Greater Toronto Area (GTA) Clinical Practice Guidelines for Antimicrobial and Immunomodulatory Therapy in Patients with COVID-19

(Last updated April 11, 2020)

Important Update Notice: This document is meant to be a living document, with the most up to date version is available at antimicrobialstewardship.com. Because epidemiology, drug availability, and scientific progress is moving rapidly, we recommend not downloading this document, but rather returning to this site for the most up to date guidelines.

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 and pharmacists, and a toxicologist—in consultation with peers, critical care physicians, pharmacists, ethicists, and patients—make the following recommendations for standardized care:

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.

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 (hospitalized, ICU-based; estimated mortality 48-67%)[2]: These patients are those who would normally be managed in an intensive care unit or step-down/step-up unit, requiring ventilatory and/or circulatory support, including ECMO (extracorporeal membrane oxygenation). Patients requiring oxygen by high-flow nasal cannula (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 (hospitalized, ward-based; estimated mortality <5%): These patients are patients who would normally be 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 (ambulatory, outpatient; estimated mortality <1%): These patients are patients who would normally be managed outside of hospital, and do not require supplemental

[1] 1. 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

[2] 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/).

oxygen, intravenous fluids, or other physiologic support. Patients hospitalized for reasons other than for medical/nursing support are included in this category.

Recommendations

INVESTIGATIONAL ANTI-COVID-19 THERAPEUTICS

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

<u>Remdesivir</u> (currently unavailable in Canada)
Recommendation
Remdesivir is not recommended for patients with COVID-19 outside of approved clinical trials.

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

<u>Chloroquine and Hydroxychloroquine (HCQ)</u>
Recommendation - Critically Ill Patients
Due to lack of consensus, no recommendations can be made on the use of chloroquine or hydroxychloroquine for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use (e.g. chronic rheumatological conditions).

Recommendation - Moderately and Mildly Ill Patients
Chloroquine and hydroxychloroquine (with or without azithromycin) are 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

Recommendation - Critically Ill Patients

Ceftriaxone 1g IV q24h x 5 days is recommended for patients with COVID-19 pneumonia outside of approved clinical trials, and should be de-escalated on the basis of microbiology results and clinical judgment. (Alternative for severe beta-lactam hypersensitivity: moxifloxacin 400mg IV q24h x 5 days).

Recommendation - Critically Ill Patients

Azithromycin is not recommended for patients with COVID-19 infection outside of approved clinical trials or where other indications would justify its use (e.g. suspected or proven Legionella pneumonia co-infection).

Recommendation - Critically Ill Patients

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 and risk for drug-resistant organisms, and clinical judgment.

Recommendation - Moderately and Mildly 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

Recommendation

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, etc.).

Tocilizumab

Recommendation - 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.

Recommendation - Moderately and Mildly Ill Patients

Tocilizumab is not recommended for patients with COVID-19 outside of approved clinical trials.

Last Update April 2, 2020

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, 2020, the CFR has hovered between 1.0-1.4%.[3]

These antimicrobial treatment guidelines were created by infectious disease physicians and pharmacists, a clinical pharmacologist/toxicologist, ethicists, and patient partners in the Greater Toronto Area. 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

Amir Amiri, Patient Partner (non-voting)
Nisha Andany, MD MPH, Sunnybrook Health Sciences Centre
Sally Bean, Ethicist, Sunnybrook Health Sciences Centre (non-voting)
Pavani Das, MD, North York General Hospital
Linda Dresser, PharmD, University Health Network
Wayne Gold, MD, University Health Network
Kevin Gough, MD, St. Michael's Hospital, Unity Health Toronto
Chris Graham, MD, Trillium Health Partners
Rebecca Greenberg, Ethicist, Sinai Health (non-voting)
Shahid Husain, MD MS, University Health Network
Susan John, MD, Scarborough Health Network
Rupert Kaul, MD PhD, University Health Network
Elizabeth Leung, PharmD MSCI, St. Michael's Hospital, Unity Health Toronto
Brian Minnema, MD, St. Joseph's Hospital, Unity Health Toronto
Andrew Morris, MD SM, Sinai Health
Lesley Palmay, BSc BScPhm MSc, Sunnybrook Health Sciences Centre
Jeff Powis, MD, Michael Garron Hospital
Sumit Raybardhan, MPH, North York General Hospital
Kathryn Timberlake, PharmD, Hospital for Sick Children
Anupma Wadhwa, MD MEd, Hospital for Sick Children
Peter Wu, MD MSc, University Health Network
Ivan Ying, MD, Mackenzie Health

