Interim Guidance for the Management of Paediatric Patients with Confirmed COVID-19

Version 4.0

15th May 2020
Key changes from previously uploaded version

- Page 2 - Addition of summary statements at beginning of guidance document
- Page 4 - Addition of contents page and hyperlinks for document navigation
- Page 9 - Reformattting of table 2 (investigations) to be consistent with EPIC order wording and to increase ease of readability
- Page 9 – paragraph on prothrombotic issues and COVID-19 moved to section on page 17
- Page 12 – removal of azithromycin from treatment table due to lack of efficacy data and associations with cardiac arrest in combination with hydroxychloroquine in recent publications: statement added recommending against its use with hydroxychloroquine in antibiotic section. In cases where antiviral therapy is considered, remdesivir is now suggested as first line consideration with dosing updates based on increasing evidence for its efficacy and conflicting evidence for hydroxychloroquine efficacy in recently data from published observations and clinical trials
- Page 15 – up date to risk factor section with newly published paediatric data
- Page 16 and 22 – up dated information regarding CRS/HLH and immunomodulatory therapy with newly published data
- Page 18 – addition of new study information on ACE inhibitors/ARBs and COVID-19
- Page 19 – additional information on clinical features of COVID-19 including paediatric multisystem inflammatory syndrome temporally associated with COVID-19
- Page 22 – updated anakinra and tocilizumab dosing

Summary Statements for Management of Children with Confirmed COVID-19

**Treatment recommendations:**

1. Supportive care is the mainstay of therapy for patients with COVID-19.
2. Use of experimental therapies for children with COVID-19 should ideally be offered in the context of clinical trials.
3. Use of experimental therapies should only be considered on a case-by-case basis with caution and should only be given under expert guidance from Infectious Diseases if it is judged that the potential for unproven benefit is likely to outweigh the known and unknown risks.
4. Experimental therapies should not be offered to patients not requiring hospitalization.
5. Considerations for treatment should include severity of illness, patient and family preference, availability of antiviral therapy, risk of side effects, drug interactions, and concomitant diseases.
6. Experimental therapies should be offered only after informed consent has been obtained (and documented) as per Hospital policy.
Recommendations for COVID-19 case management specialist team involvement

7. Patient not initially requiring critical care support:

Primary medical team will direct consultation with additional services, including:

- Notification of the Infectious Diseases (ID) for all SARS-CoV-2 positive patients
- Critical Care Response Team (CCRT) should be made aware of patients upon admission irrespective of severity and subsequently if clinical deterioration.
- Notification of Respiratory Medicine, Rheumatology, Immunology, Haematology/Oncology, Thrombosis team and Clinical Pharmacology as clinically indicated.

8. Patients requiring critical care support:

Critical Care team, Respiratory Medicine, ID and Infection Control services should be engaged. An initial multidisciplinary team meeting it is strongly recommended involving services likely be engaged if the patient further deteriorates: including Rheumatology, Immunology, Haematology/Oncology, Thrombosis team and Clinical Pharmacology.

Risk factors for severe illness in children with COVID-19


10. Populations that may be at higher risk for severe infection include infants <1 year of age, and children with comorbid conditions including: lung disease, immune compromise, obesity, congenital heart disease, sickle cell disease, genetic abnormalities, neurological disease, or diabetes mellitus.

Acute respiratory distress syndrome (ARDS) and children with COVID-19

11. In general, the principles of management of paediatric ARDS secondary to COVID-19 are likely to be aligned with those of the adult population. Specific management of ARDS in children with COVID-19 should be assessed on a case-by-case basis under the direction of critical care and respiratory teams.

Management considerations for Cytokine Release Syndrome (CRS)/secondary Hemophagocytic lymphohistiocytosis (HLH) in children with COVID-19

12. The routine use of immunomodulatory agents in children with COVID-19 outside of clinical trials is not recommended

13. In exceptional circumstances, on a case-by-case basis where monitored cytokine levels or serum markers indicate clear evidence of cytokine storm, immunomodulatory agents may be considered under expert guidance from specialist teams as detailed above.

Antibiotic therapy

14. Antibiotic therapy should follow SickKids empiric guidelines for community-acquired or hospital-acquired bacterial pneumonia, as appropriate.
1. Introduction

For the majority of children, Coronavirus disease 2019 (COVID-19) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a mild illness. Current evidence from case series of affected children indicate that fewer than 10% have severe or critical disease and that death is a rare event.\(^1,2\) However, at this time, there are limited data on the full spectrum of COVID-19 in children and information on this topic is rapidly evolving.

Risk factors for severe disease in adults include older age (particularly above 70 years), male sex, and the presence of comorbidities, in particular hypertension, coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, chronic kidney disease and immunosuppression.\(^3-5\) While there have been reports of critically ill children with comorbidities such as congenital heart disease, and hydronephrosis, and one death in a child presenting with intussusception, data are still quite limited, and therefore, the potential impact of underlying medical conditions on COVID-19 severity in children is presently unknown.\(^2\) However, given the adult data on comorbidities and based on what is known about the influenza virus, there is potential for immunocompromised children, or children with underlying chronic medical conditions (i.e. chronic lung disease or asthma) to be at increased risk of complications from COVID-19. Interestingly, a recent review of 2000 children with SARS-CoV2 infection in China indicated that infants and children less than 5 years old were more likely to have severe disease compared to older children.\(^1\)

2. Background to Guidance Development

The purpose of this guideline is to provide interim guidance to support clinicians within The Hospital for Sick Children (SickKids), Toronto who will be managing paediatric patients with COVID-19. For important information and disclaimers about this document, please see last page.

