Treatment of Acute COVID-19 and COVID-19 Exposures in Children and Adolescents

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Abstract: The landscape of acute COVID-19 therapeutics has dramatically evolved since the onset of the pandemic. The treatment of acute COVID-19 in children and adolescents requires knowledge of risk factors and clinical features to appropriately select antiviral and immunomodulatory therapies. This review article provides updated guidance for emergency physicians in the treatment of acute COVID-19 in children and adolescents.

Key Words: COVID-19, SARS-CoV-2, treatment, adolescents

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TARGET AUDIENCE

This CME activity is intended for all practitioners who care for pediatric patients presenting with exposure to or symptoms consistent with acute COVID-19, which may include pediatricians, general practitioners, pediatric emergency physicians, general emergency physicians, and pediatric intensive care physicians.

LEARNING OBJECTIVES

At the completion of this article, the reader should be better able to:

1. Explain patient and family precautions and testing procedures after exposure to individuals with acute COVID-19
2. Assess the need for acute COVID-19 treatment based on a child's underlying risk factors and clinical presentation
3. Differentiate between available antiviral and immunomodulatory therapies in the treatment of acute COVID-19 for children and adolescents

BACKGROUND

As of May 2023, more than 15 million children have tested positive for SARS-CoV-2, the causative virus of COVID-19.[1] Though most infected children will be asymptomatic or experience mild illness, COVID-19 can result in severe illness for some children and adolescents. Those with underlying medical conditions are at highest risk; however, 30% of children with COVID-19–associated hospitalizations had no underlying health conditions.[2] The landscape of COVID-19 therapeutics has rapidly advanced since the onset of the pandemic, requiring clinicians to actively keep up with emerging data. This review describes current treatment strategies for COVID-19 among children and adolescents, while conveying the dynamic nature of the topic.

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TREATMENT OF COVID EXPOSURES

Currently, there are no approved pharmaceutical agents available for postexposure COVID-19 prophylaxis. Although there are several agents under development, the only available tools to prevent COVID-19 require administration before exposure. Mitigation of infection and symptoms through vaccination, in addition to general infection control strategies, such as masking and physical distancing, are the best ways to avoid infection. Unfortunately, by the time the child is presenting to the emergency department, it is often too late for these interventions. Nonetheless, every visit can be used as an opportunity to educate families regarding the benefits of vaccination, even after natural infection has occurred.[3,4]

After being exposed to COVID-19, the child should begin precautions for 10 days.[5] Precautions include wearing a high-quality mask in indoor spaces (moderate-certainty evidence) and avoiding close, physical contact with those at risk for severe disease.[6] If symptoms develop during that period, the child should isolate and get tested, staying home until the results are known. Regardless of their symptoms, the child should be tested at least 5 full days after the known exposure. If the results are positive, the decision to treat should be based on the severity of symptoms and underlying risk factors.

Understanding the strengths and limitations of currently available tests is important to guide clinical decision-making. There are 2 types of tests for acute COVID-19 infection: nucleic acid amplification tests (NAAT), such as reverse transcriptase polymerase chain reaction (RT-PCR), or antigen tests (most rapid, home test kits). Both types have high specificities. The "gold standard" for diagnosing COVID-19 is through NAAT.[7] Because the sensitivity of NAAT testing is generally higher, particularly during early or late infection when viral loads may be low, negative antigen testing in a patient with suspected COVID-19 should be confirmed with a NAAT.[7]

Because NAATs detect viral RNA that does not necessarily represent viable virus, prolonged detection can occur in children even months after their initial infection without symptoms or risk of transmission to others. This is important to recognize when a child presents with suspected reinfection within 90 days of their previous COVID-19 infection. Early reinfection can occur particularly among young, unvaccinated patients.[8] If reinfection is suspected within 90 days of previous infection, antigen-based testing is preferred, with serial testing 48 hours later if negative (total of twice for symptomatic patients, thrice for asymptomatic patients).[9]

