

Ontario Clinical Practice Guidelines



Antimicrobial and Immunomodulatory Therapy in Patients with COVID-19

Last Updated: April 24, 2020

Important Update Notice

- This is a living document, with the most up-to-date version available at antimicrobialstewardship.com
- Epidemiology, drug availability, and scientific progress are moving rapidly, we recommend returning to this site for the most up to date guidelines rather than downloading the document
- A one-page summary of these guidelines is available [here](#)

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Executive Summary

There is limited clinical evidence to guide antiviral management for ill patients with COVID-19. Using a consensus-based, evidence-informed approach, infectious diseases physicians, pharmacists, and a toxicologist—in consultation with critical-care physicians, pharmacists, ethicists, peers, and patients—make the following recommendations for standardized care.

Recommendation: The Committee recommends that Infectious Diseases consultation (where available) be obtained before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial, and that informed consent be obtained from the patient or substitute decision-maker.

Recommendation: Recommendations are made according to the site of care/severity of illness and prognosis¹, recognizing that site of care may not correlate with severity of illness.

Severity of COVID-19 Illness for Clinical Practice Guidelines

Critically Ill patients (hospitalized, ICU-based; estimated mortality 48-67%)¹:

- Patients normally managed in an **intensive care unit or step-down/step-up unit**, requiring ventilatory and/or circulatory support, including extracorporeal membrane oxygenation (ECMO). Patients requiring oxygen by high-flow nasal cannula (HFNC) (may be used), non-invasive ventilation (less likely to be used), or higher concentrations of oxygen by mask (e.g. $\geq 40\%$ or $\geq 50\%$, depending on the hospital) are also included in this category.

Moderately Ill patients (hospitalized, ward-based, estimated mortality <5%):

- Patients normally managed on a **hospital medical/general ward**. This could include low-flow supplemental oxygen (e.g. 1-6 L/min via nasal prongs).

Mildly Ill patients (ambulatory, outpatient; estimated mortality <1%):

- Patients normally managed **outside of hospital**, and do not require supplemental oxygen, intravenous fluids, or other physiologic support. Patients hospitalized for reasons other than for medical/nursing support are included in this category.

¹ For the critical care management of these patients, please see Management Principles of Adult Critically Ill COVID-19 Patients created by the Interdepartmental Division of Critical Care Medicine at the University of Toronto (which can be accessed at <https://www.criticalcare.utoronto.ca/> or <https://icu-pandemic.org/>).

Recommendations for Anti-COVID-19 Therapies

Investigational Anti-COVID-19 Therapies

Recommendation: Investigational anti-COVID-19 therapeutics (i.e. antiviral and/or immunomodulatory agents) should be used only in approved, randomized, controlled trials.

Recommendation: Infectious Diseases consultation (where available) be obtained before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial, and that informed consent be obtained from the patient or substitute decision-maker.

Antiviral Therapy

Remdesivir

Remdesivir is not recommended for patients with COVID-19 outside of approved clinical trials. *Remdesivir is currently unavailable in Canada*

Lopinavir/Ritonavir

Lopinavir/ritonavir is not recommended for patients with COVID-19 outside of approved clinical trials.

Chloroquine and Hydroxychloroquine

Critically Ill Patients: Chloroquine or hydroxychloroquine is **not recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use.

Mildly and Moderately Ill Patients: Chloroquine or hydroxychloroquine (with or without azithromycin) is **not recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use (e.g. chronic rheumatological conditions).

Antibacterial Therapy

Empiric Antibacterial Therapy

Critically Ill Patients: Empiric therapy with ceftriaxone 1 g IV q24h x 5 days is recommended if there is a **concern for bacterial co-infection**. (Alternative for severe beta-lactam hypersensitivity: levofloxacin 750 mg IV or moxifloxacin 400mg IV q24h x 5 days.)

- Add **azithromycin** 500 mg IV q24h x 5 days to ceftriaxone empiric therapy if *Legionella* infection is suspected. (Azithromycin is not needed if empiric therapy is levofloxacin or moxifloxacin).
- Empiric therapy for bacterial co-infection should be de-escalated on the basis of microbiology results and clinical judgment.
- **Empiric antibiotic treatment for secondary** (e.g. ventilator-associated pneumonia or central line-associated bloodstream infection) should be based on the clinical diagnosis, microbiology results, local antibiograms, risk for drug-resistant organisms and clinical judgment.

Mildly and Moderately Ill Patients: Antibacterial therapy (including azithromycin) is not **routinely recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use.

Immunomodulatory Therapy

Corticosteroids

Corticosteroids should not be offered to patients infected with COVID-19 outside of approved clinical trials unless there are other indications for corticosteroid use (e.g. asthma exacerbation, adrenal insufficiency, obstetrical indications).

Tocilizumab

Critically Ill Patients: Tocilizumab **should not be offered routinely** to patients infected with COVID-19 and ideally offered within approved clinical trials.

- Tocilizumab **may be considered on an individual basis** in patients with cytokine storm (with expert consultation), but known serious drug toxicities may outweigh any potential/unknown benefit.

Mildly and Moderately Ill Patients: Tocilizumab is **not recommended** for patients with COVID-19 outside of approved clinical trials.

