Guideline/Protocol Title:	Pediatric Guidelines for Treatment of Coronavirus Disease 2019 (COVID-19); Addendum to BCH Empiric Antimicrobial Therapy Guidelines
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Collaborator(s):	Pediatric COVID-19 Clinical Working Group (includes representation from BCHO and BCHSF critical care, hospital medicine, infectious diseases, rheumatology and hematology clinicians and community partner sites (Community Regional Medical Center, Zuckerberg San Francisco General).
Approving committee(s):	BCHO P&T (12/11/2020); BCH Medications Committee (12/15/2020)
P&T Approval Date:	12/11/2020
Last revision Date:	12/11/2020

PURPOSE/SCOPE:	To address specific antiviral, steroid and monoclonal antibody therapies for COVID-19 in pediatric patients. The guidelines do not at this time address supportive care and other aspects of COVID-19 management such as anticoagulation. These guidelines are an addendum to the BCHSF Pediatric Empiric Antimicrobial Therapy Guidelines (EATG) hosted at idmp.ucsf.edu; a full 2021 EATG update is in progress with plans to consolidate guidelines for both Benioff Children's Hospital campuses. This section addressing COVID-19 is prioritized for earlier review and dissemination because evidence-based treatment recommendations are needed in the setting of the current COVID-19 pandemic.

EXECUTIVE SUMMARY

Given the lower severity of illness due to COVID-19 in pediatric patients, supportive care is the primary recommendation for most pediatric patients with mild-moderate COVID-19. Remdesivir and dexamethasone are recommended for pediatric patients with severe-critical COVID-19 based on extrapolation of adult clinical trial data, national interim guidance for pediatric patients, and local expert consensus from the Pediatric Antimicrobial Stewardship Program and Pediatric COVID-19 Clinical Working Group. Monoclonal antibody therapy is not routinely recommended for pediatric patients at this time.

BACKGROUND / INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the novel coronavirus SARS-CoV-2, emerged in late 2019 and subsequently spread into a devastating pandemic that is worsening at this time. During initial stages of the pandemic, minimal evidence existed for any specific antiviral therapy. Clinical trials conducted in adults, and data on pediatric safety from compassionate use therapy have since provided sufficient evidence to define a working standard of care that can be recommended for routine management of COVID-19 in pediatric patients.

SUPPORTING EVIDENCE
Remdesivir: Recommendation for therapy in pediatric patients with severe-critical COVID-19 is based on National Institutes of Health guidelines, Infectious Diseases Society of America guidelines, and pediatric interim guidelines, which primarily draw from multiple RCTs in adults. Efficacy data has been conflicting from various RCTs without clear demonstration of mortality benefit but with some RCTs showing shorter time to improvement, often driven by specific patient subgroups. Safety data is favorable, including from compassionate access experience in pediatric patients. **Dexamethasone:** Recommendation for therapy in pediatric patients with severe-critical COVID-19 is based on the same published guidelines, drawing from adult RCT data demonstrating mortality benefit, and well-described safety profile for acute short-term treatment in pediatric patients. One distinction from current adult treatment guidelines is the recommendation for dexamethasone regardless of level of oxygen supplementation in pediatric patients. This is based on 1) registry data showing that among pediatric patients needing any level of oxygen supplementation for COVID-19, half progress to needing mechanical ventilation, suggesting that any level of oxygen requirement signals a higher risk for impending progression; and 2) lack of a commonly accepted universal standard definition of "high flow nasal cannula" in pediatric patients, due to variability in relative flow provided in proportion to body size. **Bamlanivimab:** Not recommended for routine use based on low quality of evidence in adult patients, no efficacy or safety data in pediatric patients, overall lower risk for severe outcomes of COVID-19 in pediatric patients, and insufficient evidence to define specific risk factors in pediatric patients, even those outlined in the Emergency Use Authorization. **Casirivimab and Imdevimab:** Not recommend for routine use for the same reasons outlined for bamlanivimab.

APPENDIX
Appendix 1. Pediatric Guidelines: Viral Infections – Coronavirus Disease 2019 (COVID-19)

Reference #	Citation
1	Chiotos K, et al. Multicenter interim guidance on use of antivirals for children with coronavirus disease 2019/severe acute respiratory system coronavirus 2. J Pediatr Infect Dis Soc 2020; doi:10.1093/jpids/piaa115
2	Wolf J, et al. Initial guidance on use of monoclonal antibody therapy for treatment of COVID-19 in children and adolescents. J Pediatr Infect Dis Soc 2020; [in press]
3	Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Bamlanivimab [link: http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf]

4	Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Casirivimab and Imdevimab [link: https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-hcp.pdf]
5	COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [link: https://www.covid19treatmentguidelines.nih.gov/]
6	Bhimraj A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 [link: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/]
7	American Society of Health-System Pharmacists. Assessment of evidence for COVID-19-related treatments. Available at: [link: https://www.ashp.org/COVID-19?loginreturnUrl=SSOCheckOnly] Up to date evidence summary including detail on unsupported therapies.
8	Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*. 2020;31(7):1384-1386.

Revision History	
Revision Date	**Update(s)**
11/30/20	• New section to be addended to BCH Empiric Antimicrobial Therapy Guidelines
Subsequent revisions	• Due to the emergent nature of current COVID-19 pandemic, subsequent updates will be made in real time as new treatment evidence emerges. • Minor updates including the following changes will not be re-submitted for P&T review: changes to the FDA approval status of therapies, addition of novel therapies that are *not routinely recommended* for pediatric patients, changes to the language defining treatment indications (e.g. new definitions or new criteria for use), or minor changes to medication dose, administration, monitoring or duration recommendations to reflect updates from published guidelines or manufacturer recommendations. • Changes that will be re-submitted for P&T review will include: change in the scope of recommendations (e.g. new disease manifestation(s) addressed such as multisystem inflammatory syndrome, or inclusion of other therapeutic categories such as anticoagulants), introduction of additional novel therapies that *are recommended* for use in pediatric patients, and routine re-review every 3 years.

