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## Eliminating viral hepatitis in children after liver transplants: How to reach the goal by 2030

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### Abstract

Viral hepatitis infections are a great burden in children who have received liver transplant. Hepatotropic viruses can cause liver inflammation that can develop into liver graft fibrosis and cirrhosis over the long term. Immunological reactions due to viral hepatitis infections are associated with or can mimic graft rejection, rendering the condition difficult to manage. Prevention strategies using vaccinations are agreeable to patients, safe, cost-effective and practical. Hence, strategies to eliminate viral hepatitis A and B focus mainly on immunization programmes for children who have received a liver transplant. Although a vaccine has been developed to prevent hepatitis C and E viruses, its use is not licensed worldwide. Consequently, eliminating hepatitis C and E viruses mainly involves early detection in children with suspected cases and effective treatment with antiviral therapy. Good hygiene and sanitation are also important to prevent hepatitis A and E infections. Donor blood products and liver grafts should be screened for hepatitis B, C and E in children who are undergoing liver transplantation. Future research on early detection of viral hepatitis infections should include molecular techniques for detecting hepatitis B and E. Moreover, novel antiviral drugs for eradicating viral hepatitis that are highly effective and safe are needed for

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children who have undergone liver transplantation.

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**Core Tip:** Viral hepatitis infections are a great burden for pediatric liver transplant recipients. Strategies to prevent infection include immunization, good sanitation and screening donor blood products and liver grafts for hepatitis B, C and E. In children infected with viral hepatitis who have received a liver transplant, early detection is crucial to guide proper management, as the infection can mimic or cause graft rejection. Effective antiviral therapy should be initiated when treating children with hepatitis B and C. Patients infected with hepatitis B who have undergone successful viral eradication should be revaccinated to maintain high hepatitis B surface antibodies to guarantee immunoprotection.

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## INTRODUCTION

Viral hepatitis is an infectious disease leading to high morbidity and mortality, especially in endemic areas such as Asia. Hepatitis viruses are hepatotropic and are classified into types A, B, C, D and E. In immunocompromised patients, including children who have undergone liver transplantation (LT) and typically receive lifelong immunosuppressants, nearly all viral hepatitis infections are chronic, progressing to liver fibrosis and cirrhosis in the long term. Hepatitis A is the only hepatitis virus that presents as an acute self-limiting infection but that is more severe in immunocompromised patients than in healthy individuals. Because viral hepatitis places a heavy burden on patients, strategies for prevention, early detection and prompt, effective management are crucial for graft survival and long-term outcomes in children after LT. In this review, we focus on lessons learned and future opportunities to develop effective strategies to eliminate hepatitis A, B, C and E in children after LT.

## BIOGRAPHY

Yong Poovorawan (Figure 1), MD is currently the Professor and the head of the Center of Excellence in Clinical Virology at the Faculty of Medicine, Chulalongkorn University, Bangkok. Professor Poovorawan obtained the medical degree in 1974 and his specialization in paediatrics in 1978 from King Chulalongkorn Memorial Hospital, Chulalongkorn University. In 1984, he became a research fellow on the field of paediatric hepatology at King's College Hospital Medical School, London. Professor Poovorawan has been working in the Department of Pediatrics at Chulalongkorn University, beginning as a lecturer and becoming Professor in 1991. Professor Poovorawan has received many research awards and honours, including the Outstanding Researcher Award in 1997 from the National Research Council of Thailand, Outstanding Scientist Award in 1997 from the Foundation for the Promotion of Science and Technology under the Patronage of His Majesty the King, Mahidol University-B-Braun Award in 2002, Thailand Research Fund Award in 2004 and has been nominated Senior Research Scholar by the Thailand Research Fund since 1997. He also received the Outstanding Best Teachers Award in 2004 from the Thailand National University Teacher Association. He is a leader who has been working on Viral hepatitis in Thailand. Outstanding Prof. Thailand Research Fund (2012-2014), Research Chair Grant, NSTDA (2014), Outstanding Achievement Doctor from the



**Figure 1** Yong Poovorawan, MD, Professor, Excellence Center of Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Medical Council of Thailand (2018), Achievement Award in Virology, Genetics Society of Thailand (2018), Achievement Award from the National Vaccine Institute of Thailand (2019). His work on avian influenza in Thailand also received outstanding research awards from the Thailand Research Fund in 2004 and the National Research Council in 2006. He is a member of the expanded programme on immunization vaccine, viral hepatitis and emerging diseases of the Center Disease Control, Ministry of Public Health. Professor Poovorawan has authored and co-authored more than 614 publications in the fields of hepatitis, paediatric hepatology and virology, with H-index 66 on Google Scholar.

