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MINIREVIEWS

May 2022 acute hepatitis outbreak, is there a role for COVID-19 and other viruses?

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Abstract

There has been an increasing number of reported cases of acute hepatitis of unknown origin in previously healthy children since first reported on March 31, 2022. This clinical syndrome is identified by jaundice and markedly elevated liver enzymes with increased aspartate transaminase and/or alanine aminotransaminase (greater than 500 IU/L). We conducted an inclusive literature review with respect to acute hepatitis outbreaks in children using the search terms acute hepatitis, outbreak, children, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coronavirus disease 2019 (COVID-19), and adenovirus. According to the cumulative data presented in four main studies, the median age is 4 years, with a male predominance (1.3:1). Jaundice was the most common clinical mani-

festation (69%), followed by vomiting (63%), anorexia (52.9%), diarrhea (47.2%), abdominal pain (39%), pyrexia (33.3%), pale stool (30%), and dark urine (30%). Coryza and lethargy were reported in 16.6%, while pruritus was reported in 2% of cases. Acute liver failure was observed in 25% of cases. The exact mechanism of this acute hepatitis outbreak is still not entirely clear. Adenoviruses and SARS-CoV-2 were detected in a significant number of patients. Coinfection with adenovirus and SARS-CoV-2 could be a possible underlying mechanism. However, other possible infections and mechanisms must be considered in the pathogenesis of this condition. Acute hepatitis of unknown origin in children has been a serious problem since the start of the COVID-19 pandemic but has not yet been sufficiently addressed. Many questions remain regarding the underlying mechanisms leading to acute liver failure in children, and it is likely that extensive future research is needed.

Key Words: Acute hepatitis of unknown origin; Children; Adenovirus; SARS-CoV-2; COVID-19; Hepatic failure

Core Tip: There has been an increasing number of acute hepatitis of unknown origin in children since first reported on March 31, 2022. The exact mechanism of this acute hepatitis outbreak is still unclear. Still, the increased detection rate of adenoviruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may imply a key role for these viruses in the pathogenesis of this childhood condition. Coinfection with adenovirus and SARS-CoV-2 could also play a role, but comprehensive research is still needed to reach an exact mechanism. Until an aetiology is uncovered, the focus should be placed on the prevention of this syndrome in children *via* the use of proper hygiene.

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INTRODUCTION

Since it was first reported on March 31, 2022, in Scotland, and with the recent increase in the reported cases since April 15, 2022, in the United Kingdom, a reason for acute hepatitis of unknown origin in previously healthy children has not been clearly defined. There is speculation as to whether this phenomenon represents a true increase in the number of cases or if it is an inflated statistic due to increased awareness and reporting. By the last week of April 2022, there were 169 cases of acute hepatitis of unknown origin in children aged 1 mo to 16 years reported from 11 countries, including The United Kingdom, Spain, Israel, The United States, Denmark, Ireland, Netherlands, Italy, Norway, France, Romania, and Belgium[1]. By the end of May 2022, the number of reported cases increased to 746, reported from 36 countries in 4 continents, mainly Europe and America (Figure 1)[2].

The clinical syndrome caused by acute hepatitis is identified by jaundice and markedly elevated liver enzymes, with increases in aspartate transaminase (AST) and/or alanine aminotransaminase (ALT) to greater than 500 IU/L. These findings may be preceded by gastrointestinal symptoms such as abdominal pain, vomiting, and diarrhoea. Fever is also reported in a few cases, but most affected children are afebrile. Furthermore, many patients experience more severe complications, such as liver failure[3]. Most hepatotropic viruses that cause acute hepatitis, such as hepatitis A, B, C, D, and E viruses, are not detected in acute hepatitis of unknown origin. About 10% of cases require liver transplantation, with 1 fatal case being reported. Despite most cases being reported from Europe, Israel, and The United States, there is no link between traveling to any specific country and developing the syndrome[4].

The exact mechanism of this type of acute hepatitis outbreak is still not known. However, adenovirus is reported in 74 cases, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 20 cases, and coinfection in 19 cases. Meanwhile, data from The United Kingdom and the Netherlands show an increase in adenovirus infection in the community concurrently with the rise in the number of cases of acute hepatitis of unknown origin[5]. Although there is some evidence for the role of adenovirus with or without SARS-CoV-2 coinfection in the aetiology of this syndrome, other factors, such as immunopathogenesis and non-infection-related factors, could play a role. This review aims to shed light on the understanding of this syndrome[6].