This guideline has been developed by members of the Division of Infectious Diseases, SickKids, Toronto, with input from a COVID-19 working group including representation from the following groups: \(\text{in alphabetical order}\)

- Critical Care – Dr Anne-Marie Guerguerian, Dr Gail Annich, Dr Steven Schwartz, Dr Andrew Helmers
- Emergency Medicine – Dr Kathy Boutis, Dr Suzanne Schuh
- Haematology/Oncology – Dr Jim Whitlock, Dr Ahmed Naqvi
- Immunology and Allergy – Dr Eyal Grunebaum, Dr Vy Kim, Dr Julia Upton
- Infectious Diseases – Dr Upton Allen, Dr Stanley Read, Dr Ari Bitnun, Dr Anu Wadhwa, Dr Michelle Science, Dr Shaun Morris, Dr Valerie Waters, Fellows: Dr Helen Groves, Dr Pierre-Philippe Piche-Renaud, Dr Taito Kitano
- Pharmacy – Kathryn Timberlake
- Paediatrics – Dr Jeremy Friedman, Dr Michael Weinstein, Dr Zia Bismilla, Dr Carolyn Beck
- Respiratory Medicine – Dr Felix Ratjen
- Rheumatology – Dr Rayfel Schneider, Dr Ronald Laxer
- Additional input on thrombosis management from Dr Leonardo Brandao

\(\text{input from additional divisions/stakeholders is pending}\)

This guideline is intended to cover initial case management, laboratory and radiological work-up and potential off-label and experimental use of medications in the management of paediatric patients with COVID-19. It does not provide recommendations for infection control and personal protective equipment use or guidance on testing of patients with possible COVID-19 as these are addressed in separate documents.
In developing this guideline, a scoping review of available literature on off-label and experimental therapies for use in treating patients with COVID-19 was conducted. A summary of this review is included as a separate document entitled “Summary of Scoping Review for Experimental Therapies and COVID-19.” This document details the grading system used as the basis for the current recommendations.

Please note that where mentioned, SARS-CoV-2 refers to the coronavirus species and the resultant disease/illness it causes is referred to as COVID-19.

Please note that information regarding off label use of licensed medications (e.g. hydroxychloroquine, lopinavir/ritonavir, tocilizumab, anakinra) or experimental therapies (e.g. remdesivir) in paediatric patients with COVID-19 is intended only for children who require hospital care. For paediatric patients with COVID-19 who do not require hospital care, such therapies should NOT be prescribed.

This guideline is based on the best available evidence at the time of writing, taking into consideration drug availability in Canada. However, in view of the speed at which new relevant scientific data are being produced, this guideline is intended to be a “living” guideline that will be regularly updated as new evidence emerges. SickKids anticipates that the latest version will be available via the same link (Accessible via a SickKids login). We invite readers to send additional comments, relevant publications and other contributions to the Infectious Diseases Division at covid19working.group@sickkids.ca for the purpose of maintaining this “living guideline”.
3. Algorithm for management of patients with suspected COVID-19

- Fulfills screening criteria for COVID-19*

Clinical assessment

- Isolate and initiate infection control practices as per SickKids High Risk Alert Guidance*

- No

  - Follow SickKids policy to determine if testing indicated

  - No

    - Discharge with observation and advice. Public health notification if SARS-CoV-2 testing positive.

  - Yes

    - Admit

      - Consider sending testing for all respiratory viral infections, including avian influenza or MERS if patient meets case definition**

- Yes

  - NP swab for SARS-CoV-2 testing (if other lower respiratory tract specimen e.g. BAL please also send)

  - Consider chest X-ray, CBC and differential

  - Additional blood and imaging testing as clinically indicated

  - Consult Infectious Diseases (ID) team if patient admitted to critical care with respiratory disease or multisystem inflammatory disorder of unknown cause or if ID team input judged necessary by primary clinical team

SARS-CoV-2 testing confirmed positive

- No

  - Management of patient as per standard practice

- Yes

  - Consult ID team if input not previously requested

    - Make the Critical Care Response Team (CCRT) aware of patient and notify CCRT of any clinical deterioration that may necessitate ICU care (see table 1)

    - Initiate supportive management as per standard of care

    - Perform additional investigations as clinically indicated (see table 2)

    - Additional management considerations as detailed below (see table 3)

    - For patients requiring critical care support - critical care, Respiriology, and ID consult services should be engaged with consideration for input from Rheumatology, Immunology, Haematology and Oncology teams as required

*Please see High risk alert: Novel Coronavirus (COVID-19) available from COVID-19 screening page on SickKids COVID-19 sharepoint resources

**Please see High Risk Alert: Avian influenza (H7N9) and Middle Eastern Respiratory Syndrome Coronavirus accessed via SickKids sharepoint resources
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### Table 1. Classification of Disease Severity in Children*

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>Mild disease</th>
<th>Moderate disease</th>
<th>Severe disease</th>
<th>Critical disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
<td>▪ Symptoms of acute upper respiratory tract infection and/or mild lower respiratory tract infection; may also include fatigue, myalgia, and gastrointestinal symptoms. ▪ Mild or no work of breathing ▪ No O₂ requirement</td>
<td>▪ Clinical and/or radiological signs of pneumonia present ▪ Increased respiratory rate ▪ Signs of increased work of breathing. ▪ O₂ saturation &gt;92% on room air or low flow oxygen</td>
<td>▪ Moderate or severe work of breathing or significant hypoxia: warranting ICU admission for non-invasive ventilation</td>
<td>▪ Paediatric Acute respiratory Distress Syndrome (pARDS) necessitating invasive mechanical ventilation** ▪ May also be characterized by: - Shock/requirement of vasopressors to maintain blood pressure - Multi-Organ failure - Evidence of myocardial injury or heart failure - Acute kidney injury - Coagulation dysfunction</td>
</tr>
</tbody>
</table>

* No clear consensus is yet available to define criteria for severe disease in paediatric patients with COVID-19.

