Title
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Journal
Journal of the Pediatric Infectious Diseases Society, 9(6)

ISSN
2048-7193

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Publication Date
2020-12-31

DOI
10.1093/jpids/piaa045

Peer reviewed

Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2

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Key Points: Supportive care is sufficient for nearly all pediatric patients with COVID-19 given the overwhelming tendency toward mild illness in children. Decision-making regarding antiviral therapy for severely or critically ill children should weigh individual risks and benefits, informed by available evidence.

ABSTRACT

Background: Although Coronavirus Disease 2019 (COVID-19) is mild in nearly all children, a small proportion of pediatric patients develops severe or critical illness. Guidance is therefore needed regarding use of agents with potential activity against severe acute respiratory syndrome coronavirus 2 in pediatrics.

Methods: A panel of pediatric infectious diseases physicians and pharmacists from 18 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a set of guidance statements was developed and refined based on review of best available evidence and expert opinion.

Results: Given the typically mild course of pediatric COVID-19, supportive care alone is suggested for the overwhelming majority of cases. The panel suggests a decision-making framework for antiviral therapy that weighs risks and benefits based on disease severity as indicated by respiratory support needs, with consideration on a case-by-case basis of potential pediatric risk factors for disease progression. If an antiviral is used, the panel suggests remdesivir as the preferred agent. Hydroxychloroquine could be considered for patients who are not candidates for remdesivir or when remdesivir is not available. Antivirals should preferably be used as part of a clinical trial if available.

Conclusions: Antiviral therapy for COVID-19 is not necessary for the great majority of pediatric patients. For those rare children who develop severe or critical disease, this guidance offer an approach for decision-making regarding antivirals, informed by available data. As evidence continues to evolve rapidly, the need for updates to the guidance is anticipated.

Key Words: COVID-19, SARS-CoV-2, pediatric, antiviral, guidance

INTRODUCTION

In December 2019, a novel coronavirus, since named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in Wuhan, Hubei Province, China, as the cause of a severe respiratory disease, Coronavirus Disease 2019 (COVID-19). COVID-19 has been declared a pandemic by the World Health Organization (WHO), with cases detected in over 180 countries and affecting nearly 2 million people as of April 14, 2020, including over 600,000 in the United States (US) (1). Over 126,000 people have died from the infection worldwide.

In light of this public health crisis, there has been significant interest in identifying therapies that include both novel and "repurposed" drugs with antiviral activity against SARS-CoV-2 that may mitigate disease severity. As of the writing of this guidance on April 14, 2020, no agent has been identified with proven efficacy against SARS-CoV-2. Further, while the evidence base evolves almost daily, the data supporting candidate medications for COVID-19 are sparse, based primarily on *in vitro* studies, animal models, and small clinical studies focused on adults, with only sporadic case series describing antiviral use in children (2–5).

While pediatricians are accustomed to prescribing medications that have been studied primarily in adults, using this approach for COVID-19 presents unique challenges for several reasons. First, the evidence base evaluating all potentially active antivirals for treatment of COVID-19 is extremely limited. Second, COVID-19 appears to be far milder in the great majority of children compared with adults (6), raising questions as to whether the potential benefits of antivirals are also much less—and if so, whether the threshold for using these medications should be much higher, especially given possible harms. Third, the optimal pathway for introducing novel therapies, even in a pandemic, is to do so as part of well-designed, randomized controlled trials (3). As of April 14, 2020, no clinical trials

in the US are enrolling children <12 years old, so antiviral use in children is largely limited to off-label prescribing of agents approved by the Food and Drug Administration (FDA) for other indications or Single Patient Expanded Access requests for investigational agents such as remdesivir.

Absent clinical trials, and through the SHaring Antimicrobial Reports for Pediatric Stewardship (SHARPS) Collaborative (7), the potential value of multicenter, expert guidance for use of antivirals in children with COVID-19 during this pandemic became increasingly apparent. Herein, we outline our approach to developing this guidance, summarize the relevant available evidence, and outline the rationale for our suggested treatment approach. We remind the reader that this document is *not* a guideline, and we emphasize the ongoing importance of critical review of emerging literature to inform current and future treatment decisions. We also refer the reader to guidelines published by the Infectious Diseases Society of America (8).

GUIDANCE DEVELOPMENT

Approach

A panel of pediatric infectious diseases (ID) physicians and pharmacists from 18 geographically diverse North American institutions was convened. Through a series of teleconferences and web-based surveys, a set of guidance statements was developed and refined based on best available evidence and expert opinion. Given the overall limited nature of the data, a systematic review was not performed, nor was the available evidence formally evaluated using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) or other methodology. This guidance document has been reviewed and endorsed by the Pediatric Infectious Diseases Society.

Definitions

Because the quality of evidence considered by the expert panel was generally low, the final guidance statements integrate both the panel's assessment of the evidence quality and the ratio of risk and benefit from the treatment or action. We assert that the key guiding principle should be to "first do no harm," especially given the unknown efficacy of proposed antivirals and their established—or, in the case of novel agents, not yet fully characterized—potential harms. This principle is especially important because as discussed in detail below, available evidence indicates that pediatric outcomes for COVID-19 are favorable overall. A statement of "**suggest**" reflects the panel's view that there is a weighting towards risk or benefit from the proposed therapy or action. A statement of "**consider**" reflects the panel's uncertainty as to whether there is risk or benefit from the proposed therapy or action. Within "consider" statements, the panel further delineates interventions that "**could**" be considered, meaning that different choices regarding the action or therapy are likely to be appropriate for different patients, or "**should**" be considered, meaning that the potential risks of the action or therapy would generally be accepted by most individuals, given the potential for (yet unproven) benefit.

Framework

The panel considered four major questions related to antiviral therapy for children with COVID-19:

1. Are antiviral agents indicated in children with COVID-19?
2. What criteria define the pediatric population in whom antiviral use may be considered?
3. Does presence of any underlying medical condition or characteristic warrant different criteria for antiviral use based on increased risk of COVID-19-related morbidity or mortality?
4. What agents are preferred if antiviral therapy is offered to children with COVID-19?

For each of these broad questions, we have provided one or more relevant guidance statements using the definitions above.

I. ARE ANTIVIRAL AGENTS INDICATED IN CHILDREN WITH COVID-19?

Guidance statement: The suggested approach for nearly all children with COVID-19 is supportive care. Antivirals may be considered on a case-by-case basis. When antiviral therapy is considered, we recommend enrollment in clinical trials as these become available for pediatric patients to study the efficacy and safety of potential antivirals. Otherwise, antivirals should be offered with appropriate monitoring and in consultation with a pediatric ID specialist whenever possible.

