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See AHS Insite COVID-19 resources for current version.

Current Guidance for the Management of Pediatric Patients Hospitalized For COVID-19

Contents

Introduction

This is interim guidance document will be frequently updated as new information becomes available (previous update January 12, 2021). As such, the most current web-based version of this document should preferentially be used.

This guideline has been developed by members of the Pharmacy and the Divisions of Pediatric Infectious Diseases in Calgary and Edmonton. With facilitation by the MNCY SCN, it has been reviewed with critical feedback from the relevant pediatric medical leads at Stollery and Alberta Children's Hospitals, and Regional community pediatric leads. It also has been reviewed with critical feedback from the AHS COVID-19 Therapeutics Working Group.

To date, there are limited effective partially evidence-based therapeutic agents for the treatment of the novel coronavirus, SARS-CoV-2, and this is especially true with regards to treatment of special populations such as pediatrics. **Supportive care remains the mainstay of therapy for infected individuals**. **The use of experimental treatments for patients with COVID-19 should ideally occur within the context of controlled clinical trials.** The recommendations outlined in this document do not indicate an endorsement of these agents but are meant to support case-by-case basis decision making. Only those agents that have been frequently considered in cases of pediatric case management in other jurisdictions and the literature will be mentioned.

As recommended by AHS Ethics, any off-label use of medication requires the prescriber's careful consideration of risk/benefit, consultation between experts and attending physician as needed, and documenting consent from the patient after discussion of the current state of evidence of benefit and harm.

We recommend consultation with Pediatric Infectious Diseases (ID):

- if a patient is admitted to intensive care with presumed or confirmed COVID-19,
- if a COVID-19 patient is showing progression of illness,
- if Severe, complicated, or Critical care required due to a suspicion of Multisystem Inflammatory Syndrome in Children (MIS-C),
- or if ID consultation is judged beneficial or desired by primary clinical team
- Monoclonal Antibody Physician (Sotrovimab program) will likely involve Pediatric ID for discussion on a case-by-case basis in conjunction with primary MD.

Table 1: Classification of COVID-19 clinical illness in children[1]

Mild Disease	Upper respiratory tract infection symptoms (e.g. nasal congestion, sore throat, and fever) for a short duration or asymptomatic infection May also include fatigue, myalgia, and gastrointestinal symptoms
Moderate Disease	Clinical and/or radiological evidence of pneumonia with associated clinical features such as fever, cough, fatigue, headache, and myalgia
Severe Disease	Moderate clinical features, PLUS manifestations that suggest disease progression: • Moderate to Severe Respiratory Distress • Hypoxemia (oxygen saturation less than 92% on room air)
Critical Illness	Evidence of rapid disease progression, accompanied by any of the following conditions: • Respiratory failure with need for mechanical ventilation (e.g. ARDS, persistent hypoxia despite non-invasive oxygen supplementation) • Decreased level of consciousness, depression, coma, convulsions • Significant myocardial injury • Coagulation dysfunction, rhabdomyolysis, and other manifestations suggesting injuries to vital organs • Septic or cardiogenic shock

Investigations in Children Hospitalized for COVID-19

Prior to considering COVID Specific treatment for pediatric patients hospitalized for COVID-19, the following investigations are suggested[1-3]:

1. Baseline labs as indicated based on clinical condition
2. Selected investigations for hospitalized patients with COVID-19, as indicated for increasing severity or atypical features suggesting progression beyond typical upper respiratory infection, bronchiolitis or croup:
    - CBC & differential, AST, ALT, bilirubin, Cr, urea, CRP, blood cultures
    - Nasopharyngeal Swab for: COVID-19 PCR (if not already done)
    - D-dimer; Fibrinogen, LDH (secondary infection and prognostic indicators), CK, ferritin
    - CXR
    - Arterial or venous blood gas (selected patients)
    - Echocardiogram (critically ill patients)
    - Nasopharyngeal swab for:
        - RSV & Flu A/B panel (when epidemiologically appropriate to do so)
        - Respiratory Pathogen Panel (RPP) if 1) Severely Immunocompromised, 2) Critical Respiratory Failure, 3) Suspect Hospital-acquired infection / Outbreak Investigation, 4) Acute Flaccid Paralysis, or 5) Myocarditis/Pericarditis.
            - Note: You may need to call the Virologist on Call to get permission
    - Sputum or endotracheal aspirate if intubated (avoid bronchoscopy simply for specimen acquisition) for Gram stain and culture and SARS-COV-2 PCR (if not already done)
    - If immunocompromised and clinically indicated, ET aspirate, bronchoscopy (if required) or induced sputum for PJP and other opportunistic pathogens
3. For MIS-C presentations, please see laboratory testing recommendations:
    - Multisystem Inflammatory Syndrome in Children (MIS-C): Care Guide for Children and Adolescents in Alberta (albertahealthservices.ca)

