



Review Article



Severe Acute Hepatitis of Unknown Origin in Children: What Do We Know Today?

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Abstract

In May 2022, the UK International Health Regulations National Focal Point notified World Health Organization of 176 cases of severe acute hepatitis of unknown etiology in children under 10 years of age. From that moment on, cases of severe acute hepatitis of unknown origin in children began to be reported in several countries. As of June 17, 2022, a total of 991 cases had been reported in 35 countries worldwide, 50 children needed a liver transplant and 28 patients died. According to information published by ECDC, 449 cases have been detected in 21 EU countries. The children were between 1 month and 16 years of age. Adenovirus was detected in 62.2% of the analyzed samples. So far, the cause of these cases is unknown and many hypotheses remain open, but hepatitis A–E viruses and COVID-19 vaccines have been ruled out. A possible hypothesis has been published to explain the cause of these cases of severe hepatitis, according to which it could be a consequence of adenovirus infection in the intestine in healthy children previously infected with SARS-CoV-2. No other clear epidemiological risk factors have been identified to date. Thus, at this time, the etiology of the current cases of hepatitis remains under active investigation.

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Introduction

On April 5, 2022, the United Kingdom (UK) International Health Regulations (IHR) National Focal Point notified the World Health Organization (WHO) of 10 cases of severe acute hepatitis of unknown etiology in previously healthy

children under 10 years of age in Scotland. The age of the children ranged from 11 months to 5 years. Nine cases had symptom onset during March 2022, and one had an earlier onset in January 2022. Symptoms included jaundice, diarrhea, vomiting, and abdominal pain. All 10 cases were detected while the patient was hospitalized. After initiating a nationwide investigation, by April 8, 2022, a total of 74 cases meeting the case definition had been identified in the UK.¹ As per the case definition, severe acute hepatitis was present with high levels of aminotransferases, i.e. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >500 IU/L. It is thus likely that there have been patients with milder cases of hepatitis that have not been reported. The clinical syndrome in the identified cases is acute hepatitis with very high transaminases, often with jaundice, and sometimes preceded by gastrointestinal symptoms. Some cases required transfer to specialized pediatric liver units and six children required liver transplantation. No child was reported to have died. On May 6, 2022, the UK published technical briefing, "Investigation into acute hepatitis of unknown etiology in children in England," that described 163 cases, 11 of which required liver transplantation and no deaths at that time.² From that moment on, cases of severe acute hepatitis of unknown origin in children began to be reported in several countries (Fig. 1). The latest report published by the UK Health Safety Agency indicates that there have been 260 cases, 12 of which required liver transplantation and no deaths.³

Epidemiology

Worldwide, as of June 17, 2022, a total of 991 cases had been detected by the WHO, Centers for Disease Control (CDC), and the European Center for Disease Prevention and Control (ECDC) that were detected in 35 countries. Fifty children required liver transplantation and 28 died. Eleven deaths occurred in the United States (USA), seven in Indonesia, seven in Brazil, one in Mexico, one in Ireland, and one in Palestine (Fig. 2).^{4–8}

According to information published by the ECDC,^{9–11} 449 cases have been detected in 21 EU countries, the UK, Austria, Spain, Sweden, Portugal, Belgium, Denmark, France, Ireland, Italy, Germany, Latvia, Moldova, Netherlands, Norway, Serbia, Slovenia, Poland, Romania, Greece, and Cyprus. The remaining cases were detected in Argentina, Brazil, Canada, Costa Rica, Mexico, Panama, Puerto Rico, Indonesia, Israel, Japan, Palestine, Singapore, Malaysia,

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Abbreviations: CDC, Centers for Disease Control; ECDC, the European Center for Disease Prevention and Control.

