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

Version 2.3, 7th April 2020

Key changes from previously uploaded version

- 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

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, infants and children aged under 5 years were more likely to have severe disease compared to older children.[1]

Background to guideline 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 more 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: *(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
- 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

(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.

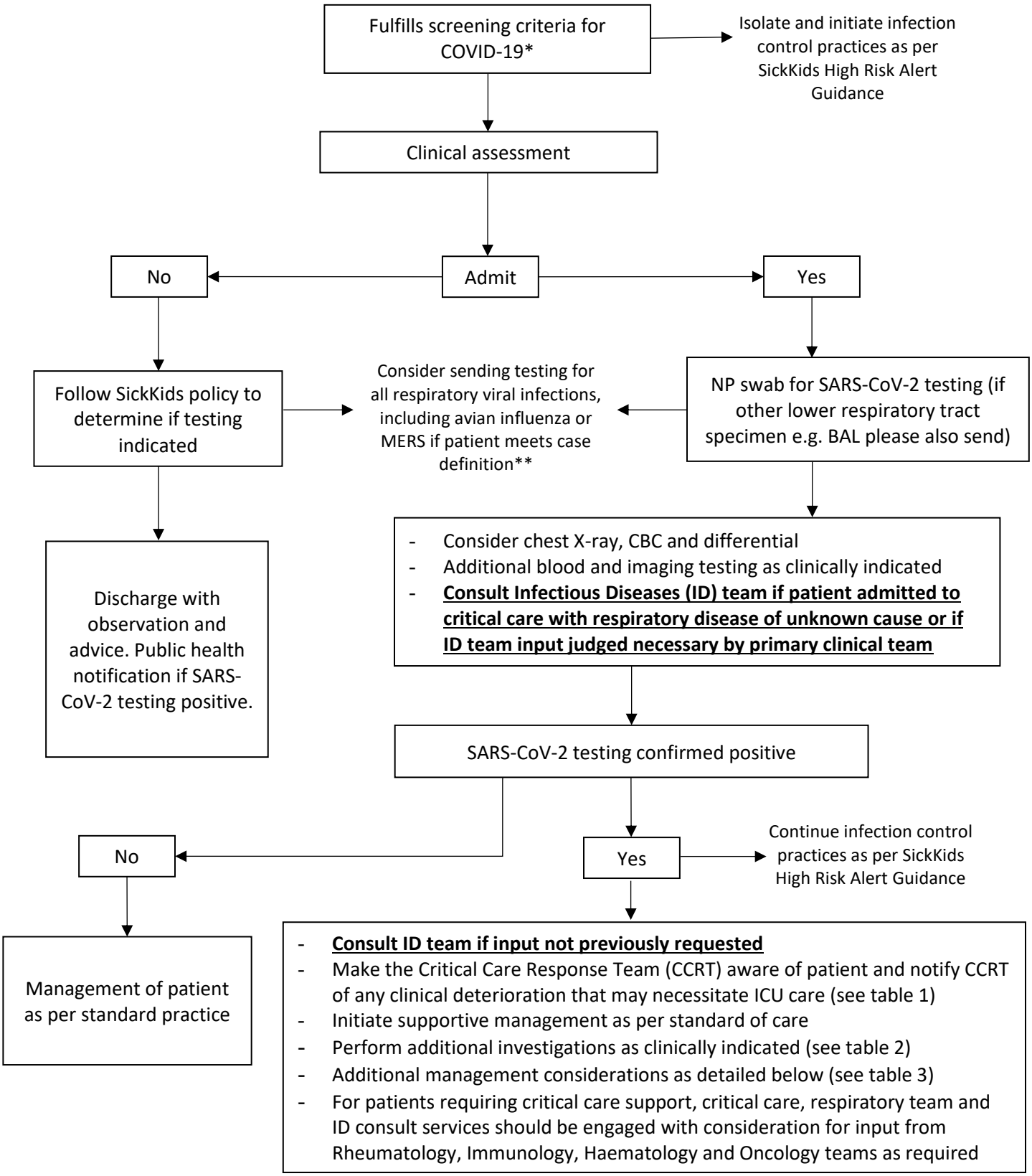
In developing this guideline, a scoping review of available literature on off-label and experimental therapies for use in treating patients with COVID-19 was conducted. A summary of this review is included as a separate document entitled "Summary of Scoping Review for Experimental Therapies and COVID-19." 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".