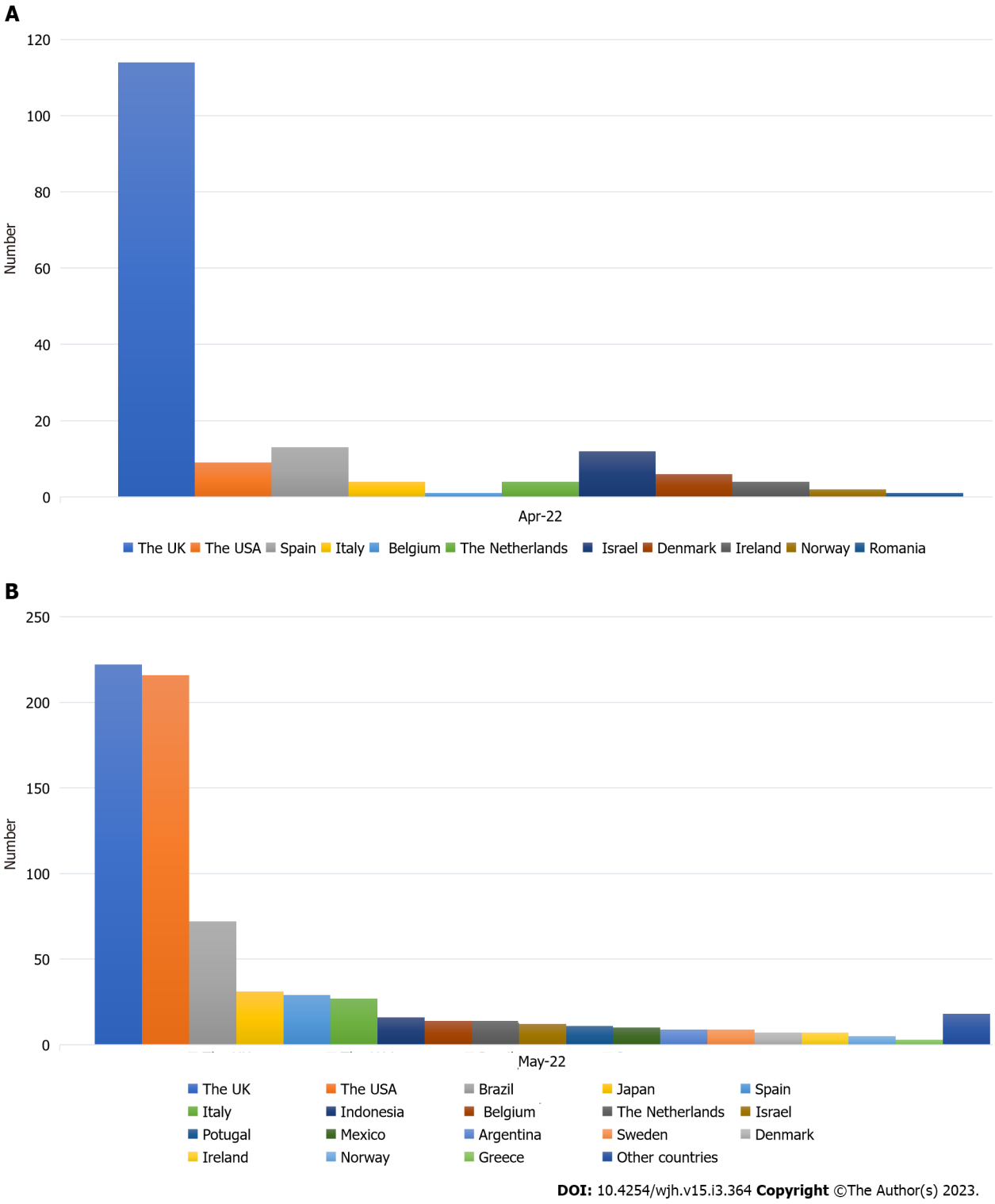

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Figure 1 Reported cases of acute hepatitis syndrome of unknown aetiology in children. A: April 2022; B: May 2022. Apr: April; The UK: The United Kingdom; The USA: The United States of America.

METHODOLOGY

We conducted an inclusive literature review by searching various electronic databases for reports on acute hepatitis outbreaks in children. Databases searched included PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Cochrane Library, Scopus, Library and Information Science Abstracts, Google search, and the National Library of Medicine catalogue. The search included reports published before August 31, 2022. Search terms utilized included acute hepatitis, outbreak, children, SARS-CoV-2, coronavirus disease 2019 (COVID-19), and adenovirus. Reference lists were inspected, and citation searches were also done on the included studies. We included open access papers published in English. Figure 2 shows a flow chart of the reviewed articles.

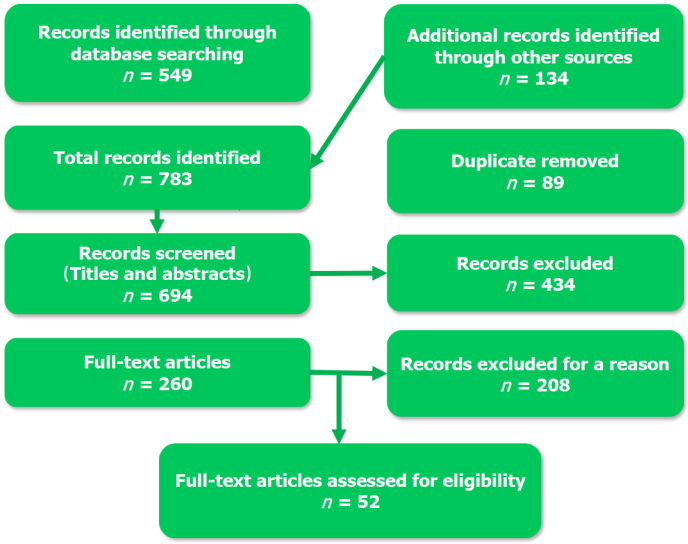

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Figure 2 Flow chart of studies included in this review.

We reviewed 260 articles concerned with acute hepatitis of unknown aetiology outbreaks in children; information from 52 was included in this review.