## HEPATITIS A VIRUS

Manifestations of hepatitis A virus (HAV) infection mainly derive from the immunologic responses to the virus and might present as severe acute liver failure in healthy children[1]. The incidence of fulminant hepatic failure from HAV infection varies from 0.1% to 1% but increases in patients with chronic liver disease[2-4]. HAV is rarely reported in children after LT. In our centre, no children have been admitted with HAV after LT[5], likely because Thailand has significantly decreased the HAV infection rate in past decades[6]. However, HAV can mimic graft rejection or presents as recurrent HAV post-LT[7]. Immunization is the mainstay of prevention and should be given before LT. Short- and long-term studies (ranging from 2-48 mo) of immunologic responses to HAV vaccines in adults post-LT have revealed variable seroprotection rates ranging from 26%-97% after 2 doses of the vaccine[8-11]. In a 4-wk assessment, Ferreira *et al*[12] compared HAV vaccine immunogenicity between children with chronic liver disease and healthy controls and found that 97% of the former and 100% of the latter showed seroconversion, with geometric mean titres of 812.4 mIU/mL and 2344.90 mIU/mL, respectively, after 2 doses of the HAV vaccine[12]. However, no study has reported HAV vaccine immunogenicity in children post-LT. Arslan *et al*[13] found that 18% and 29% of adult patients lost humoral immunity to HAV at 1 and 2 years, respectively, post-LT. Interestingly, one case study reported a 55-year-old man who was previously immunized and was HAV-IgG-positive but had an acute HAV infection in-hospital post-LT[14]. This case report suggested that rapid HAV seroconversion after LT should be regularly monitored and that revaccination should be considered for patients with a loss of HAV immunity. We recommend providing HAV vaccines to all children waiting for LT, as the humoral immune response to the HAV vaccine is favourable[12]. Nevertheless, HAV vaccines are provided only for children older than 1 year, and younger children may require LT before being eligible for the HAV vaccine. Hence, post-LT HAV immunization is needed. Further studies should be conducted regarding long-term immunologic responses of HAV to confirm the efficacy of 2-dose HAV vaccines in immunocompromised children. Apart from the vaccine, other necessary strategies include improving sanitation and avoiding uncooked food.

## HEPATITIS B VIRUS

### **Immunization: A public health weapon for preventing hepatitis B virus infection**

**Pre-LT:** Since universal hepatitis B virus (HBV) vaccination programmes began in the 1990s[15], HBV infection prevalence has rapidly decreased worldwide. HBV vaccine series that include vaccines at birth, 1-2 and 6-12 mo can reduce mother-to-child transmission, the major mode of HBV transmission in children, from 65%-90% to 3.6%-4.0%[16,17]. Indeed, the seroprotective rate after a complete HBV series is > 95%[18]. In our cohort study, although seroprotective rates decreased to 44% over a 20-year follow-up, 93.1% of the children exhibited seroconversion after a booster dose[19]. The presence of immune memory cells after the booster dose confirmed waning immunity with an anamnestic response, indicating increased levels of hepatitis B surface antibodies (anti-HBs)[19]. However, in immunocompromised patients with chronic liver diseases or cirrhosis, revaccination yields unsatisfactory outcomes, with seroconversion rates of 37.0%-90.9% on conventional schedules[20-28] and 16%-72% on accelerated/super-accelerated[29-37] schedules. Many studies on HBV schedules have been conducted to improve immunologic responses after revaccination in nonresponders, mainly using adult data, with different doses, routes, vaccine types, numbers and injection intervals. Regardless, no differences in the efficacy of these regimens have been shown[38]. Overall, time is a concern for participants awaiting LT, and super-accelerated or accelerated regimens should be considered for short-term prevention of HBV infections during and after LT[39].