Convalescent Plasma

COVID-19 convalescent plasma is not recommended for patients with COVID-19 outside of approved clinical trials. *COVID-19 plasma is currently unavailable in Canada for critically ill patients with COVID-19 and is unavailable outside of clinical trials.*

- The collection, testing, processing, and distribution of plasma in Canada is regulated by Health Canada. Facilities planning to collect plasma for transfusion must register with Health Canada and abide by the [appropriate regulations](#).
- In addition COVID-19 convalescent plasma is an unlicensed product and its use in clinical studies requires a “no objection letter” from Health Canada after submission of [a complete application](#).

Other Therapies

Numerous therapies have been shown to have a theoretical or mechanistic basis to be beneficial in the management of COVID-19. There are no clinical data that support the use of these therapies, including, but not limited to, ivermectin and ascorbic acid (vitamin C) to treat patients with COVID-19.

Other Therapies (Including Ivermectin and Vitamin C)

Other therapies (ivermectin, vitamin C, etc.) are **not recommended** for patients with COVID-19 outside of approved clinical trials.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is a new infectious disease that has resulted in a global pandemic. As with all new infectious diseases, early priorities rest on containment and mitigation, prevention (through vaccine development), and treatment of those affected.

COVID-19 carries a substantial public health burden, with a case fatality rate (CFR) that is estimated to lie between 0.5-8.9, with the best overall estimate being 0.5-1.0% by the University of Oxford's Centre for Evidence-Based Medicine. In 72 314 cases reported by the Chinese Center for Disease Control and Prevention, there were no deaths among those patients not admitted to the ICU. In Canada, from March 17-31, the CFR has hovered between 1.0-1.4%.²

These antimicrobial treatment guidelines were created by infectious disease physicians and pharmacists, a clinical pharmacologist/toxicologist, ethicists, and patient partners across Ontario. Valued input has been provided by critical care physicians, general internists, oncologists, emergency physicians, primary care providers, and pharmacists in its development. Their purpose is to evaluate current evidence, promote standardization of care, and facilitate the provision of best evidence-informed care in a rapidly changing field.

2. Committee Membership

2.1. COVID-19 Antimicrobial Therapy Guideline Standing Committee Members

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² <https://coronavirus.1point3acres.com/en>

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2.3. Standing Committee Member Conflicts of Interest Disclosures

Voting Committee members were required to update any conflicts of interest on an ongoing basis. Conflicts of interest considerations can be found in [Appendix A](#).

3. Methodology

3.1. Committee Membership Selection

- The COVID-19 Antimicrobial Therapy Standards Committee initially included members that were selected by each hospital in the Greater Toronto Area to represent their hospital on the committee. More recently, the Committee includes physicians and pharmacists representing all health regions in Ontario. We also included an academic clinical pharmacologist/toxicologist. Representation was balanced across gender and clinical experience.
- Ethicists, medical and surgical specialists, and a patient representative are consulting non-voting *ad hoc* members.

3.2. Consensus Process

- Committee members were provided with summaries of the clinical evidence. Because it is early in the development of knowledge on COVID-19, there is insufficient evidence available for a proper systematic review. Regardless, all recommendations will carry a summary and grading of the evidence. We did not implement a formal GRADE process.
- Consideration of treatment options could be provided by any member. After initial discussion, and review of the clinical evidence, proposals were made for consensus statements. These statements were then put to online votes using SimpleSurvey. If consensus was not reached, another round of conference calls and votes were performed. This was repeated until consensus was reached, or it was apparent that consensus could not be reached.
- Consensus for this process is a two-thirds ($\frac{2}{3}$) majority. Dissenting opinions were recognized, and included in the discussion of the recommendations. After committee decisions were finalized, these were created as Pre-Reviewed Draft Guidelines for External Review. External review included all relevant stakeholders (e.g. prescribers and pharmacists involved in the care of patients with COVID-19 being discussed). External review was open for 18 hours.
- After external review, the Guidelines Committee reviewed all feedback and considered whether decisions made should remain or be modified. Following this process, the Guidelines were considered complete, pending future review.

3.3. Severity of Illness Classification

Recommendations are made according to the site of care/severity of illness and prognosis³, recognizing that site of care may not correlate with severity of illness, especially as critical care unit capacity may be exceeded:

Critically Ill patients (hospitalized, ICU-based; estimated mortality 48-67%)⁴:

- Patients normally managed in an **intensive care unit or step-down/step-up unit**, requiring ventilatory and/or circulatory support, including extracorporeal membrane oxygenation (ECMO). Patients requiring oxygen by high-flow nasal cannula (HFNC) (may be used), non-invasive ventilation (less likely to be used), or higher concentrations of oxygen by mask (e.g. $\geq 40\%$ or $\geq 50\%$, depending on the hospital) are also included in this category.

Moderately Ill patients (hospitalized, ward-based, estimated mortality <5%):

- Patients normally managed on a **hospital medical/general ward**. This could include low-flow supplemental oxygen (e.g. 1-6 L/min via nasal prongs).

Mildly Ill patients (ambulatory, outpatient; estimated mortality <1%):

- Patients normally managed **outside of hospital**, and do not require supplemental oxygen, intravenous fluids, or other physiologic support. Patients hospitalized for reasons other than for medical/nursing support are included in this category.

Table 1. Severity of Illness Classification

³ Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. DOI: 10.1001/jama.2020.2648

⁴ For the critical care management of these patients, please see Management Principles of Adult Critically Ill COVID-19 Patients created by the Interdepartmental Division of Critical Care Medicine at the University of Toronto (which can be accessed at <https://www.criticalcare.utoronto.ca/> or <https://icu-pandemic.org/>).

