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Transplantation in Pediatrics Liver Failure Associated with Acute Hepatitis of Unknown Etiology

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Abstract

Introduction. On 5th April 2022, some cases of severe acute hepatitis of unknown etiology in children were reported in the United Kingdom. Since then, the number has increased rapidly, with 650 probable cases identified worldwide. This review focuses on available information about managing acute liver failure (ALF) in pediatrics with acute hepatitis of unknown etiology through the perspective of hepatobiliary surgery.

Method. A literature review proceeded on some databases, namely PubMed and Google Scholar. Epidemiological data and technical policy were obtained from World Health Organization and some government institutions.

Results. Severe acute hepatitis can progressively develop into acute liver failure, thus requiring a liver transplantation procedure immediately. There are about 30 patients have received a liver transplant. Fourteen patients reported had died. Liver transplantation is necessary to treat acute liver failure in children with acute hepatitis of unknown etiology. The need for a liver transplant can be avoided if ALF is prevented.

Conclusion. The decision to perform or not to perform a liver transplant procedure may consider indications, contraindications, possible outcomes, patient status, availability of donors, and access to transplant centers' facilities and resources.

Keywords: liver transplant, liver donor, acute liver failure, acute hepatitis, pediatrics

Introduction

Severe acute hepatitis cases of unknown etiology in children were first reported by the United Kingdom (UK) to the World Health Organization's International Health Regulations (IHR) on 5th April 2022. This called hepatitis of unknown etiology because testing results had excluded viral hepatitis types A, B, C, D, and E and other known causes of acute hepatitis.¹ Unknown hepatitis has some name, including non-A-E viral hepatitis or hepatitis X.

Acute hepatitis can progressively develop into acute liver failure (ALF). However, some lack information and reports about liver transplantation as management for pediatric ALF due to acute hepatitis of unknown etiology. Therefore, this review was made to gather current information updates and reports.

Method

We proceeded with literature searching on PubMed and Google Scholar using some keywords, including "children", "kids", "pediatrics"; and "acute liver failure", "acute hepatitis", "nonhep a-e", "nonhep a-to-e", "hepatitis unknown etiology", "hepatitis x"; and "liver transplant", "liver donor", "liver recipient", "transplantation". The current situation, policy updates, and technical briefing were obtained from World Health Organization (WHO), the European center for disease prevention and control (ECDC), the United Kingdom Health Security Agency (UKHSA), and the Ministry of Health of the Republic of Indonesia (Kementerian Kesehatan RI). Literature searching methodology was performed based on PRISMA 2020 diagram.

Results

Database searching through PubMed, Google Scholar, and health institution statement releases yielded 1813 articles which 3546 articles were excluded due to duplication, 1185 excluded due to being marked as ineligible, 14 were not retrieved, and 42 articles were excluded for other reasons. The identification of articles resulted in 26 articles included in this review.

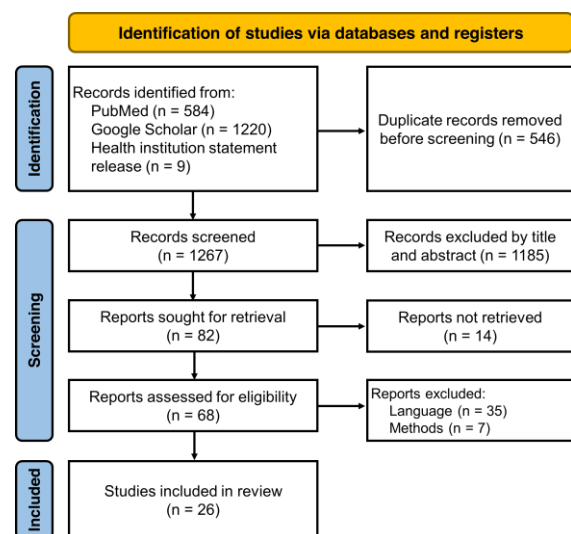


Figure 1. Literature search following Prisma flow 2020.

Epidemiological updates

Based on the communicable disease threats report released by the European center for disease prevention and control (ECDC) on 15-21 May 2022, as of 19th May 2022, there were 125 cases of acute hepatitis in children aged <16 years in 14 countries of the European Union/The European Economic Area (EU/EEA). A total of four cases required liver transplants.²

Meanwhile, based on data from the United Kingdom Health Security Agency (UKHSA), as of 12th May 2022, they have identified as many as 176 children aged <10 years with acute hepatitis of unknown etiology. A total of 11 cases have received liver transplants.²

Outside the EU/EEA and the United Kingdom, as of 19th May 2022, at least 313 cases of acute hepatitis in children have been reported from 16 countries. The cases and mortality reported worldwide were 614 and 14 cases, respectively. We have summarized the country data and the number of cases in table 1.²