Criteria to Consider COVID-19 Specific Therapy in Hospitalized Children

Pediatric patients hospitalized with COVID-19 can be considered for COVID-19 specific therapy if [1,4,5]:

- Suspected or confirmed COVID-19 and severe or critical illness presentation with pneumonia (versus croup or bronchiolitis where COVID-19 specific therapy is not usually indicated)
- Moderate COVID-19 presentation in the presence of risk factors (see Table 2. Below) that would put them at risk for severe disease

Table 2: Risk Factors for Progression to Severe Disease in Pediatric Patients

Age	Age < 1 year of age[6] 10-18 years[7] (latter reference indicates that risk of admission increases with pediatric age of those presenting to ED)
Immunocompromised	Immunosuppressive disease or of immunosuppressive therapies[6].
Comorbidities	heart disease, lung disease, (not asthma[7]), severe neurological disease, elevated Body Mass Index (BMI). [8]

Treatment of Pediatric Patients Hospitalized with COVID-19

These investigational treatments may be considered, in consultation with Pediatric Infectious Diseases, in laboratory-confirmed COVID-19 requiring hospitalization due to severe illness (see criteria above), significant clinical progression or possible significant risk factors (as summarized above). Clinical progression typically occurs between 4-7 days after symptom onset[7].

Table 3: Summary of treatment of pediatric patients hospitalized for COVID-19

Severity	**Recommendation**
Mild Disease	Supportive care only[*] On a case-by-case basis: Consider Sotrovimab in patients 12 years or older and minimum 40 kg who are at high risk for progression and have had symptoms for 5 days or less [¥]
Moderate Disease	Supportive care On a case-by-case basis: 1. Remdesivir may be useful early in disease course (day 7 or earlier) if at high risk for severe disease, especially if immunocompromised 2. Antibiotic therapy if concern for secondary bacterial infection[‡]
Severe Disease or Critical Illness	Supportive care Dexamethasone[†] On a case-by-case basis: 1. Remdesivir may be useful early in disease course (day 7 or earlier) if at high risk for severe disease and not yet ventilated , especially if immunocompromised 2. Tocilizumab[†,Φ] 3. Antibiotic therapy if concern for secondary bacterial infection

* Supportive care is effective mainstay therapy for pediatric patients with COVID-19.

[¥] See text for criteria below.

[†] For more details, please see text below. Uncomplicated, typical bronchiolitis due COVID-19 may not require the use of dexamethasone unless there is progression of symptoms or atypical features are present (more suggestive of COVID pneumonia).

[‡] Empiric antibiotics for sepsis or bacterial co-infection based on clinical assessment of the patient. See antibiotic section for details and dosing.

[Φ] Sarilumab (alternate IL-6 antagonist) or baricitinib (JAK inhibitor) have been used in this setting as alternatives. Sarilumab is not approved for use for this indication. Unfortunately, there is no data to support or refute this practice in the pediatric population. The adult guidelines provide the rationale for use in that population.

In circumstances where an adolescent patient is approaching adult physiology, and therapies proven or indicated only in adults are being considered, further guidance can be found at:

- Treatment Guidance for the Management of Adult Hospitalized Patients with COVID-19 (albertahealthservices.ca)
- One Pager Template (albertahealthservices.ca) covid therapies clinician guidance FAQ.pdf
- Casirivimab-imdevimab FAQ (albertahealthservices.ca)

Additional Treatment Information

Dosing information is provided in Table 4. Below.

Corticosteroids

In severe illness with risk factors requiring respiratory support including supplemental oxygen or critically ill patients requiring mechanical ventilation dexamethasone may be of benefit.

As the RECOVERY trial only included a small number of pediatric patients, and mortality rates are low in pediatric COVID-19 patients, treatment with dexamethasone in this population should be considered on a case-by-case basis[9-11], but it now widely used in moderate to severe COVID patients. In adult patients, dexamethasone is strongly recommended in those severely and critically ill with COVID.

Antivirals

Remdesivir

A 5-10 day course of remdesivir is recommended by some for use in adults (≥18 year olds) hospitalized with COVID-19 pneumonia who are NOT mechanically ventilated who are admitted to hospital with acute illness or any admitted patient who is immunocompromised (including ventilated). Its use has shown a reduction in recovery time, faster clinical improvement, and reduced hospital stay[12-15].