4. Recommendations for Anti-COVID-19 Therapies

- For specific recommendations concerning **special populations** refer to **section 5**.
- For information on dosing regimens, relative contraindications, and other pharmacotherapy considerations, refer to the accompanying document:
 - [Dosing and Pharmacologic Considerations for Medications Under Investigation Against COVID-19](#)

4.1. Unproved Investigational Therapies

4.1.1. Recommendations

Recommendation: Investigational anti-COVID-19 therapeutics (i.e. antiviral and/or immunomodulatory agents) should be used only in approved, randomized, controlled trials.

Recommendation: Infectious Diseases consultation (where available) be obtained before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial, and that informed consent be obtained from the patient or substitute decision-maker.

4.1.2. Clinical Evidence Review

Clinical Evidence Review	Not applicable
Evidence Grading	Not applicable
Expert Discussion and Rationale	The Committee recognizes the lack of clinical data presently available to guide COVID-19 treatment. Accordingly, to advance the development of high quality knowledge in this field, priority should be placed on enrolling patients into well-designed clinical trials addressing clinically relevant questions. While investigator-initiated, randomized, blinded clinical trials with peer-reviewed funding represent the gold standard for treatment studies, the group recognized that other designs may provide valuable evidence even if of lower certainty.

4.2. Antiviral Therapy

4.2.1. Remdesivir

- Remdesivir was available through the Special Access Program via Health Canada in partnership with Gilead Sciences but is currently unavailable (including for pregnant women or children less than 18 years of age with confirmed COVID-19 and severe manifestations of the disease.) Changes to remdesivir access may change without notice, and should be checked on the [Health Canada](#) and [Gilead](#) websites.

4.2.1.1. Recommendations

Remdesivir is not recommended for patients with COVID-19 outside of approved clinical trials. *Remdesivir is currently unavailable in Canada*

4.2.1.2. Clinical Evidence Review

No. of clinical studies	1 study
Reference #1	Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. <i>N Engl J Med</i> . 2020. DOI: 10.1056/NEJMoa2007016
Study Design	Observational case-series.
Population	53 out of 61 patients receiving remdesivir through a compassionate use program through the manufacturer, Gilead Sciences. Forty patients (75%) were men, median age was 64 years (interquartile range, 48 to 71). Thirty-four (34 [64%]) were receiving invasive ventilation, including 30 (57%) receiving mechanical ventilation and 4 (8%) receiving extracorporeal membrane oxygenation [ECMO]. Median duration of symptoms before the initiation of remdesivir treatment was 12 days (interquartile range, 9 to 15).
Intervention	10-day course of remdesivir, consisting of a loading dose of 200 mg intravenously on day 1, plus 100 mg daily for the following 9 days. Supportive therapy was to be provided at the discretion of the clinicians.
Primary outcome	None
Secondary Outcomes	None. Authors reported changes in oxygen-support requirements (ambient air, low-flow oxygen, nasal high-flow oxygen, noninvasive positive pressure ventilation [NIPPV], invasive mechanical ventilation, and ECMO), hospital discharge, and proportion of patients with clinical improvement (defined by live discharge from the hospital, a decrease of at least 2 points from baseline on a

	modified ordinal scale (as recommended by the WHO R&D Blueprint Group), or both.
Safety Outcomes/ Balancing Measures	Those leading to discontinuation of treatment, serious adverse events, and death.
Results	During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died.

4.2.1.3. Evidence Summary

Level of Evidence	Not applicable
Evidence Grading	Not applicable
Expert Discussion and Rationale	<p>Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity. It was initially developed for Ebola, but development was halted prior to completion of Phase 3 clinical trial because of vaccine and other therapeutics development. There is <i>in vitro</i> evidence of activity against SARS-CoV-2 (the virus causing COVID-19).</p> <p>Early in the COVID-19 pandemic, remdesivir was available through the Special Access Program (SAP) from Health Canada; 1 of the patients in the case series above was from the GTA. During the development of these guidelines, Gilead, the makers of remdesivir, temporarily withdrew the availability of remdesivir via SAP, and are funding an RCT. The initial sample size was 400, with outcomes of oxygenation and defervescence; they have since amended their protocol, with a revised sample size of 2400 and clinical improvement endpoints.</p> <p>Accordingly, the committee chose not to recommend remdesivir outside of a clinical trial at this time other than the two patient populations for whom it is available: pregnant women and children under age 18. Those interested in further information about compassionate use of remdesivir (currently unavailable in Canada) should contact Gilead Canada or Health Canada.</p>

4.2.2. Lopinavir/ritonavir

4.2.2.1. Recommendations

Lopinavir/ritonavir is not recommended for patients with COVID-19 outside of approved clinical trials.

4.2.2.2. Clinical Evidence Review

No. of clinical studies	1 study
Reference #1	Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir/Ritonavir in Adults Hospitalized with Severe Covid-19. <i>N Engl J Med</i> . 2020. DOI: 10.1056/NEJMoa2001282 .
Study Design	Randomized, controlled, open-label trial
Population	199 patients with oxygen saturation (SaO ₂) ≤ 94% on room air or Pao ₂ /Fio ₂ <300 mmHg. Median age: 58 years, with 60% male. At admission, 0.5% required mechanical ventilation and/or ECMO, and 15.6% required high-flow nasal cannula (HFNC) oxygen or non-invasive ventilation.
Intervention	Patients were randomly assigned in a 1:1 ratio to receive either lopinavir/ritonavir (400 mg/100 mg) bid for 14 days, in addition to standard care, or standard care alone.
Primary outcome	The primary end-point was time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever came first.
Secondary Outcomes	Clinical status (seven-category ordinal scale) on days 7 and 14, 28-day mortality, duration of mechanical ventilation, duration of hospitalization in survivors, and the time (in days) from treatment initiation to death. Virologic measures included the proportions with viral RNA detection over time and viral RNA titre area under-the-curve (AUC) measurements.
Safety Outcomes/ Balancing Measures	Adverse effects, including drug discontinuation.
Results	Treatment with lopinavir/ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs.