[3] https://coronavirus.1point3acres.com/en

2.2. COVID-19 Antimicrobial Therapy Guideline *Ad Hoc* Committee Members

Neill Adhikari, MDCM MSc, Sunnybrook Health Sciences Centre (Critical Care)
Jon Barrett, MBBCh MD, Sunnybrook Health Sciences Centre (Obstetrics)
Philippe Bedard, MD, University Health Network (Oncology)
Zia Bismilla, MD, Hospital for Sick Children (Paediatrics)
Ari Bitnun, MD MSc, Hospital for Sick Children (Paediatric Infectious Diseases)
Laurent Brochard, MD, Unity Health Toronto (Critical Care)
Steven Chan, MD PhD, University Health Network (Oncology)
Rob Fowler, MDCM MS, Sunnybrook Health Sciences Centre (Critical Care)
Helen Groves, MD, Hospital for Sick Children (Paediatric Infectious Diseases)
Elaine Gilfoyle, MD MMEd, Hospital for Sick Children (Paediatric Critical Care)
Sasan Hosseini, MD, University Health Network (Transplant Infectious Diseases)
Kevin Imrie, MD, Sunnybrook Health Sciences Centre (Oncology)
Arjun Law, MBBS MD DM, University Health Network (Hematology)
Natasha Leighl, MD MMSc, University Health Network (Oncology)
John Marshall, MD, Unity Health Toronto (Critical Care)
Cynthia Maxwell, MD, Sinai Health (Obstetrics)
Elad Mei-Dan, MD, North York General Hospital (Obstetrics)
Maral Nadjafi, MD, North York General Hospital (General Internal Medicine)
Peter Scheufler, MD, Trillium Health Partners (Obstetrics)
Steve Shadowitz, MD MSc, Sunnybrook Health Sciences Centre (General Internal Medicine)
Prakesh Shah, MSc MBBS MD, Sinai Health (Neonatal Intensive Care)
Lianne Singer, MD, University Health Network (Solid Organ Transplantation)
Simron Singh, MD MPH, Sunnybrook Health Sciences Centre (Oncology)
Miranda So, PharmD, University Health Network (Oncology)
Santhosh Thyagu, MD DM, University Health Network (Oncology)
Wendy Whittle, MD PhD, Sinai Health (Obstetrics)
Mark Yudin, MD MSc, Unity Health Toronto (Obstetrics)

2.3. **Standing Committee Member Conflicts of Interest Disclosures:** Conflicts of Interest considerations can be found in Appendix 1

3. Methodology

3.1. Committee Membership Selection

The COVID-19 Antimicrobial Therapy Standards Committee Members were selected by each hospital to represent their hospital on the committee. These hospitals represent the majority of acute care hospitals in the Greater Toronto Area. Each hospital is represented by one physician. Senior infectious diseases pharmacists were also invited to join the committee; we did not include an equal number of pharmacists as physicians for feasibility. We also included an academic clinical pharmacologist/toxicologist. Ethicists, general internists, critical care physician leaders, and patient representatives are non-voting members. Representation was balanced across gender and clinical experience.

