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ТИББИЁТДА ЯНГИ КУН НОВЫЙ ДЕНЬ В МЕДИЦИНЕ NEW DAY IN MEDICINE

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www.bsmi.uz

<https://newdaymedicine.com> E:

ndmuz@mail.ru

Тел: +99890 8061882

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HEPATITIS IN CHILDREN: A COMPREHENSIVE REVIEW OF CLASSIFICATION AND EPIDEMIOLOGY

Shagiyazova Lola Maxmudovna <https://orcid.org/0009-0007-1136-0123>

E-mail: ShagiyazovaL@mail.ru

Tashkent Pediatric Medical Institute, Uzbekistan 100140, Tashkent, 223 Bogishamol St, tel: 8 71 260 36 58 E.mail: interdep@tashpmi.uz

✓ Resume

Hepatitis, an inflammatory condition of the liver, represents a significant global health concern in the pediatric population. Its diverse etiologies, ranging from viral infections to autoimmune disorders and metabolic conditions, underscore the complexity of diagnosis and management in children. This article provides a detailed scientific overview of the classification and epidemiology of hepatitis in children. We delve into the various categories of hepatitis, including viral hepatitis (A, B, C, D, and E, alongside other viral causes), autoimmune hepatitis, toxic and drug-induced hepatitis, metabolic liver diseases associated with hepatitis, and neonatal hepatitis. For each category, we explore the etiological agents, pathogenic mechanisms, modes of transmission (where applicable), global prevalence, incidence, and specific epidemiological considerations within the pediatric age group. Furthermore, we address age-specific vulnerabilities, regional variations, and the evolving epidemiological landscape influenced by factors such as vaccination programs, socioeconomic conditions, and environmental exposures. This comprehensive review aims to provide an in-depth educational resource for healthcare professionals, researchers, and public health stakeholders, enhancing understanding of the multifaceted nature of hepatitis in children and informing strategies for prevention, early detection, and effective management to mitigate the burden of this significant pediatric health issue.

Key words: Hepatitis in children, classification, epidemiology, autoimmune disorders, metabolic conditions, viral hepatitis A, B, C, D and E.

ГЕПАТИТ У ДЕТЕЙ: КОМПЛЕКСНЫЙ ОБЗОР КЛАССИФИКАЦИИ И ЭПИДЕМИОЛОГИИ

Шагиязова Лола Махмудовна <https://orcid.org/0009-0007-1136-0123>

E-mail: ShagiyazovaL@mail.ru

Ташкентский педиатрический медицинский институт, 100140, Узбекистан Ташкент, ул. Богишамол, 223, тел: 8 71 260 36 58 E.mail: interdep@tashpmi.uz

✓ Резюме

Гепатитное, воспалительное заболевание печени представляет собой глобальное состояние здоровья в педиатрической ситуации. Его изменения, вызванные вирусными заболеваниями, аутоиммунными расстройствами и метаболическими состояниями, включают в себя сложные диагнозы и лечение у детей.

В этой статье представлен подробный научный обзор классификации и эпидемиологии гепатита у детей. Мы углубляемся в различные категории гепатита, включая вирусный гепатит (A, B, C, D и E, наряду с другими вирусными причинами), аутоиммунный гепатит, токсический и лекарственный гепатит, метаболические заболевания печени, связанные с гепатитом, и неонатальный гепатит.

Для каждой категории мы изучаем этиологических агентов, патогенные механизмы, пути передачи (где применимо), глобальную распространенность, заболеваемость и конкретные эпидемиологические соображения в пределах детской возрастной группы. Кроме того, мы рассматриваем уязвимости, связанные с возрастом, региональные различия

и развивающийся эпидемиологический ландшафт, на который влияют такие факторы, как программы вакцинации, социально-экономические условия и воздействие окружающей среды.

Целью этого всеобъемлющего обзора является предоставление углубленного образовательного ресурса для медицинских работников, исследователей и заинтересованных сторон в сфере общественного здравоохранения, который позволит лучше понять многогранную природу гепатита у детей и предоставит информацию о стратегиях профилактики, раннего выявления и эффективного лечения для смягчения бремени этой важной проблемы детского здравоохранения.