25.0%; difference, –5.8 percentage points; 95% CI, –17.3 to 5.7). Percentages of patients with detectable viral RNA at various time points were similar. Lopinavir/ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.

4.2.2.3. Evidence Summary

Level of Evidence	1 RCT of 199 Patients
Evidence Grading	Not applicable
Expert Discussion and Rationale	<p>Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor with <i>in vitro</i> inhibitory activity against SARS-CoV-2; ritonavir, another protease inhibitor, is combined with lopinavir to boost lopinavir levels by inhibiting its metabolism via cytochrome P450 isoform 3A4. Lopinavir was found to have virological activity against the original SARS coronavirus in 2004, but was inadequately studied to establish clinical benefit.</p> <p>This study was stopped at 199 patients for reasons outside of individual trial considerations. The trial was powered for, but failed to show a difference in its primary outcome, time to clinical improvement, and showed no difference in virological clearance. Concerns with this trial include the fact that therapy was not initiated early in the disease course, and critically ill patients were not well represented in this trial (at enrollment, only 16% of patients required oxygen by HFNC, mechanical ventilation or ECMO). Members of the committee believe that there is still potential that lopinavir/ritonavir could prove beneficial, but that the available evidence fails to demonstrate overwhelming benefit in critically ill patients. Members of the committee were also cognizant of the fact that the Canadian CATCO trial, as part of the WHO SOLIDARITY trial, would be examining the role of lopinavir-ritonavir in patients with COVID-19.</p>

4.2.3. Hydroxychloroquine

4.2.3.1. Recommendations

Critically Ill Patients: Chloroquine or hydroxychloroquine is **not recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use.

Mildly and Moderately Ill Patients: Chloroquine or hydroxychloroquine (with or without azithromycin) is **not recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use (e.g. chronic rheumatological conditions).

4.2.3.2. Clinical Evidence Review

No. of clinical studies	Five studies
Reference #1	Gautret P, Lagier J-C, Parola P, et al. (In press) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. <i>International Journal of Antimicrobial Agents</i> 2020. DOI:10.1016/j.ijantimicag.2020.105949 .
Study Design	Prospective microbiological cure trial with unmatched controls.
Population	Hospitalized patients over age 12 with confirmed COVID-19. 42 patients were enrolled (26 to hydroxychloroquine, and 16 to supportive care), but 6 patients enrolled to hydroxychloroquine did not complete therapy, including 3 transferred to the ICU. Only the 20 completing therapy were included in the analysis. 42% male, mean age 45 years. 17% were asymptomatic, 61% had upper respiratory tract symptoms, and 23% had lower respiratory tract symptoms.
Intervention	Hydroxychloroquine 200 mg tid orally x 10 days. Comparator arm was standard care. 6 patients in the hydroxychloroquine arm also received azithromycin.
Primary outcome	Nasopharyngeal viral clearance at day-6 post-inclusion.
Secondary Outcomes	Virological clearance over time during the study period, clinical follow-up (body temperature, respiratory rate, length of stay at hospital and mortality).
Safety Outcomes/ Balancing Measures	Occurrence of side-effects were mentioned but not reported.
Results	At day 6 post-inclusion, 70% of hydroxychloroquine-treated patients demonstrated nasopharyngeal viral clearance compared with 12.5%

	in the control group ($p= 0.001$); because the authors censored 1 cases in the hydroxychloroquine group and 5 in control group, a conservative estimate of effect is 68% vs. 18% ($p= 0.02$). This comparison was unadjusted for baseline characteristics. No clinical outcomes were reported.
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Reference #2	Chen Jun LD, Lie Li, Lie Ping, Xu Qingnian, Xia Lu, Ling Yun, Huang Dan, Song Shuli, Zhang Dandan, Qian Zhiping, Li Tao, Shen Yinzong, Lu Hongzhou. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020;49(1):0-Doi: 10.3785/j.issn.1008-9292.2020.03.03
Study Design	Randomized controlled unblinded study.
Population	Hospitalized patients with confirmed COVID-19 infection. 30 patients were randomized .
Intervention	Hydroxychloroquine 400 mg daily x 5 days with standard care. Comparator arm was standard care. Standard care included inhaled alpha-interferon, arbidol (an inhibitor of virus-mediated fusion with target membrane and a resulting block of virus entry into target cells), with or without lopinavir/ritonavir.
Primary outcome	Virological clearance at day 7 post-inclusion.
Secondary Outcomes	Median time to normothermia, CT radiographic progression
Safety Outcomes/ Balancing Measures	Diarrhea and LFTs.
Results	At day 7 post-inclusion, 86.7% of hydroxychloroquine-treated patients were virologically cured compared with 93.3% in the control group ($p>.05$). Median duration from hospitalization to viral nucleic acid clearance was 4 days in the hydroxychloroquine group, 2 days in the control group 2 ($P>0.05$). The median time for body temperature normalization in the hydroxychloroquine group and control group was 1 day after hospitalization. Radiological progression was shown on CT images in 5 cases (33.3%) in the hydroxychloroquine group and 7 cases (46.7%) of the control group. Four cases (26.7%) in the hydroxychloroquine group and 3 cases (20%) in the control group had transient diarrhea and abnormal liver function ($P>0.05$)