** pARDS Classification

| Age | Exclude patients with peri-natal related lung disease |
| Timing | Within 7 days of known clinical insult |
| Origin of Edema | Respiratory failure not fully explained by cardiac failure or fluid overload |
| Chest Imaging | Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease |
| Oxygenation | Non Invasive mechanical ventilation ▪ PARDs (No severity stratification) ▪ Full face-mask bi-level ventilation or CPAP ≥5 cm H₂O

\[
PF \text{ ratio} \leq 300
\]

\[
SF \text{ ratio} \leq 264
\]

<table>
<thead>
<tr>
<th>Invasive mechanical ventilation</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 ≤ OI &lt; 8</td>
<td>8 ≤ OI &lt; 16</td>
<td>OI ≥ 16</td>
<td></td>
</tr>
<tr>
<td>5 ≤ OSI &lt; 7.5</td>
<td>7.5 ≤ OSI &lt; 12.3</td>
<td>OSI ≥ 12.3</td>
<td></td>
</tr>
</tbody>
</table>

**Special Populations**

| Cyanotic Heart Disease | Standard Criteria above for age, timing, origin of edema and chest imaging with an acute deterioration in oxygenation not explained by underlying cardiac disease. |
| Chronic Lung Disease | Standard Criteria above for age, timing, and origin of edema with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline which meet oxygenation criteria above. |
| Left Ventricular dysfunction | Standard Criteria for age, timing and origin of edema with chest imaging changes consistent with new infiltrate and acute deterioration in oxygenation which meet criteria above not explained by left ventricular dysfunction. |

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<table>
<thead>
<tr>
<th>Mild disease</th>
<th>Moderate disease</th>
<th>Severe disease</th>
<th>Critical disease</th>
</tr>
</thead>
</table>
| - No routine investigations  
- If admitting to hospital due to presence of risk factors or underlying conditions, consider performing investigations as for moderate disease. | - Consider continuous Pulse Oximetry and ECG monitoring  
- CBC with Differential, Serum Creatinine, and ALT at baseline and repeat as clinically indicated.  
- Consider Chest X-ray at baseline  
- Blood cultures prior to initiation of antibiotics, and as clinically indicated  
- In consultation with Infectious Diseases, Immunology and Rheumatology consider additional testing to help identify early signs of disease progression, including:  
  - Urea  
  - Electrolytes,  
  - Liver panel: AST, Bilirubin, GGT, Albumin  
  - Lactate,  
  - Ferritin,  
  - CRP, ESR,  
  - Fasting triglycerides,  
  - LDH,  
  - Coagulation panel** (including fibrinogen, PT/INR, PTT and D-  
  - Chemokine/cytokine panel, including: IL-1b, IL-10, IL-6, IFN-g, CD163, and Soluble IL-2 Receptor Level (CD25), CXCL-9  
  Selected investigations should be performed at baseline and repeated as clinically indicated. | - All investigations considered for moderate disease should be performed at baseline for patients with severe disease. These tests should be repeated as clinically indicated based on regular clinical assessment.  
**The following additional investigations should be considered:**  
- Consider baseline 15 lead ECG to assess for evidence of myocarditis and to monitor QTc if using QTc-prolonging medications. ECG should be performed at baseline and more frequently if clinically indicated.  
- Consider Cardiac enzymes including Troponin I and CK  
- If patient requires intubation and bronchoalveolar lavage as part of clinical care consider sending samples for SARS-CoV-2 PCR. (Notify microbiologist on call)  
- In addition to chemokine/cytokine panel testing, lymphocyte subsets testing should be considered following discussion with infectious diseases and rheumatology teams  
**Note: due to the significant infection control risk with intra-hospital transport for CT chest scanning, this should only be performed in exceptional circumstances where results will significantly impact patient management  
**Note: Avoid bronchoscopy in proven cases of COVID-19: no clear diagnostic benefit and significant added risk of the procedure for healthcare workers | - Investigations as for severe disease plus:  
- Consider echocardiography if signs of myocardial dysfunction |

**Table 2. Suggested investigations in children with COVID-19**

* For some experimental therapies being considered, additional testing may be advised as directed in table 3 below  
** Please refer to Prothrombotic Events and COVID-19 section on page 17
4. Management of hospitalised patients with confirmed COVID-19

Supportive care
For patients with COVID-19, supportive care and treatment of complications should be provided as per standard clinical practice. At present, supportive care is the mainstay of therapy for patients with COVID-19.

General principles of using off-label/experimental therapies
- There is no randomized controlled trial evidence on which to base recommendations for antiviral treatment in persons with COVID-19.
- The use of experimental treatments for patients with COVID-19 should ideally occur within the context of controlled clinical trials.
- In patients not enrolled in clinical trials, use of experimental therapies, for example through compassionate use, should be considered on a case-by-case basis with caution and such treatments should only be given under expert guidance from Infectious Diseases if it is judged that the potential for benefit is likely to outweigh the risk.

Consideration for discussions should include evaluation of severity of illness, availability of experimental anti-viral therapy for off-label or compassionate use, side effect profile of anti-viral therapy and interactions with other treatments as well as family preferences.

When using licensed medications (e.g. hydroxychloroquine, tocilizumab, anakinra) for off-label indications or experimental therapies (e.g. remdesivir), their use should be in line with SickKids policy and procedure for compassionate use of medications. The patient and/or parent(s)/legally authorized substitute decision maker(s) should be informed of the potential anticipated benefits and potential adverse effects of the proposed therapy and the health practitioner should ensure a thorough consent discussion in accordance with SickKids consent to treatment policy. The process of discussion and verbal consent should be clearly documented in the patient's record. (policies.sickkids.ca/published/Published/clinh34/main%20document.pdf)

Note: as stated above, for paediatric patients with COVID-19 who do not require hospital care, antiviral therapy should NOT be prescribed.

