Ontario COVID-19 Clinical Practice Guideline

Important Update Notice Last Updated: **June 29, 2020**

- 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 prognosis[1], 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. ≥40% or ≥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

Critically Ill Patients: Remdesivir is not routinely recommended for patients who are critically ill. The benefit in this group remains uncertain and enrolment in approved clinical trials is encouraged. Remdesivir **can be considered for use** if it is available and clinical trials are unavailable.

Moderately Ill Patients: Remdesivir is recommended for patients who are moderately ill with COVID-19 if it is available.

Mildly Ill: Remdesivir is not recommended for patients who are mildly ill with COVID-19.

- Remdesivir is not licensed for use in Canada, and is currently unavailable to most patients in Canada.
- This recommendation is based on the best available data and may change as additional evidence becomes available.

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 - Dexamethasone

Critically Ill Patients: Dexamethasone 6 mg daily po/iv for 10 days (or until discharge if sooner) is recommended for patients who are critically ill with suspected or confirmed COVID-19.

Moderately Ill Patients: Dexamethasone 6 mg daily po/iv for 10 days (or until discharge if sooner) is recommended for patients who are moderately ill with suspected or confirmed COVID-19.

Mildly Ill: Dexamethasone is **not recommended** for patients who are mildly ill with suspected or confirmed COVID-19.

- In pregnant or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.
- In the RECOVERY trial it was permitted to switch between the two routes of administration according to clinical circumstances.
- Other corticosteroids should not be offered to patients with COVID-19 outside of approved clinical trials unless there are other indications for corticosteroid use (e.g. asthma exacerbation, adrenal insufficiency, obstetrical indications).
- This recommendation is based on the best available data and may change as additional evidence becomes available.

Tocilizumab

Critically Ill Patients: Tocilizumab should not be offered routinely to patients 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.

Interferon (with or without combination of lopinavir ritonavir and ribavirin)

Interferon beta-1b 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

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.

- 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.

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

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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 (⅔) 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 prognosis[3], 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. ≥40% or ≥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

4.2.1.1. Recommendations

Critically Ill Patients: Remdesivir is **not routinely recommended** for patients who are critically ill because of uncertainty, and enrolment in approved clinical trials is encouraged. Remdesivir **can be considered for use** if it is available, where clinical trials are unavailable.

Moderately Ill Patients: Remdesivir is **recommended** for patients who are moderately ill with COVID-19 if it is available.

Mildly Ill: Remdesivir is **not recommended** for patients who are mildly ill with COVID-19.

- Remdesivir is currently not licensed for use in Canada and is unavailable for most patients. According to Gilead, William Osler Health Sciences and The Ottawa Hospital are registered to access remdesivir through registration in an open label clinical trial (no longer enrolling additional sites). Access to remdesivir may change without notice, and should be checked on the Health Canada and Gilead websites.
- This recommendation is based on the best available data and may change as additional evidence becomes available.

4.2.1.2. Clinical Evidence Review

No. of clinical studies	Two studies
Reference #1	Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020;395(10236):1569-78. DOI: 10.1016/s0140-6736(20)31022-9
Study Design	Randomized, double-blind, placebo-controlled, multicentre in 10 hospitals in China
Population	Adults admitted to hospital with confirmed SARS-CoV-2 infection, less than 12 days from symptom onset, with SaO2≤94% on room air or PaO2:FiO2≤300mmHg, and radiographic pneumonia. 237 patients enrolled with 2:1 treatment:standard care randomization.
Intervention	Patients were randomly assigned to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids.

Primary outcome	Time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. Primary analysis was done in the intention-to-treat (ITT) population and safety analysis was done in all patients who started their assigned treatment.
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	Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]).

Reference #2	Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med. 2020. DOI: 10.1056/NEJMoa2007764
Study Design	Randomized, double-blind, placebo-controlled, multicentre in 60 sites in 10 countries (with 45 sites in US).
Population	Adults admitted to hospital with confirmed SARS-CoV-2 infection, less than 12 days from symptom onset, with SaO2≤94% on room air or requiring supplemental O2/mechanical ventilation/ECMO and/or radiographic pneumonia. 1063 patients enrolled with 1:1 treatment:standard care randomization.
Intervention	Patients were randomly assigned to intravenous remdesivir (200 mg on day 1 followed by 100 mg daily for up to 10 days in single daily infusions) or the same volume of placebo infusions for up to 10 days. Patients were permitted concomitant use of medications according to institutional guidelines.
Primary outcome	Time to recovery (i.e. discharge or only in hospital for infection control purposes, categories 1-3 on 8-point ordinal scale). Primary

	analysis was done in the ITT population using a log-rank, stratified by disease severity
Secondary Outcomes	Secondary outcomes: 14- and 28-day mortality after enrolment.
Safety Outcomes/ Balancing Measures	Grade 3 and 4 adverse events
Results	Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04).