Reference #3	Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. 2020:2020.03.22.20040758 .
Study Design	Randomized controlled unblinded study.
Population	62 adults with laboratory-confirmed COVID-19 (RT-PCR), chest CT demonstrating pneumonia, and SaO ₂ /SPO ₂ ratio > 93% or PaO ₂ /FiO ₂ ratio > 300mmHg. Exclusions: Severe and critical illness patients, retinopathy and other retinal diseases, conduction block and other arrhythmias, severe liver disease, pregnant or breastfeeding, severe renal failure, or received any trial treatment for COVID-19 within 30 days before trial.
Intervention	Hydroxychloroquine 200 mg bid x 5 days compared with standard care. Standard care included oxygen therapy, antiviral agents, antibacterial agents, and immunoglobulin, with or without corticosteroids.
Primary outcome	Primary outcome was not specified. Time to clinical recovery (normothermia + relief of cough), clinical characteristics, and radiographic characteristics were identified as endpoints.
Secondary Outcomes	None specified.
Safety Outcomes/ Balancing Measures	None specified.
Results	Compared temperature recovery time 2.2 days in hydroxychloroquine group vs. 3.2 days in control group. For cough, 15 patients in the control group and 22 patients in the hydroxychloroquine treatment group had a cough at day 0.

Reference #4	Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. 2020. medrxiv.org 10.1101/2020.04.10.20060558v1
Study Design	Multicentre randomized controlled unblinded study.
Population	150 adults with laboratory-confirmed COVID-19 (RT-PCR), stratified by severity (mild/mod/severe) in 16 centers across 3 provinces in China.

	Exclusions: Allergy to hydroxychloroquine or existing conditions that could lead to severe adverse events (e.g. severe liver or renal diseases that could impair the ability to metabolize high doses of hydroxychloroquine), pregnancy or lactation.
Intervention	Hydroxychloroquine 1200 mg PO loading dose x 3 days, followed by 800 mg daily x 2 weeks (mild/moderate) or 3 weeks (severe) compared with standard care (SOC). Standard care not described.
Primary outcome	Negative conversion of SARS-CoV-2 RT-PCR by day 28
Secondary Outcomes	<p>Alleviation of <i>clinical symptoms</i> (defervescence, normalization of SpO₂ (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production and shortness of breath), <i>laboratory parameters</i> (CRP, ESR, IL-6 and TNF-α level), and <i>chest radiology</i> by day 28.</p> <p>For severe cases: all-cause mortality, clinical status as assessed with the six-category ordinal scale (on days 7, 14, 21 and 28), days of mechanical ventilation, ECMO, supplemental oxygenation, and hospital stay</p>
Safety Outcomes/ Balancing Measures	Mentioned but not specified.
Results	<p>28-day RT-PCR negative conversion rate was not different between hydroxychloroquine+SOC vs SOC group (Kaplan-Meier estimates 85.4% versus 81.3%, P=0.341). No difference in the 28-day symptom alleviation rate was observed between the two groups.</p> <p>Adverse events were found in 30% hydroxychloroquine+SOC group (with 2 serious events) vs 8.8% SOC. The most common adverse event in the hydroxychloroquine recipients was diarrhea (10%).</p> <p>Study was stopped early because median time to alleviation of symptoms was favourable in the hydroxychloroquine+SOC group (19 days) vs SOC group.</p>

Reference #5	<p>Borba MGS, Val FdA, Sampaio VS, Alexandre MAA, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial. 2020. medrxiv.org/10.1101/2020.04.07.20056424v2</p>
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Study Design	Parallel, double-blinded, randomized trial to assess safety/efficacy of 2 doses of chloroquine.
Population	Hospitalized adults with respiratory rate >24 rpm, and/or heart rate >125 bpm, and/or peripheral oxygen saturation <90% in ambient air, and/or shock (defined as mean arterial pressure <65 mmHg, with the need for vasopressor medicines or oliguria or a lower level of consciousness) were included in Manaus, Brazilian Amazon. Out of a pre-defined 440 patients sample size, 81 patients were enrolled before discontinuation due to safety.
Intervention	High dose chloroquine (600 mg bid x 10 days) or low dose chloroquine (450 mg bid x 1 day, then 450mg daily). All patients received ceftriaxone + azithromycin.
Primary outcome	28-day mortality.
Secondary Outcomes	Mortality on day 13, participant's clinical status, laboratorial exams, and ECG on days 13 and 28, daily clinical status during hospitalization, duration of mechanical ventilation (if applicable) and supplementary oxygen (if applicable), and the time (in days) from treatment initiation to death.
Safety Outcomes/ Balancing Measures	None specified.
Results	The high dose chloroquine arm presented more QTc>500ms (25%), and a trend toward higher lethality (17%) than the lower dosage. Fatality rate was 13.5% (95%CI=6.9-23.0%), overlapping with the CI of historical data from similar patients not using chloroquine (95%CI=14.5-19.2%) Two patients in the high dosage chloroquine arm evolved with ventricular tachycardia before death.