CLINICAL SPECTRUM OF ACUTE HEPATITIS OF UNKNOWN CAUSE IN CHILDREN

The World Health Organization (WHO) has classified cases of severe acute hepatitis of unknown origin in children occurring during the current outbreak into three categories: (1) Confirmed; (2) Probable; and (3) Epi-linked. As there are no well-defined diagnostic criteria for this clinical entity, the probable case definition is the most widely used. Probable cases are those which present with manifestations of acute hepatitis with elevated serum aminotransferase levels of greater than 500 IU/L and without evidence of infection with hepatitis A-E viruses. The patient population is defined as children aged 16 years or younger as of October 1, 2021, with the youngest reported patient being 1 mo old. An epi-linked case is defined as a patient of any age presenting with acute hepatitis who has had a history of close contact with a probable case since October 1, 2021, and has no evidence of hepatitis A-E virus infection[7]. Three-quarters of reported cases in European countries are younger than age 5, as many studies have been focused on children younger than 10 years[8]. According to cumulative data presented in 4 main studies (2 from The United Kingdom and 2 from The United States), the median age of presentation is 4 years, with a male predominance (1.3:1). Jaundice is the commonlyommon reported clinical manifestation (69%), followed by vomiting (63%), anorexia (52.9%), diarrhoea (47.2%), abdominal pain (39%), pyrexia (33.3%), pale stool (30%), and dark urine (30%). Coryza and lethargy are reported in 16.6%, while pruritus is reported in 2% of cases. Acute liver failure is reported in 25% of these cases. See Table 1 for an overview of these data[9-12].

Kelgeri *et al*[9] found that in 44 cases of childhood acute hepatitis of unknown origin, hepatitis most commonly resolved. However, progression to fulminant liver failure requiring liver transplantation is reported in 14% of these cases. This finding underscores the severity of this condition and emphasizes the importance of recognizing its potential outcomes. In affected children, a prodromal phase is typically indicated by biochemical testing. Ultrasound findings of gallbladder wall thickening, pericholecystic fluid, mesenteric lymphadenopathy, and mild hepatosplenomegaly indicate a potential viral aetiology. If these findings are present, an extensive viral workup is required, especially if infection with an adenovirus is suspected. Laboratory tests essential to the diagnosis of suspected acute hepatitis of unknown origin are summarized in Table 2.

GUT-LIVER AXIS AND HEPATIC DISEASES

The gut microbiome affects various essential processes, including immunological, structural, metabolic, and neurological functions. For this reason, gut microbiome status can considerably impact physical and mental health. The gut is colonized by over 1000 microbial species, a process that starts *in utero* and continues after birth in an ongoing, complex, dynamic manner to promote gut maturation and development[13]. Although the number of microbial species in the gut microbiota of children and

Table 1 Clinical data from various studies, *n* (%)

Ref.	Kelgeri *et al*[9], 2022	Cates *et al*[10], 2022	Marsh *et al*[11], 2022	Baker *et al*[12], 2022	Cumulative data
Demographic data					
Country	UK	USA	Scotland, UK	Alabama, USA	
Number of patients	44	296	13	9	362
Age (yr), median (range)	4 (1-7)	2.2 (0–9.7)	3.9 (3-5)	2 (1.66-5.7)	3 (0-9.7)
Male/female ratio	0.83:1	1.42:1	1.2:1	0.28:1	1.3:1
Clinical findings					
Jaundice	41 (93)	71/123 (57.7)	8/9 (88.9)	8/9 (88.9)	128/185 (69)
Vomiting	24 (54)	76/123 (61.8)	4/4 (100)	7/9 (77.8)	113/180 (63)
Diarrhoea	14 (32)	61/123 (49.6)	4/4 (100)	6/9 (66.7)	85/180 (47.2)
Pale stools	13 (30)	/	/	/	13/44 (30)
Abdominal pain	12 (27)	48/123 (39.0)	7/9 (77.8)	/	69/176 (39)
Lethargy	10 (23)	15/123 (12.2)	4/4 (100)	1/9 (11.1)	30/180 (16.6)
Dark urine	6 (14)	44/123 (35.8)	/	/	50/167 (30.0)
Coryza	6 (14)	20/123 (16.3)	/	3/9 (33.3)	29/176 (16.5)
Pyrexia	4 (9)	51/123 (41.5)	0/4 (0)	5/9 (55.6)	60/180 (33.3)
Pruritus	1 (2)	/	/	/	1/44 (2.0)
Anorexia		65/123 (52.9)	/	/	65/123 (52.9)
Acute live failure	6 (14)	37/123 (30.1)	/	1/9 (11.1)	44/176 (25)

UK: The United Kingdom; USA: The United States of America.

adolescents mirrors that of adult, the relative abundance of species varies. In children and adolescents, there are more abundant *Faecalibacterium spp.*, *Bifidobacterium spp.*, and subspecies of *Lachnospiraceae*[14]. In addition, fungi and viruses are also present in the gut. Virobiota of the gut include bacteriophages that can infect prokaryotic cells, viruses that can infect eukaryotic host cells, and virus-derived genetic particles embedded in host chromosomes; the term "virome" refers to the entire complement of viral genetic elements found in the human genome[15].

In the oro- and nasopharyngeal areas, bacteriophages, coronaviruses, herpes viruses, adenoviruses, respiratory syncytial viruses, picornaviruses, influenza A viruses, and other uncharacterized eukaryotic viruses are frequently encountered. Common gastrointestinal viruses include bacteriophages, adenoviruses, caliciviruses, parvoviruses, picornaviruses, papillomaviruses, astroviruses, plant viruses, and other uncharacterized eukaryotic viruses[16]. Some eukaryotic DNA viruses, such as anelloviruses, herpesviruses, human bocavirus, and adenoviruses, and some RNA viruses, such as picobirnaviruses and parechoviruses can continue shedding for months. For this reason, these viruses form a significant fraction of the typical human virome due to their capacity for persistent infection[17]. Unfortunately, human adenoviruses in the gut can be reactivated and cause persistent infection, leading to serious morbidity and mortality, especially in immunosuppressed patients (*e.g.*, children with hematopoietic disorders)[18].

