Management of children with acute novel coronavirus 2019 disease (COVID-19) admitted to IWK Health: Third Interim guidance

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Preamble

The purpose of this guideline is to provide recommendations for assessment and management of pediatric patients with acute COVID-19 requiring admission to IWK Health. **The focus of this guidance is patients with moderate, severe, and critical disease due to acute COVID-19 infection.** This guidance does not apply to children with confirmed or suspected multisystem inflammatory syndrome temporally associated with SARS-CoV-2 infection.

These recommendations are based on a literature review of targeted therapies for COVID-19, review of other pediatric guidelines, and discussion with infectious disease specialists and infectious disease pharmacists across Canada. They reflect the consensus of the Division of Infectious Diseases at the IWK, with input from the Departments of Emergency Medicine and Critical Care, and Divisions of General Pediatrics, Immunology, Rheumatology, Hematology, and Cardiology.

Recommendations

The standard of care for children with COVID-19 is supportive therapy, as most recover without antiviral or immunomodulatory treatment. **There are no proven therapies for acute COVID-19 infection in children at this time**. See Table 1 for recommended approach to investigations and management of pediatric patients hospitalized with COVID-19. Further resources are available from AMMI Canada/Public Health Agency of Canada and the Canadian Paediatric Society.

Investigational COVID-19 therapies

- Use of off-label or experimental therapies for children with COVID-19 outside of approved, randomized, controlled clinical trials ***is not recommended*****.**
- **Hydroxychloroquine is *not recommended***
- **Lopinavir-ritonavir is *not recommended***

Remdesivir

- **Remdesivir should *not* be considered outside of a randomized controlled clinical trial.** There are limited published data on the safety or effectiveness of remdesivir in children, while clinical trials in adults suggest only modest clinical benefit in those requiring oxygen who do not require mechanical ventilation.
- Remdesivir is approved by Health Canada for use in adolescents and adults >12 years of age with severe COVID-19 (with pneumonia and requiring supplemental oxygen).

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Antibiotic treatment

- Antibiotics should only be considered in patients with evidence or suspicion of secondary bacterial infection. Antibiotics have no effect against the SARS-CoV-2 virus and concomitant bacterial pathogens at presentation have not been widely described.
- Azithromycin is **not** recommended for treatment of COVID-19.
- In patients with suspected secondary bacterial pneumonia, IV ampicillin or po amoxicillin is appropriate first-line empiric antibiotic therapy.
- In severely or critically ill patients with suspected sepsis, IV ceftriaxone is recommended.

Corticosteroids

- **Corticosteroids are not generally recommended for the treatment of pediatric patients with COVID-19 outside of a clinical trial**.
- Though randomized controlled trials in adults suggest that dexamethasone reduces mortality in patients with severe COVID-19, there are currently no data on the use of dexamethasone in children with severe disease who require supplemental oxygen or mechanical ventilation.
- Given the breadth of immunosuppression associated with glucocorticoid use in this setting and the risk for impairing antiviral immunity, caution is warranted, especially when early after onset of COVID-19 symptoms.
- Dexamethasone *may be considered* on a case by case basis weighing benefits and risks in children requiring mechanical ventilation and in those requiring non-invasive respiratory support who are considered at high risk of further deterioration.
- Outside of clinical trials, corticosteroids should generally be used only in patients with COVID-19 who have other indications for corticosteroids, such as asthma exacerbation or croup; use low to moderate doses for short courses (e.g., 1-2 mg/kg/day methylprednisolone equivalent for 3-5 days or 0.6mg/kg dexamethasone x 1-2 doses).

