**KARAMUS, Kornelia, REJAMAK, Rafał, BIŁOGRAS, Jan, BOROWSKA-ŁYGAN, Martyna, STRUŻEK, Konrad, URBAN, Wojciech and TOMASZEWSKI, Jakub. Long-Covid in Children and Adolescents: Clinical Challenges and Treatment Perspectives. Journal of Education, Health and Sport. 2025;77:56640. eISSN 2391-8306.**
**https://doi.org/10.12775/JEHS.2025.77.56640**
**https://apcz.umk.pl/JEHS/article/view/56640**

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu). 
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 05.12.2024. Revised: 02.01.2025. Accepted: 03.01.2025. Published: 03.01.2025.

# Long-Covid in Children and Adolescents: Clinical Challenges and Treatment Perspectives

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# Abstract

**Introduction:** Long COVID is a complication of the coronavirus disease. As a relatively new medical condition, it presents challenges in establishing consistent principles for its classification, diagnosis, and treatment.

**Objective:** The aim of this paper is to review the current knowledge regarding the new medical condition known as Long COVID in children.

**Materials and Methods:** The review includes works published between 2020 and 2024, available in the PubMed database, identified using relevant keywords, as well as the WHO publication *"World Health Organization. A clinical case definition for post COVID-19 condition in children and adolescents by expert consensus, 16 February 2023."*

**Results:** The literature review revealed that Long COVID is a relatively common issue, affecting up to 25.24% of children and adolescents. Identified risk factors include age over 10 years, severe primary infection, MIS-C, female gender, allergic diseases, obesity, living in polluted areas, comorbidities, poor physical and mental health, and prior respiratory infections. The spectrum of LC symptoms is broad and includes many nonspecific manifestations. The diversity of symptoms complicates diagnosis and necessitates a more holistic approach to patient care. Treatment of LC in children also poses a challenge. Most available studies focus on adults, with limited reports suggesting the efficacy of lactoferrin in managing gastrointestinal symptoms of LC in children. Physical activity is also suggested as an effective rehabilitation method for addressing reduced physical capacity and chronic fatigue.

**Conclusions:** There is an urgent need for large-scale studies on the risk factors, causes, symptoms, and treatment of LC in children and adolescents. Developing cohesive guidelines would improve patients' quality of life, facilitate diagnosis, and streamline treatment processes.

**Keywords**: pediatric; long-covid; post covid-19, after covid complication, children, long-covid treatment

# Introduction

Coronavirus disease is caused by the SARS-CoV-2 virus. In children, the course of the illness is typically milder than in adults; however, it carries a risk of serious complications [1,2]. The term "long-Covid" (hereafter referred to as LC) was first used on social media to describe symptoms persisting for weeks or even months following SARS-CoV-2 infection [3]. The World Health Organization (WHO) defines LC based on the Delphi consensus: LC is a condition occurring after Covid-19 in individuals with probable or confirmed SARS-CoV-2

infection, typically three months after the onset of symptoms, with symptoms lasting at least two months and not explainable by an alternative diagnosis [4].

Available research on LC is predominantly focused on adult populations. However, there is a significant lack of comprehensive studies conducted in pediatric populations [1]. This article aims to explore the risk factors, causes, symptoms, and the treatment of LC.

# Risk Factors

LC is characterized by a relatively high prevalence. A meta-analysis conducted by Zheng et al. revealed that LC symptoms can occur in up to 25.24% of children and adolescents who survived a Covid-19 infection. Identifying risk factors is crucial for distinguishing groups of patients requiring regular health monitoring [5].

Studies have shown an increased frequency of LC in children aged over 10 years [5,6], those with severe primary disease courses [5,6,8], and those affected by MIS-C (Multisystem Inflammatory Syndrome in Children) [5]. Higher LC risk was also observed in children with allergic diseases, including allergic rhinitis [5,7,8], obesity [8], a history of respiratory system diseases [8], poor mental or physical health [5], comorbid conditions [8], female gender [5,8], and residence in polluted areas [7].

Interestingly, a study conducted at the Department of Pediatrics, Nutrition, and Metabolic Disorders at the "Memorial-Children's Health Institute" in Warsaw demonstrated that children with immunodeficiencies were less likely to develop LC compared to healthy children [9].

# Causes of LC

The causes of LC are not fully understood. Numerous hypotheses suggest possible pathophysiological mechanisms underlying the development of LC. An article published by Ortona and Malorni outlines several potential causes of LC. The authors propose that organ damage resulting from an excessive inflammatory response during the infection could lead to LC. Another explanation might involve SARS-CoV-2 virus reservoirs in organs that reactivate after a certain period. Additionally, researchers have suggested potential causes such as hemostatic disorders, autoimmunity due to molecular mimicry of the virus, and alterations in the host microbiome [10]. Another study, known as the Mount Sinai–Yale Long COVID Study, highlights a connection between LC and the reactivation of herpesviruses (e.g., EBV, VZV), particularly Epstein-Barr Virus (EBV) [11].