However, as of 26th May 2022, the World Health Organization (WHO) updated the data, with 650 probable cases fitting the WHO case definition. The total number of cases requiring liver transplantation was 38 (6%).³

Table 1. Summary of acute hepatitis cases in children worldwide¹⁻³

Date	Country	No. of cases	No. liver transplant
19 th May 2022	Fourteen countries in the European Union/The European Economic Area (EU/EEA).	125	4
	Austria	14	0
	Belgium	2	0
	Cyprus	6	0
	Denmark	2	0
	France	3	0
	Greece	6	<5
	Ireland	35	<5
	Italy	6	<5
	The Netherlands	4	0
	Norway	3	0
	Poland	12	0
	Portugal	<5	<5
	Romania	26	<5
	Spain	9	0
	Sweden		
	12 th May 2022	The United Kingdom	176
19 th May 2022	16 countries outside the EU/EEA and the UK	313	
	Argentina	9	<5
	Brazil	44	No data
	Canada	11	<5
	Costa Rica	2	No data
	Indonesia	14	0
	Israel	12	<5
	Japan	12	0
	Malaysia	1	No data
	Maldives	<5	0
	Mexico	21	0
	Moldova	1	0
	Palestine	1	0
	Panama	2	0
	Serbia	1	<5
	Singapore	1	0
	South Korea	1	0
The United States	180	15	
19 th May 2022	Mortality over the world	14	No data
	Ireland	1	
	Indonesia	6	
	Mexico	1	
	Palestine	1	
The United States	5		

The distribution of cases of acute hepatitis in children is sporadic, and the trend of increasing chances also remains unclear. Thus, the risk of transmission, mortality, and even prognosis in the pediatric population becomes challenging to estimate accurately.¹

Likewise, the case in Indonesia. Based on data from the Ministry of Health of the Republic of Indonesia. As of 13th May 2022, there were 18 cases of acute hepatitis in children in Indonesia.

Table 2. Subjects' characteristics of acute hepatitis among children in Indonesia

	No. of cases	
Location	North Sumatera	One pending classification
	West Sumatera	One pending classification
	Bangka Belitung island	One discarded
	West Java	One pending classification
	East Java	One pending classification
	DKI Jakarta	One probable
		Five pending classifications
		Five discarded
		One waiting for surveillance
	East Kalimantan	One discarded
Age	0–4 years	4 cases
	5–9 years	6 cases
	10–14 years	4 cases
	15–20 years	4 cases

From <https://sehatnegeriku.kemkes.go.id/baca/umum/20220513/0539829/kemenkes-temukan-18-orang-dugaan-kasus-hepatitis-akut/>

Nine cases are pending classification status, seven are discarded, 1 in the verification process, and one is probable. The characteristics of pediatric patients

with acute hepatitis in Indonesia are shown in table 2. However, it is known that most patients are categorized as severe, and none of these cases receive liver transplantation procedures. Common signs and symptoms complained by patients are fever, vomiting, loss of appetite, acute diarrhea, nausea, gastrointestinal illness, myalgia, arthralgia, icterus, jaundice, white stool, pruritus, bilirubinuria, and loss of consciousness.⁴

Discussion

Liver transplant indication

Indications for liver transplant are pediatric patients with acute liver failure (ALF). As in 3 out of 4 cases of ALF due to unknown hepatitis in The Netherlands, which required a liver transplant. Health centers usually perform 3–4 transplantation procedures in children annually. Thus the number of transplants in ALF due to unknown hepatitis is considered above average.¹ Rarely, ALF with hepatic encephalopathy and coagulopathy (INR >1.5) due to acute hepatitis should be discussed with the hepatology team about the transfer to a liver transplant center. There are criteria evaluation tools (e.g., King's College Criteria) to decide the need for a liver transplant referral.⁵⁻⁷

King's College criteria for liver transplantation in acute liver failure caused by non-acetaminophen etiology consist of: (1) prothrombin time >100s (INR >6.5), irrespective of the grade of encephalopathy; or any three of the following, (2) age <11 or >40 years; (3) indeterminate etiology of hepatitis or drug-induced; (4) duration of jaundice >7 days before the onset of encephalopathy; (5) prothrombin time >50s (INR >3.5); or (6) serum bilirubin levels >17 mg/dl (300 μmol/l).⁸

In general, indications for liver transplants in patients with acute liver failure meet 3 of 5 criteria. They are unknown etiology hepatitis, age <10 years, interval jaundice encephalopathy >7 days, bilirubin >300 mol/L (17 mg/dl), and INR >3.5.⁹ Contraindications for liver transplant in children are: (1) non-resectable extrahepatic malignant tumor; (2) concomitant end-stage organ failure that a combined transplant cannot correct; (3) uncontrolled sepsis; and (4) irreversible neurological severe damage.¹⁰

Most children with acute hepatitis in Scotland presented high transaminase serum of more than 2000 IU/L, where the normal range is 10–40 IU/L. Still, only one received a liver transplant from three children that transferred to quaternary pediatric liver units in England.¹¹ We still have not found any reports or documents mentioning the cut-off level of laboratories marker for indication of a liver transplant.