**During LT:** External sources of HBV transmission, such as blood products, medical instruments and transmission by hospital personnel or close contacts, are concerns. Anti-HBs may decline after excessive plasma loss during surgery, and occult HBV infections from positive hepatitis B core antibody (anti-HBc) blood products have been reported[40].

**Post-LT:** Immunologic loss of HBV is common after LT [41], and *de novo* hepatitis B infection (DNH) was observed in our paediatric LT centre[42]. DNH is likely related to acquired HBV infections from endemic environments or from HBV reactivation from positive anti-HBc allografts during immunologic loss[43-47]. In our centre, the anti-HBs loss rate increased rapidly after LT, and 46%, 57% and 82% of patients had anti-HBs levels of < 10 mIU/mL at 1 year, 2 years and > 3 years after LT, respectively. One case of DNH was detected at 3 years after LT, though anti-HBs levels were > 1000 mIU/mL before LT[42]. Hence, regular monitoring for anti-HBs and revaccination after LT are crucial. Studies of immunogenicity to HBV revaccination after LT have reported higher humoral immune responses in children than in adults (up to 100% *vs* 33.3%-63.8%); however, immunity waned, and the patients needed frequent booster doses to maintain high seroprotective levels[43]. In healthy adults not responding to conventional vaccine schedules, a systematic review found no differences in seroconversion rates according to dosage or vaccine administration route[38]. However, to date, no study has been conducted involving children in this population. We conducted studies of immunologic responses to standard *vs* double-dose HBV vaccine series (at 0, 1 and 6 mo) in children after LT exhibiting anti-HBs loss and found response rates of 91.6% and 85% after a 6-mo follow-up, with no statistically significant difference in anti-HBs level between the two regimens (unpublished data). Hence, short-term assessment revealed that HBV revaccinations in children after LT are highly effective and safe.

Positive anti-HBc allografts are considered a major risk factor of DNH after LT, especially in patients without prior seroprotection or rapid anti-HBs loss after LT. In addition to being revaccinated 3-6 mo after LT, other strategies to prevent DNH include antiviral therapy and/or passive immunity with hepatitis B immunoglobulin (HBIG). Unlike the many studies that have used adult data and investigated several strategies, few studies of prophylactic strategies against DNH have been conducted in children who receive positive anti-HBc allografts[43,44,48-51]. Song *et al*[48] reported the efficacy of pre- and post-LT HBV vaccinations to prevent DNH and recommended a prophylactic strategy to maintain anti-HBs levels at  $\geq 1000$  mIU/mL pre-LT and  $\geq 200$  mIU/mL post-LT without antiviral consideration. The DNH rate when using this strategy was 1.3%[48]. However, anti-HBs levels may rapidly decline after LT owing to the massive immunosuppression involved. In such cases, antiviral therapy should be added in parallel until the appropriate revaccination time after LT (usually 3-6 mo) and until anti-HBs levels increase to  $\geq 200$  mIU/mL after revaccination.

Children with chronic HBV infections are rarely indicated for LT because they are usually asymptomatic in the stage of hepatitis B e-antigen (HBeAg)-positive chronic

infection or HBeAg-positive chronic hepatitis. Thus far, immunoprophylaxis data on recurrent HBV infections after LT are mainly based on adult data.

In summary, strategies to prevent HBV infection before, during and after LT mainly include active immunization. Super-accelerated and accelerated vaccines may be considered for timely protection prior to LT (to keep anti-HBs levels  $\geq 1000$  mIU/mL if possible). However, in children, anti-HBs levels should be regularly monitored, and revaccinations should be provided to maintain high anti-HBs levels ( $\geq 200$  mIU/mL).

### **The future of HBV elimination after LT**

Despite antiviral HBIG and active HBV immunization strategies, DNH has been reported in 0.9%-4.0% of both paediatric and adult LT patients[48,52,53]. Table 1 summarizes the risk factors for DNH. An escape mutation in the “a” determinant region within the hepatitis B surface antigen (HBsAg) that develops before LT, after HBV vaccination, or after HBIG administration post-LT should be considered[54]. In this situation, antiviral agents play a major role in preventing DNH, and long-term assessment for drug resistance should be considered. We recommend including pre-LT evaluations for HBV by serological, molecular and virological methods. Liver donors and allografts should be evaluated for covalently closed circular DNA (cccDNA) and HBV viral loads in cases of suspected occult infection with an escape mutant.

