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Anti-interferon α-antibodies in pediatric patients with COVID-19 and long COVID

Oksana Boyarchuk ✉, Vita Perestiuk, Tetiana Kosovska, Liubov Volianska

Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ukraine

Abstract

Introduction: The involvement of neutralizing antibodies against type I interferon (IFN-I) in the development of severe coronavirus disease 2019 (COVID-19) in adult patients has been well documented. However, the role of anti-IFN-α autoantibodies, especially non-neutralizing types, remains underexplored, especially in children. Our study aimed to determine the frequency of antibodies against IFN-α in children with COVID-19 and long COVID, as well as their potential role in the development of long COVID.

Material and methods: The study included 78 children aged 1 to 17 years with a documented history of COVID-19 from September 2022 to August 2023. All patients were divided into three groups: hospitalized with COVID-19, hospitalized with long COVID symptoms, and monitored in an outpatient care department for mild COVID-19 or symptoms of long COVID. Human anti-IFN-α antibodies were detected using enzyme-linked immunosorbent assay.

Results: Binding anti-IFN-α antibodies were detected in 2/78 (2.6%) children with COVID-19 of varying severity. One patient with anti-IFN-α antibodies had comorbidities (obesity, allergic rhinitis) and critical COVID-19 pneumonia (SpO_2 – 80%), significant inflammatory changes (neutrophil-to-lymphocyte ratio: 18.8, C-reactive protein: 95.5 mg/l), and a high D-dimer level, and later developed long COVID symptoms. In the second case, COVID-19 in a 13-year-old girl without significant comorbidities was not severe, but leukopenia and lymphopenia were observed. Subsequently, she developed pronounced long COVID symptoms (fatigue, reduced appetite, insomnia, headache, decreased attention, difficulty concentrating, weight loss, tachycardia, dizziness), which persisted for up to 6 months after the acute infection. The detection rate of binding anti-IFN-α antibodies among hospitalized COVID-19 patients was 4%, compared to 25% among patients with severe/critical disease. Among children who developed long COVID symptoms, anti-IFN-α was found in 3.4%.

Conclusions: Further studies in larger cohorts are needed to assess the role of anti-IFN-α antibodies (both neutralizing and non-neutralizing) in the development of long COVID symptoms, to understand their clinical significance, and to examine their dynamics over time.

Key words: COVID-19, type I interferons, long COVID, anti-interferon-α antibodies.

Introduction

Interferons (IFNs) are a group of cytokines that play a crucial role in modulating immune responses and antiviral immunity [1, 2].

They were first described in 1957 by the British scientist Alick Isaacs and the Swiss researcher Jean Lindenmann. Based on their receptor types, IFNs are classified into 3 types: I, II, and III [1]. Type I IFNs (IFN-I) include IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω. Interferon I is produced by plasmacytoid cells, monocytes, and fibroblasts in response to viral infections. Type II IFN includes only IFN-γ, activated by interleukin-12. Type III IFNs consist of IFN-λ1, IFN-λ2, and IFN-λ3. The receptors for IFN-λ are predominantly expressed on epithelial cells, contributing to the protection of mucosal surfaces [3].

Inborn errors in the IFN-I system, as well as the presence of neutralizing autoantibodies against IFN-I, can

Corresponding author

Oksana Boyarchuk, Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, 1 m. Voli, Ternopil, 46001, Ukraine, e-mail: boyarchuk@tdmu.edu.ua

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lead to severe viral infections, including critical coronavirus disease 2019 (COVID-19) [4]. Studies have shown that impaired IFN signaling compromises gut barrier integrity and facilitates the development of severe West Nile virus infection [5].

Autoantibodies against IFN-I may be detected in patients who have received IFN-based treatments (e.g., IFN-α2 or IFN-β) or in individuals with certain inborn errors of immunity that affect immune regulation, such as autoimmune polyendocrinopathy type I (APS-1) [6, 7]. They can also be found in patients with autoimmune diseases, such as systemic lupus erythematosus.