Algorithm for management of patients with suspected COVID-19



*Please see updated High Risk Alert: Novel Coronavirus (COVID-19) accessed via SickKids sharepoint at:
Sickkids.ca.sharepoint.com/sites/IPAC/Documents/Alerts/High%20Risk%20Alert-Novel%20Coronavirus%20-%20COVID-19.pdf

**Please see updated High Risk Alert: Avian influenza (H7N9) and Middle Eastern Respiratory Syndrome Coronavirus: MERS-CoV accessed via SickKids staff support resources.

Table 1. Classification of Disease Severity in Children*

Disease severity	Mild disease	Moderate disease	Severe disease	Critical disease
Criteria	▪ 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 O_2 requirement	▪ Clinical and/or radiological signs of pneumonia present ▪ Respiratory rate: increased ▪ Signs of increased work of breathing. ▪ O_2 saturation >92% on room air or low flow oxygen	▪ Moderate or severe work of breathing or significant hypoxia: warranting ICU admission for non-invasive ventilation	▪ 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

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

** **pARDS Classification**[6]

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**	**Invasive mechanical ventilation**		
	PARDS (No severity stratification)	Mild	Moderate	Severe
	Full face-mask bi-level ventilation or CPAP ≥5 cm H_20 [2] PF ratio ≤ 300 SF ratio ≤ 264 [1]	4 ≤ OI < 8 5 ≤ OSI < 7.5[1]	8 ≤ OI < 16 7.5 ≤ OSI < 12.3[1]	OI ≥ 16 OSI ≥ 12.3[1]
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. [3]			
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.[3]			
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.			

Table 2. Suggested investigations to consider in children with COVID-19 according to disease severity*

Mild disease	Moderate disease	Severe disease	Critical disease
▪ No routine investigations ▪ If admitting to hospital due to presence of risk factors consider performing investigations as for moderate disease	▪ Consider continuous cardiorespiratory monitoring ▪ CBC and differential, serum creatinine, ALT at baseline and repeat as clinically indicated based on regular assessment ▪ Consider Chest X-ray ▪ In consultation with Infectious Diseases, Immunology and Rheumatology consider additional serum markers testing to help identify early signs of disease progression, including: urea and electrolytes, liver panel, lactate ferritin, CRP, ESR, fasting triglycerides, LDH, fibrinogen, INR, PTT and D-dimer and cytokine panel (includes IL-1, IL-6, IL-10, IL-18, TNF alpha, CD 163, CXCL 9, and IFN-gamma) at baseline and repeated as clinically indicated.	▪ Continuous cardiorespiratory monitoring ▪ CBC and differential, serum creatinine, urea and electrolytes, liver panel, lactate, ferritin, CRP, ESR, fasting triglycerides, LDH, fibrinogen, INR, PTT, D-Dimer at baseline. Repeat as clinically indicated based on regular clinical assessment. ▪ Consider blood cultures if clinically indicated ▪ Perform Chest X-ray ▪ Consider ECG in view of the risk of myocarditis and the need to monitor QTc if using hydroxychloroquine therapy: ECG should be performed at baseline and more frequently if clinically indicated (e.g. use of hydroxychloroquine plus azithromycin or quinolone antibiotic, concern for myocarditis) ▪ Consider cardiac enzymes monitoring via troponin levels ▪ If patient requires intubation and bronchoalveolar lavage as part of clinical care consider sending samples for SARS-CoV-2 PCR. (Notify microbiologist on call) ▪ Send chemokine/cytokine panels to include IL-1, IL-6, IL-10, IL-18, TNF alpha, CD 163, CXCL 9, and IFN-gamma and lymphocyte subsets following discussion with Infectious Diseases, Immunology 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 on 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 <u>plus</u>:** ▪ Consider ECHO if other signs of myocardial dysfunction

***For some experimental therapies being considered, additional testing may be advised as directed in table 3 below**

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, lopinavir/ritonavir, 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.

Table 3. Experimental Treatment Considerations for Hospitalised Paediatric Patients 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.