The liver-gut microbiome axis, which also includes virobiota, is a bidirectional pathway in which portal veins transport gut-derived products directly from the gut to the liver, and bile and antibodies produced in the liver are transported back to the gut (Figure 3). Gut microbiome products preserve the immune homeostasis of the intestine and liver. Conversely, some microbial-derived metabolites such as ethanol, trimethylamine, short-chain fatty acids, and secondary bile acids may play a role in liver disease. Meanwhile, liver diseases such as cirrhosis can induce significant changes to the gut microbiome due to impairment of the vascular, epithelial, and immune barriers of the intestine[19]. Accordingly, gut dysbiosis can induce an abnormal mucosal immune response and lead to homeostatic imbalance. This resulting imbalance causes microbes and immune cells to migrate to the liver, provoking inflammation and associated hepatic injury, and may also influence neoplastic processes[20, 21].

Table 2 Suggested workup in the diagnosis of acute hepatitis of unknown aetiology

Item		Sample test
History		To be taken according to WHO for case definition, probable or confirmed case. History of traveling to high-risk areas endemic to hepatitis viruses, exposure to a local outbreak, household contact, sharing personal items with an infected person, attendance at day-cares, history of transfusion-dependent illness, or exposure to tattoos and/or body piercing using nonsterile techniques
Clinical examination		Low-grade fever, fatigue, anorexia, nausea, vomiting, enlarged and tender liver with/without splenomegaly, jaundice, abdominal pain, dark urine, pale or clay-coloured stool
Liver Functions		Total bilirubin, conjugated bilirubin, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase), albumin, and prothrombin time
Liver biopsy		Staining with haematoxylin and eosin in selected cases
Imaging studies		Usually not required; may be needed to rule out biliary obstruction and other aetiologies for elevated liver enzymes and to exclude complications such as cirrhosis and hepatocellular carcinoma. Abdominal ultrasound: Shows enlarged liver with decreased (acute) or increased (chronic) echogenicity, brighter portal vein, periportal oedema, gallbladder wall thickening, and ascites. CT findings of acute hepatitis are nonspecific: Hepatomegaly, gallbladder wall thickening, periportal oedema, and ascites
Tests for autoimmune hepatitis		Autoantibodies such as ANAs and anti-SMAs
Detecting viral causes of hepatitis	Serology	Antibodies against Hepatitis A-E, Epstein-Barr virus, cytomegalovirus, HIV, varicella, adenovirus, SARS-CoV-2 (anti-S and anti-N antibodies)
	Culture	Blood: Adenovirus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, influenza viruses. Rectal Swab: Adenovirus, rotavirus, enteroviruses
	PCR	Blood: For hepatitis A, C, E, adenovirus, cytomegalovirus, enteroviruses, Epstein-Bar virus, Parechovirus, Herpes simplex virus, HHV 6 and 7. Throat Swab: Respiratory virus screening by multiplex assay (including Adenovirus, Influenza, Parainfluenza, Respiratory Syncytial Virus, Rhinovirus, Human bocavirus 1-3, Human metapneumovirus, Enteroviruses, SARS-CoV-2, *etc.*). Stool: For enteric viruses screening by multiplex assay (including Norovirus, Enteroviruses, Rotavirus, Astrovirus, Sapovirus)
Detecting bacterial causes of hepatitis	Serology	Antibodies against: *Brucella spp., Bartonella henselae, Borrelia burgdorferi* (when epidemiologically appropriate)
	Culture	Blood: Routine procedures for bacterial pathogens, when clinically applicable. Throat Swab: *Streptococcus* group A. Stool: *Salmonella, Shigella, Campylobacter, E. coli* 0157. Urine: Routine procedures for bacterial pathogens, when clinically applicable
	PCR	Stool or rectal swab: Enteric bacterial pathogens. Urine: *Leptospira spp*
Toxicological screening		Blood and urine by different methods, including mass spectrometry: Drugs (*e.g.*, acetaminophen, antibiotics, antiepileptics, herbal medicines) or toxins (*e.g.*, carbon tetrachloride)
Metabolic work-up		Ceruloplasmin; 24 h of urinary copper excretion; Celiac disease screening; Urine organic acid profile; Plasma amino acids; Plasma acylcarnitine; Whole exome and mitochondrial gene examination to rule out other inborn metabolic disorders that can cause liver injury; Other metabolic work-up according to the clinical scenario

ANA: Antinuclear antibody; CT: Computerized tomography; HIV: Human immunodeficiency virus; HHV: Human herpesvirus; PCR: Polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2; SMA: Smooth muscle antibody; WHO: World Health Organization.

ADENOVIRUS HEPATOTROPIC EFFECTS

Adenoviruses are medium-sized, nonenveloped, double-stranded DNA viruses. They are named for their first isolation from the adenoid in 1953. Adenoviruses are widespread viruses that classically trigger mild cold- or flu-like disease, pneumonia, conjunctivitis, and acute gastroenteritis in all age groups throughout the year[22]. Adenoviruses are not typically hepatotropic in immunocompetent children. However, they can still cause hepatitis in children with liver stem cell transplantation, immunosuppressed children (*e.g.*, with severe combined immune deficiency), and children receiving chemotherapy for solid malignant neoplasms.