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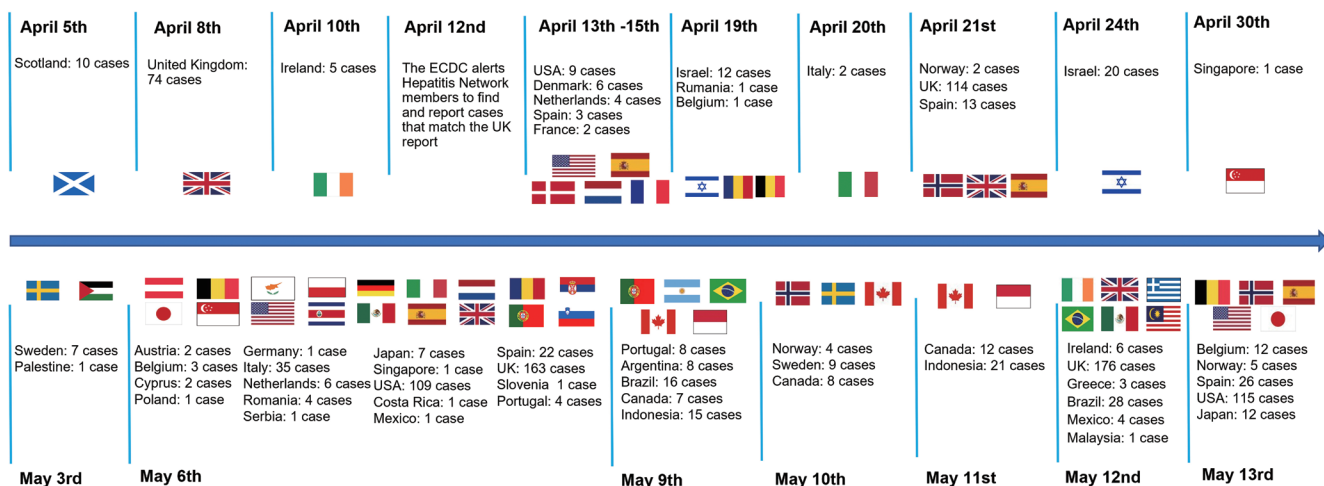


Fig. 1. Timeline of reported cases of hepatitis of unknown origin in children from April 5 to May 13.

South Korea, and the USA (Table 1).

The cases reported in the European Union included children between 1 month and 16 years of age. The majority (76.6%) were under 5 years of age, 31.2% were admitted to the intensive care unit and 8.4% received a liver transplant. There was one death associated with this disease. Adenovirus was detected in 52.4% of the analyzed samples, and most of the positive samples were whole blood. SARS-CoV-2 PCR assays were positive in 10.6%, and antibodies against SARS-CoV-2 were detected in 63.5%. A total of 85.9% were not vaccinated against COVID-19.⁹⁻¹¹

The clinical syndrome in all identified cases was acute hepatitis with markedly elevated liver enzymes. Many cases reported gastrointestinal symptoms including abdominal pain, diarrhea, and vomiting that preceded presentation with severe acute hepatitis, elevated liver enzyme levels (aspartate transaminase (AST) or alanine aminotransami-

nase (ALT) > 500 IU/L) and jaundice. Most cases did not have fever. Hepatitis is an inflammation of the liver that can be caused by viral infections, alcohol consumption, toxins, medications, and certain other medical conditions. So far, the cause of these cases is unknown, and many hypotheses remain open, but hepatitis A-E viruses have been ruled out. COVID-19 vaccines have also been ruled out, as most of the children are too young and had not been vaccinated. Other possible causes, including other types of coronaviruses, other infections, or environmental causes, are being actively investigated. At this stage the role of the viruses found in some of the cases in the hepatitis pathogenesis is still unclear. No other clear epidemiological risk factors have been identified to date, including recent international travel. Thus, at this time, the etiology of the current cases of hepatitis is still considered unknown and remains under active investigation. Laboratory testing for many infections,

