Management of Pediatric Patients with COVID-19
Pediatric COVID-19 Treatment Considerations

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Disclaimer

• Data presented is current as of April 15.

• No proven therapies for COVID-19 exist.

• Pediatric data extremely limited, largely extrapolated from adult studies

• Data presented may reflect unpublished, non-peer-reviewed studies
Learning Objectives

1. Understand the epidemiology and risk factors of COVID-19 in pediatric and neonatal patients.

2. Evaluate pediatric considerations of COVID-19 specific therapies in pediatric patients across Canada.

3. Assess factors in devising a dose in pediatric patients of a novel drug or indication.

4. Identify useful resources when searching for Pediatric COVID treatment options.
Useful Links

• COVID-19 SickKids Internal Website [HERE](External link Coming Soon)
  • Hydroxychloroquine Suspension Recipe available [HERE](#)

• GTA COVID Treatment Guidance Document [HERE](#)
  • Linked Medication Table including Pediatric Dosing COMING SOON

• Drug Interactions Calculator for COVID-therapy [HERE](#)

• Canadian Clinical Trials Google Doc [HERE](#)

• CSHP COVID-19 PSN [HERE](Do not need to be a member)
  • Discussions on everything from PPE for Pharmacy Staff to Webinars to Nebs vs MDI, and treatment options and recipes.
The SickKids Interim Guidance Document

- A scoping review of the literature, guidelines, grey literature was done to evaluate possible treatment options for COVID-19

- To support clinicians within SickKids managing COVID-19 patients, Infectious Diseases consulted with physicians across the spectrum (e.g. ED, Critical Care, Hematology, Immunology) to gain consensus and expert opinion

- Includes assessment and evaluation of patients outside of antiviral and immunomodulatory therapies.

- Routine use of experimental therapies is not routinely recommended.
Greater Toronto Area (GTA) Clinical Practice Guidelines for Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19

**Recommendations in this document apply to patients >18 years of age. For recommendations in special populations, refer to the complete guidelines.**

- There is limited clinical evidence to guide antiviral management for ill patients with COVID-19.

The guidelines recommend 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.

<table>
<thead>
<tr>
<th>SEVERITY OF ILLNESS</th>
<th>ANTIVIRAL THERAPY</th>
<th>ANTIBACTERIAL THERAPY</th>
<th>IMMUNOMODULATORY THERAPY</th>
</tr>
</thead>
</table>
| **Critically Ill Patients**  
Hospitalized, ICU-based  
Patients requiring ventilatory and/or circulatory support; also includes patients requiring high-flow nasal cannula, non-invasive ventilation, or higher concentrations of oxygen by mask
| No recommendations can be made on use of chloroquine or hydroxychloroquine outside of approved clinical trials or where other indications would justify its use  
**Lopinavir/ritonavir is not recommended outside of approved clinical trials**  
**Remdesivir** is not recommended outside of approved clinical trials | Empiric therapy with ceftriaxone 1 g IV q24h x 5 days is recommended if there is concern for bacterial co-infection (Alternative for severe beta-lactam hypersensitivity: moxifloxacin 400 mg 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 moxifloxacin)  
De-escalate on the basis of microbiology results and clinical judgment | Corticosteroids should not be offered outside of approved clinical trials unless there are other indications for its use  
Tocilizumab (IL-6 receptor blocker) should not be offered routinely outside of approved clinical trials; may be considered on an individual basis in patients with cytokine storm (with expert consultation) |
| **Moderately Ill Patients**  
Hospitalized, ward-based  
Patients requiring low-flow supplemental oxygen
| Chloroquine or hydroxychloroquine (with or without azithromycin) is not recommended outside of approved clinical trials or where other indications would justify its use  
**Lopinavir/ritonavir is not recommended outside of approved clinical trials**  
**Remdesivir** is not recommended outside of approved clinical trials | Antibacterial therapy is not routinely recommended outside of approved clinical trials or where other indications would justify its use | Corticosteroids should not be offered outside of approved clinical trials unless there are other indications for its use  
Tocilizumab (IL-6 receptor blocker) is not recommended outside of approved clinical trials |
| **Mildly Ill Patients**  
Ambulatory, outpatient  
Patients who do not require supplemental oxygen, intravenous fluids, or other physiological support
| | | |

