PURPOSE: To outline consensus recommendations on the management of pediatric patients with suspected or confirmed COVID-19 infections at CHKD. For information on the treatment and management of multisystem inflammatory syndrome in children (MIS-C), please refer to the MIS-C specific guideline available on KDnet.

PATIENT PRESENTATION:

Range from uncomplicated upper respiratory tract viral infection to pneumonia, acute respiratory distress syndrome (ARDS), sepsis, and septic shock (Table 1). No specific data is available establishing risk factors for severe COVID-19 disease in children.[23]

Table 1. Clinical Symptoms Associated with COVID-19:

Symptoms	Description
Uncomplicated Illness	Uncomplicated upper respiratory tract viral infection with nonspecific symptoms including: ▪ Fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain, anosmia, hyposmia Without signs of dehydration, sepsis, or shortness of breath
Mild Pneumonia	Non-severe pneumonia presenting with cough or difficulty breathing + tachypnea Without signs of severe pneumonia
Severe Pneumonia *Diagnosis is clinical*	Adolescent: fever or suspected respiratory infection + one of the below: ▪ RR > 30 breaths/min ▪ Severe respiratory distress ▪ SpO_2 < 90% on room air Child: cough or difficulty breathing + one of the below: ▪ Central cyanosis ▪ SpO_2 < 90% ▪ Severe respiratory distress ▪ Clinical signs of pneumonia + inability to breast feed or drink, lethargy, convulsions
ARDS	New or worsening respiratory symptoms within one week of known clinical insult Chest imaging consistent with ARDS Respiratory failure not explained by cardiac failure or fluid overload
Sepsis/Septic Shock	Diagnosis made clinically

Source: World Health Organization

Table 2. COVID-19 SPECIFIC THERAPY

Class	Agent	Route	Patient Status	Details
Antivirals	**Remdesivir (Veklury)***	IV	Either◊	**EUA:** < 12 years and ≥ 3.5 kg or > 12 years and < 40kg **FDA Approved**: ≥ 12 years and ≥ 40 kg
	Nirmatreivir/ritonavir (Paxlovid)*	PO	Out-pt	**EUA**: Mild-moderate ***High-Risk*** COVID-19 (+) patients: a) ≥ 12 years and ≥ 40 kg, AND b) Confirmed (+) COVID-19 test, AND c) High risk for progression to severe COVID-19, AND d) Within 5 days of symptoms onset
	Molnupiravir*	PO	Out-pt	**EUA**: Mild-moderate ***High-Risk*** COVID-19 (+) patients: a) ≥ 18 years of age b) Confirmed (+) COVID-19 test, AND c) High risk for progression to severe COVID-19, AND d) Within 5 days of symptoms onset
JAK-1 Inhibitor	**Baricitinib (Olumiant)**	PO	In-pt	**EUA: ≥** 2 years in combo **with** Remdesivir *Reserved for contraindications to corticosteroids, Not FDA approved for COVID-19*
mAbs	**Bebtelovimab***	IV	Out-pt	**EUA:** ≥ 12 years of age and ≥ 40 kg Anticipated CHKD shipment arrival (4/8-4/11)
	Pre-Exposure			
	Tixagevimab/Cilgavimab*	IM	Out-pt	**EUA:** ≥ 12 years of age and ≥ 40 kg **NOT** for treatment, adjunctive w/ vaccine

IM, intramuscular; In-pt, inpatient; IV, intravenous; mAbs, COVID-19 monoclonal antibodies; out-pt, outpatient; PO, orally
** Refer to drug specific guidelines, available on Kdnet*
◊ refer to remdesivir specific guideline on KDnet

COVID-19 SUPPORTIVE CARE & ANTICOAGULATION:

Supportive Care:
Sufficient fluid and calorie intake, and additional oxygen supplementation should be used in the treatment of children infected with COVID-19. The aim is to prevent ARDS, organ failure, and secondary nosocomial infections. If bacterial infection is suspected, broad-spectrum antibiotics may be used.[22]