Rationale: As discussed below, multiple large epidemiologic studies have demonstrated that the overwhelming majority of children with COVID-19 experience a mild, self-limited illness, with only rare reports of more severe disease manifestations in children, including respiratory failure or shock. Given the lack of evidence of efficacy for any antiviral and the possible harms of these medications, the risk-benefit ratio for most pediatric patients therefore tips toward supportive care as the primary management strategy, especially outside the setting of a clinical trial. Absent availability of clinical trials, and per the WHO, provision of experimental therapies to individual patients on an emergency basis can be appropriate if

"no proven effective treatment exists; it is not possible to initiate clinical studies immediately;

the patient or his or her legal representative has given informed consent; and the emergency

use of the intervention is monitored, and the results are documented and shared in a timely

manner with the wider medical community (2)."

II. WHAT CRITERIA DEFINE THE PEDIATRIC POPULATION IN WHOM ANTIVIRAL USE MAY BE CONSIDERED?

Confirmed COVID-19

Guidance statement: The panel suggests antiviral agents be considered only in children with positive virologic COVID-19 testing.

Rationale: The clinical presentation of COVID-19 in children overlaps significantly with other infections. No clinical, radiographic, or laboratory criteria are sufficiently specific to distinguish COVID-19 from these other pediatric conditions. Administration of potentially active antivirals without confirmation of SARS-CoV-2 infection poses a significant risk of exposing patients to unnecessary harms from these medications without the possibility of benefit. Further, such an approach depletes finite—and in some cases scarce—supplies of possibly efficacious agents for COVID-19, as well as supplies for patients reliant on them for other conditions. A *rare* exception might be made for critically ill patients with a high suspicion for COVID-19 (based on a highly consistent clinical presentation combined with high local prevalence or known contact with a confirmed case) for whom a significant delay in COVID-19 test results is anticipated. In such a scenario, empiric initiation of antiviral therapy could be considered.

Clinical evidence of lower respiratory tract disease based on respiratory support requirement

Guidance statement: The panel suggests that clinical criteria, and specifically respiratory support requirements, be used to define scenarios in which use of antiviral agents is considered.

Rationale: Because no available evidence supports a benefit of antiviral treatment for pediatric patients with COVID-19 with specific clinical features or disease severity, the panel concluded that the risks of unproven therapy were most tolerable in those patients with more severe illness, such as those with evidence of lower respiratory tract disease requiring escalation of respiratory support. Both clinical and radiographic criteria were considered to define this population, but because radiographic infiltrates are common, even among well-appearing children with respiratory viral infections, respiratory support requirement was favored as the more objective and therefore relevant measure (9).

Management of mild or moderate COVID-19

Guidance statement: Outpatients and hospitalized patients with mild or moderate COVID-19 should be managed with supportive care only, without antiviral agents.

Rationale: We regard COVID-19 cases as "mild" or "moderate" if there is no new supplemental oxygen requirement (or no increased requirement for patients who require supplemental oxygen at baseline) (Table 1). Available data suggest that the overwhelming majority of children with mild or moderate disease recover with supportive care alone. Administration of antivirals early in the disease course to prevent progression thus does not seem warranted, especially given that use of these agents would expose large numbers of patients unnecessarily to the possible harms of these

drugs. A rare exception might be outpatients who require an increase from baseline chronic respiratory support that can be managed at home with family expertise and/or home nursing.

Evidence summary

COVID-19 in most children is of mild or moderate severity (6,10–12). A Chinese report including 72,314 patients revealed that patients aged ≤19 years accounted for only 2.1% of all cases, despite this age group's comprising approximately 23% of the country's population (12,13). A case series published by Dong and colleagues demonstrated that among 2,143 confirmed and suspected pediatric cases in China, >90% had asymptomatic, mild, or moderate infections, where moderate disease was defined as pneumonia with fever, cough, and possible abnormalities on chest imaging but no hypoxemia or shortness of breath (11). The experience thus far in the US parallels that from Chinese reports. Among 508 patients hospitalized with COVID-19 between February 12 and March 6, only 2%-3% were ≤19 years of age, and none in this age group required admission to an intensive care unit (ICU) or died (6). A subsequent report on COVID-19 in US children indicated that among 745 with available hospitalization status, only 147 (estimated range 5.7%-20%) were hospitalized (14).

Management of severe COVID-19

Guidance statement: Supportive care alone is appropriate for the majority of children with severe COVID-19. Use of antivirals could be considered on a case-by-case basis, preferably as part of a clinical trial if available.

Rationale: We regard COVID-19 cases as "severe" if there is a new significant requirement for supplemental oxygen (or an increased requirement from baseline) without the need for new or increased non-invasive or invasive mechanical ventilation (Table 1). Most children with this disease severity will recover with supportive care alone. Use of potentially active antivirals could be considered on a case-by-case basis, taking into account underlying medical conditions and health status that *may* confer risk for progression to more serious illness, as well as the overall clinical trajectory. Of note, there is no robust evidence at this time that *any* underlying pediatric medical condition is associated with a more severe disease course. We discuss below considerations for hypothesized at-risk populations of concern to help inform case-by-case assessments.

Management of critical COVID-19

Guidance statement: Supportive care alone may be appropriate for some children with critical COVID-19. Use of potentially active antivirals should be considered, preferably as part of a clinical trial if available.

Rationale: We regard COVID-19 cases as "critical" if there is a new or increased need for non-invasive or invasive mechanical ventilation, or there is sepsis or multi-organ failure, *OR* there is a rapidly worsening clinical trajectory that does not yet meet these criteria (Table 1). The contribution to critical COVID-19 of direct viral infection versus a deleterious immune response is not yet well understood (15). However, in contrast with mildly or moderately ill patients, those with critical disease have to some extent already failed supportive therapy, such that to the degree that antiviral effects might be helpful, the risks of these therapies may be more acceptable and outweighed by the potential benefits.

Evidence summary

Although rare, critical disease and fatalities have been reported in a small number of children with COVID-19 (14,16). In the pediatric case series by Dong and colleagues, 13 (0.6%) of the 2,143 cases had respiratory failure, acute respiratory distress syndrome (ARDS), encephalopathy, myocardial injury or cardiac failure, acute kidney injury, shock, or coagulation dysfunction (11). The US pediatric case series demonstrated that of 745 COVID-19 infected patients, 15 (estimated range 0.58%-2.0%) were admitted to an ICU, and 3 died (14).

III. DOES PRESENCE OF ANY UNDERLYING MEDICAL CONDITION OR CHARACTERISTIC WARRANT DIFFERENT CRITERIA FOR ANTIVIRAL USE BASED ON INCREASED RISK OF COVID-19-RELATED MORBIDITY OR MORTALITY?

Guidance statement: There are no definitive data to support any specific risk factor for severe COVID-19 in children.

Rationale: There are no robust data demonstrating specific risk factors for severe disease in children, nor are there data that antivirals mitigate disease severity in any population. To therefore avoid treatment misallocation in the absence of well-defined pediatric risk factors, we have instead summarized *proposed* risk factors (Table 2). These include risk factors for severe illness extrapolated from adult data (including cardiovascular disease, pulmonary disease, diabetes, cancer, and obesity) or identified for other respiratory viral infections (including young age, immunocompromise, cardiovascular disease, and pulmonary disease). Rather than impose a classification scheme for initiation of antivirals based on these proposed risk factors, we have summarized considerations relevant to each hypothesized risk factor to inform case-by-case discussions.