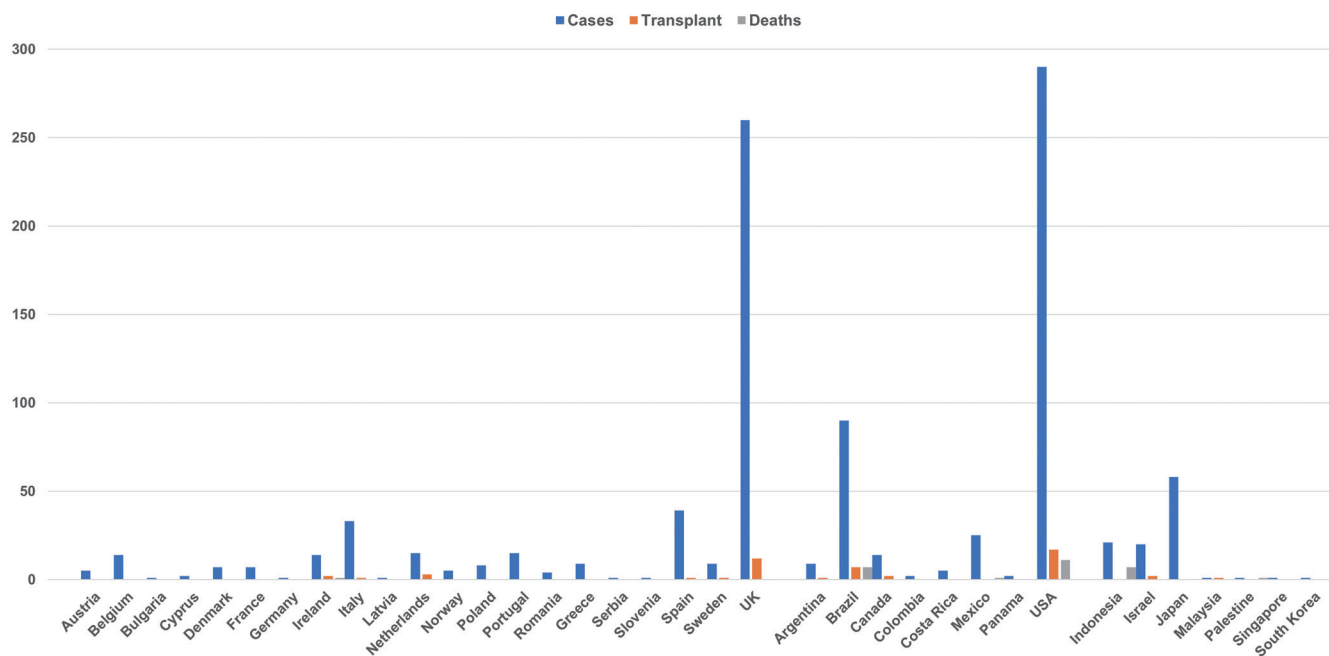


Fig. 2. Worldwide distribution of cases, transplants, and deaths from severe acute hepatitis of unknown origin in children as of June 17, 2022.

Table 1. Summary of reported cases of severe acute hepatitis of unknown origin in children worldwide as of June 17, 2022

Country	Children, n	Reporting age criteria	Reporting protocol time frame	Age of pediatric patients	Transplants, n	Deaths, n	Age at death	Sex	Ethnicity
<i>Europe</i>									
Austria	5			<10 years	0	0			
Belgium	14			≤10 years	0	0			
Bulgaria	1				0	0			
Cyprus	2				0	0			
Denmark	7			6 <10 years and 1 >10 years	0	0			
France	7			<10 years	0	0			
Germany	1			5 years	0	0			
Ireland	14			1-12 years	2	1			
Italy	33			<16 years	1	0			
Latvia	1				0	0			
Netherlands	15			11 months-8 years	3	0			
Norway	5			1-5 years	0	0			
Poland	8			7 years	0	0			
Portugal	15				0	0			
Romania	4			4 years	0	0			
Greece	9	Under 16 years			0	0			
Serbia	1				0	0			
Slovenia	1				0	0			
Spain	39			18 months-16 years	1	0			
Sweden	9				1	0			
United Kingdom	260	Up to 16 years	Since October 2021	2-5 years (median 3 years)	12	0		49% Female	88.2% White
Total	451				20	1			
<i>Americas</i>									
Argentina	9			8 years rec transplant	1	0			
Brazil	90			2 months-16 years (average 6 years)	7	7			
Canada	14	1 month-16 years	Since October 1 2021		2	0			
Colombia	2				0	0			
Costa Rica	5				0	0			

(continued)

Table 1. (continued)