The species C adenoviruses are the most commonly implicated in adenovirus-associated hepatitis, with type 5 being the most frequently encountered[23]. Furthermore, human species F adenoviruses (*e.g.*, types 40 and 41) are well-known causes of paediatric gastroenteritis. Chhabra *et al*[24] showed that F adenovirus type 41 is more widespread than type 40 in the setting of viral gastroenteritis in children younger than 5 years. Despite mainly causing respiratory infections, adenoviruses can produce transient nonspecific "reactive hepatitis" findings in children during an active infection, with AST and ALT levels used as markers of hepatitis severity[25]. Adenovirus infection can be diagnosed by direct antigen detection (in blood, stool, or respiratory samples), polymerase chain reaction (PCR) amplification, virus culture and isolation, and serology. Specimens are ideally collected within 1 week of symptom onset. Positive serology is expected in most children by the age of 4 years, but a 4-fold or more increase in the titre of adenovirus-specific antibodies is considered evidence of a recent infection. Adenovirus typing

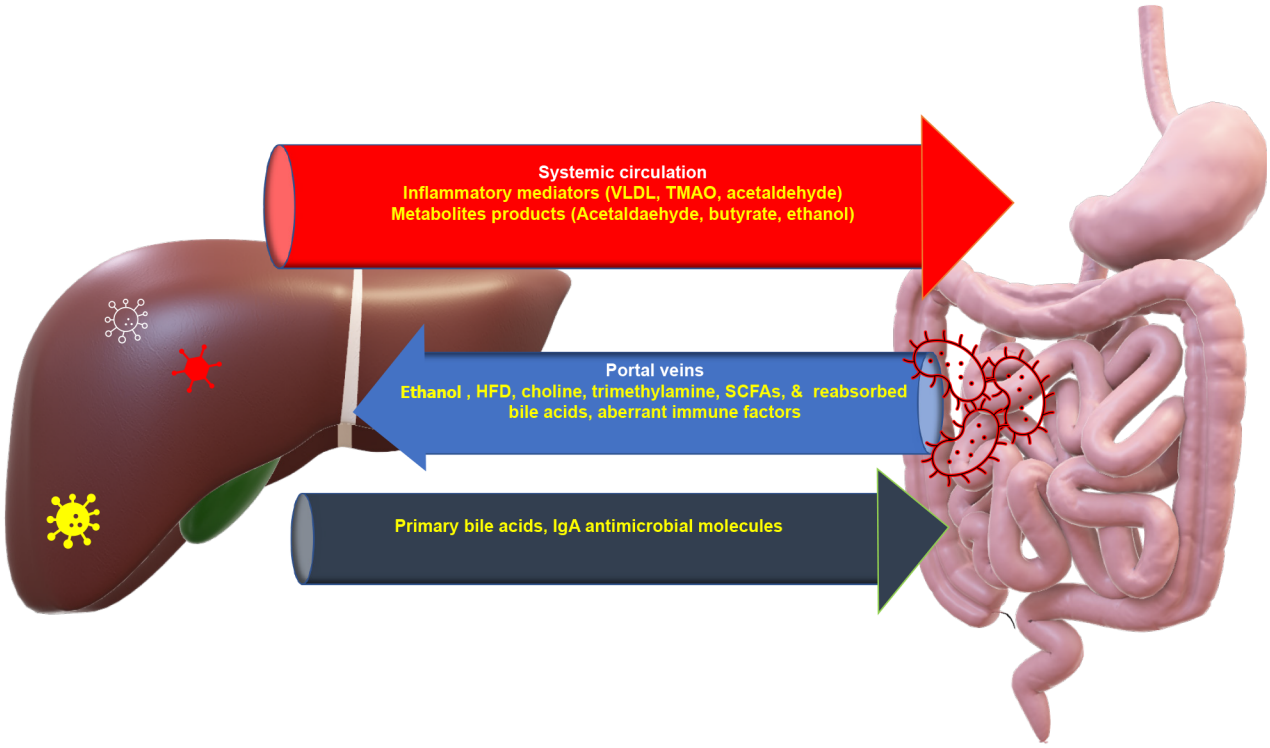

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Figure 3 Gut-liver axis. Mutual effects of the gut and liver through systemic and portal circulation and biliary enterohepatic circulation. HFD: High-fat diet; IgA: Immunoglobulin A; SCFAs: Short-chain fatty acids; TMAO: Trimethylamine N-oxide; VLDL: Very-low-density lipoprotein.

can be performed with molecular tests, and is essential from an epidemiological point of view[26]. When performing adenovirus molecular testing in suspected cases of acute hepatitis of unknown cause, whole blood samples instead of serum or plasma should be used as it has a higher viral yield[12].

Out of 74 cases of acute hepatitis of unknown aetiology with detected adenovirus, 18 patients were identified by molecular tests as serotype F41, and a few others were serotype F40[27]. This finding may indicate that enteric adenoviral infection may be related to hepatic infection by means of the gut-liver axis, a topic that warrants further research[28]. The low viral load in the clinical samples necessitated PCR amplification of part of the viral hexon gene followed by Sanger sequencing for the detection of adenoviruses. However, notably, children presenting with acute hepatic failure had a high viral load. Importantly, there are also intratypic genetic variations in adenoviruses of serotype F type 41[29]. A study at an Alabama hospital in August 2022 showed three different strains of adenovirus serotype F41, observed in 5 patients with acute hepatitis of unknown aetiology. This finding may indicate a low probability with regard to an outbreak being caused by a specific adenovirus serotype[30].

