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

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Key Points: Supportive care is sufficient for the majority of children with COVID-19 given that most will experience a mild illness. Remdesivir is suggested for children with severe disease, weighing individual risks and benefits, and should be considered for children with critical disease.

ABSTRACT

Background: Although Coronavirus Disease 2019 (COVID-19) is a mild infection in most children, a small proportion develop severe or critical illness. Data evaluating agents with potential antiviral activity continue to expand, such that updated guidance is needed regarding use of these agents in children.

Methods: A panel of pediatric infectious diseases physicians and pharmacists from 20 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 the best available evidence and expert opinion.

Results: Given the typically mild course of COVID-19 in children, supportive care alone is suggested for most cases. For children with severe illness, defined as a supplemental oxygen requirement without need for non-invasive or invasive mechanical ventilation or extra-corporeal membrane oxygenation (ECMO), remdesivir is suggested, preferably as part of a clinical trial if available. Remdesivir should also be considered for critically ill children requiring invasive or non-invasive mechanical ventilation or ECMO. A duration of 5 days is appropriate for most patients. The panel recommends against the use of hydroxychloroquine or lopinavir-ritonavir (or other protease inhibitors) for COVID-19 in children.

Conclusions: Antiviral therapy for COVID-19 is not necessary for the great majority of pediatric patients. For children with severe or critical disease, this guidance offers an approach for decision-making regarding use of remdesivir.

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

INTRODUCTION

In December 2019, the novel coronavirus 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). As of August 22, 2020, over 23 million people worldwide have been infected, including over 5.6 million in the United States (US) alone, with over 800,000 deaths reported globally (1). In light of this public health crisis, there has been significant interest in identifying potentially efficacious antiviral therapies, including novel and "repurposed" medications. To guide pediatric clinicians in the use of these agents, and leveraging the SHaring Antimicrobial Reports for Pediatric Stewardship (SHARPS) collaborative, we developed an initial antiviral guidance document, published in April 2020, based on best available evidence and expert consensus (2,3).

In the few months since this initial publication, new evidence has emerged demonstrating the efficacy of the antiviral medication remdesivir in shortening time to clinical recovery in adults with COVID-19, while several other studies have shown ineffectiveness of hydroxychloroquine and lopinavir-ritonavir (4–8). Based on these data, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for remdesivir, and the previously issued EUA for hydroxychloroquine was revoked (9,10). Further, additional observational studies have provided insight into the clinical epidemiology of COVID-19 in children, demonstrating that while most young patients experience mild illness, a small proportion develop severe illness associated with adverse clinical outcomes, including need for pediatric intensive care unit (PICU) admission and mortality (11–24). Finally, in April 2020, a newly recognized hyperinflammatory syndrome seemingly associated with COVID-19 emerged, referred to by the Royal College of Paediatrics and Child Health as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) and by the World Health Organization and US Centers for Disease Control and Prevention as Multisystem Inflammatory Syndrome in Children (MIS-C) (25–32). Affected children present with evidence of multisystem inflammation, with variable manifestations that may include fever, cardiovascular shock, gastrointestinal symptoms, or dermatologic or mucocutaneous changes (25–29). The syndrome, while fortunately rare with an estimated incidence of 2 in 100,000 persons <21 years of age often necessitates PICU admission and has resulted in rare mortalities (33).

Considering the rapidly expanding evidence base regarding optimal antiviral therapy for COVID-19, yet an ongoing paucity of pediatric-specific data, we reconvened the expert panel to update our initial guidance document. 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 treatment decisions. We additionally refer the reader to guidelines published by the Infectious Diseases Society of America and the National Institutes of Health (34,35).

GUIDANCE DEVELOPMENT

Approach

A panel of pediatric infectious diseases physicians and pharmacists from 20 geographically diverse North American institutions developed and refined a set of consensus guidance statements through a series of teleconferences and web-based surveys. The panel considered three major questions:

1) What criteria define the pediatric population in whom remdesivir should be prescribed?
2) Does the presence of any underlying medical condition or characteristic warrant different criteria for remdesivir use based on an increased risk of COVID-19-related morbidity or mortality?
3) Should any other agents with potential antiviral activity be used to treat COVID-19?

Following each consensus statement, we summarize our rationale and the relevant available evidence, prioritizing human studies. Given the overall limited nature of pediatric 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. Of note, this panel considered only antiviral use, with use of corticosteroids and other immunomodulatory therapies reviewed elsewhere (36). This guidance document has been reviewed and endorsed by the Pediatric Infectious Diseases Society.

Definitions

A statement of **"recommend"** reflects the panel's view that the evidence base for or against a therapy is sufficiently strong that departures from these recommendations could be viewed as outside the range of usual practice. A statement of "**suggest**" reflects the panel's view that there is weighting towards risk or benefit from the therapy. A statement of "**consider**" reflects the panel's uncertainty about the risk or benefit from the therapy.

I. WHAT CRITERIA DEFINE THE PEDIATRIC POPULATION IN WHOM REMDESIVIR USE SHOULD BE PRESCRIBED?

Confirmed COVID-19

*Guidance statement**:** The panel recommends remdesivir be used only in children with* positive SARS-CoV-*2 viral testing.*

Rationale: The clinical presentation of COVID-19 in children is heterogeneous and overlaps significantly with other infections. Administration of remdesivir without confirmation of SARS-CoV-2 infection poses a significant risk of exposing patients to unnecessary harms without the possibility of benefit and may deplete scarce remdesivir supplies. 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 contact with a confirmed case) for whom a significant delay in SARS-CoV-2 test results is anticipated. In such a scenario, empiric initiation of remdesivir could be considered while awaiting test results.

Assessment of disease severity based on clinical criteria

Guidance statement: The panel recommends that clinical criteria, particularly respiratory support requirements, be used to define scenarios in which treatment with remdesivir is considered.