Biologic immunomodulators

- **Tocilizumab, anakinra or other biologic immunomodulatory drugs are not generally recommended for use in critically ill patients with COVID-19 outside of approved clinical trials.**
- There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients. Therefore, no guidance can be provided to support the use of one immunomodulatory therapy over another.
- Biologic immunomodulators *may be considered* in patients with critical COVID-19 and evidence of hyperinflammation on a case by case basis where immunologic investigations suggest potential benefit and in consultation with Immunology and Rheumatology. More guidance can be found here: Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients.
- The decision to modify existing biologic regimens in patients with underlying chronic inflammatory or autoimmune conditions should be made in consultation with the prescribing subspecialist and must take into account the risk of flare of the underlying auto-inflammatory condition or macrophage activation syndrome.

Monoclonal Antibodies

- Monoclonal antibodies designed specifically to block infectivity of SARS-CoV-2: Bamlanivimab is **not recommended** for use.

Casirivimab and Imdevimab (REGEN-COV) is approved under an Interim Order for children and youth 12 years of age and older with mild-to-moderate COVID-19.
For children ≥12 years of age who do not have access to a clinical trial, combination casirivimab-imdevimab may be considered. Its use should be in accordance with criteria set out by NS public health.

Antipyresis/analgesia

- The use of either acetaminophen or ibuprofen is recommended for the symptomatic relief of fever and pain in patients with suspected or confirmed COVID-19.

Patients on antimalarials or antiretrovirals to treat underlying chronic conditions

- Children taking antimalarials (e.g., hydroxychloroquine) to treat an underlying chronic inflammatory or autoimmune condition or taking antiretrovirals (e.g., lopinavir/ritonavir) to treat HIV infection should continue their regular medications.
- The decision to modify current treatment regimens should be made in consultation with the prescribing subspecialist and must take into account the risk of flare of underlying auto-inflammatory condition or infectious disease.

Background

Following the recognition of an outbreak of severe pneumonia in Wuhan, China in late 2019, the SARS-CoV-2 virus, the cause of COVID-19, was first isolated in January 2020. The disease then rapidly spread around the world, leading the WHO to declare a global pandemic on March 11, 2020. As of May 30, 2021, there have been over 170 million cases worldwide, including over 3.56 million deaths, and over 1,370,000 cases and 25,512 deaths (in adults) in Canada.

Worldwide evidence to date shows that most cases in children are asymptomatic, mild or moderate in severity, with <2% requiring ICU admission and mortality of ~0.1%. In Canada, up until May 14,2021, there have been 243,377 cases of SARS-CoV-2 in children with 1.7% of these cases resulting in hospitalization and a mortality rate of <0.000% (total number of deaths in children positive for SARS-CoV-2 is 12 to date). Canadian data from Canadian Paediatric Surveillance Program, published September 10 2020, confirm that the hospitalization rate is low (1.3%) and half of these children were admitted for another reason, with COVID identified only through routine screening. There were no deaths in this Canadian cohort. The CPSP has not released a subsequent report to date.

Additional observational studies have provided insight into the clinical epidemiology of COVID-19 in children, demonstrating that while most young patients experience mild illness, a small proportion develop severe illness associated with adverse clinical outcomes, including need for pediatric intensive care unit (PICU) admission and mortality. Risk factors for severe disease have not been fully defined in children. Severe or critical illness appears to be more common in adolescents and children with co-morbidities such as obesity, diabetes, medical complexity (e.g., technology-dependent), chronic respiratory, cardiac, neurological diseases, and immunosuppression, with the risk increasing with the

number of co-morbidities present. Though infants <3 months of age have the highest rate of hospitalization with COVID-19, severe respiratory disease appears to be rare in this age group.

Manifestations of severe disease include fever, cough, poor feeding, hypoxemia, tachypnea and increased work of breathing. Critical illness has been associated with respiratory failure, acute respiratory distress syndrome, multiorgan failure, encephalopathy, myocardial dysfunction and coagulopathy, often with evidence of hyperinflammation. Adults with COVID-19 also appear to be at increased risk of thrombotic events; the risk in children is not defined. Monitoring of coagulation studies in children with severe to critical disease is therefore recommended.