- The limited evidence for use of antiviral medications includes in vitro and animal model research pertaining to SARS-CoV-2 and other novel coronaviruses, a limited number of open label observational human trials and extrapolation from theoretical mechanistic knowledge.
- Experience with other viral infections suggests that for antiviral therapy to be maximally effective, it should be administered as early as possible in the illness course. Presently there is no evidence on the optimal timing for anti-viral therapy in persons with COVID-19.

COVID-19 case management specialist team involvement
Patient not initially requiring critical care support:
Patients will be admitted under the care of the paediatric medical team or other primary care team who will direct subsequent consultation with additional services. This includes notification of the Infectious Diseases (ID) consult service and Infection control team for all SARS-CoV-2 positive patients. Additionally, the Critical Care Response Team (CCRT) should be made aware of patients upon admission irrespective of severity and subsequently if there is evidence of clinical deterioration that might necessitate ICU care. Notification of other services is prudent. These include Respiratory Medicine, Rheumatology, Immunology, Haematology/Oncology, Thrombosis team and Clinical Pharmacology.
Patients requiring critical care support:
The Critical Care team, Respiratory Medicine, ID consult and Infection Control services would have been engaged. In addition, it is strongly recommended that there is an initial multidisciplinary team meeting involving services that will likely be engaged if the patient further deteriorates. These services include Rheumatology, Immunology, Haematology/Oncology, Thrombosis team and Clinical Pharmacology.
Table 3. Experimental Treatment Considerations for Hospitalised Paediatric Patients (4 weeks-18 years) with Confirmed COVID-19 According to Clinical Severity

Please note experimental anti-viral therapies should not be routinely recommended for paediatric patients with COVID-19. This table is intended solely for the use of infectious diseases and specialist consulting teams at the hospital for sick children, Toronto, to provide structured guidance in decision-making for the management of exceptional cases of paediatric COVID-19.

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>First-line antiviral therapy to consider</th>
<th>Other antiviral therapies/Other Treatment considerations</th>
<th>Additional comments and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild disease</td>
<td>Supportive care only</td>
<td>For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer the use of hydroxychloroquine can be considered in discussion with infectious diseases on a case-by-case basis, if no contra-indications (e.g. prolonged QTc, history of torsades de pointes, known azithromycin or other macrolide/ketolide hypersensitivity, history of hepatic dysfunction with prior azithromycin use)</td>
<td>Acetaminophen should be used as first-line for fever or temperature management, unless contraindicated. NSAIDS can be considered with caution pending further data (see section below for more detailed discussion)</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Routine use of experimental therapies not recommended</td>
<td>Remdesivir</td>
<td>Details on inclusion criteria for remdesivir compassionate use and application process can be accessed at: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a> Contraindications for remdesivir: ALT/AST &gt;5 x ULN, eGFR &lt;30ml/min Consult Pharmacist prior to submission of remdesivir application. Remdesivir dosing: &lt; 40 kg: 5 mg/kg IV q24h x1, then 2.5 mg/kg IV q24h for 9 days ≥40kg: 200 mg IV q24h x1, then 100 mg IV q24h for 9 days - It is likely that benefit from remdesivir (if any) will occur from receiving this treatment earlier in the disease course - Note that information on the adverse effects of remdesivir are still limited and risk-benefit of using this should be assessed on an individual basis with close monitoring of toxicity</td>
</tr>
<tr>
<td>Mild disease</td>
<td>Consider use of remdesivir in patients considered at high risk for severe infections if there are no contra-indications for use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors for severe disease present*</td>
<td>Hydroxychloroquine: Paediatric dosing: 6.5 mg/kg/dose (max 400 mg/dose) PO BID x 1 day, followed by 3.25 mg/kg/dose (max 200 mg/dose) PO BID x 4 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Note:
Do not crush tablets. Extemporaneous suspension can be compounded if unable to take tablets.

### Contraindications and Warnings for hydroxychloroquine
- QTc>500 msec
- Myasthenia gravis
- Porphyria
- Retinal pathology
- Known G6PD deficiency (HCQ is considered generally safe in patients with G6PD deficiency, G6PD testing is not currently considered necessary prior to use)

Perform ECG prior to commencing therapy and assess frequency of repeat on a case-by-case basis (especially if initial QTc is 450-500 msec).
- If adding additional QTc prolonging drugs e.g. azithromycin with hydroxychloroquine, daily ECG monitoring is required due to possible drug interactions causing QTc prolongation.

### Routine use of experimental therapies not recommended

<table>
<thead>
<tr>
<th>Disease Level</th>
<th>Therapy Details</th>
</tr>
</thead>
</table>
| Moderate      | In discussion with Infectious Diseases on a case-by-case basis:  
- For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer:  
  the use of hydroxychloroquine can be considered if no contra-indications as detailed above  
- If contra-indication to hydroxychloroquine or no hydroxychloroquine available and ongoing consideration for antiviral therapy, consider lopinavir/ritonavir (LPV/r) [if early in disease course]  
- Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases |
|               | Remdesivir dosing and access considerations as detailed above  
- HCQ dosing, contra-indications and monitoring considerations as detailed above |
|               | Lopinavir/ritonavir (LPV/r) dosing:  
- < 6 months:  
  300 mg/m²/dose PO BID (dose limit: 800 mg/day) x 10-14 days  
  6 months to 12 yrs and <35kg:  
  230mg - 300 mg/m²/dose PO BID (dose limit: 800 mg/day) x 10-14 days/day  
- > 12 yrs or ≥ 35 kg:  
  400 mg PO BID x 10-14 days  
Additional Testing Requirements for LPV/r:  
- Amylase, and lipase and liver enzymes at baseline and thereafter as clinically indicated. under Infectious Diseases guidance. Contra-indications to LPV/r include previous hypersensitivity. Care should be taken if history of cardiac disease and/or presence of drug interactions.** |