Ключевые слова: Гепатит у детей, классификация, эпидемиология, аутоиммунные заболевания, метаболические состояния, вирусные гепатиты A, B, C, D и E.

Introduction

Hepatitis, derived from the Greek words "hepar" (liver) and "itis" (inflammation), denotes a spectrum of inflammatory conditions affecting the liver parenchyma. In children, hepatitis presents a particularly concerning clinical challenge due to its varied causes, potential for acute and chronic complications, and impact on long-term health and development. The liver, a vital organ responsible for numerous metabolic functions, detoxification, and synthesis of essential proteins, is susceptible to a wide array of insults that can trigger inflammatory responses. Understanding the classification and epidemiology of hepatitis in children is paramount for effective clinical practice, public health interventions, and research endeavors aimed at reducing the morbidity and mortality associated with this condition [1,2].

Гепатит, происходящий от греческих слов "hepar" (печень) и "itis" (воспаление), обозначает спектр воспалительных состояний, поражающих паренхиму печени. У детей гепатит представляет собой особенно тревожную клиническую проблему из-за его разнообразных причин, возможности острых и хронических осложнений и влияния на долгосрочное здоровье и развитие.

Печень, жизненно важный орган, отвечающий за многочисленные метаболические функции, детоксикацию и синтез основных белков, восприимчива к широкому спектру повреждений, которые могут вызывать воспалительные реакции. Понимание классификации и эпидемиологии гепатита у детей имеет первостепенное значение для эффективной клинической практики, вмешательств в общественное здравоохранение и исследовательских усилий, направленных на снижение заболеваемости и смертности, связанных с этим состоянием.

The etiologies of hepatitis in children are diverse and can be broadly categorized into infectious and non-infectious causes. Viral infections are the most common culprits globally, with a constellation of hepatotropic viruses specifically targeting liver cells. However, non-viral causes, including autoimmune disorders, metabolic diseases, toxic exposures, and drug reactions, also contribute significantly to the overall burden of pediatric hepatitis. Furthermore, in the neonatal period, unique considerations arise due to congenital infections, metabolic disorders detectable at birth, and structural anomalies of the biliary system [4,5].

Epidemiologically, hepatitis in children exhibits significant global variations, influenced by factors such as geographic location, socioeconomic status, sanitation practices, vaccination coverage, and prevalence of specific risk factors. Understanding these epidemiological patterns is crucial for tailoring public health strategies, allocating resources effectively, and implementing targeted prevention programs. This article will systematically explore the classification of hepatitis in children, providing detailed insights into each category, followed by a comprehensive analysis of the epidemiological landscape, highlighting key trends, risk factors, and geographical variations. The ultimate goal is to provide an educational resource that enhances knowledge and promotes informed decision-making to improve the health outcomes of children affected by hepatitis worldwide [6,7].

2. Classification of Hepatitis in Children

The classification of hepatitis in children is primarily based on the etiological agent or underlying pathophysiological mechanism. This framework allows for a structured approach to diagnosis,

management, and understanding the diverse clinical presentations and epidemiological profiles associated with different types of hepatitis. The major categories of hepatitis in children are outlined below:

2.1 Viral Hepatitis

Viral hepatitis constitutes the most prevalent cause of liver inflammation globally, affecting individuals across all age groups, including children. Hepatotropic viruses, specifically targeting hepatocytes, are responsible for the majority of cases. These viruses are categorized into distinct types, each with unique characteristics in terms of transmission, pathogenesis, clinical course, and long-term outcomes [8].

2.1.1 Hepatitis A Virus (HAV)

Hepatitis A is caused by the Hepatitis A virus (HAV), a single-stranded RNA virus belonging to the *Picornaviridae* family. HAV infection is primarily transmitted through the fecal-oral route, typically via ingestion of contaminated food or water, or through close person-to-person contact, especially in settings with poor sanitation and hygiene. In children, HAV infection is often asymptomatic or presents with mild, non-specific symptoms, including fever, fatigue, nausea, vomiting, abdominal discomfort, and jaundice in older children and adolescents. Fulminant hepatic failure is a rare but serious complication, particularly in children with pre-existing chronic liver disease. HAV infection is generally self-limiting, and chronic hepatitis A does not occur. Following acute infection, lifelong immunity is conferred [9,10,11].