Disease Severity	First-line antiviral therapy to consider	Other antiviral therapies/Other Treatment considerations	Additional comments and precautions
▪ Mild disease ▪ No risk factors for severe disease present*	▪ Supportive care only		Acetaminophen should be used as first-line for fever or temperature targeted management, unless contraindicated. NSAIDS can be considered with caution pending further data (see section below for more detailed discussion)
▪ Mild disease ▪ Risk factors for severe disease present*	**Routine use of experimental therapies not recommended** In discussion with Infectious Diseases and COVID-19 consultation team on a case-by-case basis: ▪ Consider use of **hydroxychloroquine** in patients considered at high risk for severe infections If no contra-indications for use	▪ If considering anti-viral therapy with hydroxychloroquine, consider addition of **azithromycin**[#] 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)	Hydroxychloroquine dosing: Paediatric dosing: 6.5 mg/kg/dose (max 400mg/dose) PO BID x 1 day, followed by 3.25 mg/kg/dose (max 200mg/dose) PO BID x 4 days Note do not crush (extemporaneous solution compounding if unable to take tablets) Contra-indications to hydroxychloroquine ▪ QTc>500 msec ▪ Drug-interactions: check at http://www.covid19-druginteractions.org (Liverpool) interactions potential of hydroxychloroquine is likely the same as chloroquine ▪ Myasthenia gravis ▪ Porphyria ▪ Retinal pathology ▪ Epilepsy Perform ECG prior to commencing therapy and assess frequency of repeat on a case-by-case basis (especially if initial QTc is 450-500msec). ▪ If adding azithromycin with hydroxychloroquine, daily ECG or cardiac monitoring is required due to possible drug interactions causing QTc prolongation Note: hydroxychloroquine is considered generally safe in G6PD deficiency,[7] G6PD testing not currently considered necessary prior to use

▪ Moderate disease	**Routine use of experimental therapies not recommended** In discussion with Infectious Diseases and COVID-19 consultation team on a case-by-case basis: ▪ Consider use of **hydroxychloroquine** <u>in patients considered at high risk for severe infections</u> If no contra-indications for use	In discussion with Infectious Diseases on a case-by-case basis: ▪ Consider parallel application for compassionate use of **remdesivir,** particularly in patients with risk factors for severe COVID-19 ▪ If considering anti-viral therapy with hydroxychloroquine, consider addition of **azithromycin**[#] if no contra-indications (see above) ▪ If contra-indication to hydroxychloroquine or no hydroxychloroquine/chloroquine available and ongoing consideration for antiviral therapy, consider **lopinavir/ritonavir (LPV/r)** <u>(if early in disease course)**</u> ▪ Consider need for antibiotic therapy if concern for secondary bacterial pneumonia - Please discuss with Infectious Diseases before commencing (see recommendations below)	▪ Dosing and considerations for hydroxychloroquine as detailed above in mild disease section ▪ If adding azithromycin with hydroxychloroquine, daily ECG is required due to possible drug interactions causing QTc prolongation ▪ Use of remdesivir is currently restricted and supply is limited, note below table regarding inclusion and exclusion criteria:[$] for remdesivir compassionate use apply through portal at https://rdvcu.gilead.com/ <u>Remdesivir dosing</u> < 40 kg: 5mg/kg loading dose; then 2.5mg/kg IV q24h x 10-14 days ≥40kg: 200mg IV q24h x1 then 100mg IV q24h for days 2 to 20 - For paediatric cases of COVID-19 remdesivir is available for compassionate use - process from application to receipt of drug takes approximately 72 hours: in view of the exclusion criteria many if not all paediatric cases in ICU be ineligible for remdesivir. - 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 ▪ <u>Lopinavir/ritonavir dosing:</u> <6 months: 300 mg/m^2/dose PO BID (dose limit: 800 mg/day) 6 months to 12 yrs: 230mg - 300 mg/m2/dose PO BID (dose limit: 800 mg daily) >12 yrs or ≥35 kg: 400mg PO BID, Continue for up to 10-14 days <u>If using LPV/r therapy check amylase, lipase and liver enzymes at baseline and thereafter as clinically indicated under Infectious Diseases guidance.</u> Contra-indications to lopinavir include previous hypersensitivity. Care should be taken if history of cardiac disease history and there is potential for drug-drug interactions with this medication.