4.2.1.3. Evidence Summary

Level of Evidence	Low
Evidence Grading	Not applicable
Expert Discussion and Rationale	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 *in vitro* evidence of activity against SARS-CoV-2 (the virus causing COVID-19). 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. Remdesivir is currently unavailable in Canada, though it is available in the United States. The Committee discussed remdesivir at length. There was consensus that it should be offered to moderately ill patients with COVID-19 if the drug were to become available in Canada. Concerns were expressed regarding uncertainty of cost, and therefore cost-effectiveness. Additionally, there was a high degree of uncertainty regarding its role in critically ill patients with COVID-19. The Beigel et al. trial suggested no benefit, but Committee members acknowledged the

	uncertainty around the trial estimates, as well as the lack of a harm signal in the existing RCTs. Accordingly, the Committee could not recommend remdesivir in critically ill patients, but also noted that prescribing it when clinical trials are unavailable is reasonable.

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	One 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. *N Engl J Med*. 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 Pao2/Fio2 <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	Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor with *in vitro* 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. 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.

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	Six 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. *International Journal of Antimicrobial Agents* 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.

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 Yinzhong, 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 SaO2/SPO2 ratio > 93% or PaO_2/FiO_2 ratio > 300mHg. 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	Alleviation of *clinical symptoms* (defervescence, normalization of SpO_2 (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production and shortness of breath), *laboratory parameters* (CRP, ESR, IL-6 and TNF-α level), and *chest radiology* by day 28. 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
Safety Outcomes/ Balancing Measures	Mentioned but not specified.
Results	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. 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%). Study was stopped early because median time to alleviation of symptoms was favourable in the hydroxychloroquine+SOC group (19 days) vs SOC group.

Reference #5	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
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.

Reference #6	Horby B, Landry P. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020.
Study Design	Randomized, controlled, open-label, adaptive platform trial

Population	Hospitalized patients were eligible for the trial if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. Initially, recruitment was limited to patients aged at least 18 years but the age limit was removed from 9 May 2020.
Intervention	Hydroxychloroquine 800 mg po once, 800 mg 6 hours later, then 400 mg q12h for 9 days vs usual care.
Primary outcome	28-day mortality
Secondary Outcomes	Duration of hospital stay; the need for (and duration of) ventilation; and, among patients not on ventilation at baseline, the composite endpoint of death or need for mechanical ventilation or ECMO.
Safety Outcomes/ Balancing Measures	None specified.
Results	A total of 1542 patients were randomised to hydroxychloroquine and compared with 3132 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98-1.26]; p=0.10). There was also no evidence of beneficial effects on hospital stay duration or other outcomes.

4.2.3.3. Evidence Summary

Level of Evidence	Five RCTs and one controlled observational study, with microbiological primary outcomes.
Evidence Grading	Not applicable
Expert Discussion and Rationale	Chloroquine and hydroxychloroquine are antimalarial drugs with *in vitro* activity against SARS-CoV-2. 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 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. As of June 22, 2020, World Health Organization (WHO), generic hydroxychloroquine (HCQ) maker Novartis and the U.S. National Institutes of Health (NIH) have ended recruitment for their COVID-19 hydroxychloroquine studies in hospitalized patients citing lack of benefits for patients and enrollment challenges. On June 15, 2020, the US FDA revoked the emergency use authorization of HCQ and CQ to treat COVID-19 based on results from the RECOVERY trial showing no mortality benefit or improving recovery. The full results of the RECOVERY trial have been submitted, but not yet published, in a peer-reviewed journal.

[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

4.4. Immunomodulatory/Immunosuppressive Therapy

4.4.1. Corticosteroids - Dexamethasone

4.4.1.1. Recommendations

Critically Ill Patients: Dexamethasone 6 mg daily po/iv for 10 days (or until discharge if sooner) is recommended for patients who are critically ill with suspected or confirmed COVID-19.

Moderately Ill Patients: Dexamethasone 6 mg daily po/iv for 10 days (or until discharge if sooner) is recommended for patients who are moderately ill with suspected or confirmed COVID-19.

Mildly Ill: Dexamethasone is not recommended for patients who are mildly ill with suspected or confirmed COVID-19.

- In pregnant or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.
- In the RECOVERY trial it was permitted to switch between the two routes of administration according to clinical circumstances.
- Other corticosteroids should not be offered to patients with COVID-19 outside of approved clinical trials unless there are other indications for corticosteroid use (e.g. asthma exacerbation, adrenal insufficiency, obstetrical indications).
- This recommendation is based on the best available data and may change as additional evidence becomes available.