There are currently no randomized controlled trials or cohort studies evaluating the use of remdesivir in pediatric patients with COVID-19 to indicate if it is effective and safe as a treatment modality in this population. It may be considered on a case-by-case basis. Those more likely to benefit are hospitalized, have increasing need for supplemental oxygen, risk factors for severe disease, and are not mechanically ventilated[16].

Paxlovid (Nirmatrelvir/ritonavir)

Paxlovid is not approved for use in pediatrics. It has an indication for preventing progression of mild COVID-19 disease to hospitalization in high risk adults only.

Agents targeting inflammatory Cascade

Tocilizumab (Interleukin 6 receptor antagonist)

There are currently no randomized controlled trials or cohort studies evaluating the use of tocilizumab in pediatric patients with COVID-19 to indicate if tocilizumab is effective and safe as a treatment modality in this population. A limited number of case studies and series have used tocilizumab in children. Tocilizumab may be considered on a case-by-case basis for worsening critical disease and high inflammatory markers under guidance of a specialist.

Tocilizumab is approved for use in adults with severe COVID-19 pneumonia based on results from RECOVERY and REMAP-CAP studies[17,18]. Patients with rapidly progressing severe disease and high markers of inflammation may be most likely to benefit. See adult guidelines for criteria for use (Treatment Guidance for the Management of Adult Hospitalized Patients with COVID-19 (albertahealthservices.ca)).

Sarilumab (Interleukin 6 receptor antagonist)

Sarilumab has been used as an alternate IL6 receptor antagonist in setting where Tocilizumab is limited. Although the data has more certainty for tocilizumab, mechanistically we would anticipate similar effects from both agents. Sarilumab is current not approved in AHS for COVID-19 indications.

Baricitinib (Janus Kinase Inhibitor)

Baricitinib is approved for use in adults with severe COVID-19 pneumonia with rapidly progressing respiratory failure based on results from the COV-BARRIER study[19]. Its use has only been examined in adults. See criteria for use in the AHS Provincial Drug Formulary[20]. It should not be used in patients who receive tocilizumab.

Anti-SARS COV2 Monoclonal Antibodies

Sotrovimab

Sotrovimab is indicated for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to hospitalization and/or death[21].

This monoclonal antibody neutralizes all sarbecoviruses, maintaining potency against Alpha (B.1.1.7), Beta (B.1.351), Gamma (p.1), Delta (B.1.617.2), and Omicron (B.1.1.529) variants. It is indicated for use in the first 5 days (flexible to 6) following onset of symptoms, confirmed by positive PCR test. It has been demonstrated to reduce progression to hospitalization and death by 85% in adult patients with the indicated underlying conditions[22].

In Alberta Health Services sotrovimab is currently being used and administered (primarily in the community via the EMS Mobile Integrated Health):

Sotrovimab is approved for use in patients 12 years or older and minimum 40 kg with mild to moderate COVID-19 symptoms who have a positive PCR test and are able to receive treatment within 5 days of symptom onset.

Pediatric criteria are evolving but use should be considered in the following patients[20]:

a) All lung transplant recipients
b) Other solid organ transplant recipients still on significant immunosuppression
c) Bone marrow or stem cell transplant recipients on immunosuppression
d) Children on chemotherapy (other than maintenance chemotherapy for ALL)
e) Other immunocompromised children with major comorbidities, especially chronic lung disease

In Discussion with the COVID-19 therapeutics working group, use in pediatrics should include a discussion with Pediatric Infectious Diseases, as data is significantly limited in this group. Sotrovimab is only approved in Alberta for outpatients or for patients admitted for other indications who are found to have SARS-CoV-2.

Other immunomodulators

Use of convalescent sera, immunoglobulin therapy (IVIG), colchicine, ivermectin, fluvoxamine, and inhaled budesonide for COVID-19 is not currently recommended. Their use should only be considered in the setting of controlled clinical trials. Updates to the discussion of possible agents will be updated as data and recommendations emerge.

Table 4: Dosing of potential COVID-19 therapeutics

Medication	Dose
Dexamethasone	0.15 mg/kg IV or PO once daily (max 6 mg) until stable on room air (maximum 10 days)
Remdesivir	***Pediatrics (<12 years):*** 3.5 kg to <40 kg: 5 mg/kg IV q24h x1, then 2.5 mg/kg IV q24h ≥40 kg: 200 mg IV q24h x1, then 100 mg IV once daily ***Adults and adolescents (≥12 years of age):*** <40 kg: 5 mg/kg IV q24h x1, then 2.5 mg/kg IV q24h once daily ≥40 kg: 200 mg IV q24h x1, then 100 mg IV q24h Total treatment for 5-10 days
Tocilizumab	Lexicomp: Pediatric (≥2 years) and Adolescents: <30 kg: 12 mg/kg/dose IV once, if no improvement, may repeat dose once ≥8 hours after initial dose ≥30 kg: 8 mg/kg IV once (max dose 400 mg/dose), if no improvement, may repeat dose once ≥8 hours after initial dose Adult guideline AHS (restricted to one dose per patient per hospitalization): ≤ 40 kg: 8 mg/kg IV once > 40 kg: 400 mg IV once
Sarilumab	2-4mg/kg IV once. (currently not approved in AHS for COVID-19 indications)
Baricitinib	Lexicomp: 2 to <9 years: 2 mg po once daily x14 days or until discharge (whichever is shorter) in combination with remdesivir ≥9 years and adolescents: 4 mg po once daily x 14 days or until discharge (whichever is shorter) in combination with remdesivir