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[4], recognizing that site of care may not correlate with severity of illness, especially as critical care unit capacity may be exceeded:

Critically Ill (hospitalized, ICU-based; estimated mortality 48-67%)[5]: These patients are those who would normally be managed in an intensive care unit or step-down/step-up unit, requiring ventilatory and/or circulatory support, including ECMO (extracorporeal membrane oxygenation). 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 (hospitalized, ward-based; estimated mortality <5%): These patients are patients who would normally be 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 (ambulatory, outpatient; estimated mortality <1%): These patients are patients who would normally be 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.

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[4] 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

[5] 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/).

Last Update April 2, 2020

4. RECOMMENDATIONS

Please look at Special Populations at the End of the Document for further Recommendations.

4.1. Unproved Investigational Therapeutics

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.***

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

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

4.2.1.2. Clinical Evidence Review:

No. of clinical studies: 1

Reference: Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. New England Journal of Medicine. 2020.
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 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 200mg 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 extracorporeal membrane oxygenation [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.
Level of Evidence: Not applicable
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. 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.

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

https://www.gilead.com/purpose/advancing-global-health/covid-19) or Health Canada (https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/remdesivir.html) for further information.

4.2.2. Lopinavir/ritonavir

4.2.2.1. Recommendations

Critically Ill: ***Lopinavir/ritonavir is not recommended for patients with COVID-19 outside of approved clinical trials.***
Moderately Ill: ***Lopinavir/ritonavir is not recommended for patients with COVID-19 outside of approved clinical trials.***
Mildly Ill: ***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.
Reference: 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.
Population: 199 patients with COVID-19 with oxygen saturation (Sao2) ≤ 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 oxygen by high-flow nasal cannula (HFNC) 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.

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: ***Due to lack of consensus, no recommendations can be made on the use of chloroquine or hydroxychloroquine for patients with COVID-19 outside of approved clinical trials or where other indications would justify its use (e.g. chronic rheumatological conditions).***

Moderately Ill: ***Chloroquine and hydroxychloroquine are not recommended for patients with COVID-19 outside of approved clinical trials.***

Mildly Ill: Chloroquine and hydroxychloroquine ***are not recommended for patients with COVID-19 outside of approved clinical trials.***

4.2.3.2. Clinical Evidence Review

No. of clinical studies: 3.

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 HCQ, and 16 to supportive care), but 6 patients enrolled to HCQ 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 200mg tid orally x 10 days. Comparator arm was standard care. 6 patients in the HCQ 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, LIU Li,LIU 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. 30 patients were randomized .
Intervention: Hydroxychloroquine 400mg 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 HCQ group, 2 days in the control group 2 (P>0.05). The median time for body temperature normalization in HCQ group and control group was 1 day after hospitalization. Radiological progression was shown on CT images in 5 cases (33.3%) in the HCQ group and 7 cases (46.7%) in the control group. Four cases (26.7%) inthe HCQ group and 3 cases (20%) inf 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 PaO2/FiO2 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 200mg 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: Not specified. Time to clinical recovery (normothermia + relief of cough), clinical characteristics, and radiographic characteristics were identified as endpoints.
Secondary Outcomes: Not specified
Safety Outcomes/Balancing Measures: None specified.
Results: Compared temperature recovery time 2.2 days in HCQ group vs. 3.2 days in control group. For cough, 15 patients in the control group and 22 patients in the HCQ treatment group had a cough in day 0,

Level of Evidence: 2 RCT and 1 controlled observational study, with microbiological primary outcomes.
Evidence Grading: Not applicable
Expert Discussion and Rationale: Chloroquine and hydroxychloroquine (HCQ) 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." (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.) 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 HCQ be adopted as therapy for COVID-19. The Committee struggled to reach consensus, and were evenly divided for critically ill patients: On one side was the view that HCQ is a relatively safe drug, has a low potential for relative harm in critically ill patients, and it offers hope for patients, their advocates, and health care providers in the face of a poor prognosis. Although the preferred route was entry into a clinical trial, there was also a strong belief that clinical trials may not be as accessible as hoped. On the other side was the view that HCQ has limited data supporting its consideration, and was as likely to cause harm as benefit. Supporters of this view believed that the only way to properly assess the benefit of HCQ would be enrolment in a clinical trial. Those opposing a recommendation to consider HCQ in critically ill patients noted that an endorsement would promote widespread adoption of HCQ, prevent the ability of the drug to be studied appropriately, and increase the likelihood of HCQ shortages for patients who need it for their chronic rheumatologic conditions. Those supporting a recommendation to consider HCQ noted that--at the time of recommendation--there were several efforts to increase availability of HCQ.