Country	Chil- dren, n	Reporting age criteria	Reporting proto- col time frame	Age of pedi- atric patients	Trans- plants, n	Deaths, n	Age at death	Sex	Ethnic- ity
Mexico	25			< 8 years	0	1	3 years		
Panama	2			≤2 years	0	0			
USA	290	Up to 10 years			17	11	All 10 years		
Total	437				27	19			
Asia									
Indonesia	21				0	7	2		
Israel	20				2	0			
Japan	58			<17 years	0	0			
Malaysia	1	1 month-18 years		4 years	1	0			
Palestine	1			8 years	0	1	8 years		
Singapore	1			10 months	0	0			
South Korea	1				0	0			
Total	103				3	8			
TOTAL	991				50	28			

chemicals, and toxins continues to be performed in the identified cases (Table 2).¹²

The UK has established a case definition and has developed a survey for the investigation of cases that meet the definition, which have been shared by the IHR with the rest of the countries.¹² The provisional confirmed case definition is a person presenting, after January 1, 2022 with an acute hepatitis which was not caused by hepatitis A–E viruses, or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause with serum transaminases >500 IU/L (AST or ALT), and ≤10 years of age. A possible case definition is a person presenting with acute hepatitis after January 1, 2022 with acute hepatitis not caused by hepatitis A–E viruses, or an expected presentation of metabolic, inherited, or genetic, congenital or mechanical cause with serum transaminases >500 IU/L (AST or ALT), who is 11–15 years of age. The Epi-linked case definition is a person presenting after January 1, 2022 with acute non-A–E hepatitis who is a close contact of a confirmed case. To prevent double-counting of cases, a person who is epi-linked but also meets the confirmed or possible case definition is recorded as a confirmed or possible case and the epi-link noted in their medical record.

As far as what we know today about liver biopsies and treatment of some of the children who have suffered from severe acute hepatitis, we have two studies conducted in Israel and in the UK.^{13,14} In the study carried out in Israel, the authors reported five pediatric patients who recovered from COVID-19 and later presented with liver injury. Two types of clinical presentations were distinguishable. Two previously healthy infants 3 and 5 months of age presented with acute liver failure that rapidly progressed to liver transplantation. Their liver explants showed massive necrosis with cholangial proliferation and lymphocytic infiltrate. Three children, two were 8 years of age and one was 13 years of age, presented with hepatitis with cholestasis. Children had a liver biopsy significant for lymphocytic portal and parenchyma inflammation, along with bile duct proliferation. All three were started on steroid treatment. Their liver enzymes improved, and they were weaned successfully from treatment. For all five patients, extensive etiology workup for infectious and metabolic etiologies were negative.¹³

In the study conducted in King’s College Hospital in the UK, the authors describe the course of eight children admitted to pediatric intensive care unit from February to May 2022.¹⁴ The main reason for admission was neurologic deterioration (hepatic encephalopathy) with rising ammonia, lactate, and international normalized ratio. Patients were neuro-monitored with transcranial Dopplers (TCD) and reversed jugular venous saturation. Four patients had abnormal pulsatility index on TCD and six had low reversed jugular venous saturation, with the lowest being 25.9%, that required intervention. They were neuroprotected by early initiation of high-volume continuous kidney replacement therapy (CKRT) with a minimum CKRT dose of 60 mL/kg/h initiated within 24 h of admission, plasma exchange, use of hypertonic saline, noradrenaline to maintain cerebral perfusion pressure, temperature control and thiopentone infusion. All received N-acetylcysteine, and those positive for adenovirus received at least two doses of cidofovir. All eight children survived, with six requiring liver transplantation. One was re-transplanted and two survived without liver transplantation, one of who was delisted after 6 days on the super-urgent list as his clinical and biochemical condition improved.