*Currently unavailable in Canada*

Note: This document is dynamic and will be updated as changes to recommendations occur. The complete and most up-to-date version of the guidelines is available at [www.antimicrobiastewardship.com/covid-19](http://www.antimicrobiastewardship.com/covid-19). Last updated on April 3, 2020.
GTA COVID Management Guideline

• Executive Summary
  • There is limited clinical evidence to guide antiviral management for critically 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:

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

• The Multicenter Initial Guidance on use of Antivirals for Children with COVID-19/SARS-CoV-2 submitted for publication to JPIDS

• 38 Pediatric Infectious Disease Physicians (31) and Pharmacists (7) from 18 geographically diverse sites developed consensus on recommendations and considerations

• Pediatric outcomes for COVID-19 are favorable

• Key guiding principle "Do no harm"
Clinical Equipoise

Clinical Equipoise *(TCPS-2 2018)*

- Clinical equipoise means a genuine uncertainty exists on the part of the relevant expert community about what interventions are most effective for a given condition. This uncertainty necessitates the conduct of research to determine the comparative therapeutic merits of different interventions (not all of which may be represented in a given clinical trial). Clinical equipoise provides a link between the duty of care of a clinician and the need to do research to ensure that the therapies or interventions offered are demonstrably safe and effective.
Severity in Pediatrics  
(Dong et al Pediatrics Pre-Print)

• As of Feb 8:  
2143 pediatric patients of suspected and confirmed cases

- 56.6% Male

- Median age 7 (IQR 2-13)

<table>
<thead>
<tr>
<th>Age group*</th>
<th>Asymptomatic</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Critical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>7 (7.4)</td>
<td>205(18.8)</td>
<td>127(15.3)</td>
<td>33(29.5)</td>
<td>7(53.8)</td>
<td>379(17.7)</td>
</tr>
<tr>
<td>1-5</td>
<td>15(16.0)</td>
<td>245(22.5)</td>
<td>197(23.7)</td>
<td>34(30.4)</td>
<td>2(15.4)</td>
<td>493(23.0)</td>
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<tr>
<td>6-10</td>
<td>30(31.9)</td>
<td>278(25.5)</td>
<td>191(23.0)</td>
<td>22(19.6)</td>
<td>0(0)</td>
<td>521(24.3)</td>
</tr>
<tr>
<td>11-15</td>
<td>27(28.7)</td>
<td>199(18.2)</td>
<td>170(20.5)</td>
<td>14(12.5)</td>
<td>3(23.1)</td>
<td>413(19.3)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>15(16.0)</td>
<td>164(15.0)</td>
<td>146(17.5)</td>
<td>9(8.0)</td>
<td>1(7.7)</td>
<td>335(15.7)</td>
</tr>
<tr>
<td>Total</td>
<td>94</td>
<td>1091</td>
<td>831</td>
<td>112</td>
<td>13</td>
<td>2141(100)</td>
</tr>
</tbody>
</table>

Data were presented with number and percent (%); *Two cases had missing values.
Pediatric Incidence/Severity

Italian Data March 17 [JAMA Network](https://www.jamanetwork.com)
Role of Risk Factors in Pediatrics

• Guidance Statement:

There are no definitive data to support any specific risk factor for Severe COVID-19 in children

• Proposed Risk Factors
  • Age
  • Immunocompromise
  • Underlying cardiac or pulmonary disease
  • Obesity
  • Diabetes
Role of Risk Factors in Pediatrics- Age

• Of the Chinese experience, the majority 89% (329/379) of infants <1 year had mild-moderate symptoms or were asymptomatic.

• Italian data similarly report no mortality in children.

• Among US children hospitalized, 8% (5/59) <1 year required ICU-level support, compared to 12% (10/88) children > 1 year of age.