Evidence summary

The early report on COVID-19 in US children offered limited analyses of age and underlying conditions. Among 95 children aged <1 year with known hospitalization status, 59 (estimated range 15%-62%) were hospitalized, and five required ICU admission. In contrast, among those aged 1-17 years, the percentage hospitalized was lower (estimated range 4.1%-14%) and varied little among age groups. Among the 345 children with available information on underlying conditions, 80 (23%) had ≥1 underlying condition, with the most common including chronic lung disease, cardiovascular disease, and immunosuppression. However, the authors note significant potential sources of bias, including missing data on severity and underlying conditions for a majority of cases, with data unlikely to be missing at random; incomplete follow-up for many patients; and geographic variation in test practices, with many areas prioritizing testing for more severely ill patients, probably leading to overestimates of the percentage of patients hospitalized in all age groups (14).

Young age

The pediatric cohort described by Dong and colleagues is the largest to date and included 379 children in the <1-year category. Of these, a majority (339, 89.4%) had mild to moderate symptoms or were asymptomatic. Multiple other reports also have described children 1 to 11 months of age with only mildly symptomatic infection who improved without intervention (17,18). Similarly, early data from Italy report no mortality in the 0- to 19-year age group (19). In the preliminary description of COVID-19 in US children described above, among 147 hospitalized children, 5 out of 59 (8%) infants <1 year of age required ICU-level care, compared with 10 of 88 (11%) children >1 year of age, suggesting that young age is not associated with increased risk of severe disease (14).

Immunocompromise

Currently available data are insufficient to establish whether immunocompromised children are at greater risk of severe COVID-19 than healthy children or those with other comorbidities (6,20). Limited data suggest that children with mild or moderate immunocompromise are not at high risk of severe infection (21). Reports from China demonstrate that adults with COVID-19 and malignancies have increased mortality compared with patients of similar ages (22,23). In a nationwide Chinese cohort, malignancy was an independent risk factor for mortality after adjusting for age and smoking status (24). However, many other confounding risk factors were present, including other comorbid conditions (25).

While a relationship between immunocompromised status and severe COVID-19 disease has not been established in the pediatric population, several studies have demonstrated this association for other respiratory viruses. In a study of seasonal coronavirus cases in children, immunocompromise was a risk factor for severe lower respiratory tract disease (26). Similarly, investigations of respiratory syncytial virus (RSV) in adult and pediatric hematopoietic stem cell transplant recipients have indicated that characteristics associated with profound immunocompromise, including steroid dose >2 mg/kg/day, absolute lymphocyte count <100-300 10^9/L, hematopoietic cell transplantation within 30 days, and graft-versus-host disease, are risk factors for poor outcomes (27–30). Similar risk factors also predict poor outcomes in parainfluenza virus infection (31,32).

Considering the limited available data in SARS-CoV-2-infected patients, and extrapolating from other viruses, children with severe T-cell deficiency or dysfunction may be at risk of more severe disease and may exhibit longer viral shedding than non-immunocompromised children (Table 3). To the extent possible, we suggest reducing T-cell immunosuppression in infected children. Finally, the

potential for drug toxicity and drug-drug-interactions given the numerous medications that immunocompromised patients receive warrants special consideration prior to initiation of antiviral therapy.

Underlying cardiac or pulmonary disease

Adult data suggest that, in addition to older age, presence of cardiovascular disease, chronic respiratory disease, hypertension, or cerebrovascular disease is associated with COVID-19-related morbidity and mortality (25,33–35). In contrast, no available data have demonstrated an association between any underlying medical condition and morbidity and mortality in children with COVID-19. However, there is evidence to support more severe outcomes from other respiratory viral infections, such as influenza (36,37), parainfluenza (38), RSV (39–42), and non-COVID-19 coronaviruses (26,43), in children with chronic cardiac and pulmonary conditions. These conditions could therefore be considerations when weighing risks and benefits of potential antiviral therapy (Table 3).

Obesity

There are limited data on overweight (BMI >85th-95th percentile for age and sex) or obesity (BMI ≥ 95th percentile for age and sex) as independent risk factors for severe manifestations of COVID-19 in adults; some of these data derive from retrospective studies that are awaiting peer review (44–46). Overweight and obesity may be independent risk factors of more severe COVID-19, as well as severe pneumonia during hospitalization due to COVID-19. While the authors report controlling for potential confounders, patients had several related comorbidities, including diabetes; hypertension; cardiovascular, renal or liver disease; and cancer. Overweight and obesity are common conditions in the pediatric population, but comorbid cardiovascular disease in particular does not commonly complicate these conditions in children. Overweight and obesity may, however, put pediatric

patients at higher risk for poor respiratory outcomes due to impaired lung mechanics (47). When contemplating use of a potentially active antiviral in a pediatric patient with COVID-19, we suggest that overweight and obesity, with their associated comorbidities, could be considered in the decision-making process but should not be the sole rationale for choosing to administer antiviral therapy.

Diabetes

Based on observational data in adults, individuals with diabetes mellitus appear to be at elevated risk for several complications of COVID-19, including progression to severe disease, development of ARDS, and in-hospital death (23,25,48). However, adult patients in these early case series often have had comorbid conditions in addition to diabetes mellitus, including cardiovascular and/or renal disease; multiple comorbidities were common among the patients with severe disease. Caution is warranted in extrapolating these data to pediatric patients with diabetes mellitus. Important differences between children and adults may include the prevalence of associated cardiovascular disease and use of concomitant medications acting on the renin-angiotensin-aldosterone system (which are hypothesized to affect individual risk for development of severe COVID-19-associated complications) (49). Additionally, possible differences in risk for severe COVID-19 disease between individuals with type 1 versus type 2 diabetes are not understood at this time. When considering use of a potentially active antiviral in a pediatric patient with COVID-19, we suggest that diabetes mellitus and associated comorbidities could be considered in the decision-making process but should not be the sole rationale for choosing to administer antiviral therapy.

IV. WHICH ANTIVIRALS SHOULD BE CONSIDERED?

There are no antivirals with proven efficacy for the treatment of COVID-19 as of April 14, 2020. All antiviral use should therefore be considered experimental. Antivirals should be tested in clinical trials, as this is the only way to establish efficacy and safety of these therapies for COVID-19. Use of antivirals outside of a clinical trial, either through Single Patient Expanded Access ("compassionate use") requests, expanded access programs, or off-label use of FDA-approved medications, provides no way to evaluate the efficacy of these therapies, exposes patients to potential harms with no mechanism to quantify these harms, and does not offer human subjects protections that would be provided in clinical trials. However, as of April 14, 2020, no randomized trials studying potentially active antivirals were enrolling children <12 years old in the US. The panel therefore acknowledges that there may be clinical scenarios in which providers may accept the potential harms of experimental therapy for a chance of (yet unproven) benefit in a child. If used, we remind the reader of the importance of compliance with local institutional and regulatory policies for experimental therapies, with appropriate monitoring for toxicity and the input of a pediatric ID consultant. To aid clinicians in decision-making surrounding antiviral therapy, we provide a narrative summary of available evidence for several proposed antiviral agents. We have prioritized discussion of studies conducted on SARS-CoV-2 and those conducted in humans to the extent possible.