APPROACH TO TREATMENT

The treatment of acute COVID-19 can be guided by 2 considerations: the patient's risk factors and severity of illness. Immunocompromised children, or those with comorbidities such as obesity, pregnancy, severe chronic lung disease, neurodevelopmental disorders, severe heart disease, or multiple severe chronic medical conditions are at highest risk for severe COVID-19 (Table 1).[10] Although less clearly established, children with sickle cell disease, poorly controlled diabetes, chronic kidney disease, and nonsevere cardiac, neurologic,

TABLE 1. Risk Factors and Initial Treatment for COVID-19 in Children and Adolescents, as Established by the NIH COVID-19 guidelines[9]

	High Risk or Consistent Association With Progression to Severe Disease	Moderate Risk or Inconsistent Association With Progression to Severe Disease	Weak or Unknown Association With Progression to Severe Disease

Risk factors	• Immunocompromised
	  • Examples: Malignancy undergoing active chemotherapy, solid organ transplant requiring immunosuppressive therapy, hematopoietic stem cell transplant within 2 y of procedure, advanced or untreated HIV, active treatment with high-dose corticosteroids, moderate to severe primary immunodeficiencies like SCID, DiGeorge, common variable immunodeficiency (CVID)
	• Obesity
	  • BMI ≥ 95th percentile for age
	• Severe neurodevelopmental conditions impairing airway clearance
	• Severe chronic lung disease
	  • Includes severe asthma
	• Severe congenital or acquired heart disease
	• Multiple medical chronic diseases
	• Children with dependency on respiratory technology
	• Pregnancy
		• Age <1 y
		• Prematurity for those ≤2 y
		• Sickle cell disease
		• Poorly controlled diabetes
		• Nonsevere cardiac, neurologic, or metabolic disease
			• Mild asthma
			• Overweight
			• Well-controlled diabetes

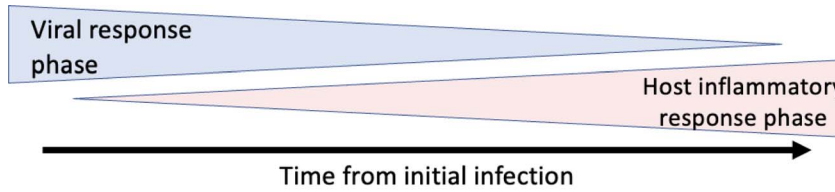
Risk mitigation through vaccination	Risk decreases to intermediate for those with COVID-19 vaccination (exception: immunocompromised children who are not expected to mount appropriate immune response to vaccination)		
Outpatient treatment	1. If ≥12 y and weighs >40 kg, offer PO Paxlovid (nirmatrelvir/ritonavir) within 5 d of symptom onset 2. If <12 y, <40 kg, or medical contraindications to Paxlovid, offer IV remdesivir (3-d course within 7 d of symptom onset)	Not enough data to support or deny antiviral treatment, use shared decision-making with patient and family based on individual benefit/risk profile	Supportive care
Inpatient treatment	Depends on disease severity, refer to NIH therapeutic management table for children hospitalized with COVID-19[9]		

SCID, severe combined immunodeficiency.

or metabolic disease are at moderate risk for progression to severe COVID-19.[11] Demographic risk factors, including age (children <1 year) and race/ethnicity (Hispanic and non-Hispanic Black children) have been associated with more severe disease.[11] Finally, hospitalization rates among unvaccinated children are approximately double those of COVID-19 vaccinated children, making this an important parameter in risk stratification.[2] The National Institute of Health (NIH) considers both underlying comorbidities and vaccination status when making treatment recommendations.[10]

The second principle in guiding treatment considers the child's illness severity. The initial assessment should focus on the patient's respiratory and circulatory status. The need for respiratory support and/or fluid administration will guide the decision for admission and further stratify therapeutic interventions. For healthy children not requiring supplemental oxygen or fluids, outpatient supportive care measures are the mainstay of treatment. Caretakers should encourage oral hydration and antipyretic use as needed. If that child has risk factors for progression to severe disease, outpatient antiviral therapies should be offered (Table 1). For children requiring respiratory support or hydration, hospitalization is required and additional treatment with antivirals and/or immunomodulatory therapies should be considered. The choice of initial treatment agents will depend on the patient's stage in their disease course, oxygen requirements, and underlying risk factors.