Anticoagulation:
COVID-19 is associated with an increased risk of venous thromboembolism (VTE) in adults. There are no specific recommendations for pediatric patients with COVID-19.[15-21] Asymptomatic, mild, or moderate COVID-19 is not an indication for anticoagulant prophylaxis unless the patient qualifies based on risks outlined in Table 2. All hospitalized COVID-19 (+) patients should undergo a risk assessment as outlined in Table 3. & Figure 1.

a) Strongly consider Hematology consult to assess risk factors

b) If patient qualifies for thromboprophylaxis, obtain D-dimer, fibrinogen, PT/PTT, & Serum Creatinine (Scr), and consult Hematology

c) Thromboprophylaxis may be changed to treatment if very high risk for VTE/microvascular thrombosis. Discuss with Hematology

d) Patients with decreased renal function should have enoxaparin adjusted or changed to unfractionated heparin, discuss with Hematology

e) Length of VTE prophylaxis to be determined by Hematology

Figure 1: Anticoagulation in Pediatric Acute COVID-19

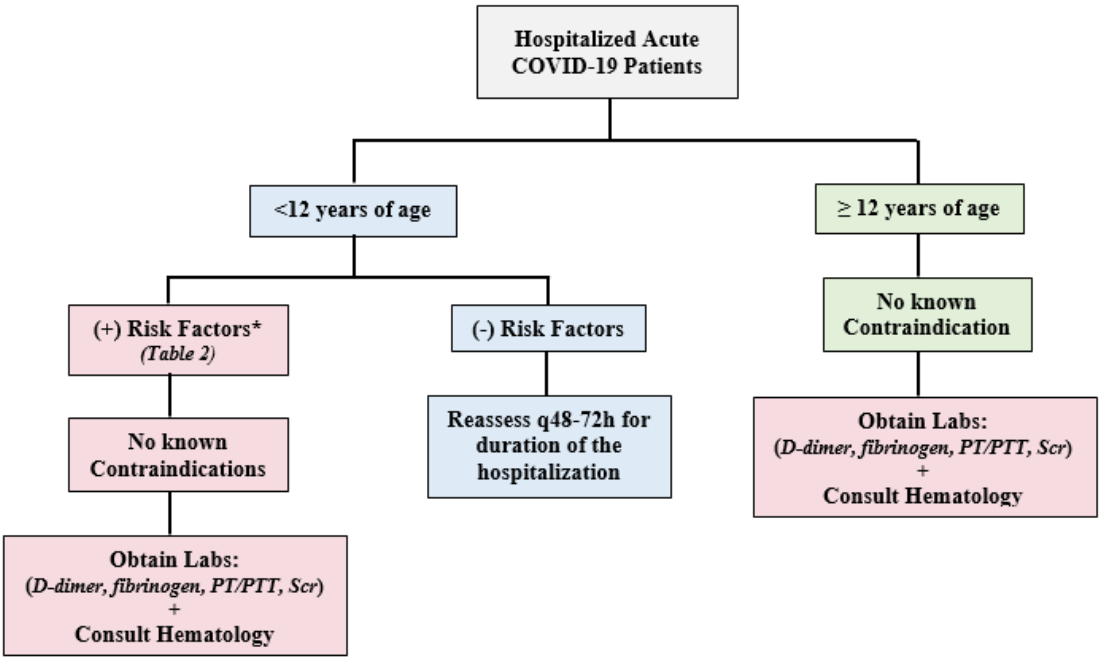


Table 3: Thromboprophylaxis should be considered in patients who meet ≥ 1 of the following

