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Considerations in Children and Adolescents Related to Coronavirus Disease 2019 (COVID-19)

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KEYWORDS

• Post-acute sequelae of SARS-CoV-2 • Long COVID • Multidisciplinary care • SARS-CoV-2 • Pediatrics • Rehabilitation • Fatigue • Quality of life

KEY POINTS

- Primary care providers should screen for post-acute sequelae of SARS-CoV-2 (PASC) in children with a history of SARS-CoV-2 infection.
- PASC is a complex multisystemic disease that benefits from a multifaceted treatment approach.
- Lifestyle interventions, physical rehabilitation, and mental health management are important in improving pediatric PASC patients' quality of life.

INTRODUCTION

Since the start of the Coronavirus Disease 2019 (COVID-19) pandemic, over 14.6 million pediatric COVID-19 cases have been reported in the United States—about 18.4% of all total cases.[1] Owing to the Omicron variant surge, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children has become increasingly prevalent, as 6.7 million of these cases have occurred in 2022.[1] Fortunately, only 0.1% to 1.5% of

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pediatric COVID-19 cases result in hospitalization, and death is rare (0%–0.02%).[1] Although most pediatric COVID-19 patients are asymptomatic or have mild symptoms in the acute period, some children present with severe and debilitating manifestations, such as multisystem inflammatory syndrome in children (MIS-C) and post-acute sequelae of SARS-CoV-2 (PASC), also known as post-COVID conditions or "long COVID."[2–4] For the purposes of this review, the authors use the term PASC. MIS-C is a multisystemic hyperinflammatory syndrome in children and adolescents that usually occurs 2 to 6 weeks after SARS-CoV-2 infection.[3,5] There have been 8862 cases of MIS-C in the United States reported to the Center for Disease Control and Prevention (CDC) as of August 29, 2022, with an incidence of less than 0.1%. Although rare, MIS-C carries significant morbidity and mortality; 72 of the cases resulted in death.[6]

PASC is the presence of symptoms that interfere with daily activities in individuals with a history of confirmed or probable SARS-CoV-2 infection that cannot be explained by an alternate diagnosis. The diagnostic criteria and time frame vary regarding when postinfectious symptoms are considered PASC. Although some (eg, World Health Organization) define PASC as symptoms lasting at least 3 months, the CDC defines PASC as symptoms (new, recurring, or persistent) present at least 4 weeks after initial infection.[7] Adult studies estimate that approximately 30% of patients develop PASC after SARS-CoV-2 infection.[8] In children, the prevalence is less well-known and challenging to study with individual studies reporting rates between 4% and 66%,[4,8–10] but larger estimates are around 5% to 25%.[9,11,12] One concern is that pediatric PASC (pPASC) is underrecognized. Children generally have mild acute illness which can result in a lack of testing for SAR-CoV-2. The lack of confirmed COVID-19 diagnosis combined with developmental limitations of children to recognize and describe nonspecific, and indolent PASC symptoms may result in underrecognition or a delay in diagnosis of PASC in children. However, PASC can be debilitating and negatively affect children's ability to attend school and participate in daily activities[8]; therefore, the importance of awareness and screening by pediatric providers cannot be understated. More information, research, and guidance are needed to improve the diagnosis and care of children with PASC. In this review, the authors consolidate what has been observed so far about pPASC.

SYMPTOMS AND PRESENTATION OF PEDIATRIC POST-ACUTE SEQUELAE OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-CoV-2)

pPASC patients display a broad spectrum of multisystemic symptoms with variable presentations, time course, and severity. pPASC symptoms can exist in children with mild or no symptoms and in both hospitalized and nonhospitalized patients.[2,8,13–16] However, some studies suggest that potential risk factors for pPASC include severity and duration of SARS-CoV-2 infection, older age, being female, allergic disease, underlying chronic disease, and higher body mass index (BMI).[8,13,16] Although adolescents have been shown to have a greater risk of PASC, it has been observed that younger children have a higher risk for respiratory symptoms and complications.[16] Multiple time courses and symptoms have been reported. PASC symptoms can linger and remain persistent after the acute infection, or the patient can fully recover after the acute infection only to later relapse or develop new postinfectious symptoms. Alternatively, the symptoms can wax and wane throughout the disease course.[2,7,8,13,14,16]