▪ Severe and critical disease	In discussion with Infectious Diseases and COVID-19 consultation team on a case-by-case basis: ▪ Consider use of **hydroxychloroquine**, particularly in patients with risk factors for severe COVID-19 if no contra-indication	▪ Consider parallel application for compassionate use of **remdesivir** ▪ If considering anti-viral therapy with hydroxychloroquine, consider addition of **azithromycin**[#] if no contra-indications (see above) ▪ If contra-indication to hydroxychloroquine or no hydroxychloroquine/chloroquine available consider **lopinavir/ritonavir (LPV/r) (**if early in disease course)****** ▪ Consider need for antibiotic therapy if concern for secondary bacterial infection - please discuss with Infectious Diseases before commencing (see recommendations below) ▪ **For patients with evidence of ARDS or cytokine release syndrome see sections below detailing further management considerations**	▪ Dosing and considerations for hydroxychloroquine as detailed above in mild disease section ▪ If adding azithromycin with hydroxychloroquine, daily ECG is required due to possible drug interactions causing QTc prolongation ▪ Remdesivir access considerations and dosing as detailed above in moderate section ▪ LPV/r dosing and considerations as detailed above in moderate section

Note: For drug interactions in the setting of COVID-19 experimental therapies check at http://www.covid19-druginteractions.org

* Please see risk factor discussion in section below.

** In a recent open-label randomised controlled trial of lopinavir-ritonavir (LPV/r) vs. placebo for treatment of severe COVID-19 in China, primary outcome of time to clinical improvement and secondary outcome of 28 day mortality was not different between groups.[8] However, a possible benefit (shorter stay in ICU) was suggested in patients who were treated early (before 12 days of symptoms). Therefore LPV/r may still be considered in exceptional cases as a second choice when hydroxychloroquine is contraindicated, but only if this treatment could be administered early in the course of the disease.

[$] Criteria for remdesivir use as per Gilead instructions for compassionate use accessed March 20th 2020: Inclusion criteria - hospitalization, confirmed COVID-19, invasive mechanical ventilation. Exclusion criteria – Evidence of multi-organ failure, pressor requirement to maintain BP, ALT levels x 5 times normal upper limit, Cr clearance <30mL/min or dialysis or continuous veno-venous hemofiltration.

[#] One study showed a small signal of possible synergistic effect with hydroxychloroquine[9], very limited and poor quality data from which it is not possible to draw firm conclusions

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.[1] A recent 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.[10] 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. Extrapolating from adult data and 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 heart disease, lung disease, neurological disease or diabetes mellitus, may be at increased risk of severe infection.[11] Of the small number of reported children with COVID-19 requiring mechanical ventilation, comorbidities mentioned included congenital heart disease, hydronephrosis and leukemia (on maintenance chemotherapy). Interestingly, to date there have been no anecdotal reports of more severe COVID-19 in children with chronic lung disease such as asthma, bronchiectasis, primary ciliary dyskinesia and cystic fibrosis and early reports from Italy suggest that children with organ transplantation have not demonstrated more severe disease.[12]

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.[1] 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.[13] 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.[14] 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 recommendations developed by the Critical Care Response Team with the Emergency Department in order to adapt systemic and oxygen therapies.

Management considerations for Cytokine Release Syndrome 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.[15] In particular, elevations in levels of IL-6 has been shown to correlate with mortality in adult patients with COVID-19.[3] 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.[16] Available evidence for some of these agents is detailed in the attached "Summary of Scoping Review for Experimental Therapies and COVID-19" document.

Presently, clinical data in patients with COVID-19 are only available for tocilizumab. 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.[17] 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. 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 and one potential advantage of this therapy is its short half-life which may reduce concerns regarding adverse effects. However, at present there are no clinical data on its efficacy in treating CRS in patients with COVID-19. Clinical trials are ongoing, such as the Swedish Orphan Biovitrum AB (SOBI) short-term clinical trial on anakinra in adult patients with COVID-19.

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 tocilizumab, anakinra or other 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.

Antibiotic therapy

Consultation with Infectious Diseases regarding antimicrobial coverage is recommended for all cases of severe or critical COVID-19

- 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 n*on-typable *Haemophilus influenzae.*

- Presently antibiotic treatment for children 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 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**
- Addition of azithromycin therapy may be considered in cases of severe or critical COVID-19 given its possible synergistic effect with hydroxychloroquine. However, caution is required due to possible drug interactions and QTc prolongation.