Rationale: Respiratory support requirement has been used to define illness severity categories in the published clinical trials evaluating remdesivir efficacy (Table 1). Because the potential benefit of remdesivir across illness severities may differ, we suggest respiratory support requirement be the primary determinant of whether remdesivir is used. The panel additionally recognizes that the spectrum of clinical presentations varies in children, and that rapid deterioration in clinical status and/or cardiovascular compromise may be additional considerations. Finally, the panel also considered radiographic criteria, but because radiographic infiltrates are common, even among well-appearing, clinically stable children, respiratory support requirement was favored as the more objective and therefore relevant measure (37).

Remdesivir for mild or moderate COVID-19

Guidance statement: The panel recommends that outpatients and hospitalized patients with asymptomatic, mild, or moderate COVID-19 should be managed with supportive care only. Remdesivir should be used only within the context of a clinical trial in these populations.

Rationale: We regard COVID-19 cases as “mild” (upper respiratory tract involvement only) or “moderate” (lower respiratory tract involvement present) if there is no new supplemental oxygen requirement (or no increased requirement for patients who require supplemental oxygen at baseline) (Table 1). Available pediatric data suggest that the majority of children experience asymptomatic, mild, or moderate disease and recover with supportive care alone, with need for hospitalization, ICU admission, or mortality infrequently reported. Additionally, while a randomized trial demonstrated a statistical difference in clinical outcomes for patients with moderate COVID-19 treated with a 5-day course of remdesivir relative to standard care, no difference was detected between standard care and a 10-day duration of remdesivir. Further, it is unclear if the statistical difference measured in this study is clinically meaningful, particularly in children who generally experience favorable outcomes. Further, a subgroup analysis of a randomized trial including all hospitalized adults with COVID-19 demonstrated no difference in time to clinical recovery among those with moderate disease. Based on currently available data, therefore, administration of remdesivir in children with mild or moderate illness is not warranted, unless it is being administered in the context of a clinical trial.

Remdesivir for severe COVID-19

Guidance statement: Remdesivir is suggested for children with severe COVID-19.

Rationale: We regard COVID-19 cases as “severe” if there is a new requirement for supplemental oxygen (or an increased requirement from baseline) but without the need for new or increased non-invasive or invasive mechanical ventilation or ECMO (Table 1). Remdesivir is suggested in this population based on a randomized trial demonstrating a shorter time to clinical recovery in hospitalized adults treated with remdesivir, with the greatest benefit in the subgroup requiring supplemental oxygen without need for mechanical ventilation. However, the clinical course of severe COVID-19 may be milder in children, and therefore the benefit of remdesivir is less certain, necessitating continued case-by-case assessments of benefit and risk in children. This assessment should be informed by illness severity, illness trajectory, hypothesized risk factors for poor clinical outcomes as detailed in section II, and remdesivir availability. When available, patients should be enrolled in clinical trials.

Management of critical COVID-19

Guidance statement: *Remdesivir should be considered for all children with critical COVID-19, unless there are contraindications.*

Rationale: We regard COVID-19 cases as "critical" if there is a new or increased need for non-invasive or invasive mechanical ventilation, hemodynamic instability requiring vasoactive agents, multisystem organ failure, or a rapidly worsening clinical trajectory (Table 1). The aforementioned randomized trial demonstrated no difference in time to clinical recovery among the subgroup of adults requiring mechanical ventilation or ECMO. The benefit of remdesivir therapy is therefore uncertain in this population. However, given extreme illness severity and lack of pediatric-specific data evaluating efficacy, remdesivir should be considered on a case-by-case basis in all critically ill children. This assessment should be informed by illness severity, illness trajectory, duration of ventilation (with initiation earlier in the intubation course favored), and remdesivir availability. When available, patients should be enrolled in clinical trials.

Duration of remdesivir therapy

Guidance statement: The panel recommends a duration of up to 5 days of remdesivir therapy for children with severe COVID-19. If remdesivir is used for children with critical COVID-19, the panel suggests a *duration of 5-10 days, with durations of up to 10 days considered on a case-by-case basis for children not improving after 5 days of therapy.*

Rationale: Based on the duration recommended in the FDA EUA and no difference in outcomes in a randomized trial comparing 5 versus 10 days of therapy in adults, we suggest a duration of up to 5 days for most children with COVID-19 who are treated with remdesivir. For children requiring mechanical ventilation or ECMO, a duration of up to 10 days is recommended in the FDA EUA and was the duration studied in the placebo-controlled trial establishing remdesivir's efficacy in hospitalized adults. However, given data suggesting no difference in outcomes between 5 versus 10 days of therapy, and uncertainty as to whether remdesivir provides any clinical benefit at all for critically ill patients, we suggest a duration of 5-10 days, with up to 10 days considered on a case-by-case basis for those patients not improving after 5 days of therapy (Table 2).

Evidence summary

General

Remdesivir is a nucleoside analog prodrug which, when activated, binds to viral RNA polymerase, resulting in premature RNA chain termination (38,39). The FDA issued an EUA for remdesivir on May 1, 2020 for adults and children with severe or critical COVID-19, which was subsequently expanded to include all hospitalized patients on August 28, 2020 (9). Prior to the EUA, remdesivir could be obtained through Single Patient Expanded Access ("compassionate use") requests through the manufacturer, Gilead Scientific.

In vitro data

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 maintains activity despite the existence of this exoribonuclease (40,41). *In vitro* studies also demonstrate a low likelihood of developing resistance, further supporting use of remdesivir (40). 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 remdesivir specificity for viral RNA polymerase and a wide therapeutic index (42).