Remdesivir

Guidance statement: If an antiviral is used, the panel suggests use of remdesivir as the preferred agent, preferably as part of a clinical trial if available.

Rationale: *In vitro* and animal data support the biologic plausibility of remdesivir's activity against SARS-CoV-2, and available published data suggest that it is generally well tolerated (50,51). Use of

remdesivir under Single Patient Expanded Access ("compassionate use") requests, the major mechanism currently available to patients <18 years of age, offers the additional advantages (relative to off-label use of other antivirals) of a mechanism for monitoring at least serious adverse events (SAEs) through data collection by the manufacturer, oversight by local Institutional Review Boards, and a requirement for informed consent.

Evidence summary

Remdesivir is a nucleoside analog prodrug which, when activated, binds to viral RNA-dependent RNA polymerase, resulting in premature RNA chain termination. While other nucleoside analogs (e.g., ribavirin) are ineffective against coronaviruses due to the proofreading capability of a unique 3'-to-5' exoribonuclease and resultant high-fidelity viral replication, remdesivir appears to maintain activity despite this exoribonuclease (52,53). Moreover, *in vitro* studies demonstrate a high threshold for developing resistance, and when present, resistance results in a loss of viral fitness, further supporting the potential role of this agent (53). Remdesivir is not FDA approved for any indication but has been studied for the treatment of Ebola virus disease (EVD) (50).

In vitro and animal data

Potent antiviral activity has been demonstrated in several *in vitro* studies evaluating remdesivir's activity against SARS-CoV-2, as well as the other betacoronaviruses SARS-CoV-1 and MERS-CoV (54–57). Half-maximal effective concentration (EC_{50}) for SARS-CoV-2 was low in Vero E6 cells (0.77 μM), while cytotoxic concentration was high, suggesting specificity for viral RNA polymerase and a wide therapeutic index (55). Animal data are limited to models of SARS-CoV-1 and MERS-CoV, with no published studies of SARS-CoV-2 (54,56,58). In a murine model of SARS-CoV-1, remdesivir reduced viral titers and improved lung function when administered one day prior to infection and one day

after infection but impacted only viral titers when administered two days after infection (54). A second study compared the effect of remdesivir and lopinavir-ritonavir activity in MERS-CoV infected mice, demonstrating that remdesivir improved both virologic and clinical outcomes when given one day prior to infection and one day after infection, whereas the impact of lopinavir-ritonavir on these outcomes was inconsistent and, when present, was of a lesser magnitude (56). Finally, remdesivir prophylaxis (given 24 hours prior to infection), treatment (given 12 hours after infection), and placebo were compared in 18 non-human primates infected with MERS-CoV. Prophylactically treated animals had improved clinical scores and reduced histopathologic infiltrates, while animals receiving both prophylaxis and treatment demonstrated reduced viral loads and fewer radiographic infiltrates, supporting remdesivir's potential role for both treatment and prophylaxis in MERS-CoV (58).

Human data

Pharmacokinetic studies of remdesivir have been performed, but primary data have not been published (59). Remdesivir has been studied in a randomized trial comparing it to three monoclonal antibodies (mAb114, Zmapp, and REGN-EB3) for the treatment of EVD. The remdesivir arm of this study was terminated early after a total of 681 patients were enrolled in the trial, as both MAb114 and REGN-EB3 were superior. Among 175 patients treated with remdesivir, 43 were under age 18, including two patients less than a week old. There was a single SAE potentially attributed to remdesivir, which was infusion-related hypotension in a 41-year-old man (50).

Published data describing use of remdesivir for COVID-19 include a case report and case series (60–62). In a non-peer-reviewed case series describing the early US experience with COVID-19, three adults were treated with remdesvir. All recovered, but all developed transaminase elevations (61). A

larger case series recently published by Gilead Scientific described 53 adults requiring some level of respiratory support who received remdesivir, 34 of whom required mechanical ventilation. Sixty-eight percent of patients showed improvement in level of respiratory support, and overall mortality in the cohort was 13%. Transaminase elevations were identified in 23% (62).

As of April 14, 2020, there are three randomized controlled trials evaluating remdesivir in the US, including: 1) an adaptive trial sponsored by the National Institutes of Health comparing treatment with remdesivir for up to 10 days to placebo in hospitalized adults with confirmed COVID-19 (NCT04280705); 2) an industry-sponsored trial comparing standard care versus five days of remdesivir versus ten days of remdesivir for hospitalized adults and children ≥12 years of age and ≥40 kg with confirmed COVID-19 without supplemental oxygen requirements (mild/moderate disease) (NCT04292730); and 3) an industry-sponsored trial comparing five days versus ten days of remdesivir for hospitalized adults and children ≥12 years of age with supplemental oxygen requirements (severe disease) (NCT04292899). There are also two expanded access protocols (NCT04302766 and NCT04323761) in the US. As of April 14, 2020, remdesivir is available to patients <18 years of age through Single Patient Expanded Access ("compassionate use") requests to the manufacturer, Gilead Scientific, Inc (https://rdvcu.gilead.com), in addition to the clinical trials above.

Hydroxychloroquine

Guidance statement: *Use of hydroxychloroquine could be considered, in particular for patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer, preferably as part of a clinical trial if available. The panel recommends against use of hydroxychloroquine in combination with azithromycin.*

Rationale: *In vitro* studies suggest possible efficacy of hydroxychloroquine and chloroquine for the treatment of SARS-CoV-2. Published human studies are conflicting and hampered by lack of peer review, small sample sizes, and significant methodologic limitations. Despite unclear efficacy at this time, advantages of hydroxychloroquine include significant pediatric clinical experience for other indications and a generally acceptable side effect profile. Combination therapy with azithromycin, however, is not supported by available evidence and introduces the risk of additive toxicity, in particular related to prolongation of the QTc (63–65), such that the panel recommends against use of this combination.

Evidence summary

Hydroxychloroquine and chloroquine have been FDA approved and widely used for decades for treatment and prophylaxis of uncomplicated malaria. Hydroxychloroquine is additionally FDA approved for discoid lupus erythematosus, systemic lupus erythematosus, and rheumatoid arthritis. These two medications differ in their pharmacologic properties and dosing, with hydroxychloroquine generally associated with fewer adverse events and drug-drug interactions. Because of improved tolerability and availability in the US, the panel has focused its guidance on hydroxychloroquine; however, both agents have the same hypothesized antiviral mechanism of action and could be considered depending on availability. The proposed mechanisms of antiviral activity are 1) inhibition of viral entry into human cells by increasing the pH of endosomes required for cell entry, 2) broad anti-inflammatory and immunomodulatory effects, and 3) inhibition of glycosylation of the ACE-2 receptor, the binding site for SARS-CoV-2 (53,66).