pPASC does not affect just one organ system; symptoms can occur in the cardiorespiratory, dermatologic, gastrointestinal, otolaryngologic, musculoskeletal, neurologic, psychiatric, renal, and general systems.[8,13] The most common symptoms

include fatigue (3%–87%), cognitive difficulties (2%–81%), headaches (3%–80%), abdominal pain (1%–76%), muscle and joint pain (1%–68%), sleep disturbance (2%–63%), post-exertional malaise (53%), rash (2%–52%), dizziness and lightheadedness (19%–48%), heart palpitations (4%–40%), and mood disorders (5%–59%) such as anxiety and depression.[2,8,14,16–18] Other notable symptoms include school performance decline, anosmia, ageusia, respiratory symptoms (eg, dyspnea, cough), persistent chest pain, nausea, vomiting, and diarrhea.[4,8,16,18] The extensive scope of clinical manifestations observed suggests that pPASC may be a multifactorial disease.[15]

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Although rare, MIS-C is a life-threatening post-acute complication of SARS-CoV-2 infection and early identification and treatment are critical.[3] The CDC defines MIS-C as the presence of clinically severe illness requiring hospitalization, fever for over 24 hours, laboratory evidence of systemic inflammation, and multisystemic organ involvement within 4 weeks of acute SARS-CoV-2 infection, all of which cannot be explained by another diagnosis.[3,19] Organ systems affected by MIS-C include cardiovascular (66.7%–86.5%), gastrointestinal (80%–90%), neurologic (12.2%), respiratory (36.5%), hematologic (47.5%), and mucocutaneous systems (74%–83%).[3,19,20]

Common symptoms include erythematous rashes, persistent fever, diarrhea, abdominal pain, and mucocutaneous lesions. Some children present with more severe manifestations such as hypotension, vasogenic shock, myocarditis, coronary artery aneurysm, cardiac dysfunction, and acute kidney injury.[3,19,21] Of note, MIS-C presents similarly to Kawasaki disease (KD) and toxic shock syndrome, and some studies show that MIS-C and KD may share the same host immune response.[22] The most common age of onset is between 6 and 12 years, and MIS-C often affects previously healthy children (70%–80%).[3,20,23,24] One theory on why school-age children are more affected is that MIS-C may be underreported in older age groups because those patients tend to be seen at adult hospitals, and many of the MIS-C statistics are reported from children's hospitals.[24] Another theory is that KD is more prevalent in school-age children, and if MIS-C does have a similar pathogenesis to KD, then this may give insight into why MIS-C is present more commonly in younger children.[23] Some studies show that obesity and previous genetic disposition to hyperinflammation may be risk factors for MIS-C.[3,20] In addition, the gastrointestinal microbiome in children differs in composition from adults, and it has been hypothesized to play a role in not only the development of MIS-C in this population but also as a potential factor for the more mild initial COVID-19 disease in pediatric patients in general.[25,26]

Optimal treatment of MIS-C is still being studied due to MIS-Cs low incidence. However, early and aggressive treatment regimens have been recommended to prevent potential long-term cardiovascular sequelae.[3,19] Current treatment is similar to KD protocols, focusing on immunomodulation, such as intravenous immune globulin (IVIG) and corticosteroids, and supportive care.[3] Despite the potential severity of MIS-C, the outcomes for children affected by MIS-C are overall very good.[3,6,19] Studies have shown that most children completely recover after treatment, and the mortality rate has been less than 1%.[3,6,19] One study showed that by 6 months, most of the symptoms from patients' initial acute illness resolved. However, some sequelae have been reported to linger, including muscle fatigue, reduced functional exercise capacity, proximal myopathy, dysmetria, abnormal saccades, anxiety, and emotional lability.[27] In particular, when tested 6 months after hospitalization on the 6-minute-walk test, 45% of the patients scored below the third percentile for age,

demonstrating functional impairment. Ninety-eight percent of the children returned to full-time education, but formal neuropsychological testing was not done to assess school performance.[27] More research needs to be done to characterize the potential long-term effects of MIS-C.