Risk Factors for VTE
• Age ≥12 years or post-pubertal
• Patients on PICU service
• Mechanical Ventilation
• Obesity
• Central Line(s)
• Decreased mobility
• Sickle Cell Disease
• Autoimmune Disorders
• Nephrotic Syndrome
• CF Exacerbation
• Prolonged Length of Stay (anticipated > 3 days)
• First degree family history of unprovoked VTE
• Personal and/or family history of thrombosis/thrombophilia
• Concomitant estrogen-containing medication
• Inotropic infusion requirement
• Any heart rhythm abnormalities
• Congenital or acquired heart disease with venous stasis or impaired venous return

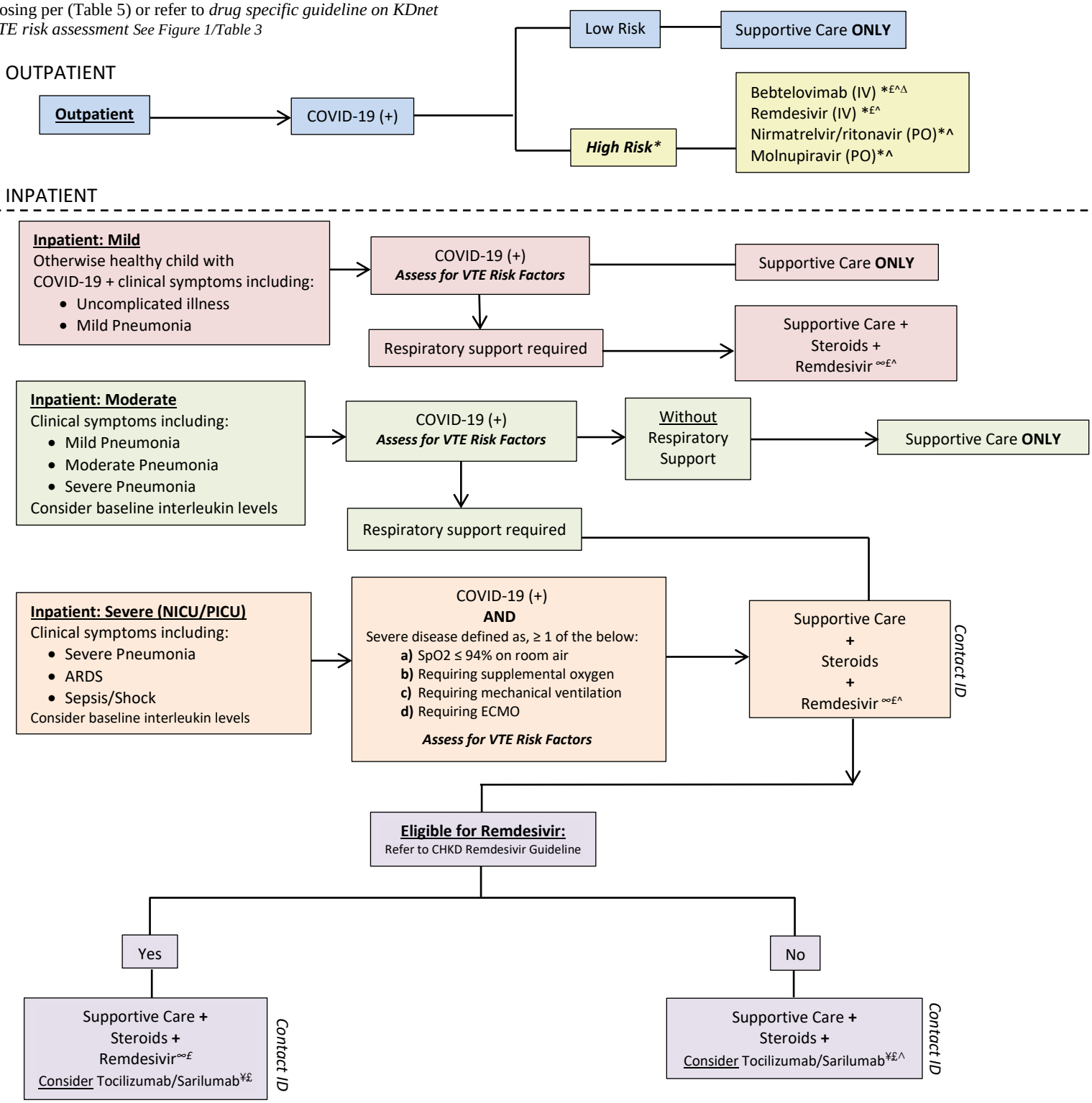
Table 4. Bleeding Risk Factors: [15-22]