In April 2020, a newly recognized hyperinflammatory syndrome emerged as a suspected post-infectious syndrome following SARS-CoV-2 infection in children. It was referred to by the Royal College of Paediatrics and Child Health as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), by the World Health Organization and US Centers for Disease Control and Prevention as Multisystem Inflammatory Syndrome in Children (MIS-C) and by Canadian Pediatric Society as Paediatric Inflammatory Multisystem Syndrome Temporally associated with COVID-19 (PIMS/MIS-C). Affected children present with evidence of multisystem inflammation and fever with variable manifestations that may include cardiovascular shock, gastrointestinal symptoms, and/or mucocutaneous changes. The syndrome often overlaps clinically with Kawasaki Disease and toxic shock syndrome. Many children are SARS-CoV-2 PCR negative but have antibodies to SARS-CoV-2 or recent exposure to COVID-19. While fortunately rare, with an estimated incidence of <1% of patients <21 years of age with SARS-CoV-2 infection, this syndrome often necessitates PICU admission and mortality has been reported in 1-5% of cases.(1, 2)

Rationale for the recommendations

Management of COVID-19 is supportive. A number of investigational antiviral therapies have been found to have activity against SARS-CoV-2 *in vitro* and in animal models; however, many therapies have been shown to be ineffective and even potentially harmful in human trials, including hydroxychloroquine and lopinavir-ritonavir. Clinical trials in Canada, including CONCOR-KIDS and CATCO-KIDS, were cancelled due to lack of enrollment.

A summary of the evidence (updated on May 29, 2021) for the use of hydroxychloroquine, lopinavir/ritonavir, remdesivir, dexamethasone and immunomodulatory therapies in treatment of COVID-19 is presented in the Appendix.

Table 1. Investigation and management of pediatric patients hospitalized with COVID-19 by disease severity.*

Disease severity	Investigations	Management

Mild disease • Symptoms of acute respiratory tract and/or mild lower respiratory tract infection; fatigue, myalgia, GI symptoms • Mild to no increased work of breathing • No O_2 requirement	• No routine investigations if being managed at outpatient • If admitting to hospital due to presence of risk factor for disease severity, consider work-up as for moderate disease	• Supportive care as Outpatient
Moderate disease • Increase RR, increased work of breathing • Requires no more than low flow supplemental oxygen to maintain SpO_2 ≥90%	• Consider NP swab for influenza PCR if not done • CBC + differential, lytes, Cr, ALT, CRP (see clinical order set)† • Consider blood culture if febrile • Consider Chest X-Ray or lung ultrasound (if available) for suspicion of pneumonia • In consultation with ID and Rheumatology consider additional investigations as for severe disease (see below) if concern for disease progression based on clinical status or initial labs	• Admit to Pandemic Response Unit • **See Clinical Order Set**: Orders for Confirmed Acute COVID-19 Pediatric Patients • **Consider ID consult** • Consider Rheumatology consult • **Consider PICU consult** if rapidly progressing disease • Low flow supplemental O_2 to keep SpO_2 90-95% • Supportive care • ***In consultation with ID***, consider patient's eligibility for enrollment in clinical trial

Severe disease • Moderate or severe work of breathing or significant hypoxia warranting non-invasive ventilation (i.e., more than low flow supplemental O_2)	• Swab for influenza PCR if not done • Consider extended respiratory panel (requires NP swab) • **Labs as per moderate disease** (clinical order set) **PLUS**: Urea, AST, GGT, albumin, bilirubin, Lactate, LDH, ferritin, ESR, triglycerides, INR, PTT, fibrinogen, D-dimer† • Blood culture if febrile • Chest X-ray or lung ultrasound • Consider ECG due to risk of myocarditis • Consider lymphocyte subsets and other immunologic work-up in consultation with Immunology‡	• Admit to PRU • **See Clinical Order Set**: Orders for Confirmed Acute COVID-19 Pediatric Patients • **ID consult** • **Consider PICU consult** if no early response to HFNC or escalating requirements • Consider Rheumatology consult • Consider Immunology consult • Consider Respirology consult • Consider Hematology consult • Consider Cardiology consult • Empiric ceftriaxone IV pending cultures if secondary bacterial sepsis suspected • Supportive care as per PRU/PICU • ***In consultation with ID***, consider patient's eligibility for enrollment in clinical trial
Critical disease • Respiratory failure, acute respiratory distress syndrome • Shock • Multi-organ failure including myocardial dysfunction, AKI, coagulation dysfunction	• Recommendations as per severe disease to be enacted at discretion of PICU	• Admission / transfer to PICU • Recommendations as per severe disease to be enacted at discretion of PICU