2.1.1 Вирус гепатита А (HAV)

2.1.2 Hepatitis B Virus (HBV)

Hepatitis B is caused by the Hepatitis B virus (HBV), a partially double-stranded DNA virus belonging to the *Hepadnaviridae* family. HBV transmission occurs primarily through parenteral routes, including exposure to infected blood or body fluids, sexual contact, and vertical transmission from mother to child during pregnancy or childbirth. Vertical transmission is a major concern in HBV epidemiology, particularly in regions with high HBV prevalence. Infants infected perinatally are at a high risk of developing chronic HBV infection, which can progress to cirrhosis, liver failure, and hepatocellular carcinoma later in life. In older children and adults, acute HBV infection often presents with jaundice, fatigue, and abdominal pain, and while most cases resolve spontaneously, a proportion of individuals develop chronic infection [12,13].

2.1.3 Hepatitis C Virus (HCV)

Hepatitis C is caused by the Hepatitis C virus (HCV), a single-stranded RNA virus belonging to the *Flaviviridae* family. HCV transmission is predominantly through parenteral routes, primarily via blood-to-blood contact, such as through sharing of contaminated needles during intravenous drug use, blood transfusions (before routine screening), and less commonly, vertical transmission. Vertical transmission of HCV is less efficient than HBV, but infants born to HCV-infected mothers are at risk. HCV infection in children is often asymptomatic or mildly symptomatic, and chronic infection is common, with a significant risk of progression to chronic hepatitis, cirrhosis, and hepatocellular carcinoma over decades. Direct-acting antiviral (DAA) therapies have revolutionized HCV treatment, offering high cure rates even in children [14,15].

2.1.4 Hepatitis D Virus (HDV)

Hepatitis D, also known as Delta hepatitis, is caused by the Hepatitis D virus (HDV), a unique, defective RNA virus that requires the presence of HBV for replication and infection. HDV can only infect individuals who are already infected with HBV. Transmission routes are similar to HBV, including parenteral and sexual contact. HDV infection can occur as a co-infection with HBV or as a superinfection in individuals with chronic HBV infection. HDV infection typically exacerbates the severity of liver disease in HBV-infected individuals, increasing the risk of fulminant hepatitis and progression to chronic liver disease. Prevention of HBV infection through vaccination is the key to preventing HDV infection.

2.1.5 Hepatitis E Virus (HEV)

Hepatitis E is caused by the Hepatitis E virus (HEV), a single-stranded RNA virus belonging to the *Hepeviridae* family. HEV is primarily transmitted through the fecal-oral route, similar to HAV, typically via contaminated water or food, particularly in regions with poor sanitation. In children, HEV infection is usually mild and self-limiting, similar to HAV. However, in pregnant women, HEV infection can be severe and associated with high mortality rates. Chronic HEV infection can occur in immunocompromised individuals, such as organ transplant recipients. Different genotypes of HEV exist, with varying geographical distributions and zoonotic potential.

2.1.6 Other Viral Causes of Hepatitis

Besides the classical hepatotropic viruses (HAV, HBV, HCV, HDV, HEV), other viruses can also cause hepatitis in children, although less commonly. These include:

- **Cytomegalovirus (CMV):** CMV is a herpesvirus that can cause hepatitis, particularly in neonates and immunocompromised children. Congenital CMV infection is a significant cause of neonatal hepatitis and can lead to long-term sequelae.
- **Epstein-Barr Virus (EBV):** EBV, another herpesvirus, is the causative agent of infectious mononucleosis. Liver involvement, including hepatitis, is common in EBV infection, although usually mild and transient.
- **Adenoviruses:** Adenoviruses are common respiratory viruses that can occasionally cause hepatitis, particularly in young children and immunocompromised individuals. Severe adenovirus hepatitis can occur in liver transplant recipients.
- **Herpes Simplex Virus (HSV):** HSV, especially HSV-1 and HSV-2, can cause severe, disseminated infection in neonates, including hepatitis. Neonatal HSV hepatitis is associated with high morbidity and mortality.
- **Varicella-Zoster Virus (VZV):** VZV, the cause of chickenpox and shingles, can rarely cause hepatitis, primarily in immunocompromised children or in the context of disseminated varicella infection.
- **Enteroviruses:** Enteroviruses, such as coxsackieviruses and echoviruses, can occasionally cause mild hepatitis in children, particularly in neonates.