Bleeding Risk Factors	Description
Not Recommended	Intracranial hemorrhage Active bleed
Consider with caution	Intracranial mass Lumbar puncture w/in 24 hours Coagulopathy Neurosurgical procedure w/in 24 hours

Figure 2. Treatment Algorithm:

Dosing per (Table 5) or refer to *drug specific guideline on KDnet*

VTE risk assessment See Figure 1/Table 3



* Reserved for High Risk Patients- See drug specific guideline on kdnet
£ ID Restricted. Contact for approval
Δ Pending available supply
ᵐConsider Baricitinib if steroids are contraindicated[46]
¥ Patients with signs and symptoms of cytokine storm
^ Must meet individual criteria for use, see specific guideline on KDnet

Criteria for risk high-risk of cytokine storm[10]

≥1	Description
IL-6	≥3x upper normal limit
Ferritin	>300 ug/L with doubling in 24 hr
Ferritin + LDH	>600 ug/L at presentation >250
D-dimer	Elevated

Table 5. Agents Approved & Under Investigation for Treatment of COVID-19[50]

COVID-19 Treatment: Drugs[50]	Dosing & Duration[23,47]	Comments
Remdesivir*(Veklury®)- (IV only) **Restricted to:** a. **Infectious Disease** b. **≤ 7 days of illness,** (do not use in patients with signs and symptoms for > 7 days) unlikely to reap benefits of therapy, risk vs. benefit **Outpatient Use:** a. **High-risk** patients with confirmed (+) COVID-19 b. **≤ 7 days of illness** (symptom onset) FDA approved ≥ 12 years & ≥ 40 kg as of 1/21/22. Patients ≥ 3.5 kg to < 40 kg with confirmed COVID-19 may utilize under the EUA, revised as of 1/21/2022.[61, 64] ***Restricted to Infectious Disease*** ***Refer to Remdesivir Guideline on KDnet***	**Adult dosing:** ▪ 200 mg load, then 100 mg q24h **Pediatric dosing*:** **Weight** / **LD** (once) / **MD** (q24h) <40 kg / 5 mg/kg / 2.5 mg/kg ≥40 kg / 200 mg / 100 mg LD-Loading Dose, Max =200 mg MD-Maintenance Dose, Max= 100 mg **Duration:** ▪ Hospitalized: 5 days ▪ Non-hospitalized: 3 days	FDA approved as of 10/22/20 **Age / wt (kg)** / **EUA Needed** **< 12 years or < 40 kg*** / YES **≥ 12 years & ≥ 40 kg** / NO * must be ≥ 3.5 kg **EUA (< 12 years):** ▪ 10/22/20: Hospitalized pediatric patients, weight ≥ 3.5 kg or < 40 kg ▪ 1/21/22: Non-hospitalized patients, weight ≥ 3.5 kg or < 40 kg, and classified as high-risk **Adverse events:** ▪ Increased liver enzymes, discontinue if ALT ≥ 10 times UNL ▪ Infusion related hypotension ▪ Drug-drug interactions CYP450 ▪ QT prolongation (possible TdP Risk)