Bastard et al. [2] identified high titers of neutralizing autoantibodies against IFN-α2 and IFN-ω in approximately 10% of patients with severe COVID-19 pneumonia. These patients ranged in age from 25 to 87 years, with the majority being male. In healthy individuals, these autoantibodies occurred in approximately 0.33%, and were not found in patients with mild or asymptomatic COVID-19.

Studies investigating autoantibodies to IFNs in pediatric patients during viral infections are limited [8, 9]. Available evidence suggests that high levels of autoantibodies against IFN-α2 in children and adolescents with multisystem inflammatory syndrome in children (MIS-C), severe COVID-19, or mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are rare but may occur in patients with inborn errors of immunity [8]. Most research has focused on neutralizing autoantibodies, while only a few studies have examined general antibodies against IFN-α in COVID-19 patients.

It remains uncertain whether autoantibodies associated with viral infections, including SARS-CoV-2, play a regulatory role in acute infections or post-infection physiological processes [10].

The presence of natural or therapeutically induced antibodies against cytokines, including anti-IFN-α, can suppress cytokine functions and result in varying degrees of deficiency. It is widely accepted that antibodies against any autoantigen or therapeutic agent are undesirable immune reactions that can influence the course of infectious and autoimmune diseases [11, 12]. Additionally, such antibodies may diminish the pharmacological effects of drugs, particularly exogenously administered cytokines [11]. Non-neutralizing anti-cytokine antibodies may hold clinical significance, but their role in SARS-CoV-2 infection remains unclear [10]. Key uncertainties include the factors that trigger their production and the duration of their persistence over time. Furthermore, the clinical implications of most anti-cytokine antibodies are not well understood.

Autoantibodies and autoinflammation have also been implicated in the development of long COVID [13, 14]. Symptoms of long COVID often overlap with autoimmune diseases. Regarding anti-cytokine antibodies, there was no evidence indicating that they play a role in long COVID development [10]. Identifying biomarkers of autoimmunity is essential for improving the understanding and management of multifactorial disorders, including long COVID.

Our study aimed to determine the frequency of antibodies against IFN-α in children with COVID-19 and long COVID, as well as their potential role in the development of long COVID.

Material and methods

The study included 78 children aged 1 to 17 years with evidence of prior COVID-19 infection between September 2022 and August 2023. Severe acute respiratory syndrome coronavirus 2 infection was confirmed by polymerase chain reaction (PCR; nasal swab), rapid antigen tests, or positive serological analysis. None of the patients included in the study had been vaccinated against COVID-19.

All participants were divided into three groups (Table I): hospitalized due to COVID-19, hospitalized due to symptoms of long COVID, and monitored in an outpatient care department for mild COVID-19 or symptoms of long COVID. Among the participants, two children were diagnosed with MIS-C associated with COVID-19. All children were hospitalized or observed in children's hospitals in Ternopil, Ukraine.

The severity of COVID-19 was assessed according to the World Health Organization (WHO) criteria and categorized as mild, moderate, severe, or critical [15].

After hospital discharge, patients were monitored for long COVID symptoms. Follow-up assessments were conducted using the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)/IP4C Global Pediatric COVID-19 follow-up case report form at 1, 3, 6, and 12 months after discharge. For children under 6 years old, survey responses were provided by their parents. The diagnosis of long COVID was based on the WHO criteria, defined as the persistence or emergence of new symptoms 3 months after the initial SARS-CoV-2 infection, lasting for at least 2 months without an alternative explanation [16].

The quantitative detection of human anti-IFN-α antibodies was performed using the enzyme-linked immunosorbent assay (ELISA) kit: Anti-IFN-α Antibody Human ELISA Kit (Invitrogen, Thermo Fisher Scientific Inc., Vienna, Austria). Antibodies detected by this method are referred to as binding antibodies against IFN-α, which include both neutralizing and non-neutralizing autoantibodies.