*Adapted from guidelines developed by the World Health Organization, Pediatric Infectious Diseases Society, Division of Infectious Diseases, Hospital for Sick Children, and PHAC Clinical management of patients with COVID-19: Second interim guidance.
†Recommended to monitor for early signs of disease progression and end-organ dysfunction
‡To evaluate for signs of cytokine storm and/or inborn error of immunity

Appendix: Summary of the evidence for antiviral therapy and immunomodulatory therapy (current as of May 31, 2021)

Corticosteroids

The RECOVERY trial evaluated the safety and efficacy of 6 mg of dexamethasone given once daily for up to ten days among more than 6,400 patients randomly allocated (1:2) to receive dexamethasone or usual care.(10) The primary outcome was 28-day mortality. While the trial demonstrated benefit of dexamethasone over standard care in patients who required supplemental oxygen (mortality of 23.3% vs 26.2%; rate ratio 0.82, 95% CI 0.72-0.94) or mechanical ventilation (mortality of 29.2% vs 41.4%; RR 0.64, 0.51-0.81), dexamethasone did not reduce mortality in patients who did not require respiratory support at randomization (17.8% vs. 14%, RR 1.18 [95% CI 0.91 to 1.55]). A meta-analysis of 3 trials involving 1282 patients similarly found a decrease in 28-day mortality among adult COVID19 patients treated with dexamethasone versus placebo (summary OR 0.64; 95% CI 0.50-0.82).(11) Dexamethasone 6 mg IV daily for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose is now recommended for hospitalized adult patients who have COVID-19 and require supplemental oxygen or mechanical ventilation.

There are **currently no data** on the use of dexamethasone in children with severe disease who require supplemental oxygen or mechanical ventilation, hence clinical judgement should be applied if considering use. The mortality rate among children hospitalized with COVID19 is also much lower than adults (0–4% vs. 25–30%). Given the breadth of immunosuppression associated with glucocorticoid use in this setting and the risk for impairing the immune response, caution is warranted, especially early after onset of COVID-19 symptoms. Furthermore, we have yet to see data assessing the potential long term effects of corticosteroid therapy and subsequent immunosuppression in neither adults nor children who receive it for COVID-19 pneumonia treatment.

Corticosteroids are therefore **generally not** recommended for the treatment of pediatric patients with COVID-19 outside of a clinical trial. However, dexamethasone may be considered on a **case by case basis** weighing benefits and risks in children requiring mechanical ventilation and in those requiring non-invasive respiratory support considered at high risk of further deterioration. More guidance can be found here: Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients.(2)

Outside of clinical trials, corticosteroids should generally be reserved for patients with COVID-19 who have other indications for corticosteroids, such as asthma exacerbation or croup; use low to moderate doses for short courses (e.g., 1-2 mg/kg/day methylprednisolone equivalent for 3-5 days or 0.6mg/kg dexamethasone x 1-2 doses).(1, 2)

Remdesivir

Remdesivir is an antiviral treatment against SARS-CoV-2 that recently received emergency use authorization from Health Canada for adolescents and adults 12 years of age and older. This decision was based on data from a preliminary report of a multinational, randomized, placebo-controlled trial (the Adaptive COVID-19 Treatment Trial [ACTT]) of hospitalized adult patients with severe disease who who received Remdesivir.(3) This study showed a shorter median time to clinical recovery among patients treated with 10 days of IV remdesivir compared to those who received placebo (11 days, 95% CI