Corticosteroids (IV/PO) **Dexamethasone** ▪ Preferred in adults, ▪ No known superior agent in children **Methylprednisolone** ▪ Preferred in COVID-19 + asthmatic patients[54] Alternatives: a. Breastfeeding/Pregnant: Prednisolone or methylprednisolone b. Preterm infant: Corrected GA < 40 weeks: Hydrocortisone Indicated for patients with: a. Respiratory support: oxygen or invasive mechanical ventilation b. Continuation for underlying condition requiring chronic steroid treatment c. Additional diagnosis where steroid therapy is appropriate	**Dosing:** **Preferred Drug** / **Dose** [33-34, 54] Dexamethasone / 0.15mg/kg once daily (Max: 6 mg) Methylprednisolone / 2 mg/kg/day divided q12h (Max: 60 mg/day) **Alternative Drugs** / **Dose** [33-34] Prednisolone / 1 mg/kg once daily (Max: 40 mg) Hydrocortisone / 0.5 mg/kg q12h X 7 days 0.5 mg/kg daily X 3 days **Duration:** up to 10 days	**Adverse events:** ▪ Hypertension ▪ Hyperglycemia
Paxlovid (nirmatrelvir/ritonavir) (PO)[62] **EUA** for the treatment of mild-to-moderate COVID-19 in patients: a. ≥ 12 years and ≥ 40 kg b. Confirmed (+) COVID-19 test c. *High risk* for progression to severe COVID-19 d. Within 5 days of symptoms onset **NOT** authorized: ▪ Hospitalized due to severe/critical COVID-19 ▪ Use for > 5 consecutive days ▪ Pre or post-exposure prophylaxis ***Refer to Oral Antivirals Guideline on KDnet*** ***Not available at CHKD, outpatient only***	**Dosing:** ▪ Nirmatrelvir 300 mg (two 150 mg tablets) + ▪ Ritonavir 100 mg (one 100 mg tablet) ▪ Twice daily **Renal Dosing: CrCl** **CrCl** (mL/min) / **Adjustment** **≥ 60** / None **≥ 30 to < 60** / Nirmatrelvir 150mg + Ritonavir 100mg **< 30** / Avoid **Hepatic Dosing:** ▪ Avoid in severe impairment (Child-Pugh Class C) **Duration:** ▪ 5 days **Administration:**	**Contraindications:** a. History of significant hypersensitivity reactions to any ingredient b. **Highly metabolized CYP3A drugs**: Elevated concentrations associated with serious and/or life-threatening reactions c. **Potent CYP3A Inducers**: associated with the potential for loss of virologic response and resistance. Cannot be started immediately after discontinuation due to the delayed offset of the recent CYP3A inducer **Warnings:** ▪ Hepatotoxicity ▪ HIV Resistance No data in pregnancy or breast feeding **Adverse Effects** (≥5%):