Meanwhile, serotyping data obtained from 4 adenovirus-positive patients in the European cohort showed 2 with serotype F41, 1 with serotype F40, and 1 with a serotype of "other." This supports the potential of adenovirus to negatively affect the liver after reaching it through the gut-liver axis. This adenovirus pathogenicity could be attributed to the development of mutations that promote hepatotropism, but this hypothesis needs to be confirmed by whole genome sequencing to detect any such mutation[28]. Despite being isolated from a significant number of children with acute hepatitis of unknown origin, the exact role of adenoviruses in the pathogenicity of this condition still needs to be confirmed. Infection with adenoviruses is usually mild and resolves spontaneously. However, the infection can be associated with high morbidity and mortality in immunocompromised children, particularly those with allogeneic stem cell transplants. Although adenoviruses have been widely studied, there is currently no anti-adenoviral treatment approved by the United States Food and Drug Administration. As of this review, cidofovir and ribavirin are the only antiviral drugs used as first-line therapy to treat adenoviral infections. Brincidofovir has no nephrotoxicity and has better bioavailability than cidofovir, but this drug is no longer manufactured[31,32].

CORONAVIRUSES HEPATOTROPIC EFFECTS

Despite pulmonary symptoms being the dominant finding in the clinical presentation of COVID-19, SARS-CoV-2 may also affect other organs such as the liver[33]. The liver is affected by 14%–53% of SARS-CoV-2 infections, regardless of preexisting liver disease[34]. SARS-CoV-2 accesses the liver *via*

binding angiotensin-converting enzyme-2 receptors, which are strongly expressed on cholangiocytes, minimally expressed on hepatocytes, and absent on Kupffer cells[35]. COVID-19-associated liver injury could be related to immune-mediated damage with a severe inflammatory response to SARS-CoV-2 infection, direct cytotoxicity due to active viral replication inside the liver cells (Figure 4), COVID-19-associated anoxic liver damage, drug-associated liver injury, or reactivation of preexisting liver infections (*e.g.*, Hepatitis B)[30]. SARS-CoV-2 infection can also activate autoimmune hepatitis *via* systemic immune hyperstimulation, molecular mimicry, or both[31].

Meanwhile, few cases of autoimmune hepatitis have been reported after SARS-CoV-2 vaccination, and those that have been reported all showed complete remission with steroid therapy[36]. Crisan *et al* [37] showed that patients who presented with elevated liver enzymes and abnormal chemistries on arrival were more likely to have worse disease and poorer outcome. The presence of fibrosis in hospitalized patients with COVID-19 is associated with increased mortality. Therefore, regular monitoring of liver function should be standard for all COVID-19 patients, and serological testing for specific hepatotropic viruses (*e.g.*, Hepatitis B or C according to the local epidemiological status) should be strongly considered[38].

Figure 4 shows the effects of COVID-19 infection on the liver, which is first evidenced by increased liver enzymes. The virus reaches the liver from the gut-liver-lung axis, which may be re-shed back to the gut through the bile. These effects are mediated through the impact of hypoxia, systemic venous congestion, immune-mediated hepatic damage by inflammatory mediators induced by SARS-CoV-2 infection, the direct hepatic cytopathic effect of SARS-CoV-2, and the hepatotoxic effects of some medications used to treat SARS-CoV-2 infection such as azithromycin, chloroquine, lopinavir, ritonavir, and tocilizumab. Hepatic damage can also result from SARS-CoV-2 reactivation of pre-existing liver diseases such as hepatitis B or C[39,40].

SYNERGISM BETWEEN SARS-COV-2 AND ADENOVIRUS

Many studies have shown an increased incidence of adenovirus among children infected with SARS-CoV-2. Coinfection with SARS-CoV-2 and adenovirus may also occur. Mohammadi *et al*[41] showed that the rate of SARS-CoV-2 and adenovirus coinfection is 1.1%, and all cases had mild respiratory disease. Another study from The United States showed a 0.4% rate of SARS-CoV-2 and adenovirus coinfection, being the third most common coinfection after rhinovirus/enterovirus and influenza A viruses[42]. Another study from the United Kingdom showed a 2% rate of coinfection with SARS-CoV-2 and adenovirus which increased the odds of death by 1.22[43]. Finally, a study from China found a slightly higher coinfection rate of 2.8%, associated with a worse diagnosis than bacterial coinfection[44].

EPSTEIN-BARR VIRUS AS A POSSIBLE CAUSE

Epstein-Barr virus (EBV) is a member of the herpesvirus family. It causes a heterogeneous group of infections in children and adults with a classic presentation (infectious mononucleosis) or other atypical presentations. Baker *et al*[12] showed that EBV was identified in 6 out of 9 children with acute hepatitis of unknown cause, verified using molecular methods. However, due to the absence of IgM, these cases could represent the reactivation of an old EBV infection and not a primary infection. However, EBV was reported to cause acute hepatitis in adults as well. García-Martínez *et al*[45] reported coinfection of SARS-CoV-2 and EBV in a 19-year-old woman who presented with pyrexia and bilateral eyelid and hemifacial swelling and was found to have splenomegaly, cervical lymphadenopathy, and elevated AST and ALT. In addition, Nadeem *et al*[46] described the reactivation of an EBV infection in a 62-year-old man attributed to coinfection with SARS-CoV-2. This patient was also found to have elevated AST and ALT. Despite these cases, the role of EBV in the pathogenesis of hepatitis is unclear, as many other confounding factors were present.