In vitro and animal data

Data from SARS-CoV-2-infected Vero E6 cells demonstrate the *in vitro* efficacy of both chloroquine and hydroxychloroquine with EC_{50} concentrations potentially achievable with available dosing regimens, though data are conflicting as to which of the two agents is more potent against SARS-CoV-2 (55,67,68). In a murine model of SARS-CoV-1, intraperitoneal chloroquine failed to inhibit viral replication in the lungs (69). Finally, and of note, despite demonstrated *in vitro* inhibition of chikungunya virus (a plus-strand RNA virus, like SARS-CoV-2), use of chloroquine prior to and during acute chikungunya infection in non-human primates resulted in delayed viral clearance, higher levels of viremia, and delayed immune response, as well as more persistent temperature instability and weight loss than in placebo-treated animals (70).

Human studies

These supportive *in vitro* data have spurred use of both chloroquine and hydroxychloroquine off-label and in multiple randomized trials. Until late March 2020, supportive human data were limited to announcement of "more than 100 patients [demonstrating] that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course," from Chinese health authorities with no presentation of primary data (71). Since, limited primary data from small randomized controlled trials and observational studies have become available with conflicting results (72–77). A randomized trial was performed at Wuhan University and included 62 adults with mild illness (defined as no supplemental oxygen requirement but radiographic evidence of pneumonia on computed tomography scan). Thirty-one were randomized to hydroxychloroquine 400 mg daily for five days plus standard care, and the other 31 patients received standard care only. "Standard care" in this study was broadly defined as use of antiviral agents, antibacterial agents, and

immunoglobulin, with or without steroids. The primary endpoints were measured five days after randomization. Time to clinical improvement was shorter in the hydroxychloroquine-treated patients compared with the control group (fever, 2.2 days versus 3.2 days; cough, 2.0 days vs 3.1 days; and radiographic improvement, 81% versus 55%) (72). This study has not yet undergone peer review at the time of writing of this guidance. A second randomized trial enrolled 150 patients from 16 Chinese hospitals and compared clinical and virologic outcomes between those treated with hydroxychloroquine 1200 mg daily for three days, followed by 800 mg daily for 2 or 3 weeks—a higher dose and substantially longer duration than those used in other studies—as compared to standard care. Randomization was stratified based on illness severity, and mild, moderate, and severe cases were included. The primary outcome was virologic clearance by PCR from respiratory secretions at day 28, with key secondary outcomes including fever resolution (<36.6°C), attainment of normal oxygen saturation, and resolution of respiratory symptoms. There was no difference in virologic clearance by PCR at 28 days (85% versus 81%) or time to virologic clearance between the two groups (median of 8 versus 7 days). Further, while the authors report improved clinical outcomes, this difference seems only qualitatively apparent during the second week of therapy and on a *post-hoc* analysis limited to 28 patients not treated with other antivirals (73). This study also has not undergone peer review. Finally, a smaller randomized trial compared 15 patients who were treated with chloroquine to 15 treated with standard therapy. While no difference was detected in virologic clearance seven days after randomization (87% versus 93%), it is difficult to view this as a "negative" trial, given the high cure rate in the control group (74).

Hydroxychloroquine also has been evaluated in several non-randomized studies. Mahevas and colleagues performed a multicenter observational study that included 181 hospitalized adults with severe COVID-19. They used inverse probability of treatment weighting (IPTW) to evaluate the impact of hydroxychloroquine started within 48 hours of admission on a composite outcome of

death or ICU transfer within 7 days of admission. There was no difference in outcome between the two groups after IPTW (21% versus 22%; RR 0.93, 95% confidence interval 0.48-1.81), though a noted limitation is that center was not included in the model. This study has not yet undergone peer review (75). Gautret and colleagues performed a non-placebo-controlled, open-label study comparing patients >12 years old treated with hydroxychloroquine 200 mg three times daily for 10 days at the primary study site to 16 controls, who were patients at the primary center who refused or were not candidates for hydroxychloroquine or patients hospitalized at surrounding centers. The primary outcome was virologic clearance at six days as measured by nasopharyngeal PCR for SARS-CoV-2; of note, the authors used PCR cycle threshold as a proxy for viral load. Twenty patients receiving hydroxychloroquine were included in the analysis (three were excluded due to intensive care unit [ICU] transfer, one because of death [on day 3], one because they decided to leave the hospital, and one because they developed nausea). At day 6, 70% of the hydroxychloroquine-treated patients versus 12.5% of the control group had a negative nasal PCR (*P*=0.001). Significant methodologic flaws, including the approach to control group selection as well as exclusion of six of the 26 patients in the treatment arm, raise concerns about the validity of the findings of this primary analysis.

The authors also presented a subgroup analysis comparing six patients who received both hydroxychloroquine and azithromycin to 14 patients receiving hydroxychloroquine alone. Six of six patients (100%) treated with combination therapy were PCR negative on day 6, as compared to eight of 14 (57%) in the hydroxychloroquine monotherapy group. However, the azithromycin-treated patients had significantly higher viral cycle thresholds at baseline, suggesting that they had a lower baseline viral load and were more likely to experience viral clearance, independent of azithromycin use (76). While this manuscript was published in a peer-reviewed journal, individuals and professional societies have raised concerns about the authors' conclusions (78).

A larger case series was published by the same group, which reported clinical and virologic outcomes for 80 patients with mild to moderate disease treated with the same combination of hydroxychloroquine and azithromycin. While 83% of patients in the study tested negative for SARS-CoV-2 by PCR by day 7, it is difficult to draw any conclusions related to efficacy given that there was no control group and individual-level cycle thresholds were not reported (77). Another group of investigators performed a similar study evaluating virologic clearance at day 7 in 11 hospitalized adults (10 of whom required supplemental oxygen) treated with hydroxychloroquine and azithromycin. In contrast to the findings of Gautret et al., 80% of survivors were persistently positive for SARS-CoV-2 after six days of therapy. While a small, uncontrolled study, these data raise the possibility that the rapid virologic clearance observed in the Gautret et al. study could perhaps have been driven by the relatively mild illness severity, and perhaps correspondingly high baseline viral cycle thresholds, of included patients (79). Finally, emerging data demonstrate that QTc prolongation >40 ms occurs in up to 30% of patients receiving the combination of hydroxychloroquine and azithromycin, with 11% developing QTc prolongation >500 ms (63). Further highlighting safety concerns, an RCT comparing safety of high-dose chloroquine (600 mg twice daily for 10 days) versus low-dose chloroquine (450 mg twice daily on day 1, followed by 450 mg daily for a total of 5 days) in combination with azithromycin demonstrated more frequent QTc prolongation >500 ms (19%) and higher mortality in the high-dose arm, leading to termination of that treatment arm (64). Of note, patients randomized to the high-dose treatment arm more often had underlying cardiovascular disease.