Appendix 1: Pediatric Guidelines: Viral Infections – Coronavirus Disease 2019 (COVID-19)

[format intended for online display – see example here: https://idmp.ucsf.edu/pediatric-guidelines-viral-infections-influenza]

The following guidelines are based on evidence assessment and published guidance at the time of review, and are subject to further changes as new COVID-19 treatment evidence emerges and new guidance is published.

These guidelines are currently focused on specific antiviral, steroid and monoclonal antibody therapies for COVID-19 and do not at this time address supportive care and other aspects of management such as anticoagulation.

The recommendations below were updated 11/30/20.

Condition	Major Pathogen(s)	First Choice Therapy	Alternative Therapy/(Details)	Comments
Coronavirus disease 2019 (COVID-19), **mild-moderate** Mild: No new or increased supplemental oxygen requirement, with symptoms limited to upper respiratory tract Moderate: No new or increased supplemental oxygen requirement, with symptoms involving the lower respiratory tract, or radiographic findings on chest X-ray	SARS-CoV-2	Supportive care is recommended for most patients. Antiviral therapy may be considered on a case-by-case basis as outlined in pediatric multicenter guidance [link] Monoclonal antibody therapy per Emergency Use Authorizations: Bamlanivimab [link to EUA info] OR Casirivimab and Imdevimab [link to EUA info] Not recommended routinely, may be considered on a case-by-case basis. See severe-critical section below if treating with antiviral therapy		ID consultation recommended for any treatment questions in patients hospitalized with COVID-19
Coronavirus disease 2019 (COVID-19), **severe-critical** Severe: new or increased requirement for supplemental oxygen	Same	Age <12 years and/or wt < 40 kg: Remdesivir lyophilized powder only Wt 3.5-40 kg: 5 mg/kg/dose IV on day 1, then 2.5 mg/kg/dose IV q24h	Remdesivir is FDA approved for treatment of hospitalized patients >= 12 years and >= 40kg Treatment for hospitalized patients not meeting above criteria remains available via	ID consultation recommended ID approval is required for remdesivir use **Duration**: Remdesivir: Severe disease: 5 days

Critical: new or increased requirement for invasive or noninvasive mechanical ventilation, sepsis, multiorgan failure, or rapidly worsening clinical trajectory that does not yet meet these criteria		Age ≥12 years and wt >40 kg: Remdesivir Injection solution or lyophilized powder Wt >40 kg: 200 mg/dose IV on day 1, then 100 mg/dose IV q24h See 4th column for emergency use authorization treatment details and monitoring, last column for duration AND Dexamethasone* 0.15 mg/kg/dose (max 6mg/dose) IV or enterally q24h (see last column for duration)	emergency use authorization (EUA) which includes specific requirements: Provide fact sheet to patient's caregiver. English and Spanish versions available here. Obtain informed assent from caregiver including discussion that medication is not yet FDA approved for patients < 12 years or <40 kg Use the age-appropriate remdesivir order panel to ensure adherence to criteria. Monitoring for remdesivir: Monitor hepatic panel at baseline and during therapy ALT >10 times the upper limit of normal and asymptomatic: Consider discontinuing remdesivir. ALT elevation AND signs or symptoms of liver inflammation: Discontinue remdesivir. Although the manufacturer's labeling recommends against use in patients with eGFR <30 mL/minute, significant toxicity with a short duration of therapy (e.g., 5 to 10 days) is unlikely.	Critical disease: 5-10 days, guided by clinical course Dexamethasone: Up to 10 days or until hospital discharge, whichever comes first *Consider risks vs. benefits of dexamethasone in relationship to underlying conditions (e.g. prior immunosuppression, metabolic disease, etc.) especially in patients with less severe respiratory illness e.g. not requiring mechanical ventilation.
Multisystem inflammatory syndrome in children (MIS-C)	Post-infectious phenomenon following SARS-CoV-2 infection	Antiviral treatment is not routinely indicated, unless acute COVID-19 is also a diagnostic consideration, and patient would meet		ID and Rheumatology consults recommended

		above criteria for severe or critical disease. Other management of MIS-C is currently outside the scope of this guideline.		

This is a subsection of the UCSF Benioff Children's Hospitals Empiric Antimicrobial Therapy Guidelines, developed by the Pediatric Antimicrobial Stewardship Programs at each campus to inform initial selection of empiric antimicrobial therapy for children at the UCSF Benioff Children's Hospitals and affiliated outpatient sites.

These are guidelines only and not intended to replace clinical judgment. Modification of therapy may be indicated based on patient comorbidities, previous antibiotic therapy or infection history. Doses provided are usual doses but may require modification based on patient age or comorbid conditions. Refer to Pediatric Antimicrobial Dosing Guideline for further guidance on dosing in children, and Neonatal Dosing Guideline for infants < 1 month of age. Consult a pediatric pharmacist for individualized renal or hepatic dose adjustment. For additional guidance, please contact Pediatric Infectious Diseases (ID) or the Pediatric Antimicrobial Stewardship Program (ASP) at the campus where your patient is receiving care.

For questions or feedback about these guidelines, please email primary content owners, Rachel Wattier (rachel.wattier@ucsf.edu), Pediatric ASP Medical Director at BCHSF and Prachi Singh (prachi.singh@ucsf.edu), Pediatric ASP Medical Director at BCHO.