4.2.3.3. Evidence Summary

Level of Evidence	4 RCTs and 1 controlled observational study, with microbiological primary outcomes.
Evidence Grading	Not applicable
Expert Discussion and Rationale	<p>Chloroquine and hydroxychloroquine are antimalarial drugs with <i>in vitro</i> activity against SARS-CoV-2.</p> <p>Early reports from China have suggested that chloroquine may be effective against COVID-19, including a summary statement that “results from more than 100 patients have demonstrated that</p>

chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course according to the news briefing.”⁵ This statement/evidence led to chloroquine being included in COVID-19 treatment guidelines issued by the National Health Commission of the People's Republic of China. However, the primary data leading to this recommendation are not yet available.

The study by Gautret et al., coupled with the above information, have led to consideration that hydroxychloroquine be adopted as therapy for COVID-19. The Committee had consensus (over 90% agreement) that hydroxychloroquine should not be recommended outside of clinical trials. (This is an update from an initial recommendation where consensus could not be reached, when even less data was available.)

For ward patients, using the same evidence used for considering hydroxychloroquine in critically ill patients, there was consensus that hydroxychloroquine should not be recommended: It was acknowledged by some members of the Committee that some patients/advocates may request that health care providers offer treatment with hydroxychloroquine.

⁵ (Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends*. 2020;14:72-3.)

4.3. Antibacterial Therapy

4.3.1. Empiric Antibiotic Therapy

4.3.1.1. Recommendations

Critically Ill Patients: Empiric therapy with ceftriaxone 1g IV q24h x 5 days is recommended if there is a **concern for bacterial co-infection**. (Alternative for severe beta-lactam hypersensitivity: levofloxacin 750 mg IV or moxifloxacin 400mg IV q24h x 5 days.)

- Add **azithromycin** 500 mg IV q24h x 5 days to ceftriaxone empiric therapy if *Legionella* infection is suspected. (Azithromycin is not needed if empiric therapy is levofloxacin or moxifloxacin).
- Empiric therapy for bacterial co-infection should be de-escalated on the basis of microbiology results and clinical judgment.
- **Empiric antibiotic treatment for secondary infections** (e.g. ventilator-associated pneumonia or central line-associated bloodstream infection) should be based on the clinical diagnosis, local antibiograms and risk for drug-resistant organisms, microbiology results, and clinical judgment.

Mildly and Moderately Ill Patients: Antibacterial therapy (including azithromycin) is **not routinely recommended** for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use.

4.3.1.2. Clinical Evidence Review

No. of clinical studies	0
Reference	See Gautret P, Lagier J-C, Parola P, et al. (refer to Section 4.2.3.2 Clinical Evidence Review, Reference #1) for a brief discussion of azithromycin

4.3.1.3. Evidence Summary

Level of Evidence	Not applicable
Evidence Grading	Not applicable
Expert Discussion and Rationale	The evidence supporting azithromycin--mostly to be included in combination with hydroxychloroquine--comes from the single paper by Gautret et al., whereby 6 patients were given azithromycin (500 mg on day 1 followed by 250 mg per day, the next four days) to

prevent bacterial super-infection, and demonstrated improved virological clearance. The Committee believed that this level of data was unacceptable to support a recommendation for use and would create a drug shortage for conditions for which there is clear evidence of benefit.

The Committee could not identify any clinical trials guiding empiric antibacterial therapy for patients with COVID-19. Bacterial co-infection appears to be uncommon in COVID-19, involving approximately 10% of patients.⁶ Radiographic findings in COVID-19 infection include bilateral (75%) or unilateral (25%) and/or ground-glass opacity (14%), seen on CT scan in almost all patients.⁷ Patients with secondary, drug-resistant nosocomial infections following hospitalization were more common.⁸

Recognizing that invasive lung sampling (i.e. via bronchoscopy) will rarely be performed in these patients, and bacterial co-infection would be difficult to rule out in those with clinical and radiographic evidence of pneumonia, there was consensus that critically ill patients should be treated with a short (5-day) course of ceftriaxone 1g IV q24h (unless severe beta-lactam hypersensitivity, when a respiratory fluoroquinolone would be a reasonable alternative, such as levofloxacin 750 mg IV q24h or moxifloxacin 400 mg IV q24h). Similarly, there was consensus that moderately ill patients with COVID-19 should not be prescribed antibacterials unless there was strong clinical suspicion of bacterial pneumonia.

⁶ Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395: 497-506. DOI: [10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)

4.4. Immunomodulatory/Immunosuppressive Therapy

4.4.1. Corticosteroids

4.4.1.1. Recommendations

Corticosteroids should not be offered to patients infected with COVID-19 outside of approved clinical trials unless there are other indications for corticosteroid use (e.g. asthma exacerbation, adrenal insufficiency, obstetrical indications).

4.4.1.2. Clinical Evidence Review

No. of clinical studies	0
Level of Evidence	Not applicable
Evidence Grading	Not applicable
Expert Discussion and Rationale	There is no reliable clinical data informing the management of COVID-19 infection with corticosteroids, regardless of severity. A recent review demonstrates that there is no strong evidence suggesting benefit from corticosteroids in coronavirus infections, and the signal points to potential harm. ⁷

4.4.2. Tocilizumab

4.4.2.1. Recommendations

Critically Ill Patients: Tocilizumab **should not be offered routinely** to patients infected with COVID-19 and ideally offered within approved clinical trials.

- Tocilizumab **may be considered on an individual basis** in patients with cytokine storm (with expert consultation), but known serious drug toxicities may outweigh any potential/unknown benefit.