Similar to adults, a biphasic disease course may be seen in children and adolescents with symptomatic COVID-19.[12] In general, antiviral therapies are most effective when used during the first 7 to 10 days of illness when active viral replication is



Antivirals	Immunomodulators and antithrombotic therapy
Nirmatrelavir/ritonavir (Paxlovid)	Corticosteroids (Dexamethasone)
Remdesivir	Interleukin-6 inhibitor (e.g., tocilizumab) or Janus kinase (JAK) inhibitors (e.g., baricitinib)
Molnupiriavir	Prophylactic anticoagulation (e.g., enoxaparin)

FIGURE 1. COVID-19 therapies based on stage in disease course.

occurring. Because prolonged viral replication can occur in patients with underlying immunocompromise, the window of opportunity to treat with antivirals may extend well beyond the first week of illness in this population. After the first week of illness, a subset of patients will progress to a hyperinflammatory state that results in lung injury and multisystem organ failure.[12] Immunomodulatory therapies, such as corticosteroids, are most effective when administered during this host inflammatory response stage (Fig. 1).

TREATMENT FOR ACUTE COVID-19

The first step in acute COVID-19 management involves respiratory and circulatory stabilization. Although the optimal SpO_2 for children with COVID-19–associated respiratory failure is unknown, there is no reason to believe it would differ from other processes resulting in acute lung injury. In accordance with the 2023 Pediatric Acute Lung Injury Consensus Conference (PALICC-2), an SpO_2 of 92% to 97% is recommended for those with mild to moderate pediatric acute respiratory distress syndrome, with tolerance as low as 88% to minimize FiO_2 exposure in those with severe pediatric acute respiratory distress syndrome.[13,14] In children unable to attain appropriate saturations with conventional oxygen therapy, a trial with noninvasive ventilation or high-flow (HF) nasal canula is preferred before intubation.[14] In contrast to children with multisystem inflammatory syndrome in children (MIS-C), hemodynamic compromise is uncommon in children with acute COVID-19. When shock is present, management should align with guidelines set forth by the *Surviving Sepsis Campaign*.[13,15]

Most clinical research for COVID-19 therapeutics has focused on the adult population. Thus, the efficacy and safety for many of the pharmacologic interventions are extrapolated to children, warranting further research moving forward. Until then, expert opinion and a limited number of studies have guided the use of antiviral and immunomodulatory therapies in the pediatric population. The NIH has developed pediatric treatment guidelines to guide the use of therapeutic agents in nonhospitalized and hospitalized children with acute COVID-19 (Table 2).[10]

Antivirals

Remdesivir

Remdesivir was the first FDA-approved antiviral drug for the treatment of COVID-19. It acts as a nucleotide prodrug that binds to viral RNA polymerase and prematurely stops transcription, therefore blunting replication.[16] Administration during the early viral replication stage may prevent progression to severe disease.

For outpatients, a 3-day course given within the first 7 days of illness can prevent progression to severe disease resulting in hospitalization or death.[17] Although the efficacy in preventing progression to severe disease in children is largely unknown, given its favorable adverse effect profile and the potential for efficacy, outpatient treatment of children with mild to moderate risk factors is recommended.

For those requiring hospitalization, remdesivir is recommended for select clinical situations. Early use within the first 10 days of symptoms is most beneficial; however, exceptions exist for immunocompromised children with prolonged viral replication. A 5-day course or continuation until discharge (whichever is sooner) is recommended for those requiring conventional supplemental oxygen.[10,16] Remdesivir should be considered for those with higher oxygen support (high flow or noninvasive ventilation [NIV]), especially if given early in the disease course. For those not requiring supplemental oxygen, remdesivir can be considered for those 12 years and older with underlying risk factors.[10]

Currently, remdesivir is only available as an intravenous formulation, logistically limiting its administration among children not requiring hospitalization. In general, it is well tolerated with few serious adverse reactions reported.[18] A clinical trial to assess the safety, pharmacokinetics, and efficacy of remdesivir in children younger than 18 years is ongoing; however, interim results suggest a similar adverse effect profile as adults.[19]