Clinical data

The results of four randomized trials evaluating the efficacy of remdesivir have been published at the time of this guidance document. The Adaptive COVID-19 Treatment Trial (ACTT) (NCT04280705) was a National Institutes of Health (NIH)-funded, multicenter, double-blind, placebo-controlled trial evaluating the efficacy of a 10-day course of remdesivir in hospitalized adults with COVID-19. The primary outcome was time to recovery, defined as either hospital discharge or hospitalized without need for ongoing medical care, and was measured on an eight-point ordinal scale. Preliminary results demonstrated that patients treated with remdesivir had a median time to recovery of 11 days as compared to 15 days in the placebo group (rate ratio 1.32, 95% confidence interval [CI] 1.12-1.55). In a subgroup analysis stratified by respiratory support requirement, time to recovery was reduced in the group requiring supplemental oxygen only, with no difference in patients not requiring supplemental oxygen (i.e., patients with moderate disease) or in patients requiring mechanical ventilation (invasive or non-invasive) or ECMO (i.e., patients with critical disease). No statistical difference in mortality was detected (7.1% in the remdesivir arm versus 11.9% in the placebo arm). There were no differences in key safety outcomes between treatment groups, including anemia, acute kidney injury, or hepatic transaminase elevations (4). Additional analysis of these data is ongoing.

An industry-sponsored trial compared 5 versus 10 days of remdesivir therapy in a cohort of 397 patients aged ≥12 years with severe COVID-19, defined as pulmonary infiltrates on imaging and an oxygen saturation <u><</u>94% on room air or need for supplemental oxygen at randomization (NCT04292899). The primary outcome was clinical status on day 14 using a 7-point ordinal scale, similar to the previous study. After adjustment for baseline clinical status, which was more severe in the 10-day group, no differences in the primary outcome were detected in the two treatment arms (43). A second industry-sponsored, open-label, non-placebo-controlled randomized trial compared standard care versus a 5- or up to 10-day course of remdesivir in hospitalized patients with moderate COVID-19, defined as pulmonary infiltrates on imaging and an oxygen saturation >94% at randomization (NCT04292730). The primary outcome of this study was clinical status score on day 11 following randomization on a 7-point ordinal scale, with differences in the distribution of scores across treatment groups reported as odds of a better clinical status. Relative to patients randomized to standard care, patients randomized to 5 days of remdesivir had a greater odds of a higher clinical status (odds ratio 1.65, 95% CI 1.09-2.48) at day 11, whereas no statistical difference in clinical status was detected in the 10-day group. Significant limitations to this study include 1) the unblinded nature of the trial and 2) uncertainty as to how to translate the summary odds ratio presented in the primary analysis into a quantifiable and clinically meaningful difference in outcome (44).

Finally, a double-blind, placebo-controlled randomized trial compared remdesivir to placebo in hospitalized adults with severe COVID-19, defined as radiographically confirmed pneumonia and oxygen saturation of ≤94% on room air or an arterial partial pressure of oxygen to fractional inspired oxygen of ≤300 mmHg. Similar to the previous two trials, an ordinal outcome scale was used, with the primary outcome of time to clinical improvement defined as the first day within 28 days of randomization that patients experienced improvement of ≥2 ordinal levels. This trial was halted prior to target enrollment due to the decline in COVID-19 cases in China, but there was no statistical difference in the primary outcome between treatment groups. Complicating the interpretation of these results, use of additional therapies, including antivirals, immunomodulators and corticosteroids, was permitted (45).

Additional published data describing use of remdesivir for COVID-19 include case reports and case series (46–48).

Pediatric considerations

There are no comparative clinical data evaluating the efficacy or safety of remdesivir for COVID-19 in pediatric patients. Most COVID-19 in children is asymptomatic or of mild or moderate severity (11,13,14,19–23). In a large case series of 2,135 confirmed and suspected pediatric COVID-19 cases in China, >90% had asymptomatic, mild, or moderate infections (13). Data from the US is consistent with these findings, with the majority of children managed as outpatients (11,22). Children receiving remdesivir have been included in several pediatric case series, though data related to clinical outcomes and adverse events are not specifically reported (12,14–16,21). A multinational European cohort of 582 children demonstrated that 507 (87%) had mild or moderate disease, with 48 patients requiring PICU admission and just four mortalities. Remdesivir was used in 17 patients, but the impact on clinical outcomes was not reported (14). Similarly, among a cohort of 576 hospitalized children in the US, 5.8% required ICU admission and only one mortality was reported. Among the 208 children with data on antiviral medication use, just nine received remdesivir (21). Finally, among 43 children aged <18 years enrolled in a randomized trial evaluating the efficacy of remdesivir for Ebola, there were no serious adverse events attributed to remdesivir in children (49).

The FDA-recommended dosing of remdesivir for children is summarized in Table 2 (50). These recommendations are based on adult physiologically based pharmacokinetic (PBPK) modeling and reflect those used in the aforementioned Ebola trial, as well as those recommended for use under the single-patient expanded access ("compassionate use") program. While these doses are expected to provide similar drug exposure to those observed in healthy adults, there are no published pharmacokinetic studies that validate this approach. Pediatric providers should be aware that remdesivir is available as an injectable solution and a lyophilized powder, which differ in their concentration of sulfobutylether-β-cyclodextrin sodium salt (SBECD), a renally cleared excipient. The injection solution contains 6 g SBECD per 100 mg vial, whereas the lyophilized powder formulation contains 3 g SBECD per 100 mg vial. For pediatric patients <40 kg, remdesivir lyophilized powder is used to limit cyclodextrin exposure to less than 300 mg/kg (50). Finally, while remdesivir is a substrate for CYP2C8, CYP2D6, and CP3A4 *in vitro*, it has a low potential for drug-drug interactions as its metabolism is likely mediated by hydrolase activity. That said, providers are nevertheless encouraged to check drug interactions prior to use (51). The FDA has warned of possible antagonism between remdesivir and hydroxychloroquine based on *in vitro* data, so concomitant use of these drugs is not recommended (52).