Mildly and Moderately Ill Patients: Tocilizumab is **not recommended** for patients with COVID-19 outside of approved clinical trials.

⁷Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*. [2020;395:473-5](#)

4.4.2.2. Clinical Evidence Review

No. of clinical studies	1 study
Reference #1	Xiaoling Xu, Mingfeng Han, Tiantian Li et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. 2020. chinaXiv:202003.00026v1 (Pre-print)
Study Design	Retrospective case series.
Population	21 patients – 17 categorized as severe COVID-19 (any of respiratory rate ≥ 30 breaths/min; $SpO_2 \leq 93\%$ while breathing room air; $PaO_2/FiO_2 \leq 300$ mmHg) and 4 categorized as <i>critical</i> COVID-19 (any of respiratory failure which requiring mechanical ventilation; shock; combined with other organ failure, need to be admitted to ICU).
Intervention	All patients received a single dose of tocilizumab 400 mg IV in addition to the existing standard of care (lopinavir/ritonavir, methylprednisolone, symptomatic relief).
Primary outcome	Not specified.
Secondary Outcomes	Not specified.
Safety Outcomes & Balancing Measures	None specified.
Results	Authors reported that 19/21 patients had been discharged at time of publication, with no deaths reported.

4.4.2.3 Evidence Summary

Level of Evidence	1 case series of 20 patients
Evidence Grading	Not applicable
Expert Discussion and Rationale	<p>Tocilizumab is a humanized interleukin-6 (IL-6) receptor antagonist approved for the second-line treatment of adult patients with moderate to severe active rheumatoid arthritis (RA), other rheumatologic diseases, and cancer patients with CAR (chimeric antigen receptor) T cell-induced cytokine release syndrome (CRS).</p> <p>Genentech (a subsidiary of the Roche Group) recently announced that they are launching a Phase III trial of tocilizumab in hospitalized patients with severe COVID-19 pneumonia in 330 patients globally.</p>

The Committee felt that tocilizumab's evidence is insufficient to make a recommendation for routine use, but felt that consideration could be given in critically ill patients with evidence of cytokine storm, best recognized by elevated IL-6 levels. Because IL-6 is not universally available, hyperferritinemia was believed to be a reasonable surrogate for IL-6. Serious known complications of tocilizumab include serious drug induced liver injury (DILI) ([Health Canada Safety Alert](#)), gastrointestinal perforation, hypersensitivity reactions, and increased risk of invasive infection such as tuberculosis ([FDA Risk Evaluation and Mitigation Strategy \(REMS\)](#)).

4.4.3. Convalescent Plasma

4.4.3.1. Recommendations

COVID-19 convalescent plasma is not recommended for patients with COVID-19 outside of approved clinical trials. *COVID-19 plasma is currently unavailable in Canada for critically ill patients with COVID-19 and is unavailable outside of clinical trials.*

- The collection, testing, processing, and distribution of plasma in Canada is regulated by Health Canada. Facilities planning to collect plasma for transfusion must register with Health Canada and abide by the [appropriate regulations](#).
- In addition COVID-19 convalescent plasma is an unlicensed product and its use in clinical studies requires a “no objection letter” from Health Canada after submission of a [complete application](#).

4.4.3.2. Clinical Evidence Review

- The only available evidence is a case series of 5 critically ill, mechanically ventilated patients. (Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020. [doi:10.1001/jama.2020.4783](https://doi.org/10.1001/jama.2020.4783)). Patients received transfusion with convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19.
- There is limited data supporting the effectiveness of convalescent plasma therapy in acute coronavirus infections, such as SARS and MERS.

4.4.3.3. Clinical Evidence Summary

- There was consensus that there is insufficient evidence to support a recommendation to use convalescent plasma therapy for COVID-19 in any setting.
- The Committee was informed that Health Canada will not approve convalescent plasma therapy outside of any clinical trials, and that the available clinical trials do not presently include patients in the critical care setting.
- The Committee was also informed that legal statutes prevent the collection of convalescent plasma outside of the supervision of Canadian Blood Services.

4.5. Other Therapies

4.5.1. Other Therapies (Including Ivermectin and Vitamin C)

4.5.1.1. Recommendations

Other therapies (ivermectin, vitamin C, etc.) are **not recommended** for patients with COVID-19 outside of approved clinical trials.

- Numerous therapies have been shown to have a theoretical or mechanistic basis to be beneficial in the management of COVID-19. There are no clinical data that support the use of these therapies, including, but not limited to, ivermectin and ascorbic acid (vitamin C) to treat patients with COVID-19.

5. Special Populations

5.1. Pediatrics (Under 18 years of age)

5.1.2. Recommendations

Recommendation: Investigational anti-COVID-19 therapeutics (i.e. antiviral and/or immunomodulatory agents) are not recommended for pediatric patients with COVID-19 who do not require hospital care.

Recommendation: Investigational anti-COVID-19 therapeutics (i.e. antiviral and/or immunomodulatory agents) are not routinely recommended for hospitalized pediatric patients with COVID-19 outside of approved clinical trials.