### **How to treat de novo hepatitis B infection in children after LT**

Su *et al*[54] found that after DNH occurred in children post-LT, more than half (5/9) exhibit seroconversion after lamivudine therapy. However, one child carried a tyrosine-methionine-aspartic acid-aspartic acid (YMDD) motif mutation, and the authors switched antiviral agent from lamivudine to adefovir dipivoxil. To date, no consensus treatment for DNH has been reached[43,54-56]. Antiviral therapy for DNH might follow the guidelines for treating HBV infections in children (Table 2). In our unit, one patient with DNH was treated with interferon- $\alpha$  for 1 year without a response, even though this child exhibited HBsAg seroconversion after 6 mo of entecavir therapy. We revaccinated him against HBV after HBsAg clearance following entecavir therapy. This child received an HBV revaccination series (0, 1 and 6 mo) and maintained anti-HB levels of  $> 1000$  mIU/mL without a booster at a 44-mo follow-up. Further study on the efficacy of antiviral therapy for DNH and other novel antiviral therapies with less drug resistance and high efficacy in children with DNH should be conducted to determine the best endpoints of HBsAg clearance and anti-HBs appearance. Tenofovir alafenamide (TAF) is a novel tenofovir product with improved properties for avoiding kidney and bone-related adverse events due to tenofovir disoproxil fumarate (TDF). Compared with TDF, TAF has non-inferior efficacy and a good safety profile[57]. Nevertheless, data for post-transplant adults and children receiving TAF are lacking. Only a small single-centre study of adult liver-transplant recipients found that TAF (25 mg/d) displayed high antiviral efficacy in preventing HBV recurrence without affecting immunosuppressive medications or graft functioning and had a good safety profile[58]. TAF is a promising antiviral therapy for adolescents diagnosed with DNH.

### **Other novel antiviral therapy**

As mentioned, current HBV prophylaxis and therapies do not completely eradicate HBV infections in most cases, requiring lifelong medication. Thus, effective and finite HBV treatment remains an unmet medical need, and new therapeutic approaches and drugs are necessary to achieve a functional cure (mainly defined as a loss of when HBsAg off therapy). Multiple novel drugs targeting different steps in the HBV life cycle are being developed. Antiviral and host-targeting agents are the two main drugs being studied. The major HBV-target-specific categories of antiviral drugs are hepatocyte-entry receptor inhibitors (*e.g.*, bulevirtide, formerly myrcludex B)[59,60], cccDNA inhibitors, nucleocapsid-assembly modulators (core protein allosteric modulators, *e.g.*, JNE-56136379)[61], post-transcriptional control inhibitors (RNA interference drugs, *e.g.*, ARC-520)[62], HBsAg-release inhibitors (nucleic-acid polymers, *e.g.*, REP 2139 and 2165)[63] and HBV DNA polymerase inhibitors. Therapies that target host immune responses include Toll-like receptor (TLR)-7 (*e.g.*, GS-9620, vesatolimod)[64], TLR-8 (GS-9688, selgantolimod)[65], and TLR-9 agonists, checkpoint inhibitors (anti-programmed death 1 and anti-programmed death-ligand 1) [66] and therapeutic vaccines[67]. These drugs are currently in phase I and II clinical trials that mainly include non-transplant adult patients and indicate a promising future for HBV eradication. No data are available on the efficacy of these new drugs

**Table 1 Risk factors of *de novo* hepatitis B infection in children after liver transplantation**

Risk factors
Positive anti-HBc donor[40]
Positive-intrahepatic HBV DNA[40]
Liver graft HBV DNA > 1000 copies[40]
Intraoperative fresh-frozen plasma transfusion > 400 mL[40]
Positive-anti-HBc recipients[40]
Pre-operative anti-HBs < 1000 mIU/mL[40,43,48]
Post-operative anti-HBs < 100-200 mIU/mL[48,53]
Hepatitis B surface mutation (within the “a” determinant region[54])

Anti-HBc: Hepatitis B core antibody; anti-HBs: Hepatitis B surface antibody.