• Unlike other RNA viruses, e.g. RSV, there does not appear to be an increased risk of severe disease with infants.
  • Appears to apply to Neonates as well.

• Neonatal guidelines focus on COVID + mothers and risk of exposure.
Role of Risk Factors in Pediatrics- Immunocompromise

- Limited data suggest that children with mild or moderate immunocompromise are not at high risk of severe infection.

- Adults with malignancy have been at higher risk of severe disease compared to their peers, but the data is poor.

- Other respiratory viruses have been shown to cause severe lower respiratory tract disease and associated poor outcomes.

- Severe T-cell deficiency or dysfunction may be at risk of more severe disease.

- Additional considerations for patients on immunosuppressants due to drug interactions with many of the proposed antiviral medications.
Role of Risk Factors in Pediatrics - Other

• Underlying cardiac, pulmonary disease
  • Adult data strongly suggest that in combination with older age, these diseases are associated with COVID-19 morbidity and mortality.

• Obesity and Diabetes
  • Observational data in adults indicates comorbid conditions including obesity, overweight, and diabetes
  • Obesity may impair lung mechanics

• No evidence in pediatrics but could consider these as factors when weighing risks and benefits.
ARE ANTIVIRAL AGENTS INDICATED IN CHILDREN WITH COVID-19?

• PIDS Guidance statement: The suggested approach for nearly all children with COVID-19 is supportive care.

• Antivirals may be considered on a case-by-case basis.

• When antiviral therapy is considered, we recommend enrollment in clinical trials as these become available for pediatric patients to study the efficacy and safety of potential antivirals.
Greater Toronto Area Pediatric Considerations

• 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.
Clinical Trials

- Only 1 interventional trial currently open to children 6 months to 18 years in Canada (Protocol under frequent revision)
- In the US, Remdesivir trials are open which includes ≥12 year olds
- Other trials coming soon?

<table>
<thead>
<tr>
<th>Row</th>
<th>Saved</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Recruiting</td>
<td>Clinical Characteristics and Outcomes of Pediatric COVID-19</td>
<td>COVID-19, SARS-CoV-2 Infection, Pediatric ALL, (and 2 more...)</td>
<td>Other: Exposure (not intervention) - SARS-CoV-2 Infection</td>
<td>University of Calgary/Alberta Children’s Hospital Calgary, Alberta, Canada</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Recruiting</td>
<td>Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial</td>
<td>COVID-19, Drug: Lopinavir/ritonavir</td>
<td></td>
<td>Vancouver General Hospital, Vancouver Coastal Health, Univeristy of British Columbia Vancouver, British Columbia, Canada • St Paul's Hospital Vancouver, British Columbia, Canada • The Ottawa Hospital - General Campus Ottawa, Ontario, Canada • (and 5 more...)</td>
</tr>
</tbody>
</table>
Evaluating severity of Pediatric COVID-19 Disease
# PIDS Clinical Severity Ranking