9-12 vs 15 days, 95% CI 13-16 days; rate ratio for recovery 1.32 [95% CI 1.12 to 1.55]). The benefit of remdesivir on reducing time to recovery was highest among adult patients who were not intubated but required supplemental oxygen. In mechanically ventilated adult patients who received remdesivir there was no observed decrease in time to recovery.(3) A recently published clinical trial of hospitalized patients with moderate COVID-19, most of whom did not require oxygen, found a small improvement in clinical recovery among those who received 5 days, but not 10 days of remdesivir, versus standard care.(4)

Pediatric clinical trials are ongoing. There is only one presently published study evaluating the safety of Remdesivir in the pediatric population (Goldman et al. *Pediatrics* 2021). This study examined the use of Remdesivir for 77 children with SARS-CoV-2 confirmed severe COVID-19 respiratory disease. This study demonstrated that Remdesivir is generally safe in the pediatric population, with the most common adverse event being temporary and resolving transaminitis. They were unable to assess if Remdesivir is an effective treatment agent for children based off of the small study size.(22) Children receiving remdesivir have been included in several pediatric case series, though data related to clinical outcomes and adverse events were not specifically reported. A multinational European cohort of 582 children demonstrated that 507 (87%) had mild or moderate disease, with 48 patients requiring PICU admission and just four deaths.(5) Remdesivir was used in 17 patients, but the impact on clinical outcomes was not reported. Similarly, among a cohort of 208 hospitalized children in the US with complete data, 33% required ICU admission and only one death (0.5%) was reported. Nine children received remdesivir.(6)

Based on these limited data and extrapolation from adult trials, some experts in the US and Canada recommend remdesivir be considered for children with severe to critical COVID-19 disease.(8, Toronto Hospital for Sick Children) However, Canadian guidelines preferentially recommend its use only in patients enrolled in randomized clinical trials.(9)
Remdesivir is approved by Health Canada for emergency use for adolescents and adults >12 years of age with severe COVID-19 who require supplemental oxygen. However, the drug was previously included in WHO Solidarity trial (CATCO Canada) but has since been removed due to unconvincing efficacy data.
The safety, tolerability, pharmacokinetics and clinical efficacy of Remdesivir in children is currently being assessed in a phase 2 and 3 clinical trial (CARAVAN Study - NCT04431453).

Biologic immunomodulators

Multiple studies and experience in a variety of settings have demonstrated that the majority of children with COVID-19 recover without immunomodulatory interventions and do not develop severe manifestations. Given the lack of available results from RCTs of immunomodulatory therapy in children with COVID-19, the risk-benefit ratio for most pediatric patients points toward supportive care as the key management strategy. However, a subset of pediatric patients develops severe or critical illness with acute COVID-19 characterized by hyperinflammation.

Immunomodulatory therapy should only be considered for pediatric patients in the setting of confirmed critical COVID-19 disease with evidence of hyperinflammation. In addition, patients with severe COVID-19 and hyperinflammation whose clinical status suggests imminent progression to critical COVID-19 may be considered for immunomodulatory treatment where immunologic investigations suggest potential benefit, in consultation with Immunology and Rheumatology.

One biologic immunomodulator, Tocilizumab, has demonstrated conflicting results in studies looking at adults with severe COVID-19 pneumonia. The CONVACTA trial did not result in significantly better clinical status or mortality in those randomized to Tocilizumab when compared to placebo at 28 days (23). This study demonstrated that of 438 patients, the 294 randomized to the tocilizumab group had a mortality at day 28 of 19.7% while the placebo group (144) had a rate of 19.4%. The RECOVERY trial demonstrated improved survival in those allocated to tocilizumab (n= 2022, mortality rate 31%) compared to those who had been allocated to routine care (n= 2094, mortality rate 35%) within 28 days of admission to hospital (rate ratio 0.85; 95% CI 0.76-0.94; p+0.0028). In assessing the difference in survival rates of studies investigating Tocilizumab, Ghandi proposed that the success rates of Tocilizumab in the RECOVERY and REMAP-CAP trials could be influenced by the concomitant administration of corticosteroids, which had become standard of care in adults with severe COVID-19 pneumonia at the time of those studies (25). Therefore, was tocilizumab only modestly effective when given alongside corticosteroids?