QUESTIONS NEED TO BE ANSWERED

Although both adenoviruses and SARS-CoV-2 are not typically hepatotropic viruses and rarely cause acute hepatitis in immunocompetent patients, coinfection with both viruses may produce significant effects on the liver and induce an acute hepatitis-like syndrome. Many questions remain, and further research may lead to key information regarding acute hepatitis of unknown origin. As there is an increased rate of autoimmune diseases after COVID-19 and its vaccines[47], could acute hepatitis of unknown cause be a COVID-19 immune-triggered reaction? Could this syndrome be caused by new variants of either adenovirus or SARS-CoV-2? Could coinfection with SARS-CoV-2 and adenoviruses trigger aggravated inflammatory responses affecting a sensitized liver and consequently induce acute hepatitis? Could acute hepatitis be a local form of the multisystem inflammatory syndrome, as

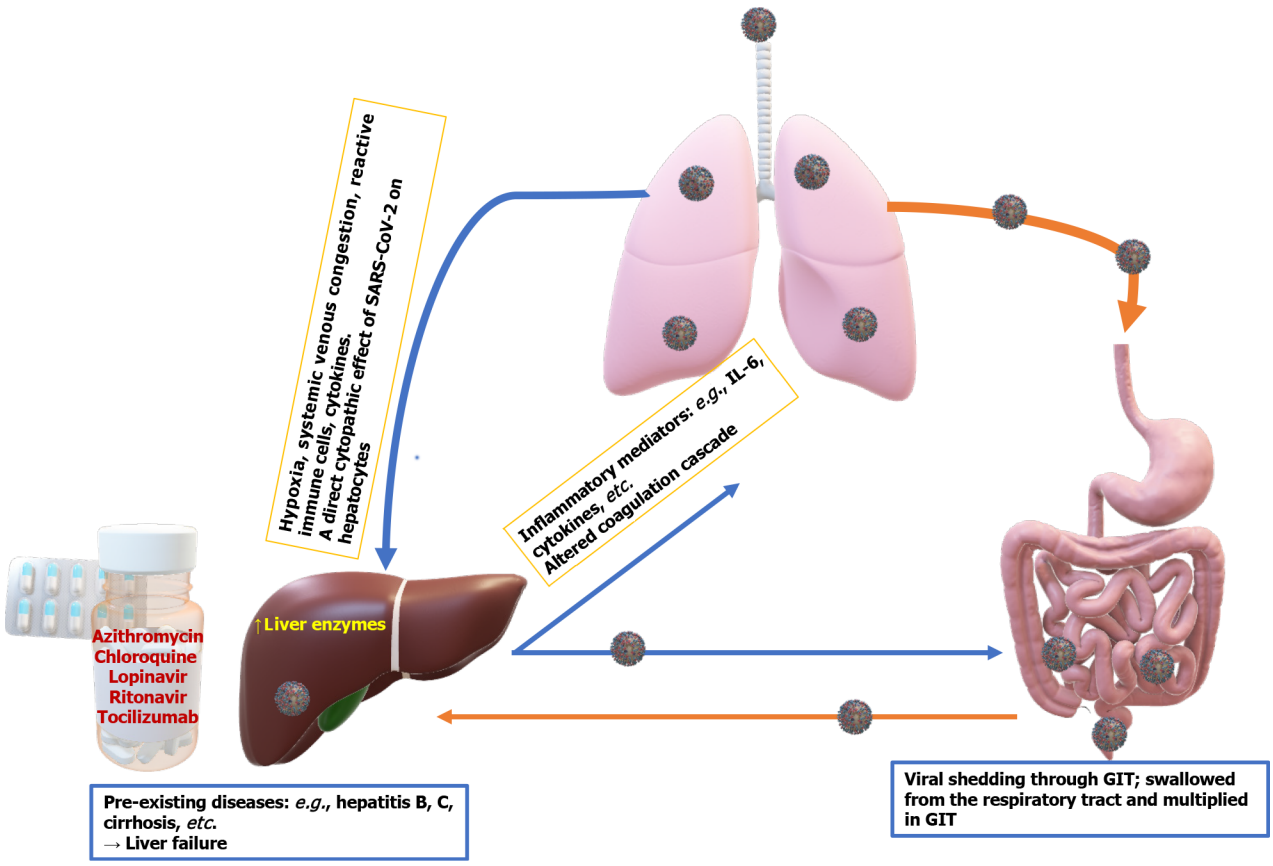

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Figure 4 Effect of coronavirus disease 2019 infection on the liver as indicated by increased liver enzymes. The virus reaches the liver from the gut-liver-lung axis and may be re-shed back to the gut through the bile. These effects are mediated through the impact of hypoxia, systemic venous congestion, immune-mediated hepatic damage by inflammatory mediators induced by severe acute respiratory syndrome coronavirus-2 infection (SARS-CoV-2), the direct hepatic cytopathic effect of SARS-CoV-2, and the hepatotoxic effects of some medications used to treat SARS-CoV-2 infection such as azithromycin, chloroquine, lopinavir, ritonavir, and tocilizumab. GIT: Gastrointestinal tract; IL-6: Interleukin 6.