Nirmatrelvir/Ritonavir (Paxlovid)

Nirmatrelvir/ritonavir (Paxlovid) is the first FDA-approved *oral* antiviral drug for the treatment of mild to moderate COVID-19 in adult patients at risk for progression to severe disease.[20] It is currently under FDA emergency use authorization (EUA) for pediatric patients aged 12 years and older weighing 40 kg or more who are within 5 days of symptom onset. There are 2 drugs that comprise Paxlovid: nirmatrelvir acts as the active antiviral component (protease inhibitor), whereas ritonavir acts as a booster to increase nirmatrelvir concentrations. Significant drug-drug interactions can exist and should be checked before prescription. Quick reference lists have been created by the NIH,

TABLE 2. Overview of NIH-Recommended COVID-19 Therapeutics for Children[9]

	NIH Recommended COVID-19 Therapeutics	Indication(s)	Age and/or Weight Limitations	Dose
Antivirals	Remdesivir	Nonhospitalized: High-risk children with symptomatic COVID-19 within 7 d of symptom onset Hospitalized: Children requiring conventional oxygen, preferably within 7–10 d of symptom onset. Consider for high-risk children or adolescents not requiring supplemental oxygen and children requiring higher levels of oxygen (HF device, NIV), especially if within 7–10 d of symptom onset	No age limitations Weight: >3 kg (limited data on neonates weighing less than this with optimal dosing not defined)	5 mg/kg on day 1 (max: 200 mg), then 2.5 mg/kg daily (max: 100 mg)
	Nirmatrelavir/ ritonavir (Paxlovid)	Nonhospitalized: High-risk children with symptomatic COVID-19 within 5 d of symptom onset	Age >12 y AND weighing ≥40 kg	Nirmatrelavir 300 mg, ritonavir 100 mg administered together twice daily (copackaged)
Immunomodulators	Dexamethasone	Hospitalized: Children requiring oxygen through HF device, NIV, MV, or ECMO. Consider for those requiring conventional oxygen therapy with increasing oxygen needs, particularly if adolescents and within the 2nd week of illness	No age or weight limitations	0.15 mg/kg IV or PO daily (max: 6 mg)
	Tocilizumab (IL-6 inhibitor)	Hospitalized: Consideration for children requiring oxygen through HF device, NIV, MV, or ECMO who do not have rapid improvement in oxygenation within 24 h of starting dexamethasone	Age >2 y	<30 kg: 12 mg/kg/dose once daily > 30 kg: 8 mg/kg/dose once daily (max: 800 mg/dose)
	Baricitinib (JAK inhibitor)	Hospitalized: Consideration for children requiring oxygen through HF device, NIV, MV, or ECMO who do not have rapid improvement in oxygenation within 24 h of starting dexamethasone	Age >2 y	2 to <9 y: 2 mg once daily ≥9 y: 4 mg once daily

in addition to the University of Liverpool Web-based interaction checker, to aid prescribers.[21,22] Paxlovid is only recommended for those 12 years and older who weigh at least 40 kg, although clinical trials are underway to study safety and dosing in younger children.[20] Paxlovid is an oral option for adolescents who are not sick enough to currently require hospitalization but have underlying risk factors that may result in disease progression (Table 2).

Paxlovid should not be used in those with hepatic impairment; reductions in dosing may be necessary for those with renal impairment.[23] Although some studies suggest the possibility of "viral rebound" with symptom recurrence after discontinuing Paxlovid, this should not impact the decision to prescribe.[23] In fact, this effect has been described during the natural course of SARS-CoV-2 infection, regardless of Paxlovid use.[24] In addition, when described with Paxlovid use, disease recurrence has not been associated with progression to moderate or severe illness.[20]

Molnupiravir

Molnupiravir is an oral antiviral drug that is available under FDA EUA for the treatment of mild to moderate COVID-19 in high-risk *adults* (≥18 years) who are unable to take alternative antiviral agents due to unavailability or medical contraindications.[25] In comparison with remdesivir or Paxlovid, the impact of molnupiravir was modest, with a 31% reduction in hospitalization or death among unvaccinated, high-risk adults.[26] Molnupiravir