Ongoing remdesivir clinical trials

Several ongoing clinical trials in the US are evaluating the efficacy of remdesivir alone or in combination with various immunomodulatory agents, including baricitinib (NCT044015799, NCT04373044), tocilizumab (NCT04409262), and merimepodib (NCT04410354). Additionally, remdesivir is being studied in the WHO-sponsored Solidarity trial (NCT04330690). Finally, an industry-sponsored study evaluating the safety, tolerability, pharmacokinetics, and efficacy of remdesivir from birth to 18 years of age is underway to inform optimal pediatric dosing (NCT04431453).

Role of remdesivir in the management of Multisystem Inflammatory Syndrome in Children (MIS-C)

Consensus statement: Remdesivir is not routinely indicated for patients with MIS-C. Therapy could be considered on a case-by-case basis in the setting of positive SARS-CoV-2 viral testing if there is diagnostic uncertainty as to whether presenting symptoms are consistent with acute COVID-19 infection versus MIS-C, or in the presence of extreme illness severity.

Rationale: MIS-C is generally hypothesized to be a post-infectious, immune-mediated inflammatory phenomenon. Therapies targeting viral replication may be ineffective, even in light of a positive SARS-CoV-2 viral test, especially given that prolonged RT-PCR positivity occurs in some patients with uncertain clinical significance. However, whether MIS-C may develop in the setting of an ongoing viral infection, or whether presence of the virus may amplify a deleterious immune response, is unknown. The symptoms of MIS-C can also overlap with those observed in severe or critical acute COVID-19. Remdesivir therefore could be considered on a case-by-case basis.

Evidence summary: The pathogenesis of MIS-C remains unknown, but the syndrome is presumed to be post-infectious based on three main observations. First, a region's incidence of MIS-C has been reported to peak about 1 month after its peak in acute COVID-19 cases (25,26). Second, some affected children have preceding symptoms consistent with acute COVID-19 (25–27). Finally, a substantial proportion of affected children have positive SARS-CoV-2 serology but negative RT-PCR assays, suggesting that their hyperinflammatory state may reflect a post-infectious phenomenon with an aberrant immune response (25,26,53). However, the SARS-CoV-2 testing profile is variable in patients meeting criteria for MIS-C, with some patients having positive RT-PCR results, sometimes without SARS-CoV-2 antibodies (25–27). It is unknown whether RT-PCR positivity in MIS-C represents replication-competent virus that may act as an ongoing inflammatory trigger. In addition, the overlap of clinical and laboratory features between acute COVID-19-associated hyperinflammatory syndrome and MIS-C can result in diagnostic uncertainty. Until the pathogenesis of MIS-C is better understood, we suggest limiting remdesivir use to select patients with MIS-C and a positive viral testing, including those with an ambiguous clinical presentation, severe illness, or an RT-PCR cycle threshold result suggestive of a high viral load. Another potential consideration for remdesivir use is concurrent use of immunosuppressive therapy - particularly corticosteroids - that may impair virologic control.

II. DOES PRESENCE OF ANY UNDERLYING MEDICAL CONDITION OR CHARACTERISTIC WARRANT DIFFERENT CRITERIA FOR REMDESIVIR 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: The majority of pediatric data related to COVID-19 remains descriptive in nature, including population-level epidemiologic studies and single- and multi-center case series describing primarily hospitalized and/or critically ill patients. The reported prevalence of *any* comorbidity in these series varies widely, ranging from 25% to 83%. Nevertheless, the panel recognizes that pediatric clinicians are likely to consider comorbidities when weighing the risks and benefits of antiviral therapy on a case-by-case basis, and in making these decisions may consider: 1) the available, albeit limited, pediatric COVID-19 literature; 2) risk factors associated with severe COVID-19 in adults; and 3) pre-existing medical conditions in children associated with worse clinical outcomes for other viral infections. We have therefore summarized relevant data and highlighted hypothesized risk factors (Table 3) that clinicians may consider in determining whether to administer remdesivir.

Evidence summary:

Medical complexity

Although there is no standard definition for children with medical complexity (CMC), this term generally refers to children who have multiple chronic health conditions, may be dependent on medical technology, and may have functional limitations (e.g., due to neurologic impairment, developmental delays, or genetic syndromes) (54). This group's risk of decompensation with pulmonary infections is likely driven by a combination of factors, including abnormalities in mucociliary clearance, muscle tone, and craniofacial structures, as well as potentially delayed recognition of illness due to impairments in communication (55). It would therefore not be unexpected if CMC experienced a more severe course following SARS-CoV-2 infections, though empiric data confirming this assumption are lacking, and interpretation of published studies is confounded by inconsistent definitions of CMC. In a cross-sectional study of 48 children admitted to North American PICUs, 19 (40%) were classified as medically complex, whereas only an estimated 0.4% of children in the US are CMC (15,56). In a large European study of 582 children, both underlying pulmonary disease and neurologic disease were associated with increased risk of PICU admission, though whether children in these categories would have met the definition for CMC based on the severity of the underlying condition was not reported (14). Similarly, two smaller US case series highlight a numerically higher prevalence of children with underlying genetic and neurologic conditions among patients requiring PICU admission, though these differences did not achieve statistical significance (12,16). Collectively, these data support the possibility that CMC may be at risk for severe COVID-19, and medical complexity therefore could be considered in making antiviral treatment decisions.