4.4.1.2. Clinical Evidence Review

No. of clinical studies	One study
Reference #1	Horby, P., Lim, W. S., Emberson, J., Mafham, M., Bell, J., … Linsell, L. (2020). Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. *medRxiv*, 2020.06.22.20137273. DOI:10.1101/2020.06.22.20137273
Study Design	Randomized, controlled, open-label, adaptive platform trial
Population	Hospitalized patients were eligible for the trial if they had clinically suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. Initially, recruitment was limited to patients aged at least 18 years but

	the age limit was removed from 9 May 2020. Pregnant or breast-feeding women were eligible.
Intervention	Usual standard of care plus dexamethasone 6 mg once daily (oral or intravenous) for up to 10 days (or until discharge if sooner). In pregnancy or breastfeeding women, prednisolone 40 mg administered by mouth (or intravenous hydrocortisone 80 mg twice daily) was used instead of dexamethasone. In the RECOVERY trial it was permitted to switch between the two routes of administration according to clinical circumstances.
Primary outcome	All-cause mortality within 28 days of randomization.
Secondary Outcomes	Secondary outcomes were time to discharge from hospital, and among patients not receiving invasive mechanical ventilation at randomization, subsequent receipt of invasive mechanical ventilation (including extra-corporeal membrane oxygenation) or death. Subsidiary clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subset), and receipt and duration of ventilation.
Safety Outcomes & Balancing Measures	None specified.
Results	Significantly fewer patients allocated to dexamethasone met the primary outcome of 28-day mortality than in the usual care group (454 of 2104 patients [21.6%] allocated dexamethasone vs. 1065 of 4321 patients [24.6%] allocated usual care; rate ratio, 0.83; 95% confidence interval [CI], 0.74 to 0.92; P<0.001). There was a significant trend showing the greatest absolute and proportional benefit among those patients receiving invasive mechanical ventilation at randomization (test for trend p<0.001) Dexamethasone reduced 28-day mortality by 35% in patients receiving invasive mechanical ventilation (rate ratio 0.65 [95% CI 0.51 to 0.82]; p<0.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (rate ratio 0.80 [95% CI 0.70 to 0.92]; p=0.002). No evidence of benefit among those patients who were not receiving respiratory support (rate ratio 1.22 [95% CI 0.93 to 1.61]; p=0.14). Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care, and a lower chance of progressing to invasive mechanical ventilation in those receiving oxygen at baseline.

	Preliminary analyses indicate no excess risk of any particular cause of death (in particular there was no excess of deaths due to non-COVID infection).

4.4.1.3. Evidence Summary

Level of Evidence	Not applicable
Evidence Grading	Not applicable
Expert Discussion and Rationale	Prior to the RECOVERY trial (unpublished data, release online) there were 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. The RECOVERY trial indicates a survival benefit for moderately and severely ill patients with COVID-19 receiving dexamethasone. These results are promising and are already being used in practice. The trial is not free from bias as it was unblinded and possibly affected by a selection bias as patients could be excluded at the treating physician's clinical judgement of dexamethasone having no benefit for that patient. The committee felt that the overall strength of the trial's design and results outweighed these concerns and determined it was in the best interest of patients to recommend dexamethasone for patients with COVID-19 who are moderately or severely ill. The committee discussed that ideally these results should be followed by a blinded RCT, but felt that another trial was unlikely to happen in the near future. These recommendations may change when the full results from the RECOVERY trial are published in a peer-reviewed journal.

4.4.2. Tocilizumab

4.4.2.1. Recommendations

Critically Ill Patients: Tocilizumab **is not routinely recommended** to patients 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.

4.4.2.2. Clinical Evidence Review

No. of clinical studies	Two studies
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 *critical* 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.

Reference #2	Christina C. Price, Frederick L. Altice, Yu Shyr, et al. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients Survival and Clinical Outcomes. CHEST. 28 June 2020. https://journal.chestnet.org/article/S0012-3692(20)31670-6/pdf
Study Design	Observational study
Population	Consecutive adults aged ≧18 years with a polymerase chain reaction- confirmed severe acute respiratory syndrome coronavirus 2 infection over the 21-day observation period were identified by using

	electronic medical records. A subgroup of tocilizumab-treated patients underwent additional pre/post assessments.
Intervention	Tocilizumab was administered 8 mg/kg intravenously, not to exceed 800 mg; a second dose could be given if the patient had a markedly elevated BMI. Patients admitted with severe disease could receive tocilizumab immediately; patients with nonsevere disease could receive it later if cytokine release syndrome evolved. Patients also received atazanavir, hydroxychloroquine, and remdesivir if available.
Primary outcome	14-day survival.
Secondary Outcomes	Secondary outcomes included MV days and post-tocilizumab CRS response
Safety Outcomes & Balancing Measures	Clinical safety variables, before and after tocilizumab administration including absolute neutrophil count, ALT, AST, and bacteremia.
Results	14-day survival of patients treated with Tocilizumab: overall 87%, severe cases 83% vs. non-severe 91% (difference not significant), ventilated patients, 75%. Survival in black and Hispanic patients, after controlling for age, was significantly higher than in white patients (log-rank test, P 1⁄4 .002).