TABLE 2. Overview of NIH-Recommended COVID-19 Therapeutics for Children[9], Continued

NIH Recommended COVID-19 Therapeutics	Duration	Administration Route	Important Adverse Effects	FDA Approval Status
	Nonhospitalized: 3 d Hospitalized: 5 d or on discharge (whichever comes first)	Parenteral (IV)	Gastrointestinal upset, transaminitis, elevated prothrombin time with normal INR, and hypersensitivity reactions	Approved for use in COVID-19 in pediatric patients ≥28 dweighing ≥3 kg
	5 d	Oral (PO)	Significant drug-drug interactions, dysgeusia, diarrhea, hypertension and myalgias	Approved for use in COVID-19 in adults ≥18 y, EUA for pediatric patients ≥12 y weighing ≥40 kg
	10 d or on discharge (whichever comes first)	Parenteral (IV) or oral (PO)	Hyperglycemia, gastrointestinal effects (including dyspepsia, gastritis, or ulceration), psychiatric disturbances, adrenal insufficiency, and infection risk	Approved for use in COVID-19
	Once with option to repeat dose once >8 h after initial dose if clinical symptoms worsen	Parenteral (IV)	Serious infections, gastrointestinal perforation, neutropenia, thrombocytopenia, transaminitis, hypersensitivity reaction	EUA
	14 d or on discharge (whichever comes first)	Oral (PO)	Serious infections, gastrointestinal perforation, cytopenia, transaminitis, hypersensitivity reaction	EUA

should not be given to children younger than 18 years due to potential effects on bone and cartilage growth.

Immunomodulators

Corticosteroids

A subset of COVID-19 patients will develop severe respiratory disease involving diffuse alveolar damage and multiorgan failure, typically after the first week of illness.[12] The pathogenesis has been partly attributed to a dysregulated host immune response resulting in severe inflammation-associated organ injury.[27,28] Immunomodulatory therapies, such as corticosteroids, may mitigate this aberrant inflammatory response. Several clinical trials have supported the use of systemic corticosteroids in hospitalized adults with acute COVID-19 receiving supplemental oxygen.[29,30] Though pediatric data are lacking, adult data have been extrapolated to recommend use of dexamethasone in hospitalized children and adolescents with COVID-19 requiring HF oxygen, NIV, mechanical ventilation (MV), or extracorporeal membrane oxygenation (ECMO).[10,11] Dexamethasone should be considered for children receiving conventional oxygen who have rapidly escalating oxygen requirements, particularly adolescents who are presenting during their second week of infection. If dexamethasone is unavailable, prednisone, methylprednisolone, or hydrocortisone can be considered, although less data support their use.[10] Asthma exacerbations triggered by acute COVID-19 infection

should be managed according to the child's asthma treatment plan. There is no evidence to support the use of inhaled corticosteroids.

There is no benefit to giving corticosteroids to patients who are not requiring oxygen, and doing so may cause harm.[29] As with all COVID-19 therapeutics, consideration for where the patient is in their disease course is important when deciding whether steroid treatment is necessary. Dexamethasone clearly benefits patients treated more than 7 days after symptom onset when inflammatory lung damage was occurring, in contrast to patients not requiring oxygen, who more commonly presented during their first week of illness as viral replication is occurring.[29] Studies have found longer hospitalizations and prolonged viral shedding when steroids are given to patients early in their disease course when supplemental oxygen is not required.[31]

Interleukin-6 Inhibitors and Janus Kinase Inhibitors

Interleukin-6 inhibitors and Janus kinase inhibitors act by blocking cellular signaling pathways involved with producing an immune or inflammatory response.[32,33] Though clinical trial data supporting a mortality benefit are limited to adults, tocilizumab (an interleukin-6 inhibitor) and baricitinib (a Janus kinase inhibitor) received FDA EUA for the treatment of children with COVID-19 who are 2 years and older, receiving systemic corticosteroids, and require supplemental oxygen, NIV, MV, or ECMO.[34,35] The NIH recommends the addition of these agents to dexamethasone for children requiring oxygen through HF oxygen, NIV, MV, or ECMO who do not have rapid improvement in oxygenation (eg, after 24 hours).