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Respiratory support requirement</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/ moderate</td>
<td>No new or increased supplemental oxygen requirement</td>
<td>Supportive care.</td>
</tr>
<tr>
<td>Severe</td>
<td>New or increase from baseline supplemental oxygen requirement without need for new or increase in baseline non-invasive/invasive mechanical ventilation.</td>
<td>Supportive care alone is appropriate for the majority of children. Use of potentially active antivirals could be considered on a case-by-case basis, preferably as part of a clinical trial if available.</td>
</tr>
<tr>
<td>Critical</td>
<td>New or increased requirement for invasive or non-invasive mechanical ventilation, sepsis, or multi-organ failure; OR rapidly worsening clinical trajectory that does not yet meet these criteria.</td>
<td>Supportive care may be appropriate for children who are severely ill with COVID-19. Use of potentially active antivirals should be considered, preferably as part of a clinical trial if available.</td>
</tr>
<tr>
<td>Disease Severity</td>
<td>SickKids Pediatric Interim Guidance</td>
<td>Pediatric Infectious Disease Society Guidance</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Mild disease</strong></td>
<td>▪ Supportive care only</td>
<td>Supportive care</td>
</tr>
<tr>
<td><strong>Mild disease</strong></td>
<td><strong>With Risk factors for severe disease</strong>&lt;br&gt;<strong>Routine use of experimental therapies not recommended</strong>&lt;br&gt;▪ Consider use of hydroxychloroquine +/- azithromycin</td>
<td>Supportive care</td>
</tr>
<tr>
<td><strong>Moderate Disease</strong></td>
<td><strong>Definition Varies</strong>&lt;br&gt;PIDS: No supplemental O&lt;sub&gt;2&lt;/sub&gt;&lt;br&gt;SickKids: May be on O&lt;sub&gt;2&lt;/sub&gt;&lt;br&gt;▪ <strong>Routine use of experimental therapies not recommended</strong>&lt;br&gt;▪ Consider use of hydroxychloroquine +/- azithromycin&lt;br&gt;▪ If rapidly progressing, consider parallel application for Remdesivir</td>
<td>Supportive care</td>
</tr>
<tr>
<td>Disease Severity</td>
<td>SickKids Pediatric Interim Guidance</td>
<td>Pediatric Infectious Disease Society Guidance</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>Severe Disease</strong>&lt;br&gt;SickKids: ICU&lt;br&gt;PIDS: New O₂ requirement</td>
<td>▪ Routine use of experimental therapies not recommended&lt;br▪ Consider use of hydroxychloroquine +/- azithromycin&lt;br▪ Consider parallel application for Remdesivir&lt;br▪ If unable to take HCQ due to contraindications or availability, consider Lopinavir/Ritonavir</td>
<td>Use of potentially active antivirals <strong>could be considered</strong> on a case-by-case basis, preferably as part of a clinical trial if available.</td>
</tr>
<tr>
<td><strong>Critical Disease</strong></td>
<td>For patients with evidence of ARDS or cytokine release syndrome, consider Tocilizumab in select cases with expert consultation.</td>
<td>Supportive care alone may be appropriate for some children with critical COVID-19. Use of potentially active antivirals <strong>should be considered</strong>, preferably as part of a clinical trial if available.</td>
</tr>
</tbody>
</table>
PIDS Recommendations

• No proven therapies for the treatment or prophylaxis of COVID-19

• However, due to lack of studies enrolling children, there may be some patients in whom potential benefit outweighs potential harms.

• Guidance statement: If an antiviral is used, the panel suggests use of remdesivir as the preferred agent, preferably as part of a clinical trial if available.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Evidence for use in COVID</th>
<th>Availability in Canada</th>
<th>Pediatric Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir A Neucloside Analogue</td>
<td>Intracellular incorporation of the pharmacologically active nucleoside triphosphate form into nascent RNA chains by the viral RNA-dependent RNA-polymerase, causing premature RNA chain termination.</td>
<td>Clinical trials ongoing in USA including a phase 3 placebo-controlled, double-blinded RCT. Mentioned as options in several guidelines worldwide. Small adult study (N=53) showed clinical improvement in some patients, difficult to distinguish from natural course Similar efficacy in virologic cure in Ebola as Placebo.</td>
<td>Not approved by Health Canada. Clinical trials ongoing. May be available on compassionate use basis Mar 24: Limited to &lt;18 years, pregnant women *Exclusion Criteria: Concomitant antivirals, CrCL&lt;30 or dialysis as per Gilead, pressors Online application <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a></td>
<td>Dosing Per Gilead: &lt; 40Kg: 5mg/kg Loading dose; Then 2.5mg/kg IV q24h for total of 10 days ≥40kg: 200mg IV x1 Then 100mg IV q24h for days 2-10 Supplied as 100mg IV vials Side effects: Elevation of ALT/AST, Acute Kidney Injury, hypotension associated with loading dose. Drug interactions with LPV/RTV</td>
</tr>
</tbody>
</table>
72 HOURS TO REMDESIVIR COVID-19 COMPASSIONATE USE