POTENTIAL MECHANISMS OF POST-ACUTE SEQUELAE OF SARS-CoV-2

Our understanding of the mechanisms underlying the pathophysiology of PASC is constantly evolving. Although much has been published describing reputed causes, few studies include broadly generalizable clinical data.[28] In addition, it is unknown if the pathophysiology behind PASC in children differs from adults. The heterogeneity of the clinical spectrum suggests that multiple mechanisms may be at play; literature demonstrating phenotypic symptomatic clustering of patients with PASC further suggests a multifactorial process.[29] Persistent symptoms may be due to virus-driven tissue damage from acute infection in certain cases, such as acute lung damage following respiratory infection or anosmia/parosmia following direct upper respiratory infection. However, alternative explanations are needed to understand persistent or late-onset symptoms in individuals lacking evidence of direct viral tissue invasion. The proposed mechanisms for the latter include immune dysregulation and inflammation in response to a restricted or persistent viral reservoir potentially leading to autoimmunity/molecular mimicry, micro-clots and endothelial damage, metabolic and gastrointestinal microbiome alterations, or autonomic nervous system dysfunction.[30–36]

TREATMENT OF PEDIATRIC POST-ACUTE SEQUELAE OF SARS-CoV-2

Current Treatment Approaches for Overall Systems

Currently, treatment of pPASC targets symptom management, rehabilitative support, and a patient/family-centered, goal-directed return to baseline physical, cognitive, academic, and social activity. pPASC management includes a healthy diet and sleep hygiene, along with environmental supports that promote healthy adjustment.

Management begins with validation of symptoms and the diagnosis, along with education about treatment options and prognosis. For most patients and families, this starts with the primary care provider, but referral to a multidisciplinary pPASC clinic may be needed in some cases. Management is then tailored to the patient's symptoms. There are a few red flag symptoms that necessitate precautions or restrictions on treatment. For example, patients with cardiac warning signs (eg., cardiac chest pain, dyspnea, or exertional desaturation) may necessitate evaluation or discussion with a cardiologist before the initiation of any physical rehabilitation program.

Lifestyle Interventions: Lifestyle interventions can be helpful for symptomatic management and to promote overall well-being. Normalizing daytime routine and optimizing sleep are important in developing a consistent schedule. Sleep should be consolidated to the evenings with limited or no napping during the day. For those with insomnia or difficulty falling asleep, sleep hygiene strategies should be discussed, including establishing a regular bedtime, maintaining a dark and quiet environment, avoiding screen time before bed, and relaxation techniques.[37] Brain fog and other cognitive symptoms should be managed with a gradual return to cognitive activity and school accommodations when indicated. Priority should be made for children to return to school and accommodations via a medical 504 plan may be needed to work up to tolerating a full school day, such as increased time for tests and homework assignments, limiting nonessential work, and scheduled rest breaks.[15]

Maintaining adequate nutrition and hydration is also important, especially for those with weight loss due to gastrointestinal symptoms and/or altered taste/smell as well as for headache prevention.[38] Olfactory training is commonplace in patients with altered smell and/or taste. This training is being studied in patients with COVID-19 post-viral olfactory dysfunction.[39,40]

For those with orthostatic intolerance, treatments such as increased salt-fluid intake, reconditioning, sleeping in an upright position, physical countermeasure maneuvers, and compression garments are additional lifestyle interventions that can help with symptom management.[41,42]

Pursed lip breathing and other breathing exercises may be recommended for respiratory symptoms and may help augment the aerobic exercise program. By focusing on slow, deep breaths with inhalation typically through the nose and exhalation through the mouth, breathing exercises can serve to strengthen respiratory muscles—particularly the diaphragm.[43]