	▪ Take all 3 tabs together with fat containing meal ▪ If hospitalization occurs after starting treatment, complete the full 5-day course per the healthcare provider's discretion ▪ If a dose is missed within an 8 hours window, take the missed dose as soon as possible, if > 8 hours, do not take the missed dose and resume normal schedule	▪ Dysgeusia, diarrhea, hypertension, myalgia **Drug Interactions!!!!!** For specific recommendations and contraindications, refer to specific guideline on KDnet
Molnupiravir (PO) [63] **EUA**: Mild-moderate COVID-19 in patients: a. ≥ 18 years of age b. Confirmed (+) COVID-19 test c. *High risk* for progression to severe COVID-19 d. Within 5 days of symptoms onset Outpatient **ONLY** **NOT** authorized: ▪ Hospitalized patients, due to COVID-19 ▪ Pre or post-exposure prophylaxis ▪ Duration > 5 consecutive days **Pregnancy testing prior to initiating** ***Refer to Oral Antivirals Guideline on KDnet*** ***Not available at CHKD, outpatient only***	**Dosing:** ▪ 800 mg (4 caps) every 12 hours X 5 days ▪ Supplied as 200 mg capsules No renal or hepatic dose adjustments required Not recommended in pregnancy or breastfeeding **Duration:** ▪ 5 days **Administration:** ▪ If hospitalization occurs after starting treatment, complete the full 5-day course per the healthcare provider's discretion ▪ If a dose is missed within an 10 hours window, take the missed dose as soon as possible, if > 10 hours, do not take the missed dose and resume normal schedule	TdP: Torsade's de pointes **Contraindications:** None known **Warnings:** (Data from animal studies) a. **Embryo-Fetal Toxicity:** Advise use of effective contraception correctly and consistently, for the duration of treatment and for 4 days after the last dose b. **Bone and Cartilage Toxicity:** Avoid age < 18 years may affect bone & cartilage growth **Adverse Effects** (< 2 %): ▪ Diarrhea, nausea, dizziness **Drug Interactions:** none known to date **Pregnancy Surveillance Program** ▪ Voluntary long-term follow up program
Baricitinib (Olumiant®)-(PO/NG/GT only) **EUA:** ≥ 2 years **in combo with Remdesivir** **At CHKD,** Baricitinib is reserved for patients who meet the stated EUA criteria and have a contraindication to corticosteroid treatment *Corticosteroids should be 1st line and Baricitinib 2nd line only when steroid use is contraindicated* [46] CBC, CMP: Required at baseline and daily while on therapy, careful attention to LFTs and Scr/BUN ***Restricted to Infectious Disease***	**Dosing:** **Age** / **Dose** **≥ 2-8 years** — 2 mg once daily **≥ 9 years** — 4 mg once daily **Dose Adjustments/Contraindications for:** a. Renal Insufficiency b. Hepatic Failure c. ALC < 200 cells/µL d. ANC < 500 cells/µL	**EUA:** Suspected or confirmed COVID-19 in patients who are: ▪ Hospitalized **AND** ▪ Adults or pediatric patients ≥ 2 years of age **AND** ▪ Require supplemental oxygen, invasive mechanical ventilation, or ECMO **Drug Interactions:** • Strong OAT3 Inhibitors **Adverse events:** ▪ Serious Infections ▪ **Thrombosis** ▪ Abnormalities in LFTs, CBC, BUN/Scr at baseline and daily required **Caution:** ▪ Avoid use of live vaccines w/ Baricitinib ▪ Hypersensitivity-Rare but has been reported
Tocilizumab (TOCI) (IV) ▪ IL-6 inhibitor ▪ Added to antiviral therapy + steroids in those meeting criteria (**Figure 2**)	**Adult Dosing (≥18 years):** ▪ 8 mg/kg X 1 (Max 800 mg) **Pediatric Dosing (<18 years):** ▪ < 30 kg: 12 mg/kg X 1 (Max 800 mg) ▪ ≥ 30 kg: 8 mg/kg X 1 (Max 800 mg) ** Round dose to nearest full vial ** **Duration**: ONCE	**Contraindications:** ▪ Avoid in pregnancy/breastfeeding ▪ Alanine aminotransferase >5 times UNL ▪ Absolute neutrophil count <500 cells/µL ▪ Platelet count <50,000 cells/µL **Caution:** ▪ Avoid live viral vaccines ▪ Caution converting from either agent to anakinra ▪ CRP & IL-6 levels not reliable post dose **Serious adverse events:** ▪ GI perforation, Anemia, Hepatitis, Infusion reaction ***Do not anticipate response for 48-72 hrs post dose***
Sarilumab (SC or IV)[23, 55-57] **2nd Line** IL-6 inhibitor ▪ Alternative during critical TOCI shortage in those ≥ 40 kg ▪ Data is limited in children Added to antiviral therapy + steroids in those meeting criteria (**Figure 2**) ***Restricted to Infectious Diseases***	**Dosing (≥ 40 kg):** ▪ 400 mg **IV** X 1 dose **Administration:** ▪ 400 mg in 100 mL of 0.9% NaCl infused over 1 hour[55-57] **Duration**: ONCE **Route of Administration:** *IV only for COVID-19* ▪ SC NOT FDA approved for CRS ▪ IV is not FDA approved, studied in a clinical trial of hospitalized patients with COVID-19	