**Moderate disease**

- In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team [see above] on a case-by-case basis:  
  Consider use of remdesivir in patients considered at high risk for severe infections if there are no contra-indications for use |
| Severe and critical disease | Routine use of experimental therapies not recommended | For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer: the use of hydroxychloroquine can be considered if no contra-indications as detailed above  
In discussion with Infectious Diseases and multidisciplinary COVID-19 case management team (see above) on a case-by-case basis:  
Consider use of remdesivir in patients considered at high risk for severe infections if there are no contra-indications for use  
If contra-indication to hydroxychloroquine or no hydroxychloroquine/chloroquine available consider lopinavir/ritonavir (LPV/r) (if early in disease course)  
Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases  
For patients with evidence of ARDS or cytokine release syndrome see sections below detailing further management considerations | Remdesivir access considerations and dosing as detailed above in mild disease section  
For patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer: the use of hydroxychloroquine can be considered if no contra-indications as detailed above  
If contra-indication to hydroxychloroquine or no hydroxychloroquine/chloroquine available consider lopinavir/ritonavir (LPV/r) (if early in disease course)  
Consider antibiotic therapy if concern for secondary bacterial pneumonia, as per recommendations below - Please discuss antibiotic choice with Infectious Diseases  
For patients with evidence of ARDS or cytokine release syndrome see sections below detailing further management considerations |

* Please see risk factor discussion in section below.  
**Note: For drug interactions in the setting of COVID-19 experimental therapies check at http://www.covid19-druginteractions.org
Risk factors for severe illness in children with COVID-19

There are some reports of moderate and severe infection in children requiring hospitalization. However, severe disease in children is uncommon and risk factors for severe disease in the paediatric population are yet to be clearly defined. One large study recently published in Paediatrics by Dong et al. noted that over 60% of severe and critical cases of COVID-19 in children occurred in those aged five years or less. A further report from the United States CDC noted that among children with COVID-19, 147 were hospitalized (estimated range 5.7-20%) with 15 (0.58%-2%) admitted to ICU. Data on underlying medical conditions and risk factors in hospitalized patients was limited. Children aged less than 1 year accounted for the highest percentage of hospitalization and all patients admitted to ICU for which there was available information, had one or more underlying medical condition, however the nature of these conditions has not yet been specified. More recently data from a multicentre Italian study of children and adolescents also showed increased hospitalisation rates in children under 1 year old. Notably, the hospitalisation rate was similar between children with comorbidities and those without and mechanical ventilation was only required in 2 out of 168 children studied, one of whom was preterm and the other had congenital heart disease. In a cross-sectional study of 46 North American PICUs with 48 children admitted secondary to COVID-19, 83% were noted to have significant pre-existing comorbidities. Of these, comorbidities included; medically complex patients (long-term dependence on technological support, developmental delay, genetic abnormalities), immune suppression, obesity, diabetes, seizures, congenital heart disease, chronic lung disease, sickle cell disease.

Extrapolating from these and adult data, as well as from risk factors for severe disease in children with other human coronavirus infections, it might be reasonable to consider that immunocompromised children or children with comorbidities, such as obesity, congenital heart disease, lung disease, sickle cell disease, genetic abnormalities, neurological disease or diabetes mellitus, may be at increased risk of severe infection.

Acute respiratory distress syndrome (ARDS) and children with COVID-19

ARDS in paediatric cases of COVID-19 is likely to be an uncommon event. In their review of over 2000 paediatric patients with COVID-19, Dong et al. reported that only 0.6% progressed to ARDS or multi-organ failure. Information on the specific management of ARDS in paediatric cases of COVID-19 is limited at present. Extensive guidelines from the Surviving Sepsis Campaign on the management of critically ill adults with COVID-19 include recommendations for the management of ARDS in this population. In brief, these guidelines recommend appropriate ventilation strategies such as use of low tidal volumes, conservative fluid strategies over liberal fluids, use of prone ventilation, appropriate neuromuscular blockade and sedation, with move to elective ECMO as needed if refractory hypoxemia despite these measures. These guidelines also recommend that in mechanically ventilated adults with COVID-19 and ARDS, use of systemic steroids may be considered.

In general, the principles of management of paediatric ARDS secondary to COVID-19 are likely to be aligned with those of the adult population. However, there are key differences between paediatric and adult physiology as well as differences in the management of ARDS to consider with respect to the paediatric population. Accordingly, specific management of ARDS in children with COVID-19 will be assessed on a case-by-case basis under the direction of critical care and respiratory teams when appropriate.

Severe respiratory failure with COVID-19 may occur in children with underlying conditions such as asthma. In patients with COVID-19 presenting with asthma, please follow the Critical Care Response Team and Emergency Department recommendations.
Management considerations for Cytokine Release Syndrome (CRS)/secondary Hemophagocytic lymphohistiocytosis (HLH) in children with COVID-19

Cytokine release syndrome (CRS) has been highlighted as an important component of the critical illness associated with COVID-19 in adults. Severe COVID-19 has also been associated with a cytokine profile resembling secondary HLH. In particular, elevations in levels of IL-6 has been shown to correlate with mortality in adult patients with COVID-19. In light of these findings a number of immunomodulatory agents have been proposed as theoretical therapeutic options for patients experiencing CRS with COVID-19. These include IL-6 receptor antagonists such as tocilizumab and the IL-1 blocker anakinra as well as JAK-pathway inhibitors. Available evidence for some of these agents is detailed in the “Summary of Scoping Review for Experimental Therapies and COVID-19” document and a brief summary is also provided in appendix 1.

The current data do not support a firm course of action regarding the use of immunomodulatory agents or timing for their implementation. Therefore, presently we do not recommend the routine use of immunomodulatory agents in children with COVID-19 pending further data. In exceptional circumstances, on a case-by-case basis where monitored cytokine levels or serum markers indicate clear evidence of cytokine storm, immunomodulatory agents may be considered under expert guidance from the respective clinical teams. Candidate agents include, but are not limited to, tocilizumab and anakinra. Please refer to appendix 1 for further details on treatment considerations for patients with CRS/HLH secondary to COVID-19.