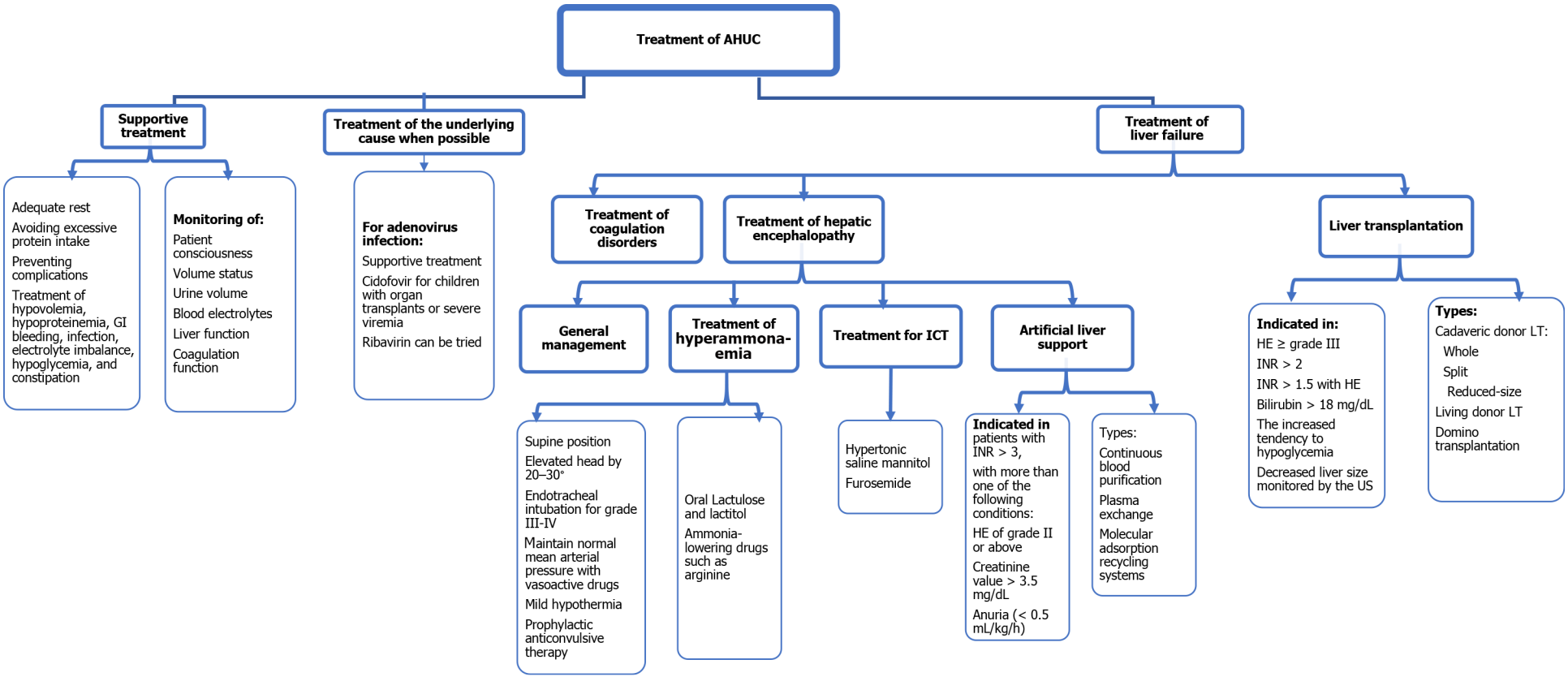
described by Cantor *et al*[47]? Could adenoviruses serve as a vector for SARS-CoV-2, easing the entry of SARS-CoV-2 in hepatocytes? Could this syndrome of acute hepatitis be related to other undiscovered microbial or non-microbial agents? Other aetiologies cannot be ignored. Despite being isolated from cases with acute hepatitis of unknown cause, the role of adenoviruses in the pathogenesis of this syndrome is not yet proven. We must strive to answer these questions and better define the correlation between SARS-CoV-2 and adenovirus infection and the development of this syndrome.

TREATMENT

Treatment of acute hepatitis of unknown cause in children is mainly symptom-based, supporting the recovery of liver function and treating complications as they arise. Cidofovir can be used when adenovirus infection is suspected, particularly in children with an organ transplant or severe viremia[48,49]. When multisystem inflammatory syndrome in children (MIS-C) is suspected to cause acute hepatitis, the treatment protocol is the same as the management of MIS-C[47]. Liver transplantation is indicated in children with acute fulminant hepatic failure refractory to aggressive therapy[50]. A summary of the treatment of acute hepatitis of unknown cause is illustrated in Figure 5.

PREVENTION

As SARS-CoV-2, adenoviruses, EBV, and other viruses are strongly suspected as potential mediators of acute hepatitis of unknown cause, appropriate hand hygiene and regular surface disinfection are essential to reduce viral spread. Hand and respiratory hygiene manoeuvres can reduce the spread of nonenveloped viruses such as adenoviruses[51]. Moreover, it is key that healthcare professionals know the signs and symptoms of hepatitis in children. In suspected cases, clinicians should order serum ALT



DOI: 10.4254/wjh.v15.i3.364

Figure 5 Summary of the treatment of acute hepatitis of unknown cause. AHUC: Acute hepatitis of unknown cause; GI: Gastrointestinal; HE: Hepatic encephalopathy; ICT: Increased intracranial tension.

and AST transaminase testing to ensure efficient detection of cases as early as possible.

CONCLUSION

There has been an increasing number of acute hepatitis of unknown origin in children since first reported on March 31, 2022. The exact aetiology of this condition in children, which was observed to increase in prevalence during the COVID-19 pandemic, is still unclear. Despite adenoviruses and SARS-CoV-2 being isolated from some patients with acute hepatitis of unknown cause, the role of these viruses in the pathogenesis of this syndrome is not yet proven. Coinfection with SARS-CoV-2 and other

viruses may relate to the pathogenesis of this condition. However, many questions remain and will require comprehensive research to better understand this correlation. Until a better understanding is reached, emphasis must be placed on preventing the development of acute hepatitis in children by using proper hygiene (*e.g.* hand washing, frequent surface disinfection) to reduce viral spread. Treatment of acute hepatitis of unknown cause in children is mainly symptom-based, supporting liver recovery and treating complications as they arise.

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FOOTNOTES

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