Passive Immunoprophylaxis

Convalescent Plasma

The use of convalescent COVID-19 plasma (CCP) to confer passive immunity and treat infection was widely studied at the onset of the pandemic. Although retrospective studies suggest that it is well tolerated without significant safety concerns, data supporting its efficacy in children and adolescents are lacking, so it is not recommended as a preventative or therapeutic agent.[36]

SARS-CoV-2 Neutralizing Antibodies

Early in the pandemic, COVID-19 monoclonal antibodies were developed as a treatment and preventive strategy, with most targeting the spike protein.[37] Unfortunately, as variants emerged with spike protein mutations, these neutralizing antibodies were deemed ineffective. At this time, no SARS-CoV-2 neutralizing antibodies are approved for the treatment or prevention of acute COVID-19.

ANTICOAGULATION

The inflammatory state associated with acute COVID-19 may result in thromboembolic events. In children and adolescents, the risk is low and generally increases with age and clinical severity, with an incidence of 0.7% among those with asymptomatic infection, 2.1% among those hospitalized with COVID-19, and as high as 6.5% among those with MIS-C.[38] In the absence of pediatric-specific data, the NIH recommends prophylactic anticoagulation to those 12 years and older with acute COVID-19 (pharmacologic and/or mechanical depending on risk factors).[10]

"FIRST, DO NO HARM"

At the onset of the COVID-19 pandemic, several therapies proposed as possibly beneficial were subsequently proven ineffective and even harmful. For example, the repurposing of older drugs, such as hydroxychloroquine, ivermectin, or colchicine, was trialed and proven to be ineffective in the treatment or prevention of COVID-19.[39] These medications should be avoided in the treatment or prevention of acute COVID-19. The same should be said for unnecessary antibiotic use. The rate of bacterial coinfection with COVID-19 at the time of presentation is low, ranging from 2% to 8% depending on the population.[40,41] Despite the low incidence, antibiotics are prescribed in up to three quarters of patients with acute COVID-19.[40] Inappropriate antibiotic prescription may result in adverse effects, antimicrobial resistance, and unnecessary burden to the patient and families.

SEQUELAE AFTER ACUTE COVID-19

Beyond the risk of acute infection, complications such as MIS-C and postacute sequelae of SARS-CoV-2 infection (PASC, post-COVID, or "long COVID") may result in ongoing health concerns among children and adolescents.

Multisystem inflammatory syndrome in children is a rare but serious complication that typically develops 2 to 6 weeks after acute infection with COVID-19, resulting in severe systemic inflammation and multiorgan dysfunction. More than 9000 cases of MIS-C have been reported since the onset of the pandemic, resulting in 79 deaths.[42] At times, it may be challenging to differentiate between severe acute COVID-19 and MIS-C given their overlapping clinical features. As previously described, children and adolescents with acute COVID-19 may progress to a hyperinflammatory state, typically within the second week of illness. This is in contradistinction to MIS-C, where the initial SARS-CoV-2 infection is often mild or completely asymptomatic, followed by a period of 2 to 6 weeks where the patient is well and then acutely develops symptoms. Patients with MIS-C tend to have higher levels of systemic inflammation and higher rates of myocardial dysfunction, gastrointestinal symptoms, and mucocutaneous involvement compared with those with acute COVID-19.[43] Distinguishing between the two is important because the management significantly differs. Although beyond the scope of this review, standard MIS-C management involves immunomodulation with corticosteroids, intravenous immunoglobulin, and/or biologics.

The number of children and adolescents affected by PASC is not well defined. Although the absolute risk of PASC in children and adolescents seems much lower than adults, ongoing symptoms have been reported.[44] Treatment is variable and should be tailored to the patient's symptoms. Fortunately, PASC improves over time for most children and adolescents.[45] Postacute sequelae of SARS-CoV-2 infection in children and adolescents remains an area of active research.