Antibiotic therapy

- General considerations:
  Other potential causes of pneumonia, such as non-SARS-COV-2 respiratory viruses, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and other bacterial pathogens should be considered in all children admitted with suspected COVID-19.
  Early data suggests that rates of secondary bacterial pneumonia in children with COVID-19 are low and thus far, adult centres are not reporting high rates of bacterial superinfection.
  Common organisms implicated in secondary bacterial pneumonia for influenza include; *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *non-typable Haemophilus influenzae*.

- Antibiotic therapy should follow SickKids antibiotic guidance for community-acquired bacterial pneumonia with additional consideration for *S. aureus* coverage.
  - Ceftriaxone or cefuroxime should be considered as first line antibiotic treatment for suspected secondary bacterial pneumonia in children at least 1 month of age with COVID-19.
  - Ceftriaxone plus vancomycin is recommended in severe cases requiring critical care management
  - For severely Beta-lactam allergic patients, macrolides or fluoroquinolones (such as levofloxacin) with or without the addition of an anti-staphylococcal agent such as vancomycin or clindamycin are appropriate options
  - **Note**: quinolones should be used with caution in patients receiving hydroxychloroquine due to risk of QTc prolongation
  - Combination azithromycin therapy with hydroxychloroquine is not recommended as its use is not supported by available evidence and introduces the risk of additive toxicity, in particular related to prolongation of the QTc and reported increased rates of cardiac arrest.
Prothrombotic Events in patients with COVID-19

Reports are emerging of a high prevalence of DVT/PE in adults hospitalized with COVID-19, particularly in critically ill patients. Anticoagulation prophylaxis is being offered to all adult patients with COVID-19 with dose escalation consideration according to D-dimer titres. In children, overall absolute thrombotic risk is much lower than adults and the risk of thrombotic events in the context of COVID-19 in children is much less clear. Coagulation panel (PT/INR, PTT, fibrinogen, platelet count, and D-dimer) should be considered at baseline in children with COVID-19 with projected stay > 24 hours and repeated as clinically indicated. Patients with limb swelling should undergo Doppler USS to exclude DVT and CTPA should be considered in patients whose respiratory parameters worsen out of keeping with other markers of COVID-19 disease severity.

Use of other therapies/areas of controversy

Convalescent sera

At present published data on use of convalescent plasma is limited to small case series.16,17 Multiple trials of convalescent plasma use in patients with COVID-19 are ongoing worldwide. Thus far, no serious adverse reactions or safety events have been recorded following COVID-19 convalescent transfusion. Presently, as per Health Canada recommendations, convalescent plasma is not available for use outside of approved clinical trial settings.

Corticosteroids

Use of systemic corticosteroids should in general be avoided due to possible harm and lack of clear evidence supporting their use. Most data on the use of corticosteroids for novel coronavirus infections are based on observational studies with significant methodological limitations showing mixed results. A retrospective observational study from Hong Kong on adult patients with SARS found that any steroid therapy was associated with increased need for ICU admission or mortality.18 However, in a separate observational study with a focus on critical care patients, corticosteroid use was associated with lower overall mortality and shorter hospitalization stay.19 No controlled clinical trials on the use of corticosteroids in COVID-19 patients or other coronaviruses have yet been reported. A recent non-peer-reviewed report of 26 adult patients with severe COVID-19 (unclear if ARDS) found that methylprednisolone for 5-7 days was associated with a shorter duration of supplemental oxygen use and improved radiological findings.20 A further observational cohort study of 201 patients in Wuhan, China found that in patients with ARDS, methylprednisolone decreased the risk of mortality.21 In view of the confusing, and inconclusive scientific data based on poor quality evidence, as well as the potential for steroid therapy to worsen outcomes, routine use of steroids is currently not recommended for paediatric patients with COVID-19.

In exceptional circumstances where steroids are indicated for other reasons, such as patients presenting with symptoms of severe asthma in the context of COVID-19, cautious use of systemic steroids may be considered on a case-by-case basis where benefits of therapy are felt to outweigh the risks. Of note, guidance from the National Health Commission of the People’s Republic of China recommends that if steroids are being considered in patients with COVID-19, this should be of low dose and short duration (e.g. methylprednisolone 1-2 mg/kg/day for 3-5 days or less) due to the risk of delayed viral clearance and immune suppression.22

Use of corticosteroids in the setting of CRS/HLH management is discussed in appendix 1 and should only be considered on a case-by-case basis under the directions of specialists with expertise in managing these conditions.
Immunoglobulin therapy (IVIG)

IVIG has not been demonstrated to be of benefit and should not be used routinely in patients with COVID-19. Some guidelines are recommending to consider the use of IVIG therapy at standard dosing in special patient populations such as those with IgG < 4g/L.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Recent commentaries have been published suggesting ibuprofen should be avoided in patients with COVID-19. There are limited data on the use of NSAIDs in the context of COVID-19 and much of the evidence is derived from work in sepsis and other respiratory diseases where complications were more common in patients taking ibuprofen. For COVID-19, there are no firm data to suggest NSAIDs worsen the course of COVID-19 and further data are needed to draw clear conclusions on this. Based on currently available information, the World Health Organization does not recommend against the use of ibuprofen.

As a pragmatic approach pending further data on this controversial issue, we suggest that acetaminophen is the preferred first line option for treatment of fever in COVID-19 provided there are no contra-indications to its use.

- For patients who are already on NSAID therapy for other medical conditions, pending further data we do not currently advise discontinuing these. If such patients develop COVID-19, they should be advised to consult with their care providers regarding continued NSAID use.

Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin Receptor Blockers (ARBs)

SARS-CoV-2 uses ACE2 as its cellular entry receptor. Controversy exists as to whether ACE inhibitors and ARBs could be beneficial in reducing COVID-19 severity or conversely exacerbate disease. One recent large study of adults with COVID-19 did not find any evidence of increased risk of severe COVID-19 and use of ACE inhibitors or ARBs. Therefore, patients on these medications should be advised to continue them as per standard practice for their care. For patients with COVID-19 who are on ACE inhibitors or ARBs, case-by-case decisions can be made regarding ongoing use based on clinical presentation and opinion from the primary medical team in consultation with Infectious Diseases or the multidisciplinary COVID-19 case management team (see above). Clinical trials on the use of ARBs e.g. losartan as therapy in COVID-19 are ongoing.
Clinical features of paediatric patients with COVID-19

One large case series has reported on the clinical characteristics of children with confirmed COVID-19.2 Of 1391 children assessed and tested from January 28th through February 26th 2020, a total of 171 had confirmed SARS-CoV-2 infection. The median age was 6.7 years with a male predominance and even spread amongst age groups. Of these 171, 48.5% had cough, 46.2% pharyngeal erythema, 41.5% fever (median duration 3 days), 8.8% had diarrhoea, 7.6% had fatigue, 7.6% had rhinorrhoea, 6.4% had vomiting and 5.3% had nasal congestion.

Another larger case series of 2143 paediatric patients with confirmed COVID-19 was reported by the Chinese Center for Disease Control and Prevention.1 The median age was 7 years (Interquartile age 2-13 years). Over 90% were asymptomatic, mild or moderate cases and no deaths were reported. Of the paediatric cases who had severe or critical disease (5.8%) approximately 60% were aged five years or less.

Provisional data from Italy on 17th March 2020 highlighted that of 22,512 cases of COVID-19, only 1.2% were in patients aged less than 18 years old and that there were no deaths in patients aged under 20 years.27

In a retrospective case series of 10 hospitalized paediatric cases from China, the mean age at hospitalization was 6 years, 80% had fever, 60% cough, 40% sore throat, 30% stuffy nose and 20% sneezing and rhinorrhea. In this series none of the children had diarrhoea or vomiting.28 The assumed incubation period was between 2 and 10 days and symptoms typically resolved within 1 week.

Symptoms of COVID-19 in children are typically milder than that of adult cases, and asymptomatic cases have also been reported. However, while severe disease is uncommon in children, there are increasing reports of children requiring intensive care support and deaths in children due to COVID-19 have also been reported.

There have been reports of atypical symptoms in adult cases of COVID-19 such as anosmia and acute conjunctivitis, with alerts being issued to otolaryngology and ophthalmology teams regarding these symptoms.29,30

Reports of vascular and dermatological phenomena in association with COVID-19 have been described in both children and adults. The Canadian Dermatological Association notes the following skin changes with COVID-19:31

- “Covid toes” (or covid hands) – similar to the type of cold related changes we have seen in the feet of people for many years, but often occurring in places where the conditions are not cold and damp. These seem to happen more commonly in younger patients.
- Rash with or without small blisters
- Widespread hives (urticaria)
- Small bruises and broken blood vessels (petechiae)

Paediatric multisystem inflammatory syndrome in the setting of the COVID-19 outbreak

There are increasing reports of children with significant systemic inflammatory response syndromes in countries experiencing COVID-19 outbreaks. Regions reporting this have noted a spike in cases that occurs approximately one month following the overall peak of COVID-19 cases.
This syndrome shares many features common to other paediatric inflammatory conditions and cases may present with features of Kawasaki disease (KD), shock and toxic-shock-like syndrome.

For further information on identification and management of this condition please refer to the document “Practice alert: Rise in cases of paediatric multisystem inflammatory syndrome in the setting of the COVID-19 outbreak” available on the SickKids Sharepoint, COVID-19 information for clinicians.

**Neonates and COVID-19**

Please refer to the SickKids Neonatal COVID-19 Management document available on the SickKids sharepoint, COVID-19, information for clinicians.
### General principles

- Careful monitoring of patient clinical status and serum markers is crucial in determining need for therapeutic intervention in exceptional cases
- **First line management of CRS/secondary HLH is supportive**, i.e. oxygen and ventilator support, fluid management, vasopressor/inotropic support and treatment of complications.
- Symptom progression should be monitored using a modified Penn Grading Scale for CRS (see table 4 below)

### Table 4. CRS status grading for children with COVID-19 (adapted from Penn CRS criteria)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild:</td>
<td>Moderate:</td>
<td>Severe:</td>
<td>Life threatening:</td>
</tr>
<tr>
<td>• supportive care only required</td>
<td>• requiring intravenous fluid (IV) support (not hypotension)</td>
<td>• Significant liver enzyme dysfunction and creatinine elevation not attributable to other condition</td>
<td>• Hypotension requiring high dose vasopressors</td>
</tr>
<tr>
<td></td>
<td>• FEVERS</td>
<td>• Hypotension requiring IV fluid support (multiple fluid boluses) or low dose vasopressors</td>
<td>• Hypoxia requiring mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td>• Neutropenia</td>
<td>• Coagulopathy requiring fresh frozen plasma, fibrinogen concentrate or cryoprecipitate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mild organ dysfunction (mild creatinine elevation and liver enzyme dysfunction)</td>
<td>• Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP, BiPAP)</td>
<td></td>
</tr>
</tbody>
</table>

- Symptoms may include high fever, rigors, myalgia, nausea, vomiting, anorexia, fatigue, headache, hypotension, encephalopathy, dyspnoea, tachypnoea and hypoxia
- Signs may include marked elevation in IL-6, interferon gamma and TNF-α