Table I. Clinical characteristics of observed children

Characteristic	Hospitalized with COVID-19 (*n* = 50)	Hospitalized with long COVID (*n* = 13)	Outpatient care for COVID-19 or long COVID (*n* = 15)	Total (*n* = 78)
Male [*n* (%)]	29 (58.0)	3 (23.1)*	7 (46.7)	39 (50.0)
Age [years] (Me, range)	12 (1–17)	11 (2–17)	8 (1–15)	8 (1–17)
Without comorbidities [*n* (%)]	23 (46.0)	4 (30.8)	5 (33.3)	32 (41.0)
Comorbidities [*n* (%)]	27 (54.0)	9 (69.2)	10 (66.7)	46 (59.0)
Overweight/obesity [*n* (%)]	9 (18.0)	2 (15.4)	2 (13.3)	13 (16.7)
Allergy [*n* (%)]	12 (24.0)	2 (15.4)	4 (26.7)	18 (23.1)
Heart diseases [*n* (%)]	3 (6.0)	3 (23.1)	0 (0)	6 (7.7)
Digestive system diseases [*n* (%)]	2 (4.0)	0 (0)	0 (0)	2 (2.6)
Nervous system diseases [*n* (%)]	0 (0)	1 (7.7)	2 (13.3)	3 (3.8)
Kidney problem [*n* (%)]	1 (2.0)	1 (7.7)	2 (13.3)	4 (5.1)
COVID-19 severity [*n* (%)]				
Asymptomatic	0 (0)	6 (46.2)	6 (40.0)	12 (15.4)
Mild/moderate	46 (92.0)	7 (53.8)	9 (60.0)	62 (79.5)
Severe/critical	4 (8.0)	0 (0)	0 (0)	4 (5.1)
ICU admission [*n* (%)]	4 (8.0)	1 (7.7)	0 (0)	5 (6.4)
Mechanical ventilation [*n* (%)]	2 (4.0)	0 (0)	0 (0)	2 (2.6)
Long COVID [*n* (%)]	35 (70.0)	13 (100.0)	11 (73.3)	59 (75.6)
Anti-IFN-α antibodies [*n* (%)]	2 (4.0)	0 (0)	0 (0)	2 (2.6)

**p < 0.05 between patients hospitalized for COVID-19 and patients hospitalized for long COVID.*
COVID-19 – coronavirus disease 2019, ICU – intensive care unit, IFN-α – interferon α.

Statistical analysis

Statistical analysis was conducted using STATISTICA 10 software. Qualitative variables were presented as absolute frequencies and percentages. The normality of quantitative variables was assessed using the Kolmogorov-Smirnov test or by examining histograms. Quantitative data are expressed as the median and range where applicable. Categorical variables were analyzed using the χ^2 test. A *p*-value of < 0.05 was considered statistically significant.

Bioethical standards

The study was conducted in compliance with the 1975 Declaration of Helsinki (revised in 2000) and was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University (Protocol No. 70, August 1, 2022). Written informed consent was obtained from all participants (children and their parents).

Results

The general characteristics of the patients included in the study are summarized in Table I. A total of 50 children were hospitalized due to COVID-19, 13 patients were hospitalized for symptoms of long COVID, and 15 children were followed up on an outpatient basis for mild COVID-19 or long COVID symptoms. Among the patients hospitalized for long COVID, females predominated (76.9% vs. 23.1%; $p = 0.006$). No significant sex differences were observed in the other groups. The median age of patients was 8 years.

Comorbid conditions were identified in 59% of the studied patients, with no significant differences between groups. The most common comorbidities were allergic conditions (23.1%), including bronchial asthma, allergic rhinitis, food allergies, and atopic dermatitis, followed by overweight/obesity (16.7%). Other comorbidities, such as heart diseases, kidney disorders, digestive and nervous system diseases, were less common (Table I).

Asymptomatic COVID-19 was observed in 12 children (15.4%). Among children who later developed long COVID symptoms, 20.3% had no COVID-19 symptoms. The diagnosis of long COVID in these cases was based on the presence of persistent symptoms, positive serological tests for COVID-19, and the exclusion of other causes of the patient's symptoms.

Mild to moderate disease severity was observed in the majority of patients across all groups, accounting for

79.5% of cases. Severe and critical COVID-19 occurred in four patients hospitalized due to COVID-19, two of whom required non-invasive mechanical ventilation.