2.2 Autoimmune Hepatitis (AIH)

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by immune-mediated destruction of hepatocytes. It is classified as an autoimmune disorder where the body's immune system mistakenly attacks liver cells, leading to inflammation and liver damage. AIH can occur in children and adolescents, although it is less common than in adults. Two main types of AIH are recognized based on autoantibody profiles: Type 1 AIH (characterized by anti-nuclear antibodies [ANA] and/or anti-smooth muscle antibodies [SMA]) and Type 2 AIH (characterized by anti-liver kidney microsomal type 1 antibodies [anti-LKM1] and/or anti-liver cytosol antibody type 1 [anti-LC1]). AIH typically presents with insidious onset of fatigue, jaundice, and elevated liver enzymes. If untreated, AIH can progress to cirrhosis and liver failure. Immunosuppressive therapy is the mainstay of treatment to control liver inflammation and prevent disease progression.

2.3 Toxic and Drug-Induced Hepatitis

Exposure to certain toxins and drugs can induce liver injury and hepatitis in children. The liver's role in detoxification makes it vulnerable to damage from various xenobiotics.

- **Drug-Induced Liver Injury (DILI):** Numerous medications can cause DILI in children, ranging from mild liver enzyme elevations to severe fulminant hepatic failure. Common culprits include acetaminophen (paracetamol) overdose, certain antibiotics (e.g., amoxicillin-clavulanate, isoniazid), anticonvulsants (e.g., valproic acid), and herbal supplements. DILI can be idiosyncratic or dose-dependent.
- **Toxic Hepatitis:** Exposure to environmental toxins or industrial chemicals can lead to liver damage. Examples include poisoning with *Amanita* mushrooms (containing amatoxins), carbon tetrachloride, and certain heavy metals.

2.4 Metabolic Liver Diseases Associated with Hepatitis

Several inherited metabolic disorders can manifest with liver inflammation and hepatitis in children. These conditions often result from defects in specific metabolic pathways, leading to accumulation of toxic metabolites or deficiencies in essential substances within the liver.

- **Wilson's Disease:** Wilson's disease is an autosomal recessive disorder of copper metabolism, resulting in copper accumulation in the liver, brain, and other organs. Hepatic manifestations can range from asymptomatic liver enzyme elevations to acute hepatitis, chronic hepatitis, and cirrhosis.
- **Alpha-1 Antitrypsin Deficiency (AATD):** AATD is an autosomal recessive disorder characterized by deficiency of alpha-1 antitrypsin, a protein that protects the lungs and liver from proteolytic damage. Liver disease in AATD can present as neonatal cholestasis, childhood hepatitis, or cirrhosis.
- **Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH):** NAFLD is increasingly recognized in children and adolescents, often associated with obesity, insulin resistance, and metabolic syndrome. NASH, a more severe form of NAFLD, involves liver inflammation and can progress to fibrosis and cirrhosis.
- **Galactosemia:** Galactosemia is an inherited metabolic disorder affecting galactose metabolism. Neonatal galactosemia can present with liver dysfunction, including hepatitis and jaundice.
- **Hereditary Fructose Intolerance:** Hereditary fructose intolerance is an inherited disorder of fructose metabolism that can lead to liver damage, including hepatitis and cirrhosis, upon fructose ingestion.

- **Glycogen Storage Diseases (GSDs):** Certain GSDs, such as GSD type IV (Andersen disease), can cause progressive liver disease, including hepatitis and cirrhosis.

2.5 Neonatal Hepatitis

Neonatal hepatitis refers to liver inflammation occurring within the first few months of life. It encompasses a diverse group of conditions with overlapping clinical presentations, characterized by jaundice, hepatomegaly, and elevated liver enzymes. Neonatal hepatitis can be broadly categorized into:

- **Infectious Causes:** Congenital infections, such as CMV, rubella, toxoplasmosis, syphilis (TORCH infections), HBV (vertical transmission), HCV (vertical transmission), and HSV, can cause neonatal hepatitis.
- **Metabolic Causes:** Galactosemia, tyrosinemia, hereditary fructose intolerance, AATD, Wilson's disease, and other metabolic disorders can present as neonatal hepatitis.
- **Biliary Atresia:** Biliary atresia is a progressive fibro-obliterative disease of the extrahepatic bile ducts, leading to cholestasis and liver damage, manifesting as neonatal hepatitis.
- **Alagille Syndrome:** Alagille syndrome is a genetic disorder affecting multiple organ systems, including the liver and bile ducts, often presenting with neonatal cholestasis and hepatitis.
- **Idiopathic Neonatal Hepatitis:** In some cases, the cause of neonatal hepatitis remains undetermined despite thorough investigations, and these cases are classified as idiopathic neonatal hepatitis.