Physical Therapies and Specific Considerations: Fatigue and exercise intolerance are commonly reported in children with PASC.[44] There are several known benefits of physical activity in overall health and well-being,[45] and recent suggestions that individualized exercise plans may help symptom management in PASC[46] with a combination of aerobic exercise and energy conservation strategies. Premorbid and current levels of physical activity should be assessed in all children with PASC, and specific goals should be determined. Some patients report a "push and crash" cycle, where they participate in an activity when they feel more able and then end up depleting their energy level to a point that leads to a period of worsened fatigue for several hours or even days.[47] In those with post-exertional malaise, pacing and energy conservation strategies should be discussed to avoid exacerbation of fatigue and other symptoms following exercise.[48] Physical activity and exercise should be slowly progressed over time based on individual tolerance. Standardized scales, such as the Borg Rating of Perceived Exertion scale, can be used to estimate the level of exertion in children.[49] In those with orthostatic intolerance, activity can be initiated in more recumbent positions with advancement to upright positions as able.[42] Physical therapy is often helpful to guide patients in exercise progression while understanding symptom limitations.[15] Modifications may be helpful to allow children to participate in preferred sports activities such as limiting time spent in practice/games, focusing on drills that require less aerobic work, incorporating more frequent rest breaks into their schedule, and allowing children frequent access to water and snacks.

Mental Health: Mood symptoms (eg, anxiety, depression, irritability) are commonly reported in children and adolescents with PASC, which has been seen in other diagnoses that are similar and may overlap with PASC (eg, myalgic encephalomyelitis/chronic fatigue syndrome, orthostatic intolerance/postural orthostatic tachycardia syndrome (OI/POTS), and concussion).[50–52] The degree to which mental health symptoms of anxiety and depression is the consequence of PASC pathogenesis itself, secondary to patients' physical symptoms, or due to the general effects of the pandemic (eg, social isolation, loss of loved ones, disruption to routine) is still unknown.[53] Although multiple, if not all, of these effects likely contribute to mood symptoms, a recent study in adults demonstrated that patients with PASC had worse mood and cognitive functioning after SARS-CoV-2 infection, even when compared with controls that had similar pandemic experiences.[54]

Given the potential impact physical symptoms may have on daily functioning and emotional well-being, it is important to screen and address any mood symptoms in children with PASC with an assessment of functioning across a variety of domains. This clinical interview may include questions regarding adjustment to medical

changes, health-related behaviors (eg, sleep, appetite, hydration, physical activity), physical symptom management, premorbid mental health concerns, behavioral concerns, and school concerns. A biopsychosocial framework[55] for assessment and intervention, which recognizes the multiple biological, psychological, and social aspects that contribute to the experience of illness, has been used in pPASC clinics[15] and can be beneficial for patients. As the symptoms of PASC can significantly impact the quality of life and daily activities of children and adolescents, many children benefit from psychotherapy. Identifying a provider who has experience working with individuals with chronic illnesses, such as chronic pain, is advantageous.[15,56]

Case Example: This case is a compilation of multiple patients with PASC designed to represent the most common symptoms and treatments. The patient is a 15-year-old boy who was diagnosed with COVID-19 in December 2021. Previously, the patient had an unremarkable medical history with only a diagnosis of mild intermittent asthma as a younger child. His family reported that he was a competitive athlete, participating in basketball and track practices five to six times a week, and had a robust social life. He earned above-average grades and did not require school accommodations. He self-reported some anxiety about the pressure of school and sports performance before his COVID-19 infection, but it did not reach a clinical level, and he described himself as well-adjusted and passionate about school, his future career, and his athletic activities.

The patient's initial COVID-19 diagnosis was characterized by mild fatigue, sore throat, congestion, and fever (T_{max} 101°F) for one day. He was not hospitalized and did not seek SARS-CoV-2-specific treatment. His acute symptoms resolved within 5 days, but fatigue remained. However, approximately 2 weeks after his initial COVID-19 diagnosis, his fatigue noticeably worsened and started to experience new daily headaches, orthostatic dizziness, nausea, and palpitations.