Histopathology studies of the liver explant and in a few patient biopsies did not find evidence of adenovirus in hepatocytes, but all revealed hepatocyte necrosis and parenchymal collapse. The lack of adenovirus in hepatocytes, but severe liver injury leading to acute liver failure, may

Table 2. Recommended laboratory tests in suspected cases of severe acute hepatitis in children

Sample type	Test	Pathogen
Blood*	PCR	Adenovirus, Enterovirus, CMV, EBV, HSV, Hepatitis A, Hepatitis C, Hepatitis E, HHV6 and HHV7
Blood*	Serology	Hepatitis A, B, C, E, CMV, EBV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available)
Blood	Culture	Standard culture for bacteria/fungi (only if clinically indicated i.e. fever)
Throat swab*	PCR	Respiratory virus panel (including adenovirus/enterovirus/influenza, SARS-CoV-2)
Stool*	PCR	Adenovirus, sapovirus, norovirus, enterovirus. Standard bacterial stool pathogen panel to include <i>Salmonella</i> spp. (or stool culture depending on local test availability)
Blood* (whole blood in EDTA and plasma separated specimens)	Toxicology	Local investigations according to history
Urine*	Toxicology	Local investigations according to history

*Earliest possible sample.

have been related to an aberrant immune response from the host's liver immune system. Detailed characterization of immune infiltrates in the liver of children who progress to liver failure may identify a subgroup that responds to immunosuppression including steroids and avoids liver transplantation.¹⁴

Investigations and main etiological hypotheses

The hypotheses being considered are that this hepatitis may be caused by: 1. An abnormal susceptibility or response of the host to adenovirus, which would cause the adenovirus to progress more frequently to hepatitis because of (a) lack of exposure during the COVID-19 pandemic; (b) prior infection with SARS-CoV-2 (including the Omicron variant) or other infection; (c) coinfection with SARS-CoV-2 or other virus; or (d) toxin, drug, or environmental exposure. (2) Increased frequency of normal adenovirus infections, which highlights a very rare or under-recognized complication. (3) A new adenovirus variant, with or without the contribution of a cofactor; (4) A post-infectious SARS-CoV-2 syndrome (including a restricted effect of Omicron); (5) Drug, toxin or environmental exposure; (6) A new pathogen acting alone or as a coinfection; (7) A new variant of SARS-CoV-2; or (8) SARS-CoV-2 envelope glycoprotein spike acting as a superantigen.

Adenovirus

Adenovirus infection together with other cofactors that would enhance its effect remains the main causal hypothesis. Thus, of all cases reported from the UK that were tested for adenovirus (some identified as adenovirus 41F), 72% were positive. In recent weeks, according to UK respiratory infection surveillance data, the incidence of adenovirus infections has increased significantly compared with previous years, especially in children 1–4 years of age and children 5–9 years of age.¹

Several hypotheses have been proposed to explain how adenoviruses might have changed their pathogenesis to cause hepatitis in healthy children: (1) Lack of exposure to pathogens during the COVID-19 pandemic may have generated an immune deficit in children and rendered them more susceptible to adenovirus infection generating a rarer and more severe condition. (2) Relaxation of restrictions has

generated a massive wave of adenovirus infections, which would allow detection of a rarer outcome of infection. (3) A past infection or coinfection with another pathogen, or exposure to a toxin, drug, or environmental factor, has altered the response to adenovirus infection. (4) Infection with a new adenovirus that is capable of causing severe liver disease in children.

Adenoviruses are common pathogens that typically cause mild respiratory or gastrointestinal symptoms. Adenoviruses 40–41F are among the most frequent causes of viral gastroenteritis in children. In some cases, adenoviruses have been implicated in hepatitis in immunocompromised children and adults, and exceptionally in healthy individuals.^{15–17} In addition, not all children have tested positive for adenovirus, and those who did test positive have often tested positive in only whole blood, and at very low concentrations, with the virus not being detected in liver and plasma samples. Adenoviruses are very common and may only be an incidental finding.

SARS-CoV-2 acting as a superantigen

Recently, a hypothesis to explain the cause of these cases of severe hepatitis has been published, according to which it could be a consequence of adenovirus infection in the intestine in healthy children previously infected with SARS-CoV-2 and carriers of other viruses.^{18,19} There is evidence that SARS-CoV-2 can persist in the gastrointestinal tract. In fact, the virus can be detected in the intestine for a much longer period in children than in adults.² Repeated release of viral protein in the intestinal epithelium would result in activation of the immune system. Specifically, part of the SARS-CoV-2 envelope, glycoprotein S, could act as a superantigen. Superantigens are a class of antigens that cause excessive and uncontrolled activation of the immune system. Specifically, they cause nonspecific (polyclonal) activation of T lymphocytes and massive release of cytokines (small proteins that regulate cell function). If a normal immune system response activates less than 0.001% of T lymphocytes, a superantigen activates up to 20%. Many bacterial toxins or viral molecules can act as superantigens that generate a massive nonspecific immune response that is not directed against a particular antigen or pathogen. Continuous and repeated activation because of adenovirus coinfection, could enhance a multisystem inflammatory syndrome (MIS-C) leading to acute hepatitis in children.