- Submit request to Gilead (online)
  https://rdvcu.gilead.com
  [no confirmation email]

- Gilead requests data, sends prescriber agreement, consent form template & drug info
  [IB, protocol, pharm manual] (email)
- Complete expanded clinical data entry for Gilead (online)
- Return prescriber agreement to Gilead (email)
  - Request eIND from FDA (phone)
  - Get patient or family consent

T0

- Gilead approves request (email)
  - Inform local IRB (email)

T+1 hour

- FDA sends Form 3926 (email)
  - Drug arrives (yay)
  - Prescribe drug, order safety labs

T+29 hours

- Gilead sends letter of agreement (email)
- FDA issues eIND (email)↑
- Send eIND to Gilead (email)
- Return Form 3926, CV, medical license, Gilead letter of authorization to FDA (email & mail)↑

T+30 hours

T+48 hours

T+72 hours

↑Note that Form 3926, CV, medical license usually returned to FDA first before eIND granted but not in this case

ANOTHER PCH GRAPHIC
PIDS Recommendations

• **Guidance statement:** Use of hydroxychloroquine could be considered, for patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer, preferably as part of a clinical trial if available.

• **The panel recommends against use of hydroxychloroquine in combination with azithromycin.**

• **Guidance statement:** The panel suggests a hydroxychloroquine dosing regimen that includes a loading dose on day 1 and a total duration of no more than five days.
### Evidence Hydroxychloroquine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Evidence for use in COVID</th>
<th>Availability in Canada</th>
</tr>
</thead>
</table>
| Hydroxychloroquine sulfate (HCQ)  | Chloroquine blocks virus infection by increasing endosomal pH required for virus/cell fusion, interfering with glycosolation for cellular receptors for SARS-CoV. In Vitro studies indicate Chloroquine inhibited viral growth in Vero cells without significant cytotoxicity. | Evidence: (Adult)  
1. In a small study (n=26 treatment, n=16 controls) of patients aged over 12 years (all 10-14yr olds were ax, no tx) with confirmed COVID-19 infection (asymptomatic, URTI and LRTI patients) Hydroxychloroquine treatment was associated with faster viral load reduction compared to control.  
2. In a randomized trial in China, (n=30) patients given HCQ 400mg BID vs Std of Care. The HCQ group was less likely to have virologic clearance, more likely to develop side effects (n=3). No benefit seen. | Marketed in Canada |


PIDS Recommendations

- Guidance statement: The panel suggests a hydroxychloroquine dosing regimen that includes a loading dose on day 1 and a total duration of no more than five days.

- Guidance statement: G6PD screening is not routinely recommended prior to initiation of hydroxychloroquine because the risk of hemolysis from short courses of hydroxychloroquine is low.
Determining a Dose for a Novel Indication

- Data from SARS-CoV-2 infected Vero cells showed in-vitro activity of Chlorquine and Hydroxychloroquine
- $EC_{50}$ concentrations achievable with available dosing regimens
- Pharmacologically-Based Pharmacokinetic Modelling (PBPK) regimen published by Yao et al used healthy Chinese Volunteers and rat lung penetration as the model for devising a dose.
Determining a Dose for a Novel Indication

• HCQ dosing proposed in initial COVID-19 treatment protocols in adults used:
  • Loading dose of 400mg PO BID x2 doses, then 200mg PO BID for 5-10 days

• Subsequent adult doses proposed include:
  • Chinese pilot trial: 400 mg PO daily x 5 days
  • In vitro data: 400 mg PO BID x 1 day, followed by 200 mg PO BID x 4 days
  • Canadian arm of SOLIDARITY trial (CATCO): 800 mg PO BID (separated by 6 hours) x 1 day, then 400 mg PO BID x 10 days (or until discharge, whichever comes first)
  • French publication: 200 mg PO TID x 10 days
  • Canadian arm of REMAP-CAP: 400 mg PO q8h x 9 doses, then 200 mg PO q12h to max of 10 days
  • Pharmacokinetic modelling study: 800 mg once daily on day 1, followed by 200 mg BID for 7 days
Determining a Dose for a Novel Indication

• HCQ has been used in Pediatrics for treatment of acute malaria

  Treatment; acute attack; uncomplicated: Infants, Children, and Adolescents: Oral: Initial: 13 mg/kg/dose hydroxychloroquine sulfate (maximum initial dose: 800 mg/dose hydroxychloroquine sulfate); followed by 6.5 mg/kg hydroxychloroquine sulfate at 6, 24, and 48 hours after initial dose; maximum dose: 400 mg/dose hydroxychloroquine sulfate (CDC 2013).