Among the examined children, only 2 (2.6%) were found to have anti-IFN-α antibodies. The first case involved an 11-year-old boy with comorbidities, including obesity (body mass index 25.2; 98th percentile) and allergic rhinitis. He experienced a critical course of COVID-19 pneumonia. The boy was admitted to the hospital on December 30, 2022, in a severe condition, presenting with respiratory distress. His oxygen saturation was 80% on room air, with a respiratory rate of 50 breaths/min and a heart rate of 120 bpm. The illness had started a week before admission, and despite outpatient treatment, no improvement was noted. He was subsequently hospitalized in the intensive care unit (ICU) and required non-invasive mechanical ventilation for 24 hours.

On admission, a complete blood count revealed leukocytosis (17.73 × 10^9/l), neutrophilia (86%) with a left shift in the neutrophil count (14% band neutrophils), lymphopenia (9.8%), and a neutrophil-to-lymphocyte ratio (NLR) of 8.8. The platelet count was 159 × 10^9/l, and the erythrocyte sedimentation rate (ESR) was 16 mm/h. During the initial days of treatment, leukocytosis persisted, neutrophilia increased to 94%, and lymphopenia worsened (0.82 × 10^9/l), with the NLR rising to 18.8, ESR increased to 33 mm/h, C-reactive protein (CRP) was elevated at 95.5 mg/l, and the D-dimer level was 6.7 µg/ml (normal range: ≤ 0.5 µg/ml).

The boy received antibacterial therapy with ceftriaxone and amikacin, along with dexamethasone (8 mg, equivalent to 1 mg/kg of prednisone). On the third day of hospitalization, his condition improved, and he was transferred from the ICU to the pulmonology department, where he continued his treatment.

After discharge from the hospital, the boy experienced fatigue, reduced activity, tachycardia, chest pain, abdominal pain, and a need for frequent rest. Cardiovascular examinations, including ECG and echocardiography, revealed no significant abnormalities. However, chest pain, intermittent abdominal pain, and tachycardia persisted for up to 2 months following COVID-19, while fatigue and reduced activity lasted up to 6 months after the infection. Given the presence of symptoms lasting more than 2 months after COVID-19 and the absence of other identifiable causes, the boy was diagnosed with long COVID.

The second case involved a 13.8-year-old girl hospitalized with a fever, sore throat, and general weakness. Coronavirus disease 2019 was confirmed by PCR testing. Her medical history included allergic rhinitis. A complete blood count revealed anemia (Hb 110 g/l), leukopenia (3.21 × 10^9/l), and lymphopenia (0.62 × 10^9/l).

After recovering from COVID-19, the girl exhibited persistent symptoms, including fatigue, loss of appetite, insomnia, headaches, difficulty focusing, impaired concentration, weight loss, tachycardia, and dizziness. These symptoms persisted for more than 3 months, leading to a diagnosis of long COVID. No other potential causes of the presence of anti-IFN-α antibodies were identified, such as the use of IFN-based antiviral therapies, immunoglobulin treatments, or evidence of autoimmune diseases.

Among children who developed long COVID symptoms, anti-IFN-α antibodies were detected in 2 out of 59 children (3.4%). Among the 19 children who did not develop long COVID symptoms, no anti-IFN-α antibodies were detected; however, the difference was not statistically significant (p = 0.4162).

Discussion

Our study demonstrated that anti-IFN-α antibodies can be detected in children. While the overall prevalence of these antibodies in the population of children with current or past COVID-19 was 2.6%, their prevalence in children with severe/critical COVID-19 was significantly higher, reaching 25%. Anti-IFN-α antibodies were detected in 3.4% of children with long COVID, although the difference compared to those without long COVID symptoms was not statistically significant.

In the first case, anti-IFN-α antibodies were identified in a patient with comorbidities (obesity and allergic rhinitis) and a critical course of COVID-19 pneumonia (SpO_2 – 80%), characterized by pronounced inflammatory changes (NLR of 18.8, CRP – 95.5 mg/l), and an elevated D-dimer level. This patient subsequently developed long COVID symptoms, including fatigue, reduced activity, tachycardia, and chest pain.

In the second case, the course of COVID-19 was not severe in a 13-year-old girl without significant comorbidities. However, she presented with leukopenia and lymphopenia during the acute phase of the infection. Over time, the patient developed persistent long COVID symptoms, including fatigue, reduced appetite, insomnia, headaches, difficulty concentrating, impaired focus, weight loss, tachycardia, and dizziness, which lasted up to 6 months after the acute infection.