CONCLUSIONS

Although many children and adolescents with SARS-CoV-2 infection will experience minimal symptoms, a subset will progress to severe disease, and even death. From 2019 through 2022, COVID-19 ranked 8th among all causes of pediatric deaths in the United States, representing 2% of total deaths among children 19 years and younger.[46] Pediatric providers must be equipped to recognize and appropriately manage children presenting with acute COVID-19. Understanding which risk factors predispose to severe disease should guide administration of therapeutics during early disease to minimize the risk for progression. For children presenting with moderate to severe disease requiring hospitalization, the stage in their disease course and their oxygen requirements should guide administration of antiviral and immunomodulatory agents.

Three years into the COVID-19 pandemic, there has been significant progress toward understanding the disease and development of therapeutic agents, yet many unknowns exist,

particularly in the management of children. It is important that providers have access to changing recommendations. Both the NIH and American Academy of Pediatrics have produced excellent pediatric guidelines for the management of acute COVID-19 that are regularly updated to reflect emerging research.[10,11] By staying informed on evidence-based recommendations, pediatric providers can mitigate the risk posed by acute COVID-19 and reduce its impact on future generations.

REFERENCES

1. American Academy of Pediatrics. Children and COVID-19: state-level data report. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/. Accessed May 30, 2023.
2. Shi DS, Whitaker M, Marks KJ, et al. Hospitalizations of children aged 5–11 years with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep*. 2022; 71:574–581.
3. Hall V, Foulkes S, Insalata F, et al. Protection against SARS-CoV-2 after Covid-19 vaccination and previous infection. *N Engl J Med*. 2022;386: 1207–1220.
4. Hammerman A, Sergienko R, Friger M, et al. Effectiveness of the BNT162b2 vaccine after recovery from Covid-19. *N Engl J Med*. 2022; 386:1221–1229.
5. Centers for Disease Control and Prevention. What to do if you were exposed to COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-health/if-you-were-exposed.html. Accessed March 13, 2023.
6. Jefferson T, Del Mar CB, Dooley L, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev*. 2020;11:CD006207.
7. Centers for Disease Control and Prevention. COVID-19 testing: what you need to know. Available at: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html. Accessed March 13, 2023.
8. Nevejan L, Cuypers L, Laenen L, et al. Early SARS-CoV-2 reinfections within 60 days and implications for retesting policies. *Emerg Infect Dis*. 2022;28:1729–1731.
9. US Food & Drug Administration. At-home COVID-19 antigen tests-take steps to reduce your risk of false negative results: FDA safety communication. Available at: https://www.fda.gov/medical-devices/safety-communications/home-covid-19-antigen-tests-take-steps-reduce-your-risk-false-negative-results-fda-safety. Accessed March 13, 2023.
10. National Institute of Health. NIH COVID-19 treatment guidelines: clinical management of children summary. Available at: https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-children/clinical-management-of-children-summary/. Accessed April 3, 2023.
11. American Academy of Pediatrics. Management strategies in children and adolescents with mild to moderate COVID-19. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/outpatient-covid-19-management-strategies-in-children-and-adolescents/. Accessed May 30, 2023.
12. García LF. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol*. 2020;11:1441.
13. Emeriaud G, López-Fernández YM, Iyer NP, et al. Executive summary of the second international guidelines for the diagnosis and management of pediatric acute respiratory distress syndrome (PALICC-2). *Pediatr Crit Care Med*. 2023;24:143–168.
14. National Institute of Health. NIH COVID-19 treatment guidelines: oxygenation and ventilation for children. Available at: https://www.covid19treatmentguidelines.nih.gov/management/critical-care-for-children/oxygenation-and-ventilation-for-children/. Accessed April 20, 2023.
15. National Institute of Health. NIH COVID-19 treatment guidelines: hemodynamic considerations for children. Available at: https://www.covid19treatmentguidelines.nih.gov/management/critical-care-for-children/hemodynamics-for-children/. Accessed April 20, 2023.
16. National Institute of Health. National Institute of Health COVID-19 treatment guidelines: remdesivir. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/remdesivir/. Accessed April 20, 2023.
17. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med*. 2022;386: 305–315.
18. Goldman DL, Aldrich ML, Hagmann SHF, et al. Compassionate use of remdesivir in children with severe Covid-19. *Pediatrics*. 2021; 147:e2020047803.
19. Gilead Sciences (Sponsor). Study of remdesivir in participants 18 years old and younger with COVID-19 (CARAVAN). Available at: https://www.clinicaltrials.gov/ct2/show/NCT04431453. Accessed April 20, 2023.
20. National Institute of Health. National Institute of Health COVID-19 treatment guidelines: ritonavir-boosted nirmatrelvir (Paxlovid). Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed April 12, 2023.
21. National Institute of Health. Drug-drug interactions between ritonavir-boosted nirmatrelvir (Paxlovid) and concomitant medications. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir–paxlovid-/paxlovid-drug-drug-interactions/. Accessed April 10, 2023.
22. University of Liverpool. COVID-19 drug interactions. Available at: https://www.covid19-druginteractions.org/checker. Accessed April 10, 2023.
23. Lexicomp. Nirmatrelvir and ritonavir (pediatric and neonatal Lexi-Drugs). Available at: https://online-lexi-com.eu1.proxy.openathens.net/lco/action/doc/retrieve/docid/pdh_f/7185832?cesid=1dicpcf85fU&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dpaxlovid%26t%3Dname%26acs%3Dfalse%26acq%3Dpaxlovid. Accessed April 10, 2023.
24. Anderson AS, Caubel P, Rusnak JM, EPIC-HR Trial Investigators. Nirmatrelvir–ritonavir and viral load rebound in Covid-19. *N Engl J Med*. 2022;387:1047–1049.
25. National Institute of Health. NIH COVID-19 treatment guidelines: molnupiravir. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/molnupiravir/. Accessed April 10, 2023.
26. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N Engl J Med*. 2022;386:509–520.
27. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846–848.
28. Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021;191:4–17.
29. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384:693–704.
30. Wagner C, Griesel M, Mikolajewska A, et al. Systemic corticosteroids for the treatment of COVID-19. *Cochrane Database Syst Rev*. 2021; 8:CD014963.
31. Shuto H, Komiya K, Yamasue M, et al. A systematic review of corticosteroid treatment for noncritically ill patients with COVID-19. *Sci Rep*. 2020;10:20935.
32. National Institute of Health. COVID-19 treatment guidelines: interleukin-6 inhibitors. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/interleukin-6-inhibitors/. Accessed April 18, 2023.

