain antiretrovirals.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Medication	Usual Side Effects	Potential Serious Side Effects	Contra-indications/ Precautions	Drug Interactions
Tocilizumab	Infusion-related reactions (during or within 24 hours): hyper or hypotension, headache, dizziness, rash Nausea, vomiting, diarrhea, abdominal pain, mouth ulceration; Potential for significant; reduction in neutrophil/ platelet count. And/or increases in liver enzymes	Hypersensitivity reactions/anaphylactic reactions (incl death). Increased risk of infection or infection reactivation	Hypersensitivity to the drug; active infections, neutropenia or thrombocytopenia; patients with history of intestinal ulceration or diverticulitis; Pre-existing CNS demyelinating disorders history of opportunistic infection, latent TB	Lower concentrations of drugs metabolized by liver cytochrome enzymes (e.g., cyclosporine, warfarin, phenytoin, simvastatin) may be observed in patients with chronic inflammatory conditions treated with tocilizumab. Significance is unknown in patients treated for COVID-19. Monitor levels/ therapeutic effects.

Medical: Pharmacologic Management Guideline · XVI

April 7, 2021

Appendix C: Infections of concern in the context of treatment with steroids or immunomodulating agents

Secondary infection with fungi, and reactivation of infections, including viral (hepatitis B and herpesviruses), parasitic (*Strongyloides stercoralis*) and tuberculosis (TB), can be seen with the use of steroids.[1] Prescribing physicians should be aware of these risks.

Aspergillus: COVID-19 associated pulmonary aspergillosis has been identified in the literature as a possible complication of infection with SARS-CoV-2.[4–6] Similar to pulmonary aspergillosis associated with influenza,[7] these patients may not have the risk factors, such as immunocompromised state secondary to transplant, that we classically see with invasive fungal infection. Thus, work-up should be considered if clinical suspicion of secondary fungal infection exists.

Hepatitis B (HBV): Consider screening all patients with COVID-19 for hepatitis B, including hepatitis B surface Ag and core antibody. If questions or concerns about active hepatitis B or risk of reactivation of hepatitis B arise, please consider contacting Infectious Diseases.

Herpesviruses (HSV, VZV, CMV): Please monitor high risk patients (ie. solid organ and post-stem cell transplant recipients) for these viral infections. Specifically, for patients at high risk of CMV reactivation, please monitor CMV viral loads by PCR weekly. These tests should be sent off weekly on Tuesday mornings. If a patient is already receiving prophylactic antivirals, please ensure these are continued.

Strongyloides stercoralis: *Strongyloides stercoralis* is a nematode infection acquired through contact with contaminated soil in tropical and subtropical regions worldwide.[2] Although most infections are asymptomatic, patients who receive immunosuppressive therapy including steroids are at risk of hyperinfection or dissemination syndrome.[2] This should be considered for those at epidemiologic risk requiring treatment with dexamethasone for COVID-19.[3] Screening, by strongyloides antibody testing, is available at TOH through the Public Health Lab, however, results often take 10-14 days to become available. Patients with an epidemiologic risk who receive steroids or immunomodulatory therapies should be monitored carefully and if active infection is suspected, work-up should be sent off (stool O&P) and consideration of empiric treatment with ivermectin if appropriate. Please consider consultation with Infectious Diseases.