Although the occurrence of life-threatening COVID-19 pneumonia has been most commonly associated with impaired IFN-I immunity due to genetic variants or the production of neutralizing autoantibodies (auto-Abs) in adults, such impairments can occur in patients of all ages [17]. Among a cohort of 168 pediatric patients with severe COVID-19, 199 with MIS-C, and 45 with mild SARS-CoV-2 infections, only one had high levels of anti-IFN-α2 antibodies [8]. In our cohort, there were only two

children with MIS-C, and neither of them had IFN-I autoantibodies.

At the same time, a high percentage (24%) of autoantibodies neutralizing IFN-I was noted in vaccinated adult patients with "breakthrough" cases of critical COVID-19 pneumonia [18]. Another study reported that 38% of ICU patients with COVID-19 pneumonia were positive for auto-antibodies neutralizing IFN-I. Of these, only 5% had auto-antibodies neutralizing IFN-α2 at any concentration, while 33% had auto-antibodies neutralizing only IFN-ω at lower concentrations [19]. Patients with auto-antibodies experienced more severe COVID-19, including a higher occurrence of renal failure, extracorporeal membrane oxygenation support, and prolonged mechanical ventilation and ICU stays, although mortality was similar to those without auto-antibodies.

Anti-IFN antibodies are believed to preexist in certain individuals rather than being generated in response to infection. Their presence underscores their potential to worsen the severity of common infections by neutralizing IFN and disrupting downstream antiviral signaling pathways [2].

A study conducted in Italy [20] assessed both autoantibodies to IFN-α using the ELISA and the presence of neutralizing antibodies against IFN-I. Autoantibodies were detected in a significant percentage of patients with COVID-19, showing fluctuations over time and associations with biochemical and hematological parameters. Specifically, anti-IFN-α antibodies were found in 7.5% of adult COVID-19 patients, while neutralizing anti-IFN-α antibodies were observed in 3.6%. Both types of antibodies were more prevalent in males and individuals over 60 years of age. Additionally, binding antibodies against IFN-α were detected in 28.6%, and neutralizing autoantibodies in 76.9% of patients admitted to the ICU. Neutralizing anti-IFN-I antibodies were associated with higher levels of CRP, lactate dehydrogenase, D-dimer, and altered hematological parameters, consistent with the findings of our study.

Considering that our study specifically identified autoantibodies against IFN-α, and comparing our findings with data from Italian researchers [20], it can be hypothesized that in the first case, the increase in autoantibody levels against IFN-α could also include an increase in neutralizing autoantibodies. This is supported by the severe course of COVID-19 pneumonia, high CRP levels, elevated D-dimer, and an increased NLR. Researchers have noted that neutralizing autoantibodies against IFN-I are associated with elevated leukocyte, neutrophil, and platelet counts, as well as low lymphocyte counts, all of which are linked to severe COVID-19 [20, 21].

A recent study examining nasal IgA1 autoantibodies against IFN-α found their presence in over 70% of mild and moderate COVID-19 cases at the onset of infection [22]. These autoantibodies followed the peak production of IFN-α and decreased with recovery, indicating a regulated balance between the response to IFN-α and the response against IFN-α. Nasal autoantibodies were associated with robust immunity against SARS-CoV-2, fewer symptoms, and effective recovery, suggesting a protective role in the immunopathology of COVID-19.

In contrast, systemic IgG1 autoantibodies against IFN-α appeared later and were detected only in a subgroup of patients with heightened systemic inflammation and worsening symptoms.

Our study demonstrated that anti-IFN-α antibodies were detected in patients with long COVID; however, the lack of statistical significance compared to fully recovered patients casts doubt on the role of these antibodies in the development of long COVID in children. Other studies investigating the role of autoantibodies against IFN-I in the adult population also largely support the view that their role in the development of long COVID symptoms is unlikely [23–25].