There are no immunomodulators with proven efficacy for the treatment of COVID-19 in pediatric patients. Therefore, **no guidance can be provided to support** the use of one immunomodulatory therapy over another. If immunomodulators are used in the treatment of COVID-19, patients should be closely monitored for adverse effects. More guidance can be found here: Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute Coronavirus Disease 2019 in Pediatric Patients

Monoclonal antibodies

Monoclonal antibodies designed specifically to block infectivity of SARS-CoV-2 such as REGN-COV have been evaluated in clinical trials. REGN-COV is a combination of two monoclonal antibodies (Casirivimab and Imdevimab). Virus-neutralizing antibodies that form REGN-COV bind non-competitively to the critical receptor binding domain of the SARS-CoV-2 virus spike protein.

The combination of casirivimab and imdevimab is not authorized for use in patients younger than 12 years of age or adolescents weighing less than 40 kg. The safety and efficacy (effectiveness) of the combination of casirivimab and imdevimab has not been directly assessed in pediatric patients (<18 years of age) in clinical trials. **Therefore we suggest against routine administration of outpatient monoclonal antibody therapy to children for COVID-19 (eg, combination casirivimab-imdevimab [REGEN-COV]. If employed, monoclonal antibody therapy ideally should occur in the context of a clinical trial and should consider risk factors supported by evidence from studies in children**. Evidence from randomized trials and observational studies in adult patients suggests that outpatient monoclonal antibody therapy soon after diagnosis reduces the need for hospitalization. However, the benefits and risks in children are uncertain .
The recommended dosing regimen in patients 12-17 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of casirivimab and imdevimab as those observed in adults based on an allometric scaling approach (which accounted for the effect of body weight changes associated with age on clearance and volume of distribution). Close monitoring in this patient population is highly recommended.

Health Canada authorized its application with conditions on an Interim Order for patients with mild-to-moderate COVID-19. It is recommended that it only be given to patients at high risk of being hospitalized or dying due to COVID-19. It is not authorized to be used in patients who are hospitalized or require oxygen therapy due to COVID 19. The recommended dose is 1200 mg of each casirivimab and imdevimab, administered together through intravenous infusion after dilution over 1 hour.
Its use should be in accordance with criteria set out by NS public health.

Hydroxychloroquine and azithromycin

The WHO Solidarity trial and UK-based RECOVERY trials have reported **no evidence of benefit** of hydroxychloroquine and an increased risk of serious cardiac adverse effects in patients with COVID-19. Multiple observational studies and randomized trials have evaluated the effectiveness of hydroxychloroquine for treatment of COVID-19, with the overwhelming majority of data demonstrating no benefit. Of equal importance, safety concerns related to cardiotoxicity have been identified, particularly in combination with other corrected QT interval (QTc)-prolonging medications such as azithromycin. The FDA withdrew their emergency use authorization for HCQ in COVID-19 in June 2020.

Lopinavir/ritonavir

Published clinical trials and observational studies **do not support** use of lopinavir-ritonavir for treatment of COVID19 and highlight a high prevalence of adverse effects, particularly gastrointestinal effects, as well as potential drug-drug interactions from prolonged cytochrome P4503A inhibition. There are no comparative observational studies or randomized trials evaluating safety or efficacy of lopinavir-ritonavir or other HIV protease inhibitors for treatment of SARS-CoV-2 infection in children. Reports of use are sparse and limited to case series, the largest of which included 14 children treated with lopinavir-ritonavir, all of whom recovered.

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