The patient presented to his PASC clinic approximately 6 months after his COVID-19 diagnosis. At the time of his appointment, he reported ongoing fatigue and headaches that were interfering with full-time school attendance and participation in extracurricular activities. He reported sleeping 10 to 11 hours every night and napping for 1 to 2 hours after school most days of the week and still feeling tired. He was unable to eat more than one meal per day plus snacks due to nausea as well as an ongoing abnormal sense of taste, indicating "everything tastes rotten." He frequently felt as though he was going to "pass out" when making transitions and noticed that his heart races at random times throughout the day. On physical examination, he was pale and tired appearing but otherwise in no acute distress. He had a moderate increase in heart rate when standing (118 bpm from 70 bpm while sitting) during orthostatic vital signs, and the remainder of his examination (cardiac, respiratory, musculoskeletal, skin, abdominal, and neurologic) was unremarkable. On a 6-minute walk test, he ambulated 430 m. For a healthy 15-year-old boy, the average ambulation is 697 ± 74 meters.[57] During psychological consultation, he reported that he was also experiencing significant cognitive dysfunction, noting that it was harder to remember things after he read them and to attend school when there were distractions around him. He also reported headaches that sometimes were exacerbated by reading on electronic screens. As a result, he has been doing school virtually from home for the past 3 months but was still struggling to keep up with coursework. He self-reported anxiety about his performance in school, sometimes resulting in significant difficulty falling asleep or getting started on school assignments. He also vocalized frustration with not being able to perform "at his level" in his sports and questioned if he even wanted to continue competitive sports. He was especially worried about experiencing more episodes of heart palpitations during practices and in the school setting. The

patient also noted frequent anxiety and distress about when he would start to "feel back to normal." On the PROMIS Pediatric Profile-37, both the patient and his mother (via parent proxy) reported clinically elevated fatigue and anxiety scores (scores >1 standard deviation [SD] above the mean) and a clinically low physical functioning/mobility score (>1 SD below the mean).

Case Example Management: Initial recommendations for the patient included increasing fluid intake to a minimum of 80oz of non-caffeinated fluid per day, daily magnesium supplementation (400 mg per day), coenzyme q10 supplementation (initially 100 mg twice daily), as well as twice daily olfactory retraining using four scent groups for a minimum of 12 weeks. He also had not previously been vaccinated against COVID-19, so it was recommended that he receive two doses of mRNA vaccine and a booster to minimize the risk of additional SARS-CoV-2 infection and potential symptom exacerbation in the future. He was also referred to a cardiology/POTS specialist for additional evaluation for POTS/dysautonomia.

The patient received an aerobic exercise prescription that started with 10 minutes of supine exercises activity per day with a titration plan of increasing the total time by 5 minutes per week, and adding walking and aquatic exercises, to a goal of 60 minutes per day, as tolerated without symptom exacerbation the following day. Energy conservation strategies including pacing during routine activities and daily schedule prioritization were discussed.

Providers also identified school accommodations that would permit the patient to return to in-person school while also reducing expectations. He had scheduled rest periods in school, reduced classwork and homework assignments as well as extended deadlines, and was able to work in a quiet/low-light room when needed for examinations. When possible, he was given the option to have printed materials rather than need to use electronic devices to complete assignments. He practiced relaxation and grounding techniques and identified times to practice and use them at home with a psychologist. The psychologist facilitated a discussion about his priorities and helped identify small steps he could take to start engaging in more of the activities that were important to him. Given his clinically elevated anxiety score, a referral for a community therapist was also provided.