There are 15 US-based trials evaluating hydroxychloroquine, including seven evaluating the effect of pre- or post-exposure prophylaxis in various populations (NCT04308668, NCT04333732, NCT04328467, NCT04328961, NCT04335084, NCT04318444, NCT04333225) and seven evaluating

efficacy for treatment (three of which include azithromycin) (NCT04329832, NCT04334382, NCT04335552, NCT04334967, NCT04334512, NCT04333654, NCT04332991). One trial (NCT04335552) includes adolescents >12 years of age.

Hydroxychloroquine dosing

Guidance statement: The panel suggests a hydroxychloroquine dosing regimen that includes a loading dose on day 1 and a total duration of no more than five days.

Rationale: We suggest one of two dosing regimens (Table 4), both of which incorporate a loading dose and no more than five days of therapy. This suggestion is based on the pharmacokinetic (PK) characteristics of hydroxychloroquine. The first is the dosing and duration used for acute uncomplicated malaria, with the option of extending to a total of five days. This three-day regimen has the advantage of substantial clinical experience and a track record of safety, which should be prioritized when administering therapy with unknown efficacy but significant potential for toxicity. The second is the dosing and duration proposed by Yao et al. based on physiologically based pharmacokinetics (PBPK) modeling (67). The divided daily doses offer the additional advantage of perhaps minimizing gastrointestinal side effects.

Evidence summary

There is a lack of data to support a specific dosing regimen or duration of therapy for treatment of SARS-CoV-2. Relevant PK properties of the drug to consider when making dosing and duration determinations include a large volume of distribution and a long terminal half-life of up to 40 days (80). As a result, it takes several weeks to achieve steady-state with once-daily dosing. Administering

a loading dose, or higher dosages on day 1, may therefore be beneficial to more rapidly achieve peak plasma concentrations, especially when treating an acute infection like SARS-CoV-2. Yao and colleagues performed simulations based on PBPK modeling using human population PK and rat lung drug penetration data. All simulated hydroxychloroquine dosing regimens tested achieved high trough lung:EC_{50} ratios. The authors concluded that a dose of 400 mg twice daily on day 1, followed by a maintenance dose of 200 mg given twice daily for four days, would be ideal for adult patients to balance efficacy, safety, and compliance (67). Pediatric simulations were not reported.

Dosing currently approved for treatment of acute malaria has the advantage of decades of clinical experience and safety. Additionally, based on Monte Carlo simulations, the acute malaria dosing regimen is more likely to achieve rapid peak plasma concentrations, which may be beneficial when treating an acute infection such as COVID-19 (81).

Optimal treatment duration is similarly uncertain, with five days being most commonly used in published reports, but anywhere from 3-14 days reported (51,71,82–85). Given the very long half-life of the drug, short courses of 3-5 days are likely to be of sufficient duration to treat an acute viral infection. Underscoring the importance of short durations of therapy, hydroxychloroquine has been associated with dose-dependent toxicities, including life-threatening cardiac arrhythmias, hemolysis, and retinopathy, though both hemolysis and retinopathy are extraordinarily rare with short durations of therapy (86,87).

G6PD screening prior to hydroxychloroquine initiation

Guidance statement: G6PD screening is not routinely recommended prior to initiation of hydroxychloroquine because the risk of hemolysis from short courses of hydroxychloroquine is low. If G6PD screening is performed, hydroxychloroquine therapy should not be withheld while awaiting the result. The panel suggests monitoring patients with known G6PD deficiencies for hemolysis during hydroxychloroquine therapy.

Rationale: Available data from small studies suggest the risk of hemolysis is low among patients with G6PD deficiencies who receive hydroxychloroquine (88,89). G6PD screening is not performed routinely for patients receiving hydroxychloroquine for FDA-approved indications (e.g., malaria, rheumatologic conditions) (90,91). If providers elect to screen for G6PD deficiency, initiation of therapy should not be delayed while awaiting this result. Patients with G6PD deficiencies should be monitored for hemolysis during hydroxychloroquine therapy.

Lopinavir-ritonavir

Guidance statement: The panel was divided as to whether lopinavir-ritonavir could or should be considered for any pediatric patient with COVID-19 infection in any clinical scenario. The panel recommends against combination therapy with lopinavir-ritonavir and ribavirin.

Rationale: While there are some favorable data from observational studies of other betacoronaviruses, *in vitro* and animal data supporting use of lopinavir-ritonavir are mixed. Further, a randomized trial demonstrated no difference in time to clinical improvement or virologic outcomes in severely ill adults with COVID-19 treated with lopinavir-ritonavir as compared with usual care (92).

Some panelists raised concerns that patients in this trial were severely ill and treated late in their disease course, suggesting that these findings were not generalizable to children with less severe disease, such that lopinavir-ritonavir may be an option for children unable to receive remdesivir or hydroxychloroquine. Others believed that that these data, coupled with the questionable efficacy *in vitro* and in animal studies, were sufficient to exclude a significant possibility of benefit in pediatric populations, such that lopinavir-ritonavir should not be considered an option in any scenario. A further consideration raised by the panelists was the harms resulting from exacerbating drug shortages for children with HIV, a pediatric infection for which lopinavir-ritonavir has demonstrated efficacy. Use of lopinavir-ritonavir with ribavirin raised concerns due to the risk of ribavirin toxicity and lack of clear efficacy data for this agent, and this combination is not recommended by the panel.

Evidence summary

Lopinavir-ritonavir is a protease inhibitor FDA approved for treatment of pediatric HIV. The ritonavir component inhibits the CYP3A metabolism of lopinavir, increasing plasma levels of lopinavir. It is a preferred therapy for children 2 weeks to 3 years of age who require antiretroviral therapy and an alternative therapy for children >3 years of age (93,94). Lopinavir-ritonavir is generally well-tolerated, with the most common adverse drug reactions (ADRs) being dysgeusia (i.e., a distorted sense of taste), nausea, vomiting, and diarrhea, with serious ADRs (hepatotoxicity, QTc prolongation, and AV block) rarely reported (95–98). Its hypothesized mechanism of action for SARS-CoV-2 is inhibition of the viral proteinases papain-like proteinase and 3C-like proteinase, which are key enzymes in coronavirus polyprotein processing.

In vitro and animal data

An *in vitro* study evaluated the antiviral activity of lopinavir in Vero E6 cells and demonstrated an EC_{50} of 26.1 μM, which is well above the trough lopinavir serum concentration with dosing used for HIV and that being studied for SARS-CoV-2 (99,100). *In vitro* data supporting use of lopinavir in SARS-CoV-1 and MERS-CoV are mixed (101–107). Relevant to the observational studies described below, Chu and colleagues demonstrated inhibition of cytopathic effect after 48 hours in Vero E6 cells infected with SARS-CoV-1 at lopinavir concentrations of 4 μg/mL and ribavirin 50 μg/mL, suggesting the possibility of synergy between the two agents (105).