- Patients with grade 2 or higher symptoms should have serum and cytokine markers sent as per investigation guidance detailed in section 3 above
- The following progression in clinical status despite supportive care should trigger notification of the COVID-19 case management specialist team as detailed on page 6:
  - Haemodynamic instability despite intravenous fluids and vasopressor support
  - Worsening respiratory distress, including pulmonary infiltrates, increasing FiO2 requirement and/or need for mechanical ventilation
  - Rapid clinical deterioration
  - Presence of hyper-inflammation:
    - Lymphocyte counts <1000 cells/mL
    - Ferritin >500 ng/mL
    - LDH >300 U/L
    - D-Dimer >1000 ng/mL
    - Marked elevation in IL-6 and other measured cytokines (as detailed in table 2, page 5)
- On an exceptional case-by-case basis, the COVID-19 case management specialist team may consider initiation of immunomodulatory therapy. Anakinra has been proposed as a potential first line choice in light of its shorter half-life. However, there is a lack of available consensus for immunomodulatory therapy use in children with COVID-19 and a number of other potential immunotherapies, including tocilizumab have also been proposed.
• If no clinical improvement with immunomodulatory treatment occurs within 12-18 hours, consideration may be given to further/increased doses of immunomodulatory therapy and/or corticosteroid therapy.
  
  o Optimal dosing of corticosteroids for use in patients with COVID-19 remains controversial. Dosing for management of CRS following CAR-T Cell therapy is suggested as 1-2 mg/Kg methylprednisolone as an initial dose, then 1-2 mg/Kg per day followed by a rapid taper after haemodynamic normalization.

• If no response within 24-48 hours, consider alternative immunomodulatory therapy options for treatment of CRS.

Table 5. Suggested paediatric dosing for anakinra and tocilizumab

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra</td>
<td>S/C or IV</td>
<td>5-10 mg/kg/day in 3-4 divided doses</td>
<td>Max total dose in 24 hours: 400mg  Stop if no clinical benefit at maximum dose</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IV</td>
<td>Weight &lt; 30 kg: 12 mg/kg IV over 1 hour</td>
<td>If no improvement at 12-18 hours, consider repeat with same dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight &gt; 30 kg: 8 mg/kg IV over 1 hour (max dose 800 mg)</td>
<td></td>
</tr>
</tbody>
</table>

* Appendix 1 was developed following the meeting of a specific COVID-19 working group on 15th April 2020 to address the management approach to patients with cytokine release syndrome in the setting of COVID-19. Key contributors to this CRS working group included; Critical care: Dr Anne-Marie Guergerian; Infectious Diseases: Dr Upton Allen, Dr Stanley Read, Dr Anupma Wadhwa, Dr Valerie Waters, Dr Shaun Morris, Dr Michelle Science; Oncology: Dr Ahmed Naqvi; Rheumatology: Dr Rayfel Schneider, Dr Ronald Laxer. The guidance presented above is a modified version of the SickKids guidance for management of CAR-T Cell therapy induced CRS (BMT4870/01 - CAR-T Cell Therapy - Administration and Management of Toxicities) on 22nd April 2020.

Summary of available literature for use of tocilizumab and anakinra in patients with COVID-19

Tocilizumab is an FDA approved agent and its use is well established for the treatment of severe or life-threatening cytokine release syndrome (CRS) induced by chimeric antigen receptor (CAR) T cell therapy. In the context of COVID-19, a small study of 20 adult patients in China treated with tocilizumab found fever resolved within one day of commencing therapy in all patients, with all but one patient being discharged from hospital within two weeks. However, the small size and lack of control group makes it difficult to draw firm conclusions on the safety and efficacy of tocilizumab in treating patients with COVID-19 from this data. In a separate small single centre study, Luo et al. reported use of tocilizumab in 15 COVID-19 patients. Of these, seven were defined as critically ill, three died within 7 days of therapy and one was clinically worse at the time of reporting. The remaining patients were classed as moderate or severe and all but one were reportedly stable or improved after 7 days. The absence of comparison groups and publication with short follow-up times, makes interpretation of efficacy from these small single-centre studies impossible. Therefore, it is unclear at this stage if possible benefits outweigh potential risks of tocilizumab therapy in treating paediatric patients with COVID-19. Anakinra has been shown to be of benefit when given early in disease course for other causes of CRS. In a recent retrospective cohort study in Milan, Italy of patients with COVID-19, moderate-to-severe ARDS, and hyperinflammation found 21 day survival was higher in the high-dose anakinra group versus the standard treatment group (p=0.009). A further potential advantage of this therapy is its short half-life which may reduce concerns regarding adverse effects. Further clinical trials of anakinra in adult patients with COVID-19 are ongoing.
7. Appendix 2. Previous Changes to Document Versions

Key changes from previously uploaded version – Version 3.1 24th April 2020

- Page 5: Update of investigation section (table 2) to include suggested cytokine testing IL-1, IL-10, IL-6, and IFN-gamma, sIL2r (CD25) and CD163
- Page 5: New statement regarding thrombosis risk in children with COVID-19 and appropriate investigations (table 2)
- Page 6/7: Statements regarding COVID-19 case management specialist team involvement
- Page 13: Comment on the use of convalescent plasma in the management of patients with COVID-19
- Page 12, 16, 17: additional suggested considerations in the management of cytokine release syndrome in patients with COVID-19

Key changes from previously uploaded version – Version 2.3 7th April

- New comment in background section highlighting that for paediatric patients with COVID-19 who do not require hospital care, antiviral therapy should NOT be prescribed.
- New comment regarding the process of informed verbal consent for parents relating to the option of experimental therapies in COVID-19 added under the section: “General principles of using off-label/experimental therapies”
- Guidance in table 3 now includes only paediatric hydroxychloroquine dosing based on weight with maximum doses included. Frequency of repeat ECGs in patients receiving hydroxychloroquine to be assessed on a case-by-case basis.
- Update on preliminary paediatric data from US CDC data added in risk factor section
8. References


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