Moreover, higher levels of IL-6, IL-1, and D-dimers have been observed in individuals with LC. The virus also exhibits an affinity for the endothelial ACE2 receptor, which triggers the coagulation cascade and increases the risk of thrombosis [11,12,13].

# Symptoms

The symptoms of Long COVID (LC) in children are similar to those reported by adults and affect multiple organs and systems. A study conducted in the Netherlands demonstrated that 92% of patients diagnosed with LC experience limitations in daily functioning due to the disease, and 29% required multidisciplinary care [14].

The complaints reported by pediatric patients are nonspecific and can also be observed in other infections and childhood diseases. The World Health Organization (WHO) provides a list of symptoms to consider when diagnosing LC in pediatric patients (the percentages in parentheses refer to the frequency of symptoms based on meta-analyses by Pellegrino et al. and Lopez-Leon et al.): cognitive impairments (6.27%), cough (3.8%), dyspnea (2–57.1%), chest pain (1.3–51%), diarrhea (1.68%), dizziness (4.4%), ear pain and tinnitus (3.41%), fever (1.87%), headache (3.5–80%), insomnia (8.42%—average frequency of sleep disorders), joint pain and swelling, muscle pain (combined muscle and joint pain 0.7–66%), light sensitivity, eye pain (ophthalmological disorders overall 3.00%), loss of appetite (6.07%), mood swings (16.5%), nausea (1.53%), heart palpitations (1.27%), rash (skin lesions overall 2.61%), abdominal pain (2.91%), sore throat (2.47%), postural disorders (musculoskeletal symptoms other than pain 1.72%) [13,15,25].

**Neurological Symptoms**

Among the neurological symptoms of LC, pediatric patients reported the following complaints: anosmia, headaches, loss of taste, muscle pain, sleep disturbances, paresthesia, dizziness, myalgia, and behavioral problems. Most of these symptoms resolved within two years of the initial infection [16].

Another neurological condition described in a case study involved vestibular migraine, as reported by J. Saniasiaya. Both children (a girl and a boy) experienced dizziness accompanied by unilateral or bilateral headaches and photophobia. The symptoms appeared after a Covid-19 infection and persisted for three months in the first case and six months in the second.

- **Case 1 (girl):** Symptoms occurred 3–4 times per week, each episode lasting 20–30 minutes, and resolved with rest.

- **Case 2 (boy):** Symptoms occurred almost daily, lasting 30–60 minutes, and resolved only with analgesics (sometimes requiring an additional dose). Both children also suffered from severe motion sickness.

In the first case, treatment included vestibular rehabilitation, magnesium and riboflavin supplementation, and lifestyle modifications, including adequate sleep, stress avoidance, physical activity, and parental monitoring of screen time and eating habits. The use of analgesics was recommended for occasional relief. During a follow-up visit, the child reported improved quality of life and good symptom control with analgesics.

In the second case, treatment involved the use of flunarizine (5 mg daily), lifestyle adjustments, home-based vestibular rehabilitation, and parental oversight of dietary habits and screen time. The treatment achieved the desired effect, and the patient reported an improved quality of life. Headache episodes occurred only twice a month and subsided after taking painkillers [17].

# Psychiatric Symptoms

It is challenging to determine whether psychiatric symptoms in LC patients result from the infection itself or are adaptive disorders associated with isolation due to illness. In the United States, Tran et al. conducted a retrospective cohort study using the Komodo Healthcare Map database. The study included children aged 3–17 years. The study group comprised patients diagnosed with LC, while the control group consisted of children who had recovered from Covid-19 without developing LC.

Researchers examined each patient for the prescription of antidepressant medications (SSRI, SNRI, TCA, or other antidepressants). The study covered the period from October 1, 2021, to April 4, 2022, and included children for whom the 12-month period after their initial Covid-19 infection fell within this timeframe.

The results of the analysis showed that children suffering from LC have a higher risk of being prescribed antidepressant medications compared to children who had a Covid-19 infection but did not develop LC [18].

# Pulmonary Symptoms

Respiratory system complaints are among the most common issues reported by children suffering from LC. In a meta-analysis conducted by Eun Kyo et al., the most frequently reported respiratory symptoms in children with LC included cough, dyspnea, sore throat, chest pain, and rhinitis [19].

# Cardiological Symptoms

Cardiovascular symptoms in LC include chest pain, heart palpitations, and arrhythmia [1]. Studies on Italian children with confirmed prior SARS-CoV-2 infection revealed an increased risk of chronic deformation and dysfunction of the left ventricle. Researchers suggested that the cause might be chronic myocarditis following the acute phase of Covid-19 [20].