Young age (<1 year)

The pediatric cohort described by Dong and colleagues remains the largest to date and included 376 children in the <1-year category (13). Of these, 89% had mild to moderate symptoms or were asymptomatic. A more recent case series of 130 children from Italy found that infants <6 months old were at increased risk of critical disease compared to older children, though no deaths occurred. In this series, 33% of the children who received ICU-level care also had comorbidities, and 3 out of the 6 infants in the ICU did not require respiratory support (17). Similarly, a multinational European study including 582 children identified an association between age <1 month and ICU admission, as compared to outpatient management or management on the general ward. However, the degree of respiratory or inotropic support was not reported, so illness severity cannot be assessed, and as in the prior report, there were no mortalities in this age group (14). In the report of COVID-19 in US children described above, among 59 infants <1 year of age, 8% required ICU-level care, compared with 11% of the 88 children >1 year of age, suggesting that young age is not associated with increased risk of severe disease (11). Likewise, the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) recently reported surveillance of 576 children hospitalized in the US with COVID-19, among whom infants <12 months of age accounted for 27.3% (157/576) of the pediatric hospitalizations. Further analysis of clinical severity in 208 of these hospitalized patients did not separate out infants <1 year but found that children aged 0-2 years did not have increased rates of ICU-level care compared to older children (31.1% vs 34%). No children 0-2 years of age required invasive mechanical ventilation (21). Several additional reports have also described infants experiencing only mild infection who frequently improved without any intervention (57–59). This includes a case series of 18 hospitalized infants <90 days, none of whom required supplemental oxygen or intensive care (59). Overall, data are insufficient to suggest that young age alone is a risk factor for severe COVID-19.

Older age (>12 years)

Initial reports of COVID-19 in the US suggested that adolescents were not at risk of severe disease (11). However, as the pandemic has unfolded, single-center reports on the US experience among hospitalized children have suggested an increased proportion of severe respiratory disease in adolescents compared with younger children and infants (12,16,23). A large multicenter report of North American PICU hospitalizations describes that the majority of PICU admissions occurred in the 11- to 21-year-old age group (15). As risk factors among adolescents similar to those identified in adults (e.g., obesity) could contribute to ICU admissions, older age could be considered a risk factor for increased COVID-19 severity and therefore could be considered in guiding antiviral treatment decisions.

Immunocompromise

In a cohort of children admitted to PICUs in New York City with acute COVID-19, 17% had hematologic malignancy/immunosuppression listed as a comorbidity (24). In a separate cohort from the North American PICU collaborative study group, 23% of patients had malignancies or were otherwise receiving immunosuppression (15). Outcomes were not stratified by co-morbidity in either study, and it remains unclear whether immunocompromised status is a risk factor for severe disease requiring ICU-level care. In a large multinational European study, children with malignancy accounted for 10% of the cohort requiring PICU admission (14). Cohorts of pediatric cancer patients from New York, Madrid, and Italy had both low rates of infection and low morbidity when infected (60–63). COVID-NET reported 5.4% of all hospitalized pediatric patients with underlying disease were immunocompromised (21). No cohort studies of pediatric solid organ transplant patients with COVID-19 have been published, though case reports and anecdotal information suggest that severe COVID-19 in this population is rare (64–67). Finally, in two electronic registries of pediatric COVID-19 cases, severe disease or death appeared uncommon in children who were immunocompromised or in those receiving treatment for cancer (68,69).

These data suggest that children who are mildly to moderately immunocompromised are not at higher risk of severe COVID-19; however, the limited number of studies and lack of comparative data preclude an assessment of risk in severely immunocompromised children (Table 4). Further, several studies have demonstrated an increased risk of severe disease in adults with malignancies and in severely immunocompromised children with other respiratory viral infections, including seasonal coronaviruses, respiratory syncytial virus, and parainfluenza (70–79).

Considering the limited available data in SARS-CoV-2-infected children, 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. These factors could be considered in deciding whether to prescribe remdesivir (Table 4). We remind clinicians to consider the potential for drug toxicity and drug-drug-interactions given the numerous medications that immunocompromised patients receive, particularly for patients receiving other experimental agents.

Underlying severe cardiac or pulmonary disease

Adult data suggest that, in addition to older age, presence of underlying cardiovascular disease, including coronary artery disease, cardiomyopathy, and hypertension, and chronic respiratory disease are associated with COVID-19-related morbidity and mortality (80–84). However, differing etiologies of cardiopulmonary disease in children make direct application adult data challenging, with congenital heart disease as well as bronchopulmonary dysplasia being additional pediatric considerations (Table 4). Patients with congenital heart disease have not consistently been reported in series describing severely or critically ill cohorts, though one large European series reported that 4% of non-PICU versus 10% of PICU patients had congenital heart disease (14,85). Limited experience suggests a high prevalence of underlying pulmonary disease among children with severe COVID-19, including children with chronic respiratory insufficiency or failure resulting in technology dependence (i.e., chronic invasive or non-invasive mechanical ventilation) (11,14,15,23). A significant prevalence of asthma among children with SARS CoV-2 infection has been described in some reports, although data are insufficient to demonstrate an association between underlying asthma and increased risk of severe COVID-19 (12,23). However, there is evidence to support more severe outcomes from other respiratory viral infections, such as influenza (86,87), parainfluenza (88), RSV (89–92), and non-COVID-19 coronaviruses (73,93), in children with chronic cardiac and pulmonary conditions. Presence of severe underlying cardiac or pulmonary disease could therefore be considered when weighing risks and benefits of potential antiviral therapy (94).

Obesity

Data from retrospective studies suggest that being overweight (BMI >85th-95th percentile for age and sex) or obese (BMI ≥ 95th percentile for age and sex) is an independent risk factor for hospitalization and severe manifestations of COVID-19 in adults (95–100). Being overweight or obese is common in children (101), but unlike adults, comorbid cardiovascular disease (e.g., hypertension, diabetes, or renal disease) less often complicates these conditions. Initial reports of hospitalized children with COVID-19 are mixed with regard to disease severity in obese children. For example, a case series of children hospitalized with COVID-19 in New York City indicated that obesity was the most prevalent comorbidity, with a significant association with mechanical ventilation in children ≥2 years of age (16), whereas other series have not demonstrated this association (12,23). Recognizing the limitations of these small series reporting unadjusted analyses, and considering the growing body of evidence supporting an association between overweight and obesity and COVID-19 severity in younger adults, an elevated BMI could be considered when determining whether to administer remdesivir, particularly when associated with cardiovascular comorbidities (96,97).