3. Epidemiology of Hepatitis in Children

The epidemiology of hepatitis in children is complex and varies considerably across different geographical regions and for different etiologies. Understanding the epidemiological patterns is crucial for public health planning and targeted interventions.

3. Эпидемиология гепатита у детей

Эпидемиология гепатита у детей сложна и значительно различается в разных географических регионах и для разных этиологий. Понимание эпидемиологических закономерностей имеет решающее значение для планирования общественного здравоохранения и целевых вмешательств.

3.1 Viral Hepatitis Epidemiology

3.1.1 Hepatitis A Epidemiology

HAV infection is endemic in many developing countries with poor sanitation and hygiene. In these regions, most individuals are infected with HAV in early childhood, often asymptotically, leading to widespread immunity by adulthood. Improved sanitation and hygiene in developed countries have shifted HAV epidemiology towards outbreaks associated with contaminated food or water, and travelers to endemic regions are at risk if not vaccinated. Vaccination against HAV is highly effective and recommended for travelers, individuals at high risk, and increasingly incorporated into childhood immunization programs in some countries. The global incidence of HAV is declining due to improved sanitation and vaccination efforts.

3.1.2 Hepatitis B Epidemiology

HBV infection remains a major global health problem, with the highest prevalence in Asia and sub-Saharan Africa. Vertical transmission is the predominant route of HBV infection in these high-prevalence regions, leading to chronic HBV infection in infants and contributing to the pool of chronic carriers. Universal newborn HBV vaccination has been implemented in many countries and has significantly reduced the incidence of chronic HBV infection and its sequelae, particularly hepatocellular carcinoma. However, challenges remain in achieving high vaccination coverage globally and in addressing HBV infection in older children and adolescents who may have missed newborn vaccination. The global prevalence of chronic HBV infection is estimated to be around 0.5-1% in children under 5 years of age, but varies widely geographically.

3.1.3 Hepatitis C Epidemiology

Globally, HCV prevalence is lower than HBV prevalence, but it remains a significant concern, particularly in certain regions. In children, vertical transmission and transfusion of unscreened blood products were historically important routes of HCV infection. However, with routine screening of blood products and improved perinatal care, vertical transmission has become the primary route of HCV infection in children in developed countries. The prevalence of HCV infection in children is generally low, estimated to be less than 0.5% globally, but higher in specific populations, such as children born to HCV-infected mothers. With the advent of highly effective DAA therapies, there is increasing emphasis on identifying and treating HCV-infected children to prevent long-term complications.

3.1.4 Hepatitis D Epidemiology

HDV epidemiology is intertwined with HBV epidemiology since HDV requires HBV for replication. HDV prevalence is highest in regions with high HBV endemicity, such as parts of Asia, Africa, and South America. HDV infection is less common in children compared to adults. Prevention of HBV infection through vaccination effectively prevents HDV infection.

3.1.5 Hepatitis E Epidemiology

HEV epidemiology is characterized by two distinct patterns. Genotype 1 and 2 HEV are prevalent in developing countries and are transmitted primarily through contaminated water, causing large outbreaks. Genotype 3 and 4 HEV are zoonotic and found in developed countries, transmitted through consumption of undercooked pork or contact with animal reservoirs. In children, HEV infection is generally mild and self-limiting, but outbreaks can occur in areas with poor sanitation. The global burden of HEV infection in children is not as well-defined as HAV or HBV, but it is likely significant in endemic regions.