• Pediatric JRA or SLE: Oral: 3 to 5 mg/kg/day divided 1 to 2 times/day to a maximum of 400 mg/day

• Serious Safety Concerns:
  • QTc prolongation – Acute or chronic therapy, along with other cardiac effects
  • Bone marrow suppression
  • Hypoglycemia
  • Retinal toxicity- Seen beyond 5 years of therapy

• Other Adverse Reactions: Nausea, vomiting, diarrhea, skin reactions, CNS effects (April 1, 2020 FDA advisory)
Determining a Dose for a Novel Indication

• Relevant PK properties include:
  • Volume of Distribution
  • Long Terminal Half-Life (up to 40 days)
  • Hepatic metabolism
  • Excreted 15-25% in urine as metabolites and unchanged
  • 40% Protein bound

• Relevant Pharmacodynamic (PD) Properties:
  • Trough Lung: EC_{50} Ratio
Determining a Dose for a Novel Indication

- Using Monte Carlo simulations, with pediatric PK parameters, different dosing profiles were simulated.
- A. 200mg TID x 10 days
- B. 400mg BID x 1 day, then 200mg BID x 4 days
- C. 400mg Daily x 10 days
- D. 13mg/kg followed by 6.5mg/kg at 6, 24, and 48 hrs
- Blue = Median population concentration
- Red = 2.5%ile and 97.5%ile
Determining a Dose for a Novel Indication

- Using Monte Carlo simulations, with pediatric PK parameters, different dosing profiles were simulated.
- A. 200mg TID x 10 days
- B. 400mg BID x 1 day, then 200mg BID x 4 days
- C. 400mg Daily x 10 days
- D. 13mg/kg followed by 6.5mg/kg at 6, 24, and 48 hrs
- Blue = Median population concentration
- Red = 2.5%ile and 97.5%ile
What is the Right Dose of HCQ?

- Growing evidence that no clinical benefit seen
- Only consider in patients in whom risks of disease outweighs the risk of toxicity.
- Monitor: QTc, LFTs, Renal function, GI tolerance, CNS toxicity
- Check for drug interactions
What is the Right Dose of HCQ?

• Pediatric dosing regimens for hydroxychloroquine proposed in the literature:

• Physiologically-based pharmacokinetic modelling: 6.5 mg/kg/dose PO BID x 2 doses (max 400 mg/dose), then 3.25 mg/kg/dose PO BID x 4 days (max 200 mg/dose)\textsuperscript{28,29}

• Acute malaria dosing: 13 mg/kg/dose PO once (max 800 mg/dose), then 6.5 mg/kg/dose PO at 6, 24, and 48 hours after initial dose (max 400 mg/dose)\textsuperscript{30}
PIDS Recommendations

- **Guidance statement:** The panel was divided as to whether lopinavir-ritonavir could or should be considered for any pediatric patient with COVID-19 infection in any clinical scenario.