For instance, one study detected IFN-α2 antibodies in 2 out of 215 adult participants with convalescent SARS-CoV-2 infection, including 121 patients with long COVID (1.6%) [23]. This finding showed no significant difference compared to the general population prevalence of these antibodies, which ranges from 0.17% to 1.1% in individuals under 70 years of age and up to 4% in those over 70 years [2].

A Danish study, which included 279 patients with long COVID and 94 adults with prior mild SARS-CoV-2 infection who did not develop long COVID symptoms, showed that 5 adults with long COVID (1.8%) and 3 of the controls (3.2%) had IFN-I autoantibodies [24].

A study conducted in Germany among 128 patients with post-COVID conditions and 38 asymptomatic patients assessed the presence of antibodies against IFN-α, IFN-β, and IFN-ω. It found that 1.56% (2/128) of patients with post-COVID conditions were positive for binding autoantibodies against IFN-β, though with no neutralizing activity. None of the participants had antibodies against IFN-α. According to the authors, this indicates a limited role of IFN-I in the pathogenesis of post-COVID syndrome. Additionally, an evaluation of IFN-stimulated gene activity showed no correlation with fatigue, suggesting that impairment of the IFN-I system is unlikely to be responsible for post-COVID syndrome in adults [25].

Thus, our study, one of the few that has assessed autoantibodies against IFN-α in children, demonstrated that these antibodies can be detected in 25% of children with severe or critical COVID-19, as well as in patients with milder disease who later developed symptoms of long COVID. Clearly, the role of autoantibodies against

IFN-α, including neutralizing autoantibodies against IFN-I, in the development of long COVID symptoms requires further investigation in larger patient cohorts. Furthermore, the differential detection of anti-IFN-α antibodies in children with varying disease severity highlights the complexity of immune responses to SARS-CoV-2 in pediatric populations. The fact that we found antibodies in children with mild COVID-19 who developed long COVID symptoms is particularly noteworthy, as it suggests that even mild cases may involve an altered immune response that can predispose to prolonged symptoms. This finding underscores the need for careful long-term monitoring of children following COVID-19, even after recovery from the acute phase.

Identifying IFN-α antibodies could serve as a biomarker for predicting severe disease and guiding therapeutic interventions [2, 4, 9]. Potential strategies include monitoring patients with severe COVID-19 or symptoms of long COVID for the presence of these antibodies. Early detection could prompt adjustments to clinical management, such as tailored use of immunomodulatory treatments or antiviral agents. Moreover, given the reported persistence of anti-cytokine autoantibodies in other diseases [5], long-term follow-up and immune surveillance might be warranted to assess their impact on health outcomes and susceptibility to future infections.

Emerging therapeutic approaches aimed at neutralizing autoantibodies against IFNs or modulating immune responses may hold promise for improving outcomes in affected patients. Continued research is necessary to explore these possibilities and refine personalized treatment strategies.

Study limitations

A limitation of our study was the ability to identify only binding antibodies against IFN-α without distinguishing neutralizing autoantibodies. Additionally, we did not measure the presence of autoantibodies before COVID-19 or several months after the infection. Nonetheless, our research is among the few that have investigated autoantibodies against IFN-α across different pediatric age groups, in children with COVID-19 of varying severity, and in patients with symptoms of long COVID.

Future studies will help determine the persistence of these autoantibodies during long-term observation and their impact on the recovery of patients with COVID-19. They will also assess their concentration in other viral infections, such as influenza.

Conclusions

Binding anti-IFN-α antibodies were detected in 2.6% of children with a history of COVID-19 of varying severity. The detection rate was 4% among hospitalized COVID-19 patients and 25% among those with severe or critical COVID-19. Anti-IFN-α antibodies are unlikely to play a significant role in the development of long COVID symptoms, despite being detected in 3.4% of patients with long COVID and none of the fully recovered patients, as the difference was not statistically significant.

This study underscores the importance of further research to distinguish between binding and neutralizing autoantibodies against IFN-α, as well as to understand their clinical significance, dynamics over time, and their potential impact on the development of long COVID symptoms.

Disclosure

Conflict of interest: The authors declare no conflict of interest.

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Ethics approval: The study was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University (Protocol No. 70, August 1, 2022).

Data availability: The data that support the findings of this study are available on request from the corresponding author (O.B.).

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