This syndrome appears in a small percentage of children for a few weeks to a few months after the child becomes ill, even if the illness is mild. It is usually quite severe, requiring hospitalization.²⁰ The liver is one of the most frequently affected organs. In fact, 43% of MIS-C cases result in hepatitis. The cause is thought to be impairment of the intestinal barrier, with the virus escaping into the bloodstream and causing inflammation.²¹

Another observation that tends to confirm this hypothesis is the presence in the spike protein of SARS-CoV-2 of a sequence not present in other coronaviruses and resembling another sequence in *Staphylococcus aureus* enterotoxin B that produces toxic shock syndrome.²² It also acts as a superantigen, binding to major histocompatibility complex class II molecules on antigen-presenting cells and to the V β chains of the specific T-cell receptor (TCR).²³ The interaction results in the activation of a large proportion (up to 30%) of T cells and the massive release of proinflammatory cytokines²⁴ that trigger a rapid and potent inflammatory reaction. It has been shown in mice that an adenovirus infection generates hypersensitivity against enterotoxin B.²³ For those reasons, Brodin and Arditi suggest that children with acute hepatitis be investigated for SARS-CoV-2 persistence in stool, T-cell receptor skewing, and interferon gamma (IFN- γ) upregulation, because that would provide evidence of a SARS-CoV-2 superantigen mechanism in an adenovirus-41F-sensitized host.¹⁸

Along the same lines, Nishiura *et al.*²⁵ suggest that prior exposure to the Omicron variant (B.1.1.529) may be associated with an increased risk of severe hepatitis in children, indicating a critical need for cofactor studies. They analyzed the correlation between reported cases of Omicron variant and cases of acute hepatitis in children in 38 Organization for Economic Cooperation and Development countries and Romania between December 1, 2021, and April 27, 2022. Twelve of the 39 countries reported at least one case of hepatitis. The confirmed diagnoses of Omicron cases ranged from 4.4 to 11.9 million between the dates studied. In the remaining 27 countries, the cumulative number of cases of this variant ranged from 0.5 to 5.5 million. For example, a seroepidemiological study published in the US reported that approximately 75% of children were infected with Omicron variant by the end of February. It concluded that countries that reported more cases of this rare condition were those with a higher proportion of the population infected with Omicron.²⁵ According to all the studies that we have to date, episodes of severe acute hepatitis can be explained by a concatenation of two circumstances. (1) A SARS-CoV-2 infection with accumulation of virus in the intestine and outflow viral proteins into the bloodstream because increased intestinal permeability. (2) An adenovirus infection that sensitizes the immune system and causes an over reaction with subsequent liver inflammation. The hypothesis is complex, but whether children with acute hepatitis are carriers of SARS-CoV-2 in the stool, and whether evidence of superantigen-mediated immune activation is found, needs further investigation. If so, early application of immunomodulatory therapies could be considered to prevent liver damage and prevent transplantation. This therapy has been shown to be effective in some cases in Israel and in a case in a 3-year-old girl in the US.^{26,27} On the other hand, if it is proven that the liver damage is directly caused by a virus, treatment with antivirals would be necessary.

For the moment all the hypotheses remain unproven. It is important to know the cause in order to identify cases as soon as possible and to find effective treatments. The lesson we draw from the available evidence is that, faced with such a complex situation, one must keep an open mind to all possible explanations. Unfortunately, the simplest one is not always the correct one.

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Conflict of interest

MTPG has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2016. The other authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (MTPG); analysis and interpretation of data (MTPG, ATP, BSG), drafting of the manuscript (MTPG, ATP, BSG). All authors have made a significant contribution to this study and have approved the final manuscript.

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