4.4.2.3 Evidence Summary

Level of Evidence	Two studies
Evidence Grading	Not applicable
Expert Discussion and Rationale	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). 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. 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. Interferon (with or without combination of lopinavir-ritonavir and ribavirin)

4.4.3.1. Recommendations

Interferon beta-1b (with or without combination of lopinavir-ritonavir and ribavirin) is not recommended for patients with COVID-19 outside of approved clinical trials.

4.4.3.2. Clinical Evidence Review

No. of clinical studies	One study
Reference #1	Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020. DOI: 10.1016/S0140-6736(20)31042-4
Study Design	Multicentre, prospective, open-label, randomized phase 2 trial.
Population	127 patients admitted to 6 hospitals in Hong Kong with COVID-19 infection.
Intervention	Patients were randomly assigned in a 2:1 ratio to receive either 14-days of lopinavir/ritonavir 400/100mg q12h, ribavirin 400mg q12h, and 3 doses of 8M IU interferon beta-1b on alternate days or to 14 days lopinavir/ritonavir 400/100mg q12h.
Primary outcome	Time to negative NP swab for SARS-CoV-2 PCT on ITT population.
Secondary Outcomes	Time to resolution of symptoms maintained for 24h, daily NEWS2 and SOFA score, length of stay, and 30 day mortality. Additional virological endpoints.
Safety Outcomes/ Balancing Measures	Frequencies and duration or adverse events.
Results	Combination therapy had a median time to negative NP swab of 7 days, compared with 12 days in the control arm (HR 4.37, 95% CI 1.86-10.24, p=0.001).

4.4.3.3. Evidence Summary

Level of Evidence	One RCT of 127 patients.
Evidence Grading	Not applicable
Expert Discussion and Rationale	This study, performed in very low risk patients, only provides benefit in microbiologic endpoints, and so is of unclear application to patients hospitalized in Canada. The Committee feels that more study is required with clinically relevant endpoints prior to making any firm recommendations.

4.4.4. Convalescent Plasma

4.4.4.1. 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.

4.4.4.2. Clinical Evidence Review

No. of clinical studies	One study
Reference #1	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)
Study Design	Case series.
Population	Five critically ill, mechanically ventilated patients.
Intervention	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. Convalescent plasma was administered between 10 and 22 days after admission.
Primary outcome	Changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), Pao_2/Fio_2, viral load, serum antibody titer, routine blood biochemical index, ARDS, and ventilatory and extracorporeal membrane oxygenation (ECMO) supports before and after convalescent plasma transfusion.
Secondary Outcomes	None specified.
Safety Outcomes & Balancing Measures	None specified.

Results	Four patients who had been receiving mechanical ventilation and ECMO no longer required respiratory support by 9 days after plasma transfusion. 3/5 patients were discharged at the time of publication.

4.4.4.3. Evidence Summary

Level of Evidence	One case series of five patients
Evidence Grading	Not applicable
Expert Discussion and Rationale	There is limited data supporting the effectiveness of convalescent plasma therapy in acute coronavirus infections, such as SARS and MERS. 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)

5.1.1. 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 (not licensed for use in Canada) is available in some other countries as an exceptional access product for pregnant women and children.
- For critically or moderately ill pregnant or breastfeeding patients with COVID-19 receiving steroids, oral prednisolone 40 mg once daily (or intravenous hydrocortisone 80 mg twice daily) should be used instead of dexamethasone.
- 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, immuno-suppression 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
June 24, 2020	• Recommendations for dexamethasone, use in critically and moderately ill patients with COVID-19 is recommended (Section 4.4.1) • Summary of the RECOVERY trial added to evidence for hydroxychloroquine Recommendation against the use of HCQ in non-clinical trial settings unchanged (Section 4.2.3) • Evidence summary updated to include information about the end of the WHO, NIH, and Novartis HCQ clinical trials (Section 4.2.3.3) • Added considerations for dexamethasone use in pregnancy (section 5.2.1)
June 17, 2020	• Recommendations for remdesivir, use in critically ill patients 'can be considered' where remdesivir is available. Use in moderately ill patients is recommended for patients who are moderately ill with COVID-19 if it is available (Section 4.2.1) • Recommendations for interferon (with or without combination of lopinavir-ritonavir and ribavirin) added (Section 4.4.3)
April 24, 2020	• Recommendations for special populations added (section 5) • Recommendations for COVID-19 convalescent plasma therapy added (4.4.4) • 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.