In a mouse model of MERS-CoV, lopinavir-ritonavir combined with IFN-β administered one day prior to infection slightly reduced viral titers but did not impact lung function or weight loss. Lopinavir-ritonavir and IFN-β given one day after infection improved pulmonary function but failed to reduce viral replication, lung hemorrhaging, or viral titers (56). In a non-human primate model of MERS-CoV, animals treated with lopinavir-ritonavir were compared to untreated animals, animals treated with mycophenolate mofetil (MMF), and animals treated with IFN-β1b. The lopinavir-ritonavir-treated animals had better clinical scores, less weight reduction, and less pulmonary infiltrate than untreated animals and animals treated with MMF. Furthermore, necropsied lung and extrapulmonary tissues from the treated group had lower mean viral loads than those of animals in the comparator groups (108).

Human data

A matched cohort study including 75 patients with SARS-CoV-1 compared mortality and rates of intubation between patients treated with lopinavir-ritonavir initially (N=44), patients treated with lopinavir-ritonavir as rescue therapy (after worsening oxygen saturation, dyspnea, radiographic findings, and after failure of pulse steroids) (N=31), and historical controls receiving standard therapy (including ribavirin and steroids). Matching criteria included age strata, sex, presence of comorbid medical conditions, lactate dehydrogenase (LDH), and for the group who received lopinavir-ritonavir as a rescue therapy, use of steroids. Lopinavir-ritonavir as an initial treatment (in combination with ribavirin, as part of standard therapy) was associated with reduced mortality (2.3% vs 15.6%) and mechanical ventilation (0% vs 11%) compared with the standardized rates in the matched cohort. The mortality, oxygen desaturation, and intubation rates of the subgroup of patients who received lopinavir-ritonavir as rescue therapy were not different from those in the matched cohort receiving standard therapy (109).

A second observational study in SARS-CoV-1 compared 41 patients treated with lopinavir-ritonavir for 10-14 days, ribavirin, and steroids to 111 historical control patients treated with ribavirin and steroids only. The treatment group was further divided into those treated with lopinavir-ritonavir as initial therapy (before needing pulse steroids, which were given for worsening respiratory symptoms in both groups) (N=12) and as “rescue” therapy (after pulse steroids) (N=29). The rate of ARDS or death at 21 days was significantly lower in the lopinavir-ritonavir treatment group (1/41, 2.4%) than historical controls (32/111, 28.8%). In addition, the lopinavir-ritonavir group had a progressive decrease in viral load, an early rise in lymphocyte count, a reduction in the cumulative dose of pulsed methylprednisolone, and fewer episodes of nosocomial infections. Of note, gastrointestinal ADRs occurred in 11 (26%) patients, including one patient who had to stop therapy due to elevated alanine aminotransferase levels. Hemoglobin reductions >2 g/dl occurred in 70%, potentially due to

concomitant ribavirin. Like the prior study, the pre/post design introduces the opportunity for confounding due to improvement in recognition and management of SARS-CoV-1 patients later in the epidemic. Further, the small number of exposed patients limited the ability to adjust for many confounders, aside from admission LDH (105).

The highest quality human study in SARS-CoV-2 is a randomized controlled trial conducted in Chinese hospitals comparing lopinavir-ritonavir to usual care in adults with COVID-19 with oxygen saturation <94%. The primary outcome was time to clinical improvement. A patient met the outcome if s/he experienced a two-point improvement on a seven-point ordinal scale from the time of randomization or was discharged from the hospital. Secondary outcomes included 28-day mortality, duration of mechanical ventilation, length of stay, and virologic measures. A total of 199 patients were included, with 99 in the lopinavir-ritonavir group and 100 in the usual care group. There was no difference in time to clinical improvement in the intention-to-treat population (16 days versus 16 days). No difference in the primary outcome was identified when the group was stratified into those treated within 12 days of illness onset and those treated beyond 12 days, with 13 days being the median duration of symptoms prior to randomization. There was no difference in 28-day mortality (19.2% versus 25%; difference, 5.8%; 95% CI, -17.3 to 5.7) or virologic outcome between the two groups, but the lopinavir-ritonavir-treated patients had a shorter ICU length of stay (six days versus 11 days) (92). Concerns about the generalizability of these findings include: 1) lopinavir-ritonavir was started late in the disease course (median of 13 days after symptom onset), while animal and human data from other coronaviruses suggested that early antiviral initiation is important; 2) higher baseline viral loads in the treatment arm, though there was no difference in the change from baseline across the two arms; and 3) a high mortality rate in this cohort, perhaps limiting ability to extrapolate these data to other, less sick patients.

There are additionally several published case reports and case series describing patients treated with lopinavir-ritonavir, including a series of 36 children in which 14 were treated with lopinavir-ritonavir. All patients recovered, and no comparisons were made between treated and untreated patients (110). Several additional adult case series report favorable clinical outcomes among lopinavir-ritonavir-treated patients, but illness severity, concomitant therapies, and the lack of comparator groups preclude any statement of efficacy (111–113). Notably, in the largest series, only one of six patients treated with lopinavir-ritonavir was able to complete therapy due to gastrointestinal adverse events (111).

As of April 14, 2020, there are no US-based clinical trials registered on clinicaltrials.gov evaluating lopinavir-ritonavir for the treatment of COVID-19, though there are multiple ongoing and planned trials in other countries.

CONCLUSION

Published data from large epidemiologic studies suggest that the overwhelming majority of children with COVID-19 experience a relatively mild and self-limited illness, with rare reports of critical illness and (thus far) near non-existent mortality. As of April 14, 2020, there are no antiviral therapies with proven efficacy for COVID-19. Absent an opportunity to participate in a clinical trial, use of investigational agents for treatment of COVID-19 through Single Patient Expanded Access requests or off-label use of medications currently approved by the FDA for other indications is possible, but such use appears to be unnecessary in most cases. Pediatricians and pediatric ID providers should therefore be guided by the principle of “first, do no harm” when considering antiviral therapy, reserving use for those children in whom the possibility for benefit outweighs risk of toxicity. Use of antivirals as part of randomized controlled trials to establish the efficacy and safety of these agents for treatment, prophylaxis, and as a strategy to reduce household transmission should be prioritized.

FUNDING

This work was supported by the Agency for Healthcare Research and Quality [K12-HS026393 to K.C.].

ACKNOWLEDGMENTS

The authors thank the SHaring Antimicrobial Reports for Pediatric Stewardship (SHARPS) Collaborative for facilitating this work. We are especially grateful to Cindy Terrill and Mirela Grabic for their invaluable logistical support.

The authors have no associations that might pose a conflict of interest.

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Table 1. Suggested management of COVID-19 by illness severity

Disease category	Respiratory support requirement	Management
Mild/ moderate	No new or increased supplemental oxygen requirement.	Supportive care.
Severe	New or increase from baseline supplemental oxygen requirement **without** need for new or increase in baseline non-invasive/invasive mechanical ventilation[a].	Supportive care alone is appropriate for the majority of children. Use of potentially active antivirals could be considered on a case-by-case basis[b], preferably as part of a clinical trial if available.
Critical	New or increased requirement for invasive or non-invasive mechanical ventilation[a], sepsis, or multi-organ failure; **OR** rapidly worsening clinical trajectory that does not yet meet these criteria.	Supportive care may be appropriate for children who are severely ill with COVID-19. Use of potentially active antivirals should be considered, preferably as part of a clinical trial if available.