Diabetes

Based on observational data, adults with diabetes mellitus appear to be at elevated risk for several complications of COVID-19, including progression to severe disease, development of ARDS, and death (22,84,102–104). However, diabetes mellitus has not emerged thus far as a clear independent risk factor for complications of COVID-19 in children (11,15–17). This may be due in part to limited pediatric data, but may also be due to a higher prevalence of type 1 versus type 2 diabetes in children relative to adults, as well as a higher prevalence of associated comorbidities in adults, including obesity (105). Based on emerging data that support obesity as a risk factor for severe COVID-19, obesity may be an important comorbidity modifying risk for complications of COVID-19 in children with diabetes mellitus (16,96). A related issue is that while use of concomitant medications acting on the renin-angiotensin-aldosterone system has been hypothesized to influence risk for COVID-19-associated complications, current evidence does not support a detrimental effect of these medications (106). When considering remdesivir in a pediatric patient with COVID-19, diabetes mellitus and associated comorbidities such as obesity could be considered in the decision-making process, but diabetes mellitus should not be the sole rationale for choosing to administer antiviral therapy. Exposure to angiotensin-converting inhibitor or angiotensin receptor blocker therapy should not influence risk assessment in decisions to administer remdesivir.

III. SHOULD ANY OTHER ANTIVIRALS BE USED FOR TREATMENT OF PEDIATRIC COVID-19?

Hydroxychloroquine

Consensus statement: The panel recommends against use of hydroxychloroquine, alone or in combination with azithromycin, for treatment of COVID-19, outside of a clinical trial.

Rationale: Multiple observational studies and randomized trials have evaluated the effectiveness of hydroxychloroquine for treatment of COVID-19, with the overwhelming majority of data demonstrating no benefit. Of equal importance, safety concerns related to cardiotoxicity have been identified, particularly in combination with other corrected QT interval (QTc)-prolonging medications such as azithromycin.

Evidence summary

General

Hydroxychloroquine and chloroquine have been FDA approved and widely used for decades for treatment and prophylaxis of uncomplicated malaria, discoid lupus erythematosus, systemic lupus erythematosus, and rheumatoid arthritis. The two drugs differ in their pharmacologic properties and dosing, with hydroxychloroquine generally associated with fewer adverse events and drug-drug interactions; as such, it has been the preferred agent for clinical use in the US. The proposed mechanisms of antiviral activity for both drugs 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 (107). The FDA issued an EUA on March 28, 2020 for use of hydroxychloroquine or chloroquine for COVID-19; on June 15, 2020, in light of data demonstrating lack of efficacy and potential safety concerns, the EUA was revoked (10,108).

Human studies

The initial human data that led to enthusiasm surrounding use of hydroxychloroquine, with or without azithromycin, included small observational studies and randomized controlled trials early in the pandemic (109–113). Subsequent large randomized trials have not demonstrated benefit with hydroxychloroquine therapy. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial is a multicenter, open-label adaptive trial supported by the United Kingdom (UK) National Health Service (NHS), which compares multiple investigational therapies for COVID-19, including hydroxychloroquine, to usual care among hospitalized patients. The majority of patients in the hydroxychloroquine arm had severe disease, with 60% of patients requiring supplemental oxygen and 17% requiring invasive mechanical ventilation. Among 1,561 patients randomized to hydroxychloroquine compared to 3,155 patients randomized to usual care, there was no difference in 28-day mortality (26.8% versus 25.0%, respectively) or hospital discharge within 28 days (60.3% versus 62.8%, respectively). These data have not yet undergone peer review (5).

A smaller, multicenter, open-label trial randomized 150 hospitalized patients with mild or moderate disease to hydroxychloroquine versus standard care, which could include other antivirals and steroids. This study was terminated prior to target enrollment due to waning of the pandemic in China, but no difference in the primary outcome of virologic clearance at 28 days (81% versus 85%) or time to virologic clearance (8 versus 7 days) was detected (6). Finally, a Brazilian trial compared the impact of hydroxychloroquine plus azithromycin versus hydroxychloroquine alone versus standard therapy on 15-day clinical status using a 7-point ordinal scale in just over 500 hospitalized patients with mild to moderate COVID-19. No difference was detected in any treatment arm (7). Also supporting the lack of efficacy of hydroxychloroquine are the results of a randomized trial comparing hydroxychloroquine to placebo for post-exposure prophylaxis following a moderate- or high-risk exposure to SARS-CoV-2. No difference in SARS-CoV-2 RT-PCR positivity or SARS-CoV-2-compatible illness within 14 days was detected (114).

Most observational studies have also demonstrated a lack of benefit of hydroxychloroquine. Mahavas and colleagues performed a multicenter study evaluating the impact of hydroxychloroquine compared to standard care on ICU-free survival at 21 days in a cohort of 173 hospitalized adults with severe COVID-19. Following inverse probability of treatment weighting (IPTW), no difference in ICU-free survival was detected (76% versus 75%; HR 0.90, 95% confidence interval 0.40-2.10) (115). Similar findings were demonstrated by Geleris and colleagues, who found no difference in a composite outcome of intubation or death with hydroxychloroquine versus standard care following IPTW in a single-center cohort of 1376 patients (HR 1.04, 95% confidence interval 0.82-1.32) (116).