Cardiovascular symptoms often overlap with complaints from the respiratory system. Baldi et al. conducted cardiovascular stress tests on children with LC, with healthy children serving as the control group. The results showed that children with LC exhibited reduced oxygen uptake at peak exertion, abnormal cardiovascular efficiency (based on the oxygen pulse ratio), and a pathological anaerobic threshold (indicating possible ventilatory or vascular pulmonary insufficiency). However, heart rate, respiratory reserve, and oxygen saturation remained normal in both groups [21].

# Gastrointestinal Symptoms

Gastrointestinal symptoms are relatively common among children with LC. The most frequently reported complaints include nausea, abdominal pain, diarrhea, constipation, vomiting, dysphagia, gastroesophageal reflux, and loss of appetite [22,23,24].

There have been reports suggesting that lactoferrin might be an effective remedy for managing LC-related gastrointestinal symptoms. At the Gemelli University Hospital in Rome, two clinical cases of children showed significant improvement after treatment with lactoferrin:

- **Case 1 (6-year-old boy):** The boy experienced gastrointestinal symptoms for 16 weeks after the acute phase of Covid-19. He was treated with high doses of lactoferrin (600 mg/day for 90 days). Diarrhea resolved within two weeks, while other LC symptoms, such as chronic fatigue, gradually subsided over the next two months.
- **Case 2 (11-month-old girl):** The infant had persistent diarrhea following Covid-19 infection (five loose stools daily). She was admitted to the hospital after four weeks of ongoing symptoms. Oral lactoferrin (400 mg/day for 90 days) was administered. Within approximately one week, bowel movements normalized to one stool of normal consistency per day[23].

An observational study was also conducted on children with gastrointestinal symptoms following Covid-19 infection. The treatment protocol involved administering lactoferrin at a dose of 600 mg/day for 90 days in children under 8 years old and 800 mg/day for 90 days in children aged 9–17 years. The study found that six months after the initial infection, children receiving lactoferrin had fewer gastrointestinal symptoms compared to those who did not.

However, this difference was not statistically significant. According to the authors, larger-scale studies would be needed to resolve the ambiguity in the results [24].

# Treatment

Due to the wide variety of symptoms presented by children suffering from LC, an individualized treatment approach is recommended, tailored to the specific symptoms exhibited [2,19]. In March 2024, an international study aimed at standardizing tools for assessing the health status of children and adolescents with LC was published. Based on a literature review and expert voting, several tools were identified for assessing the severity of some symptoms associated with LC. Over half of the experts agreed on the widespread use of the following scales:

- **PedsQL Fatigue Module:** for assessing fatigue,
- **PedsQL Gastrointestinal Symptoms Module:** for gastrointestinal disturbances,
- **PedsQL Cognitive Functioning Module:** for cognitive functioning,
- **EQ-5D:** for physical functioning.

However, consensus could not be reached on tools for evaluating other symptoms [26].

Proposed treatment methods vary significantly depending on the symptoms affecting the child. Studies suggest the effectiveness of high-dose lactoferrin in treating gastrointestinal symptoms associated with LC [1,23,24]. Additionally, research has indicated the positive effects of moderate and gradually introduced physical activity in improving exercise tolerance and treating chronic fatigue [1,27].

There is, however, a far greater number of studies focusing on LC treatment in adults, which may provide guidance in selecting appropriate treatment options for children [2].

# Conclusions

Long-Covid is a disease that poses a significant challenge to modern medicine. In this literature review, we highlighted various risk factors such as severe primary disease course, age above 10 years, history of MIS-C, presence of comorbid conditions, poor physical and mental health, female gender, obesity, and residence in polluted areas [5,6,7,8]. The literature presents several theories to explain the development of LC; however, none fully account for all the symptoms associated with the condition. It seems that the pathophysiology of the disease may be more complex and involve a combination of several proposed mechanisms [10].

LC diagnosis also presents challenges due to the broad spectrum of symptoms that may indicate the disease. The World Health Organization provides a list of symptoms to consider

when diagnosing LC. These include cognitive impairments, cough, dyspnea, chest pain, diarrhea, dizziness, ear pain and tinnitus, fever, headache, insomnia, joint pain and swelling, muscle pain, light sensitivity, eye pain, loss of appetite, mood swings, nausea, heart palpitations, rash, abdominal pain, sore throat, and postural disorders [15].

There is a notable lack of research focused on the treatment of LC in children. Limited reports suggest the potential use of high-dose lactoferrin in managing gastrointestinal symptoms caused by LC [23,24]. Additionally, physical exercise has been suggested as beneficial for alleviating symptoms of chronic fatigue syndrome and improving exercise tolerance [27].

Based on this literature review, we strongly advocate for more extensive research on LC in the pediatric population. There is a need to establish consistent guidelines for diagnosing and treating children and adolescents. Furthermore, advancing research on risk factors and the causes of LC could help reduce its prevalence.

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