Delaying the decision to perform a liver transplant on a pediatric patient with ALF can increase the risk of infection, multiple organ failure, irreversible brain damage, and even death.⁹ Although several case series have suggested that >50% of hepatocyte necrosis is associated with a risk of death, it is generally not recommended to perform the routine histological examination in patients with ALF, and the decision to transplant should not be based on biopsy findings. Liver biopsy may be indicated in cases of diagnostic doubt, especially to exclude neoplastic causes, which are contraindications to liver transplantation.⁹

Without liver transplantation, mortality in children with acute liver failure (ALF) is very high. Death was caused by fulminant hepatitis, ALF, with hepatic encephalopathy. This is associated with increasing age and preexisting liver disease. One of the classic markers of ALF is impaired coagulation with a prolonged prothrombin time. A few children with ALF have bone marrow failure ranging from mild pancytopenia to aplastic anemia.¹²

After the indications for transplantation are met, the patient is immediately included in the list of active donors in need. If donor organs are available, the transplant team should review the patient's condition to

identify the prognosis after transplantation or absolute contraindications to transplantation, especially if irreversible brain damage is found.⁹

Adenovirus infection in patients requires a liver transplant

Quantitative PCR results showed that patients who required liver transplants had adenovirus DNA levels 12 times higher than patients who did not require liver transplants.^{13,14} Human adenovirus (HAdV) infection is found in many children. Of the eight UK-based patients requiring a liver transplant, seven were tested for adenovirus in blood samples, and all were found to have the virus. HAdV serotype 41F was identified in 5 patients who underwent molecular subtype examination.¹⁵ This serotype is associated with the appearance of gastrointestinal symptoms. In addition, hepatitis due to HAdV infection is usually asymptomatic in immunocompetent children, or the clinical manifestations are mild and self-limiting. In this outbreak case, many hepatic clinical manifestations are severe and require liver transplantation to avoid multiorgan failure.^{16,17}

A comprehensive report by Baker et al. showed results of the liver biopsy from 6 children with unknown acute hepatitis without virus inclusions and adenovirus by examining electron microscopic and immunohistochemical staining. However, adenovirus was detected after real-time PCR testing in whole blood specimens from all patients. Its initial viral load range was 991–70680 copies/mL. Adenovirus type 41 was detected in all five specimens.^{18,19}

Adenovirus is recognized as a cause of hepatitis in immunocompromised children but not recognized in immunocompetent children. However, the magnitude of this relationship remains under investigation.¹⁹

Reported studies of liver transplant

De Kleine et al. observed 34 pediatric liver centers (including 25 transplant centers) in 22 European countries and Israel regarding severe acute hepatitis resulting in acute liver failure. During January–April 2022, a mean of two cases was detected (range: 0–8). A total of 11 large transplant centers with transplant volumes >16 cases per year reported that transplant procedures in 3.8 months in early 2022 reached a mean of 2.5 cases (range: 0–5). Meanwhile, in 2019, 2020, and 2021 each had a mean of 4.9 cases (range: 0–10), 3.7 cases (range: 0–10), and 4.9 cases (range: 0–10), respectively.¹⁷ A total of four children received liver transplants, and three died before the organs became available. One child with Wilson's disease (cause identified) died after transplantation.¹⁷ In the case of Alabama, in the United States, nine children were diagnosed with acute hepatitis with median age = 2 years, 11 months (interquartile range: 1 year, eight months to 5 years, nine months) at admission. Although the median of alanine aminotransferase (ALT) = 1724 U/L (range: 603–4696), aspartate aminotransferase (AST) = 1963 U/L (range: 447–4000), and total bilirubin = 7 mg/dL (range: 0.23–13.5), there were only two patients required and recovered after transplantation. Meanwhile, seven patients recovered without liver transplantation.^{18,19}