Casirivimab and imdevimab (REGEN-COV)	AHS adults and recovery trial: 40 kg and ≥12 years: 4g/4g IV x1 Range in some guidelines has been between 1200-4000mg IV x1
Sotrovimab	Children ≥12 years and adolescents weighing ≥40 kg (Lexi): 500 mg IV x1

Considerations for COVID-19 Management with Empiric Antimicrobial Therapy

Antibiotics are indicated only for:

- Empiric management of patients with possible bacterial pneumonia while COVID-19 is being confirmed and bacterial infection excluded, and
- COVID-19 pneumonia with suspected bacterial superinfection.

When antibiotics are given, the usual choice would be ampicillin or amoxicillin for patients who are not critically ill and ceftriaxone for patients who are critically ill. Addition of azithromycin is controversial. Vancomycin should be added only if MRSA pneumonia is suspected because the patient is colonized with MRSA or has a clinically compatible course.

Table 4: Doses of empiric antimicrobial therapy for patients with COVID-19 with suspicion of a secondary bacterial process

Pediatric Dosages
Amoxicillin PO 45-90 mg/kg/day div TID Ampicillin IV 200-400 mg/kg/day div q6h Azithromycin IV/PO 10 mg/kg x 1, then 5 mg/kg/day q24h x 4 days Ceftriaxone IV 50-75 mg/kg/day given q24h Vancomycin IV 60 mg/kg/day div q6h; adjust based on trough levels to target 10-20 mg/L

* Azithromycin use should be considered if the clinical and epidemiological presentation is in keeping with *Mycoplasma pneumoniae* disease

If symptoms clinically compatible with influenza and influenza RVP pending or positive, consider:

- Oseltamivir (Tamilflu®): PO, given twice daily; ≤15 kg: 30 mg, >15 to 23 kg: 45 mg; >23 to 40 kg: 60 mg; >40 kg: 75 mg
- Discontinue if influenza RVP negative.

Management of Possible Secondary Bacterial Infection/Ventilator Associated Pneumonia in Pediatric COVID-19 patients

Culture directed therapy is preferred; empiric therapy pending appropriate culture results:

Piperacillin-tazobactam 240-300 mg piperacillin component/kg/day div q6-8h

OR

Meropenem 60 mg/kg/day div q 6-8h

REASSESS at 48-72 hours WITH VIRAL AND BACTERIAL LAB RESULTS

Management of Thromboembolic risk

In the adults, COVID-19 has emerged an independent risk factor for thrombosis[23]. The estimated prevalence of venous thromboembolism (VTE) is 31% in COVID-19 patients[24].

In contrast, pediatric data is limited, and children are at low risk for VTE overall. The rate of VTE in hospitalized children is estimated at 0.58% with those between 12 to 18 years having the highest rate of 0.94%[25].

At present, hospitalized pediatric patients with COVID-19 have an increased risk of thrombosis with a reported incidence of 2.1%. Age greater than 12 years old increases the risk of thrombotic complications with COVID-19 or MIS-C (incidence 6.8%). Most thrombotic events occurred while on thromboprophylaxis[26].

The increased rate of thrombosis is a concern however, additional risk factors (age, central venous line, ward vs ICU, etc.) and risk of bleeding must be carefully evaluated before contemplating initiation of thromboprophylaxis. Therefore, Consultation with pediatric hematology (Calgary) or KidClot (Edmonton) is recommended when thromboprophylaxis is being contemplated for a child admitted with symptomatic COVID19. For MIS-C please refer to the provincial MIS-C recommendations.

Considerations for Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C is a serious delayed complication of COVID-19 infection that may develop in some children and young adults. Consultation with a specialist is recommended prior to management of suspected MIS-C with corticosteroids or other immunomodulating therapies. Please refer to the MIS-C document for further details: Multisystem Inflammatory Syndrome in Children (MIS-C): Care Guide for Children and Adolescents in Alberta (albertahealthservices.ca)

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