Use of other therapies/areas of controversy

- 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 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 shorter duration of supplemental oxygen use and improved radiological findings.[20] A further observational cohort study of 201 patients in Wuhan, China found 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]

- 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.[23,24] 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.[23] 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 patients should be advised 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.

- Ace inhibitors (ACE)/Angiotensin Receptor Blockers (ARBs):
  SARS-CoV-2 uses ACE2 as its cellular entry receptor.[25] Controversy exists as to whether ACE inhibitors and ARBs could be beneficial in reducing COVID-19 severity or conversely exacerbate disease. In view of the lack of consensus and lack of experimental or clinical data, no clear conclusions can yet be made regarding their role in COVID-19. 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 COVID-19 consultation team. Clinical trials on the use of ARBs eg. Losartan as therapy in COVID-19 are ongoing.

Additional information on COVID-19 in paediatric patients:

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 rhinorrhea, 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.[26]

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.[27] The assumed incubation period was between 2 and 10 days and symptoms typically resolved within 1 week. Symptoms of COVID-19 in children are milder than that of adult cases, and asymptomatic cases have also been reported. However, while severe disease is uncommon in children, there have been isolated reports of children requiring intensive care support and possible deaths in children due to COVID-19.

There is limited timeline data for infections in children due to the small numbers of cases. Adult literature suggests admission to hospital occurs approximately 7 days following symptom onset with onset of severe respiratory distress symptoms approximately 9 days after symptom onset.

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. Presently it is unclear if these symptoms are also a feature of COVID-19 in children.[28,29]

Neonates and COVID-19

In a case series of two pregnant physicians infected with SARS-CoV-2 during the third trimester in China, there was no evidence of vertical transmission of SARS-CoV-2 with all products of conception and the infants testing negative.[30] In one retrospective case series from Wuhan University Hospital, nine pregnant women who were positive for SARS-CoV-2 all underwent C-section and all 9 babies were well with good APGAR scores and, of the 6 tested (3 not tested), all were negative for SARS-CoV-2.[31] Thus, no evidence of vertical transmission was noted in this study. In a more recent study of ten mothers with COVID-19 there was no evidence of vertical transmission, though there were concerns regarding adverse outcomes for neonates in the setting of perinatal COVID-19.[32] Isolated cases of neonatal COVID-19 have been reported but it is unclear if severe disease can occur and thus far no deaths have been reported in this age group.[33]

Management of neonates born to mothers with suspected or confirmed COVID-19 and management of neonates with confirmed COVID-19 represent special at risk groups and detailed management advice is contained in separate documents. Extrapolating from experience with other respiratory tract viruses, such as respiratory syncytial virus, neonates with COVID-19 may be at increased risk of severe infection particularly if they have other comorbidities, including congenital heart disease, prematurity etc. Management for such cases should be determined on a case-by-case basis following discussion with the Infectious Diseases team. Particular caution should be used when considering any experimental or off-label antiviral therapies due to lack of evidence regarding safety and efficacy of experimental antiviral medications in this age group.

References

1. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics*. 2020. doi:10.1542/peds.2020-0702

2. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med*. 2020;(NEJMc2005073). doi:10.1056/NEJMc1210001

3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan , China : a retrospective cohort study. *Lancet*. 2020;6736(20):1-9. doi:10.1016/S0140-6736(20)30566-3

4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585

5. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. *Jama*. 2020;4720:2019-2021. doi:10.1001/jama.2020.4326

6. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med*. 2015;16(5):428-439. doi:doi:10.1097/PCC.0000000000000350

7. Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020:105932. doi:10.1016/j.ijantimicag.2020.105932

8. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. 2020:1-13. doi:10.1056/NEJMoa2001282

9. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open- label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;In press. doi:10.1016/j.ijantimicag.2020.105949

10. Bialek S, Gierke R, Hughes M, McNamara L, Pilishvili T, Skoff T. Morbidity and Mortality Weekly Report. Coronavirus Disease 2019 in Children United States, February 12-April 2, 2020. 2020.

11. Ogimi C, Englund JA, Bradford MC, Qin X, Boeckh M, Waghmare A. Characteristics and outcomes of coronavirus infection in children: The role of viral factors and an immunocompromised state. *J Pediatric Infect Dis Soc*. 2019;8(1):21-28. doi:10.1093/jpids/pix093

12. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. *Liver Transpl*. 2020:0-1. doi:10.1002/lt.25756

13. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign : Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020.