For ward patients, using the same evidence used for considering HCQ in critically ill patients, there was consensus but not unanimity 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 HCQ.

4.3. Antibacterial Therapy

4.3.1. Recommendations

Critically Ill Patients: 1. ***Ceftriaxone 1g IV q24h x 5 days is recommended for patients with COVID-19 pneumonia outside of approved clinical trials, and should be de-escalated on the basis of microbiology results and clinical judgment. (Alternative for severe beta-lactam hypersensitivity: moxifloxacin 400mg IV q24h x 5 days). 2. Azithromycin is not recommended for patients with COVID-19 infection outside of approved clinical trials or where other indications would justify its use (e.g. suspected or proven Legionella pneumonia co-infection). 3. Empiric antibiotic treatment for secondary (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.***

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.***

Mildly 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.***

4.3.2. Clinical Evidence Review:

No. of clinical studies: 0 (see Gautret P, Lagier J-C, Parola P, et al. above under **Recommendation 5** for a brief discussion of azithromycin)

Level of Evidence: No applicable

Evidence Grading: Not applicable

Expert Discussion and Rationale: The evidence supporting azithromycin--mostly to be included in combination with HCQ--comes from the single paper by Gautret et al., whereby 6 patients were given azithromycin (500mg on day1 followed by 250mg 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 (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). 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. (Huang et al. *Lancet* 2020; Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;**395**:507-13.) Patients with secondary, drug-resistant nosocomial infections following hospitalization were more common (Chen N et al. *Lancet.* 2020).

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 moxifloxacin 400mg 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.

4.4. Immunomodulatory/Immunosuppressive Therapy

4.4.1. Corticosteroids

4.4.1.1. Recommendations

Critically Ill Patients: ***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, etc.)***

Moderately Ill Patients: ***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, etc.)***

Mildly Ill Patients: ***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, etc.)***

4.4.1.2. Clinical Evidence Review

No. of clinical studies: 0

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 demonstrated that there is no evidence strong evidence suggesting benefit from corticosteroids in coronavirus infections, and the signal points to potential harm. (Russell 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. Tocilizumab

4.4.2.1. Recommendations

Critically Ill Patients: ***Tocilizumab should not be offered routinely to patients infected with COVID-19 outside of 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.***

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

Mildly 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: 1.

Reference: 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; SpO2 ≤ 93% while breathing room air; PaO2/FiO2 ≤ 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 400mg 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: Not specified.

Results: Authors reported that 19/21 patients had been discharged at time of publication, with no deaths reported.

Level of Evidence: 1 case series of 20 patients

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 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)).

Special Populations

Pediatrics (Under Age 18)

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.

A ‘live’ separate guidance document developed to support clinicians within the Hospital for Sick Children, Toronto in managing pediatric patients with suspected or confirmed COVID-19 can be found at:

https://sickkidsca.sharepoint.com/sites/IPAC/clinical-resources

The linked guidance document is intended solely for the use of the multidisciplinary COVID-19 team at the Hospital for Sick Children, Toronto to provide structured guidance in decision-making for the use of investigational anti-COVID-19 therapeutics in the pediatric population.

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).

Pregnancy

There is a paucity of evidence guiding the medical management of pregnant patients with COVID-19. Recommendations for antimicrobial 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).

HIV

Cancer

Solid Tumours, Lymphoma, Leukemia (and related cancers)

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 using prescribing medications.

Transplantation

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 COVI-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 1 Conflicts of Interest

Voting Committee members were required on an ongoing basis to update and conflicts of interest.