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Originated: 03/20/2020	Last Revised: **3/30/2022**

Revision History:
3/30/22: removed sotrovimab from guideline per FDA recommendations or BA.2
2/22/22: Bebtelovimab added to flow diagram and Table 2.
2/2/22: added outpatient remdesivir, adjusted outpt mgt on figure 1. Added reference. Removed remdesivir oxygen supp. requirement. Added comment to oral antiviral, not available inpatient.
1/5/22: Addition of sotrovimab and removal of BAM-E and C/I, added T-C. Removed innovative use from Sarilumab. Added Molnupiravir and Paxlovid, adjusted table 4 for additions and formatting. Updated figure 1.
11/19/21: addition of PF-07321332/Ritonavir (Paxlovid) to figure 2. and table 4.
8/23/21: remdesivir restriction added
8/20/21: clarified recommendations for dexamethasone and Remdesivir in algorithm added, sarilumab added w/ innovative use guidance, C/I ppx comment added
7/23/21: updated steroid recommendations
6/2/21:conv plasma removed, monoclonal antibodies updated to reflect variant changes, C/I recommended agent, dosing for Sotrovimab added with note to used C/I as preferred, flow diagram updated
3/24/21: Anticoagulation lab recommendations, Bamlanivimab monotherapy removed.
2/26/21: MIS-C guideline separation, update treatment to include anticoagulation recommendations and risk assessment. Added BAM-E to guideline and recommended using BAM containing first over C/I.
1/28/21: added heme-onc consult and removed ASA as initial therapy without consult. Add dosing recommendations and caveat in dosing table.
1/20/21: updated MIS-C guideline, steroids and anakinra dosing, Remdesivir ALT recommendations
12/15/20: updated Baricitinib recommendations from 12/14 NIH
11/24/20: added Bamlanivimab & Casirivimab and Imdevimab, and Baricitinib, removed nebulized recommendations, added covid specific therapy chart, removed
10/23/20: Updated MIS-C management and FDA Remdesivir approval
8/7/20: clarified recommendations for dexamethasone and Remdesivir in algorithm
7/22/20: updated Remdesivir use of CHKD product under EUA
7/17/20: updated anakinra dosing and tocilizumab information
7/8/20: added nebulized therapy guidance, renumbered tables
6/24/20: dexamethasone recommendations added, Qtc monitoring (Figure 2.) removed, organized to improve flow. Tables and figures renumbered
6/17/20: Hydroxychloroquine and azithromycin removed from guideline
6/1/20: ID consult added to MIS-C and moderate-severe criteria combine
5/29/20: Hydroxychloroquine removed from algorithm and ID will recommend as a 2nd line therapy if indicated, and moved to 2nd line in table 4. ID consult added to algorithm. Reformatting of table 4

5/22/20:addition of definition and review of treatment for MIS-C, Remdesivir EUA update, addition of chart with known indication in COVID-19 and unclear, anakinra added to list, cytokine storm table moved to tocilizumab dosing table, QTC chart updated. MIS-C severity table, guideline for MIS-C treatment and dosing. MIS-C flow diagram, Simplified tocilizumab dosing
5/4/20: Updated information on disease process in children, added EUA to Remdesivir, changed to consider Hydroxychloroquine to the treatment algorithm. Added new references. Removed Lopinavir-Ritonavir
4/9/20: NG administration for hydroxychloroquine, Remdesivir added to figure 1, azithromycin changed to (+/-) in figure 1. Tables renumbered for organization, VTE prophylaxis guidance-Reviewed by Eric Lowe MD & Jessica Price PharmD
4/3/20: Remdesivir reference to guideline, included reference for cytokine storm
03/30/20: updated Lopinavir/ritonavir dosing and duration, remove azithromycin from combination early initiation, added QT monitoring recommendations and risks, NSAID statement

The recommendations in this guide are meant to serve as treatment guidelines for use at The Children's Hospital of The King's Daughters. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information through an independent source.

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