Multidisciplinary Care Approach

Given the complex and wide-ranging nature of PASC symptoms and the impact on functioning, a multidisciplinary care team (MDT) approach to evaluation and management of PASC is preferred.[58,59] The MDT model, which has been most widely used and studied in the setting of cancer care, incorporates multiple stakeholders.[60] Beyond anecdotes and logic that support the benefits of streamlined, centralized communication and plan development that is achieved by an MDT, there is some evidence in the literature that supports improved outcomes and patient experiences with complex or rare diagnoses under the care of MDTs.[61–63] However, specialized multidisciplinary clinics for pPASC are not always available to patients; currently, there are fewer than 15 pediatric post-COVID clinics in the United States.[64] It is important to not only expand access to multidisciplinary care clinics for pPASC but also to provide guidance on the multifaceted treatment approaches that can be used by individual providers.

DISCUSSION AND LIMITATIONS

It is important to note that most studies so far have had significant limitations, and it has been difficult to determine the prevalence of different pPASC symptoms, resulting

in a wide range of data reported.[4,12] Many studies have no control groups, low response rates, inconsistent follow-up times, and ill-defined inclusion criteria.[4,12] Large-scale studies, which tend to rely on online surveys, have low response rates and select for patients from higher socioeconomic backgrounds, as they have better access to online technology.[4,12,65] Of note, many of these larger studies omit a portion of patients—some protocols exclude patients when they recover from COVID-19, which can be problematic, as there are numerous cases of pPASC where children recover only to relapse with symptoms in the future.[2] This could lead to an underreporting of prevalence. Conversely, it has been observed that in smaller cohort studies, there may be an overreporting of prevalence, as patients who are referred to or seek out pPASC clinics tend to present with more severe symptoms.[14] Different methods of gathering symptoms can also lead to variation; studies that provide patients with a predetermined list of symptoms to choose from are more likely to have a higher percentage of reported symptoms than, for example, those who have patients self-describe their clinical manifestations.[2,14] More studies need to be done to ascertain a more precise prevalence of pPASC symptoms.

There can be variability in the severity, time course, and individual symptoms that children experience with PASC, making the diagnosis and treatment challenging and possibly underreported in pediatric populations. pPASC symptoms are often missed due to numerous reasons. The symptoms are often nonspecific and encompass a broad differential, leading to misdiagnosis. Sometimes, PASC is not suspected if the patient showed complete recovery from acute illness, therefore leading to overlooking relapsed PASC symptoms. Identifying symptoms in children can be challenging in comparison to adults as well. Children are often not able to articulate or advocate for themselves due to developmental limitations, making it more challenging to interpret their symptoms.[66]

However, studies have found that children are distressed by these symptoms and that PASC can negatively impact children's quality of life and functioning.[15,67] Academic or school performance has been shown to decline in children with PASC.[68] Therefore, it is important to remain vigilant and appropriately screen children for symptoms of PASC after SARS-COV-2 infection. Primary care clinicians should obtain a history of SARS-CoV-2 infection and screen for symptoms of PASC. Although many children will be able to be managed in a primary care setting, those with more severe or refractory disease may benefit from coordinated, multidisciplinary subspecialty care to address multisystem organ involvement and to provide comprehensive functional rehabilitation.

CLINICS CARE POINTS

- Post-acute sequelae of SARS-CoV-2 (PASC) can occur in children with mild/asymptomatic acute symptoms; primary care physicians should screen for PASC symptoms in children with a history of SARS-CoV-2 infection.
- PASC is a complex multisystemic disease that affects the physical, mental, and social well-being of patients' lives; a multifaceted treatment approach is important in improving the quality of life of patients.
- Lifestyle interventions are key methods for managing pPASC, as there is not yet known curative treatment. Providers should prioritize helping patients develop daily routines and advocate for school accommodations. Other symptom-specific interventions, such as establishing good nutrition habits, olfactory training, orthostatic intolerance interventions, and breathing exercises may be beneficial.

- Physical rehabilitation and therapy are essential in improving the overall health and well-being of PASC patients. Treatment plans based on individualized tolerance are critical to avoid "push and crash," where patients experience prolonged worsened fatigue or other symptoms after activity.
- Mood symptoms and physical symptoms in tandem impact the experience of illness in PASC patients—screening for mood symptoms in all PASC patients is important in developing tailored treatment approaches to improve patients' quality of life.

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