[a]Non-invasive mechanical ventilation includes high-flow nasal canula, continuous positive airway pressure (CPAP), or bilevel positive airway pressure (BiPAP).

[b]Case-by-case considerations could include underlying medical conditions and health status that may confer risk for more serious illness.

Table 2. Patient characteristics for consideration in antiviral decision-making

Underlying condition or characteristic	Considerations for antiviral therapy
Young age	There is insufficient evidence to suggest that young age alone is a risk factor for severe COVID-19.
Severe immunocompromise	There is insufficient evidence to establish that severely immunocompromised children are at higher risk for severe COVID-19. Based on adult studies of COVID-19 and extrapolation from other viral infections, children with severe immunocompromise *may* be more likely to experience severe illness or prolonged viral shedding from COVID-19.
Mild/moderate immunocompromise	There is insufficient evidence demonstrating that mildly or moderately immunocompromised children are at higher risk for severe COVID-19.
Severe underlying cardiac disease	There is insufficient evidence demonstrating that children with underlying cardiac disease are at higher risk for severe COVID-19. Based on adult studies of COVID-19 and extrapolation from other viral infections, children with significant underlying cardiac disease *may* be more likely to experience severe illness.
Severe underlying pulmonary disease	There is insufficient evidence that children with underlying pulmonary disease are at higher risk for severe COVID-19. Based on adult studies of COVID-19 and extrapolation from other viral infections, children with significant underlying pulmonary disease *may* be more likely to experience severe illness.
Obesity	There is insufficient evidence that either overweight or obesity alone is a risk factor for severe COVID-19 in the pediatric population. Additional considerations include the presence of comorbidities, including diabetes; hypertension; cardiovascular, pulmonary, renal, or liver disease; and cancer.
Diabetes	There is insufficient evidence to suggest that either type 1 or type 2 diabetes alone is a risk factor for severe COVID-19 in the pediatric population. Additional considerations include the degree of glycemic control and presence of associated comorbidities (e.g., cardiovascular or renal disease, or transplantation).

Table 3. Examples of underlying condition or characteristics for consideration in antiviral decision-making

Underlying condition or characteristic	Examples
Severe immunocompromise	**Hematopoietic cell transplant recipient** • Duration of time post-allogenic-HCT <100 days or post-auto-HCT <30 days • Absolute lymphocyte count <300/mm^3 • Recent anti-lymphocyte therapy (e.g., ATG <3 months or alemtuzumab <6 months) or HCT with ex vivo T-cell depletion in prior <6 months • GVHD requiring systemic immunosuppressive therapy
	Solid organ transplant recipient • Recent solid organ transplant or high-level immunosuppression (risk associated with time since transplantation and degree of immunosuppression may vary by organ type) • Treatment with ATG (<3 months) or alemtuzumab (<6 months) • Recent immunosuppressive treatment for transplant rejection (<3 months)
	Receiving anticancer chemotherapy • Lymphoblastic leukemia in induction or receiving therapy for relapsed or refractory disease (especially if ALC <100/mm^3) • Other cancers including acute myeloid leukemia, acute lymphoblastic leukemia in remission, B and T cell lymphomas, and solid/brain tumors and receiving chemotherapy with ALC <100/mm^3
	Primary immunodeficiency • Severe combined immunodeficiency or other congenital disorder associated with profound T-cell dysfunction or deficiency or history of prior opportunistic infections.
	• HIV infection with CD4 count <15% or <200/mm^3
	Other immunosuppressive medications and conditions • Alemtuzumab (<6 months) • ATG (<3 months) • Co-stimulation inhibitors (e.g., belatacept, abatacept) for maintenance immunosuppression • High-dose corticosteroids (e.g., ≥2mg/kg/day prednisone-equivalent for >2 weeks) • Expected profound T-cell dysfunction or ALC <100/mm^3

Severe underlying pulmonary disease	• Listed for lung transplant • Oxygen on non-invasive ventilation while awake or asleep for lung disease, heart disease, or pulmonary hypertension • Severe chronic respiratory disease (including cystic fibrosis, bronchopulmonary dysplasia, interstitial or diffuse lung disease, bronchiectasis, scoliosis, congenital diaphragmatic hernia, pulmonary hypoplasia) with ≥3 hospitalizations in the last 12 months • Severe neuromuscular disease resulting in impaired airway clearance/cough (for example, SMA, Duchenne's and other muscular dystrophies) • Severe persistent asthma
Severe underlying cardiovascular disease	• Any cardiomyopathy • NYHA/Ross class II-IV heart failure • Unrepaired cyanotic congenital heart disease • Single ventricle physiology

Abbreviations: ALC = absolute lymphocyte count; ATG = anti-thymocyte globulin; HCT = hematopoietic cell transplant; GVHD = graft-versus-host disease; HIV = human immunodeficiency virus; NYHA = New York Heart Association; SMA = spinal muscular atrophy

Table 4. Antiviral agents

Agent	Pediatric dose/duration	Comment
Remdesivir	**Pediatric and Adult Dosing (verify dosing and preparation with manufacturer):** **<40 kg:** 5 mg/kg IV loading dose on day 1; followed by 2.5 mg/kg IV q24h **≥40 kg:** 200 mg IV loading dose on day 1; followed by 100 mg IV q24h Recommended duration: Up to 10 days, with 5-day duration favored for fast responders (5- versus 10-day duration being studied in clinical trials)	Available through Single Patient Expanded Access requests for children (as of 4/14/2020). Children >12 years old are also eligible for clinical trials at certain sites (NCT04292730 and NCT04292899).
Hydroxy-chloroquine	**Adults:** 800 mg PO followed by 400 mg PO at 6, 24, and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis) **OR** 400 mg PO BID on day 1, followed by 200 mg PO BID for up to 5 days **Infants, Children, and Adolescents:** 13 mg/kg (maximum: 800 mg) PO followed by 6.5 mg/kg (maximum: 400 mg) PO at 6, 24, and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis) **OR** 6.5 mg/kg/dose (maximum: 400 mg/dose) PO BID on day 1, followed by 3.25 mg/kg/dose (maximum: 200 mg/dose) PO BID for up to 5 days **Neonates:** dosing not established; consider use on a case-by-case basis	Consider use if patient not a candidate for remdesivir. Recommend against combination therapy with azithromycin.

	Recommended duration: No more than 5 days. The duration studied for acute malaria is 3 days.	
Lopinavir- ritonavir	**Adults:** Lopinavir 400 mg/ritonavir 100 mg (2 tablets) PO twice daily **Neonates ≥14 days and postmenstrual age ≥42 weeks** to **children <18 years of age:** Lopinavir 300 mg/m^2 (maximum 400 mg/dose) PO twice daily Recommended duration: 7-14 days	Panel was divided on whether lopinavir/ritonavir should/could be considered for any patient with COVID-19. Recommend against combination therapy with ribavirin.