- *In vitro* data showed promise, but an early randomized-controlled trial did not show any benefit in clinical improvement or virologic outcomes in severely ill adults vs Standard of Care (SOC)

- Multiple drug interactions requiring extra caution, to avoid using if possible.
# Evidence Kaletra (Lopinavir/Ritonavir)

<table>
<thead>
<tr>
<th>Drug</th>
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</table>
| Lopinavir/ Ritonavir: Kaletra | Inhibit 3-chymotrypsin-like protease of Coronavirus: Docking and molecular dynamic experiments were applied to examine the effect of inhibitors on coronavirus proteinase - of the HIV1 proteinase inhibitor tested the highest affinity for blocking the Coronavirus protease was lopinavir. | Cao et al NEJM Results of open label clinical trial on lopinavir–ritonavir versus standard care in adult patients with COVID-19 failed to show difference in primary outcome of time to clinical improvement. Severe adverse events eg. ARDS were more common in standard care group compared to lopinavir-ritonavir. Currently used in China–consensus guideline, weak recommendation. Used in Korea and reported in case reports. Also used clinically in Italy and Japan as part of consensus guideline. | Marketed in Canada On Protective allocation | Pediatric Dosing: 

- **<6 months**: 300 mg/m²/dose LPV PO BID (Dose limit: 800 mg/day)  
- **6 months to 12 yrs**: 230-300 mg/m²/dose LPV PO BID (Dose limit: 800 mg/day)  
- **>12 yrs or ≥35 kg**: 400 mg LPV PO BID

**Alternative Pediatric Dosing:**  
10 mg/kg/dose LPV PO BID (maximum 800 mg/day)  
Adult: 400/100 PO BID (up to 10-14 days, per WHO)  

Commonly reported side effects are gastrointestinal i.e. diarrhoea, nausea, vomiting.  
Also known to cause anaemia, liver dysfunction, pancreatitis, arrhythmias, prolongation of the QTc. Multiple Drug-Drug Interactions |
## Evidence Tocilizumab

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor antibody. Elevated levels of IL-6 have been associated with severe disease in COVID-19. Blockage of this is presumed to decrease the cytokine storm induced by COVID-19 and reduce lung damage.</td>
<td>Multi-center, randomized clinical trial is ongoing in China: ChiCTR2000029765. Preliminary results released by the National Health Commission showed that in 20 patients with severe COVID-19 temperature dropped within one day in all 20 and 19 patients were discharged from hospital within two weeks. However of these 20 patients only 2 patients were ventilated and one on non-invasive support and the study had no controls. Therefore difficult to draw firm conclusions regarding benefit.</td>
<td>Marketed in Canada: Licensed for Children &gt;2 yrs of age with RA Ordering restricted: Emergency Allocation available Current supplies reserved for CAR-T cell patients</td>
<td>Dosing for COVID-19 in Chinese guidelines: Initial dose is 4-8mg/kg with the recommended dose of 400mg diluted with 0.9% normal saline to 100ml. The infusion time should be more than 1 hour. One extra administration can be given after 12 hours (same dose as before). No more than two administrations should be given with the maximum single dose no more than 800mg Side Effects: Headache, diarrhea, nasopharyngitis, increased ALT noted. Risk of infections*: disseminated fungal, disseminated TB, bacterial and viral pathogens *Blackbox Warning from FDA</td>
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Other Considerations

• Steroids
• Other Interleukin Inhibitors- Anakinra, Eculizumab
• IVIG, Convalescent Serum
• Favipiravir, Arbidol, Baloxivir, Oseltamivir, Ribavirin
• Interferon alpha, Beta IV and INH
• Antibiotics

• Neonates
  • Thus far limited impact
  • Isolation precautions between COVID+ parent or siblings
Antibiotics

• Low rates of secondary bacterial infections being reported.

• Empiric use of antibiotics for Community-acquired pneumonia may be appropriate, with reassessment after 48 hours.
Summary

• Evidence developing hour by hour, day by day.
  • E.g. a Single case report published on Remdesivir in US March 5 2020, -->
  • More than 2 Million confirmed cases worldwide on April 15 2020
  • Pre-print evidence may be subsequently retracted or revised substantially

• No evidence that any therapy is definitively better than supportive care

• Clinical trials are preferable, but difficult to determine whether Pediatrics would benefit... Ethical concerns

• Treatment more likely offered in Pediatric patients than to adults in GTA

• Treatment guidance for Pediatric patients similar across North America, however, if access to Remdesivir is further limited, re-evaluation may be needed.
References

Risk Factors:


5. More to come....