33. National Institute of Health. COVID-19 treatment guidelines: janus kinase inhibitors. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/janus-kinase-inhibitors/. Accessed April 25, 2023.
34. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397:1637–1645.
35. REMAP-CAP Investigators, Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med*. 2021;384:1491–1502.
36. Jacquot C, Gordon O, Noland D, et al. Multi-institutional experience with COVID-19 convalescent plasma in children. *Transfusion*. 2023;63:918–924.
37. Huang Y, Yang C, Xu XF, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol Sin*. 2020;41:1141–1149.
38. Whitworth H, Sartain SE, Kumar R, et al. Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. *Blood*. 2021;138:190–198.
39. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. *Clin Infect Dis*. 2022;ciac724.
40. Langford BJ, So M, Raybardhan S, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin Microbiol Infect*. 2021;27:520–531.
41. Wu HY, Chang PH, Chen KY, et al. Coronavirus disease 2019 (COVID-19) associated bacterial coinfection: incidence, diagnosis and treatment. *J Microbiol Immunol Infect*. 2022;55:985–992.
42. Centers for Disease Control &Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States. Available at: https://covid.cdc.gov/covid-data-tracker/#mis-national-surveillance. Accessed May 10, 2023.
43. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA*. 2021;325:1074–1087.
44. Gurdasani D, Akrami A, Bradley VC, et al. Long COVID in children. *Lancet Child Adolesc Health*. 2022;6:e2.
45. Osmanov IM, Spiridonova E, Bobkova P, et al. Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC global follow-up protocol: a prospective cohort study. *Eur Respir J*. 2022;59:2101341.
46. Flaxman S, Whittaker C, Semenova E, et al. Assessment of COVID-19 as the underlying cause of death among children and young people aged 0 to 19 years in the US. *JAMA Netw Open*. 2023;6:e2253590.