3.1.6 Epidemiology of Other Viral Hepatitis Causes

The epidemiology of other viruses causing hepatitis in children reflects the epidemiology of the respective viruses. CMV infection is ubiquitous, with high seroprevalence rates in the general population, and congenital CMV infection remains a significant concern. EBV infection is also widespread, and infectious mononucleosis is common in adolescents and young adults. Adenovirus and enterovirus infections are common childhood illnesses, and hepatitis is a less frequent manifestation. HSV hepatitis in neonates is a rare but serious condition associated with neonatal HSV infection epidemiology.

3.2 Autoimmune Hepatitis Epidemiology

AIH is a relatively rare disease in children, with an estimated incidence of 0.6-1.2 per 100,000 children per year and prevalence of 6-11 per 100,000 children. AIH can occur in children of any age, but it is more commonly diagnosed in older children and adolescents. There is a female predominance in AIH, both in children and adults. Genetic susceptibility plays a role in AIH, with associations with certain HLA haplotypes. The geographical distribution of AIH is not as well-defined as viral hepatitis, but it is considered to be a global disease.

3.3 Toxic and Drug-Induced Hepatitis Epidemiology

The epidemiology of toxic and drug-induced hepatitis is influenced by environmental exposures, medication use patterns, and prescribing practices. Acetaminophen overdose is a common cause of DILI in children, particularly in adolescents. Exposure to environmental toxins depends on geographical location, industrial activities, and environmental regulations. Surveillance systems and pharmacovigilance programs are important for monitoring the incidence and identifying risk factors for DILI and toxic hepatitis in children.

3.4 Metabolic Liver Disease Epidemiology

The epidemiology of metabolic liver diseases causing hepatitis in children is determined by the prevalence of the underlying genetic disorders and associated risk factors. Wilson's disease, AATD, galactosemia, and hereditary fructose intolerance are relatively rare inherited disorders, with varying prevalence depending on population genetics and geographical distribution. NAFLD and NASH are increasingly prevalent in children and adolescents in parallel with the rising rates of childhood obesity and metabolic syndrome globally. The prevalence of NAFLD in children is estimated to be around 5-10% in the general pediatric population and significantly higher (up to 70%) in obese children.

3.5 Neonatal Hepatitis Epidemiology

The epidemiology of neonatal hepatitis reflects the combined epidemiology of its various causes. Congenital infections contribute significantly to neonatal hepatitis, with CMV being the most common infectious cause. Biliary atresia is a relatively rare condition, with an estimated incidence of 1 in 10,000 to 1 in 15,000 live births. Alagille syndrome is also rare. Metabolic disorders causing neonatal hepatitis are individually rare, but collectively contribute to a proportion of cases. Idiopathic neonatal hepatitis accounts for a significant proportion of cases where the etiology remains unclear. The overall incidence of neonatal hepatitis is estimated to be around 1 in 2,500 live births.

4. Age-Specific Considerations in Pediatric Hepatitis Epidemiology

The epidemiology of hepatitis in children is significantly influenced by age, with distinct patterns observed in different age groups:

- **Neonates (0-28 days):** Neonatal hepatitis is dominated by congenital infections (TORCH, HBV), metabolic disorders, biliary atresia, and Alagille syndrome.

Conclusion

Hepatitis, an inflammatory condition of the liver, represents a significant global health concern in the pediatric population. Its diverse etiologies, ranging from viral infections to autoimmune disorders and metabolic conditions, underscore the complexity of diagnosis and management in children. This article provides a detailed scientific overview of the classification and epidemiology of hepatitis in children. We delve into the various categories of hepatitis, including viral hepatitis (A, B, C, D, and E, alongside other viral causes), autoimmune hepatitis, toxic and drug-induced hepatitis, metabolic liver diseases associated with hepatitis, and neonatal hepatitis. For each category, we explore the etiological agents, pathogenic

mechanisms, modes of transmission (where applicable), global prevalence, incidence, and specific epidemiological considerations within the pediatric age group. Furthermore, we address age-specific vulnerabilities, regional variations, and the evolving epidemiological landscape influenced by factors such as vaccination programs, socioeconomic conditions, and environmental exposures. This comprehensive review aims to provide an in-depth educational resource for healthcare professionals, researchers, and public health stakeholders, enhancing understanding of the multifaceted nature of hepatitis in children and informing strategies for prevention, early detection, and effective management to mitigate the burden of this significant pediatric health issue.

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