Three large observational studies additionally considered the combination of hydroxychloroquine and azithromycin. The first was a multicenter study comparing hydroxychloroquine alone (n=97), hydroxychloroquine plus azithromycin (n=113), or no hydroxychloroquine (n=158) in a cohort of men admitted to US Veterans Affairs hospitals. Unadjusted mortality was highest in the hydroxychloroquine group (27.8% versus 22.1% in the combination therapy group versus 11.4% in the untreated group). Following propensity score adjustment, hydroxychloroquine therapy remained associated with mortality (HR 2.61, 95% confidence interval 1.10-6.17), while hydroxychloroquine plus azithromycin was not (HR 0.43, 95% confidence interval 0.16-1.12). Cause of death was not reported in this study, and given its observational design, it is possible that the association between hydroxychloroquine use and death is the result of residual confounding (117). A second study utilized data from the New York State Department of Health to compare in-hospital mortality in a cohort of 1438 patients, including 25 children. No difference in mortality was detected among patients treated with hydroxychloroquine alone (n=271), azithromycin alone (n=211), hydroxychloroquine plus azithromycin (n=735), or neither drug (n=221). Cardiac arrest was more common in the group receiving hydroxychloroquine and azithromycin relative to no treatment, but not in patients receiving either drug alone (118). Finally, a retrospective study including 2,541 hospitalized adults suggested reduced in-hospital mortality among patients treated with hydroxychloroquine (HR 0.34; 95% CI 0.25-0.46) or the combination of hydroxychloroquine and azithromycin (HR 0.29; 95% CI 0.22-0.40) relative to neither drug (119). However, a notable limitation was that the hydroxychloroquine-treated patients more often received steroids, a therapy that has been shown to reduce COVID-19 related mortality. This raises the possibility that the mortality benefit seen in the hydroxychloroquine-treated groups was, in fact, driven by the receipt of steroids, especially when considered in the context of multiple randomized trials demonstrating no benefit with hydroxychloroquine therapy.

In addition to the lack of efficacy, several reports have highlighted the potential for QTc prolongation with concomitant hydroxychloroquine and azithromycin therapy, occurring in up to 30% of treated patients (120,121). The high-dose arm of a randomized trial comparing high-dose (600 mg twice daily for 10 days) to low-dose (450 mg twice daily on day 1, followed by 450 mg daily for a total of 5 days) chloroquine was terminated after detection of higher mortality in the high-dose arm (122).

Pediatric data

There are no comparative observational studies or randomized trials evaluating safety or efficacy of hydroxychloroquine or chloroquine in children. Frequency of hydroxychloroquine use has been reported in several pediatric case series and was as high as 44% in a US cohort of critically ill children (12,14–16,18). Several authors have evaluated dosing strategies for hydroxychloroquine and chloroquine in children using pharmacokinetic modeling; however, detailed discussion of these studies is beyond the scope of this review (123).

Ongoing hydroxychloroquine clinical trials

There are 27 US-based trials currently recruiting that evaluate hydroxychloroquine, including eight evaluating the effect of pre- or post-exposure prophylaxis in various populations (NCT04341441, NCT04354870, NCT04381988, NCT04328961, NCT04363450, NCT04318444, NCT04435808, NCT04335084) and the remainder evaluating efficacy for treatment (six of which include azithromycin) (NCT04342169, NCT04353037, NCT04421664, NCT04354428, NCT04351620, NCT04334382, NCT04328012, NCT04379492, NCT04344444, NCT04373044, NCT04345692, NCT04374019, NCT04334382, NCT04370782, NCT04344457, NCT04335552, NCT04358081, and NCT04329832). One trial (NCT04335552) includes adolescents >12 years.

Lopinavir-ritonavir

Consensus statement: The panel recommends against use of lopinavir-ritonavir, alone or in combination with ribavirin, except as part of a clinical trial.

Rationale: Given that data from several randomized trials demonstrate no difference in clinical or virologic outcomes with lopinavir-ritonavir treatment among hospitalized patients with COVID-19, and the high prevalence of side effects reported in observational studies, the panel recommends against use of lopinavir-ritonavir outside of a clinical trial.

Evidence summary

General

Lopinavir-ritonavir is a protease inhibitor approved by the FDA 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 is an alternative antiretroviral agent for children >3 years of age (124). It is not FDA approved or authorized for use in the treatment of SARS-CoV-2 infection. 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 of the antiviral activity of lopinavir in Vero E6 cells demonstrated an EC_{50} of 26.1 μM, which is well above the trough lopinavir serum concentration with dosing used for HIV and doses used in studies of SARS-CoV-2 (125,126). No animal data exist evaluating lopinavir-ritonavir for SARS-CoV-2.

Human data

A randomized controlled trial compared lopinavir-ritonavir to usual care in 199 hospitalized adults with severe COVID-19. There was no difference between the groups in time to clinical improvement, defined as a two-point improvement on a seven-point clinical severity scale between the groups (16 days versus 16 days), 28-day mortality (19.2% versus 25%), or virologic clearance. The lopinavir-ritonavir group did experience shorter ICU length of stay (6 versus 11 days). Concerns about the generalizability of these findings include: 1) a relatively small sample size, such that only a large difference in outcome was detectable; 2) lopinavir-ritonavir was started late in the disease course (median of 13 days after symptom onset), perhaps beyond the time of peak viral replication; and 3) a high mortality rate in this cohort, perhaps limiting ability to extrapolate these data to other, less sick patients (8). Preliminary data, not yet peer-reviewed, from the RECOVERY trial demonstrate no difference in 28-day mortality in patients treated with lopinavir-ritonavir (n=1,596) relative to usual care (n=3,376) (22.1% versus 21.3%; relative risk 1.04; 95% confidence interval 0.91-1.18; *P*=0.58). Seventy percent of this cohort required supplemental oxygen and 26% required no respiratory support, while just 4% required mechanical ventilation (127). Two smaller trials have reported consistent findings, with no differences in virologic clearance in hospitalized adults treated with lopinavir-ritonavir or another protease inhibitor, darunavir/cobicistat (128,129).