Outcome and infection risk

The favorable outcome relates to etiology as a predictive factor. About 30% of cases with liver failure due to unknown etiology achieve spontaneous recovery.²⁰ Patients with mild encephalopathy have a better prognosis than patients with severe encephalopathy.²¹ However, the risk of failure, such as primary non-function, can occur in the early hours after transplantation which is characterized by high lactate levels, increased partial prothrombin and thromboplastin time, and decreased patient consciousness. This serious complication must be treated

immediately by administering prostaglandin E1, preventing brain edema with mannitol infusion and hyperventilation, and giving plasma and glucose to counteract the effects of liver failure. If the signs of primary non-function do not improve, then the patient needs a new transplant (retransplant).^{9,10,22}

Besides, thrombosis due to hepatic artery anastomosis can result in post-transplant necrosis of early massive liver grafts. It was reported to be four times more common in children in the first 30 days. These events can be identified immediately by doppler ultrasound examination, then treated with anastomosis or balloon angioplasty. Irreversible brain damage may also occur due to massive fluid/electrolyte displacement during hepatectomy, the anhepatic phase, and reperfusion. Signs of symptoms of rejection can be seen in the presence of elevated liver enzymes. This can be prevented by taking immunosuppressive or anti-rejection drugs for the rest of their life after transplantation and routine check-ups to monitor drug levels in the body. The risk of infection increases due to the consumption of anti-rejection drugs.^{9,10,22} The use of immunosuppressants should be of one concern because they may worsen hepatitis infection of unknown etiology.

Access to health facilities

No pediatric patients with acute hepatitis in Indonesia have received liver transplants. Although, there were 6 cases of death. Transplantation is a challenge for the referral hospital in this outbreak. In Indonesia, Sulianti Saroso Infection Center General Hospital (RSPI) has chosen to be a referral center because it has capable health personnel and adequate health facilities such as negative pressure rooms and laboratories.²³ The distribution of case findings in various regions in Indonesia requires a physician to be alert and responsive to build a diagnosis, initial management, and referral to RSPI in Jakarta.

Several cases in the EU/EEA and UK showed the high need for liver transplantation due to acute liver failure in pediatric patients with acute hepatitis. Thus access to highly specialized pediatric intensive care units (PICU) and liver transplantation centers may improve their outcomes.¹ Healthcare facilities must adhere to standard precautions and perform contact and droplet precautions for suspected or probable cases.³ Data from the specialized pediatric liver unit in England showed that the number of liver transplants for acute liver failure due to unknown cause hepatitis among children <10 years during the first quarter of 2022 is higher than the previous annual number between 2009 and 2019.^{1,14} Outside Europe, 9 cases of acute hepatitis in children aged 1–6 years have been reported in the state of Alabama in the US. Two of these cases required liver transplants.^{24,25} In the Alabama case, three patients developed ALF. Two were treated with cidofovir (off-label use) and steroids, then sent to a liver transplant facility.¹⁹

The history of pediatric liver transplantation relies on rigorous and integrated cooperation between referral pediatricians, pediatric transplant hepatologists, transplant surgeons, nurses, transplant coordinators, psychologists, and social workers.¹⁰

Knowledge Gap

We found some knowledge gaps while writing this article. First, the objective criteria for liver transplantation are still not clear. Some countries stated that patients with ALF should be performed a liver transplantation procedure. However, in Indonesia, a recommendation from the Indonesian Pediatric Society for the management of severe acute hepatitis and fulminant hepatitis was not mentioned liver transplantation. This may be why no liver transplantation was performed in Indonesia during this acute hepatitis outbreak.²⁶ Second, the selection

criteria for liver transplant recipients have not yet been published or reported in many journals, even a single case report. Third, laboratory findings correlated with liver transplantation in acute hepatitis of unknown etiology remain unclear.

Conclusions

Liver transplantation is necessary to treat acute liver failure in children with acute hepatitis of unknown etiology. The need for a liver transplant can be avoided if ALF is prevented. The liver transplant procedure performed during the outbreak has been reached fifteen times. Indonesia has become the country with the highest mortality and is one country that does not do liver transplants at all. The decision to perform or not to perform a liver transplant procedure may consider indications, contraindications, possible outcomes, patient status, availability of donors, and access to transplant centers' facilities and resources. The examination results from patients who received liver transplantation found many cases of adenovirus infection, specifically serotype 41F. Due to unknown etiology, current knowledge about liver transplantation in pediatric patients with acute hepatitis is still limited. Thus, the various information in this review still needs to be clarified.

Disclosure

The authors declare no conflict of interest.

Role of authors

Conceptualization ABP ASP, Data curation ABP MR LAN, Formal analysis ABP MR LAN, Funding acquisition ABP ASP, Investigation ABP MR LAN, Methodology ABP, Project administration ABP, Resources MR LAN, Software ABP MR LAN, Supervision. ASP, Validation ABP, ASP, Visualization ABP, Writing original draft preparation ABP MR LAN, Writing review and editing ABP ASP MR LAN.

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