- The use of investigational treatments for children with COVID-19 should ideally occur within the context of controlled clinical trials. It is recognized by the consensus group, however, that opportunities to enroll children into clinical trials is limited.
- Due to this limitation and other notable differences in the pediatric population, for hospitalized children not enrolled in clinical trials, use of investigational therapies may be considered on a case-by-case basis with caution.
- Infectious Diseases consultation should be obtained before any investigational antiviral treatment is offered to a pediatric patient outside of a clinical trial. Input from other services such as Rheumatology, Haematology and Immunology should also be sought if immune modulatory treatments are being considered. Informed consent should be obtained from the patient or substitute decision-maker.
- Consideration should include evaluation of severity of illness, availability of investigational treatments for children, side effect profile, drug interactions and family preferences.
- For the vast majority of pediatric patients with COVID-19 the course is mild and self-limited. Serious illness, ICU admission, and death, however have been reported and further understanding of severe COVID-19 in children is limited.
- If further guidance with the management of a child with COVID-19 is required, please page Infectious Diseases through locating at the Hospital for Sick Children (416-813-6621). For critically ill patients, please contact the pediatric ICU through CritiCall (1-800-668-4357).

5.2. Pregnancy

5.2.1. Recommendations

Recommendation: There is a paucity of evidence guiding the medical management of pregnant patients with COVID-19. Recommendations for anti-COVID-19 therapy are generally no different for pregnant patients compared with non-pregnant patients.

- The Committee noted that remdesivir (currently unavailable in Canada) is available in some other countries as an exceptional access product for pregnant women and children.
- The Committee also noted that initiation of antepartum corticosteroids for fetal maturation could be considered (as per current guidelines if preterm delivery is indicated or anticipated based on maternal condition).

5.3. HIV

5.3.1. Recommendations

Recommendation: There is a paucity of evidence to guide the medical management of patients with HIV and COVID-19 co-infection. The presence of HIV in patients with COVID-19 should not influence management of COVID-19 antiviral therapy.

Recommendation: A pharmacist or HIV specialist should be consulted when new medications are being considered for patients receiving antiretroviral therapy for HIV infection.

Recommendation: Antiretroviral therapy for HIV infection should not be initiated in the setting of acute COVID-19 outside of a clinical trial.

- The Committee noted that antiretroviral therapy has the potential for significant drug-drug interactions with investigational anti-COVID-19 therapies.
 - For more information about drug interactions and other pharmacologic considerations, refer to the accompanying [Dosing and Pharmacologic Considerations for Medications Under Investigation Against COVID-19](#).

5.4. Cancer - Solid Tumors, Lymphoma, Leukemia (and related)

5.4.1. Recommendations

Recommendation: For patients undergoing medical treatment for cancer, careful attention for drug-drug interactions is required if antiviral therapy is being considered.

- There is limited experience of managing patients with solid tumours, lymphoma, or leukemia, and who are infected with COVID-19. The Committee had consensus that there are generally no unique differences in antimicrobial or immunomodulatory recommendations for patients with cancer.
- The Committee did want to highlight that some chemotherapy regimens have significant drug interactions with medications being considered in treatment of COVID-19. Potential for interactions should always be investigated prior to prescribing medications.

5.5. Transplantation

5.5.1. Recommendations - Solid Organ Transplantation

Recommendation: For solid organ transplant recipients with COVID-19, investigational anti-COVID-19 therapeutics (i.e. antiviral and/or immunomodulatory agents) are not routinely recommended outside of approved clinical trials.

Recommendation: For solid organ transplant recipients moderately or critically ill with COVID-19, empiric therapy for suspected bacterial infection is recommended. Empiric therapy should use Clinical Practice Guidelines for Solid Organ Transplantation.

Recommendation: For solid organ transplant recipients with COVID-19, immunosuppression and cell-cycle inhibitors should not be reduced.

Recommendation: For solid organ transplant recipients receiving chronic corticosteroids and with moderate or severe COVID-19, stress-dose corticosteroids should be used if applicable.

- There is limited evidence regarding solid organ transplant recipients with COVID-19. The Committee--supported by *Ad Hoc* members with expertise in solid organ transplantation--find no evidence to make specific therapeutic recommendations separate from the general population.
- Committee members noted that care of these patients requires expert care or input. Considerations that differ from the routine care of patients with COVID-19 include considerations of immunosuppression and immunomodulation. The Committee consensus was patients should not have any changes to immunotherapy, but should receive stress doses of steroids if moderately or critically ill with COVID-19. Solid organ transplant recipients on chronic corticosteroids--because of inhibition of their adrenal axis--should receive stress doses of corticosteroids if moderately or critically ill.
- Solid organ transplant recipients also require special considerations because of drug-drug interactions. Accordingly, lopinavir-ritonavir (a strong CYP3A4 inhibitor) should generally be avoided because of potential drug-drug interactions.

Appendix A. Conflicts of Interest

No conflicts of interest have been declared by any Committee members. An updated list is kept on file.

Appendix B. Summary of Revisions

The table below provides a summary of revisions with each guideline update.

Revision Date	Summary of Revisions
April 24, 2020	<ul style="list-style-type: none"> • Recommendations for special populations added (section 5) • Recommendations for COVID-19 convalescent plasma therapy added (4.4.3) • Recommendations for “Other Therapies” (ivermectin, vitamin C) added (4.5) • Recommendation on use of hydroxychloroquine in critically ill patients revised (previous recommendation “due to lack of consensus, no recommendations can be made on the use of chloroquine or hydroxychloroquine for patients with COVID-19 outside of approval clinical trials or where other indications would justify its use”)

Appendix C. Pharmacological Considerations

For information on dosing regimens, relative contraindications, and other pharmacotherapy considerations for medications under investigation against COVID-19, refer to the accompanying document: [Dosing and Pharmacologic Considerations for Medications Under Investigation Against COVID-19](#).