Published observational studies largely do not support use of lopinavir-ritonavir for treatment of COVID-19 and highlight a high prevalence of adverse effects, particularly gastrointestinal effects, as well as potential drug-drug interactions from prolonged cytochrome P4503A inhibition (130–132).

Pediatric data

There are no comparative observational studies or randomized trials evaluating safety or efficacy of lopinavir-ritonavir or other HIV protease inhibitors for treatment of SARS-CoV-2 infection in children. Reports of use are sparse and limited to case series, the largest of which included 14 children treated with lopinavir-ritonavir, all of whom recovered (14,133).

Ongoing lopinavir-ritonavir trials

As of July 20, 2020, there are five US-based clinical trials registered on clinicaltrials.gov evaluating lopinavir-ritonavir for the treatment of COVID-19 in both the inpatient and outpatient setting (NCT04455958, NCT04372628, NCT04328012, NCT02735707, and NCT04459702). None are enrolling children.

CONCLUSION

This interim guidance for use of antiviral agents in children with COVID-19 provides an update to the initial guidance published in April 2020, integrating results of several randomized trials as well as the growing body of literature characterizing the epidemiology of COVID-19 in children. Optimal evidence-based practices surrounding antiviral therapy will undoubtedly continue to change over time as more data are available. We encourage pediatric providers to consider enrolling patients in clinical trials to evaluate these and other therapies whenever possible.

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

Disease category	Respiratory support requirement	Management
Mild	No new or increased supplemental oxygen requirement, with symptoms limited to the upper respiratory tract.	Supportive care.
Moderate	No new or increased supplemental oxygen requirement, with symptoms involving the lower respiratory tract, or radiographic findings on chest x-ray.	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].	Remdesivir is suggested for all children with severe COVID-19, unless there are contraindications.
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.	Remdesivir should be considered for all children with critical COVID-19, unless there are contraindications.

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

Table 2. Remdesivir dosing and administration

Pediatric dose/duration (50)	**Contraindications** (50)	**Warnings** (50)
Pediatric and Adult Dosing: **3.5-40 kg:** 5 mg/kg IV loading dose on day 1; followed by 2.5 mg/kg IV q24h of lyophilized powder only **≥40 kg:** 200 mg IV loading dose on day 1; followed by 100 mg IV q24h; lyophilized powder or solution may be used <u>Recommended duration</u>: Severe disease: up to 5 days Critical disease: 5-10 days	Hepatic impairment: Remdesivir should not be administered to patients with ALT $\geq$ 5 times the upper limit of normal OR to patients with ALT elevations associated with elevated conjugated bilirubin, alkaline phosphatase, or INR. Renal insufficiency: Remdesivir is not recommended for patients >28 days old with an eFGR <30 ml/minute or term neonates (7 to 28 days of life) with a serum creatinine ≥ 1 mg/dL, unless the benefit outweighs the risk. No dose adjustments have been performed for patients with eGFR >30 ml/minute.	Potential adverse events include elevation in hepatic transaminases and hypersensitivity reactions. Hepatic function tests should be monitored daily. Co-administration of hydroxychloroquine may reduce antiviral activity of remdesivir (52).

Kg, kilogram; mg, milligram; IV, intravenous; q, every; h, hours; ALT, alanine aminotransferase; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; ml, milliliter

Table 3. Hypothesized risk factors for severe COVID-19

Underlying condition or characteristic	Considerations for antiviral therapy
Medical complexity	There is insufficient evidence to definitively support medical complexity as a risk factor for severe COVID-19. Based on the high prevalence of medically complex children in reported critically ill pediatric COVID-19 cohorts and extrapolation from other viral infections, medical complexity could be considered in making antiviral treatment decisions.
Young age	There is insufficient evidence to support young age alone as a risk factor for severe COVID-19.
Older age	There is insufficient evidence to definitively support older age (i.e., the adolescent age group) as a risk factor for severe COVID-19. However, based on the higher prevalence of adolescents in published pediatric cohorts relative to younger children, older age could be considered in making antiviral treatment decisions.
Severe immunocompromise	There is insufficient evidence to definitively support severe immunocompromise as a risk factor for severe COVID-19 in children. However, given the limited evidence base, and based on adult studies of COVID-19 and extrapolation from other viral infections, severe immunocompromise could be considered in making antiviral treatment decisions.

Mild/moderate immunocompromise	Evidence to date suggests that mild/moderate immunocompromise should not be considered a risk factor for severe COVID-19 in children.
Severe underlying cardiac disease	There is insufficient evidence to definitively support underlying cardiac disease as a risk factor for severe COVID-19 in children. However, based on adult studies of COVID-19, extrapolation from other viral infections, and limited data in children with COVID-19, presence of underlying cardiac disease could be considered in making antiviral treatment decisions.
Severe underlying pulmonary disease	There is insufficient evidence to definitively support underlying pulmonary disease as a risk factor for severe COVID-19 in children. Based on adult studies of COVID-19, extrapolation from other viral infections, and limited data in children with COVID-19, underlying pulmonary disease could be considered in making antiviral treatment decisions.
Obesity	There is insufficient evidence to definitively support isolated overweight or obese as a risk factor for severe COVID-19 in the pediatric population. Current reports indicate that obesity is prevalent among pediatric COVID-19 hospitalizations, particularly in critically ill cohorts. Obesity could be considered in making antiviral treatment decisions.
Diabetes	There is insufficient evidence to definitively support diabetes alone

as a risk factor for severe COVID-19 in children.

Table 4. 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 with ≥3 hospitalizations in the last 12 months (including cystic fibrosis, bronchopulmonary dysplasia, interstitial or diffuse lung disease, bronchiectasis, scoliosis, congenital diaphragmatic hernia, pulmonary hypoplasia) • 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