14. Cheifetz IM. Pediatric ARDS. *Respir Care*. 2017;62(6):718-731. doi:10.4187/respcare.05591

15. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5

16. Mehta P, Mcauley DF, Brown M, et al. Correspondence COVID-19 : consider cytokine storm syndromes and. *Lancet*. 2020;6736(20):19-20. doi:10.1016/S0140-6736(20)30628-0

17. Xu X, Han M, Li T, et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Pre print (non-peer reviewed). http://doi.org/10.1093/ofid/ofaa105. Published 2020. Accessed March 20, 2020.

18. Auyeung T, Lee J, Lai W, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. *J Infect*. 2005;51:98-102.

19. CHen R, Tang X, BL L, ZY W, JQ F, N Z. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. *Chest*. 2006;129(6):1441-1452.

20. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, Dong N, Tong Q, (2020) Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. *medRxiv*. 2020. doi:https://doi.org/10.1101/2020.03.06.20032342

21. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020:1-10. doi:10.1001/jamainternmed.2020.0994

22. National Health Commission (NHC) of the People's Republic of China. The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection 7th Edition, published March 3rd, 2020. Translanted to English. http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm.

23. Day M. Covid-19 : ibuprofen should not be used for managing symptoms , say doctors and scientists. *Br Med J*. 2020;1086(March):2020. doi:10.1136/bmj.m1086

24. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir*. 2020;2600(20):30116. doi:10.1016/S2213-2600(20)30116-8

25. Tian X, Li C, Huang A, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect*. 2020;9(1):382-385. doi:10.1080/22221751.2020.1729069

26. Livingstone E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA - J Am Med Assoc*. 2020;(March 17). doi:10.1001/jama.2020.4344

27. Cai J, Xu J, Lin D. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. 2020. doi:https://doi.org/10.1093/cid/ciaa198

28. American Academy of Ophthalmology. Alert: Important coronavirus updates for ophthalmologists. https://www.aao.org/headline/alert-important-coronavirus-context. Published 2020. Accessed March 27, 2020.

29. ENTUK. Loss of smell as marker of COVID-19 infection. https://www.entuk.org/sites/default/files/files/Loss of sense of smell as marker of COVID.pdf. Accessed March 27, 2020.

30. Fan C, Lei D, Fang C, et al. Perinatal Transmission of COVID-19 Associated SARS-CoV-2: Should we Worry? *Clin Infect Dis*. 2020. doi:10.1093/cid/ciaa226

31. Chen H, Guo J, Wang C. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020;395:809-815.

32. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr*. 2020;1(9):51-60. doi:10.21037/tp.2020.02.06

33. Wang S, Guo L, Chen L, et al. A case report of neonatal COVID-19 infection in China. *Clin Infect Dis*. 2020:ciaa225. doi:10.1093/cid/ciaa225

Important Information and Disclaimers About This Document:

This Guidance Document is intended solely for healthcare providers at The Hospital for Sick Children ("SickKids"). Any use of this Guidance Document must be subject to the judgment of a patient's attending physician, taking into consideration all available information related to the condition of the patient and after review of the benefits and risks of the proposed course of action with the patient (if of an appropriate age) and/or the patient's parents or guardians.

The Guidance Document is NOT intended for use by patients or their families and is not designed or intended to constitute medical advice or to be used for diagnosis. The Guidance Document is NOT a substitute for the personalized judgment and care of a trained medical professional. SickKids does not recommend or endorse any information, procedure, or product that may be mentioned in this Guidance Document.

Every reasonable effort has been made to ensure that the information provided in the Guidance Document is accurate and in accordance with the standards accepted at the time it was created, however new and emerging research and experience may result in changes to these standards. You are responsible for ensuring that the materials are current and comply with all applicable laws.

The Guidance Document is provided "as is" with no representations or warranties of any kind, express, statutory or implied, as to the content or information produced by the Guidance Document. By viewing and using any information derived from the Guidance Document, you hereby waive any claims, causes of action and demands, whether in tort or contract, against SickKids (including its employees, physicians, directors and agents) in any way related to use of the Guidance Document or the information derived from it.