**Table 2 Antiviral agents for hepatitis B infection in children[44]**

Medication	Licensing	Dose and duration	HBsAg loss (%)	Resistance (%)
IFN- $\alpha$ -2b	$\geq 1$ yr	6 million IU/m <sup>2</sup> three times weekly for 6 mo	1-2	0
Lamivudine	$\geq 2$ yr	3 mg/kg daily for $\geq 1$ yr	0	19-64
Entecavir	$\geq 2$ yr	0.25-0.5 mg daily for $\geq 1$ yr	0.52	0.7-1.2
Tenofovir dipovaxil fumarate	$\geq 12$ yr	300 mg daily for $\geq 1$ yr	0.02	0
Adefovir	$\geq 12$ yr	10 mg daily for $\geq 1$ yr	0	0.9-20

HBsAg: Hepatitis B surface antigen.

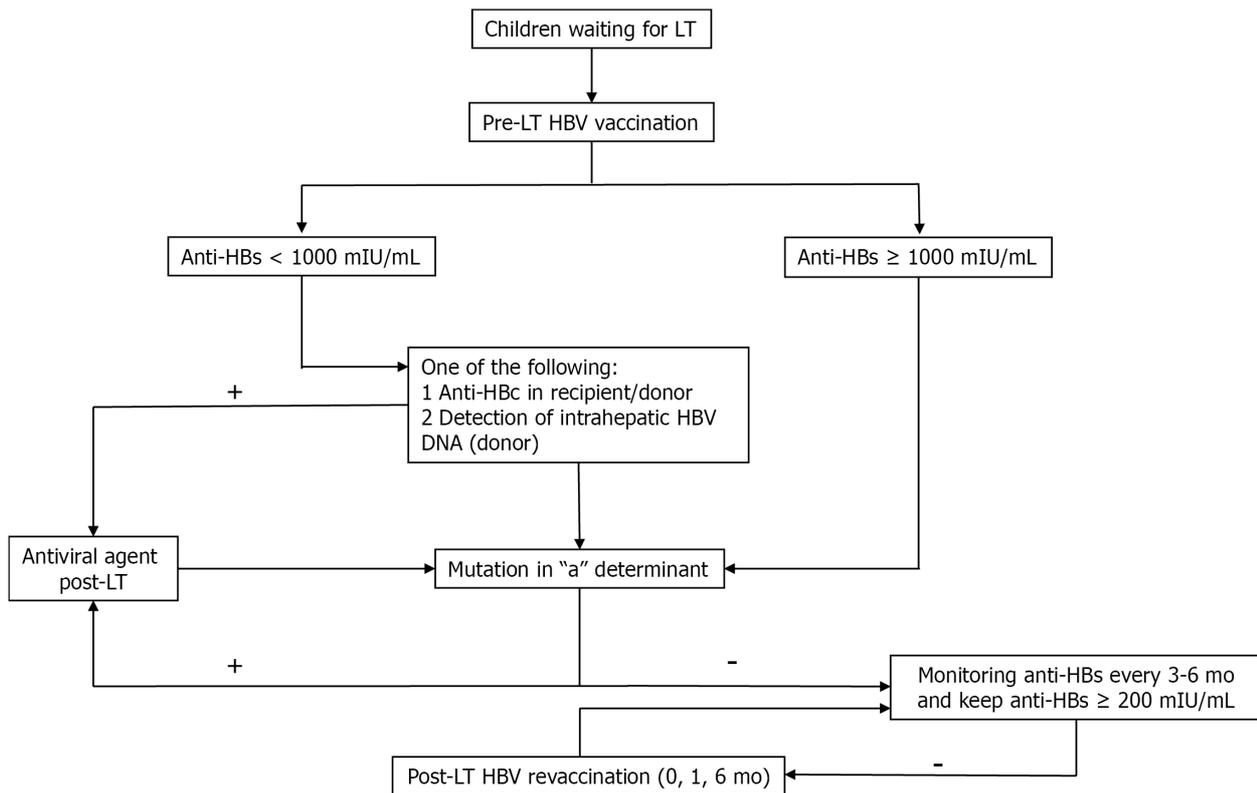
against HBV recurrence or *de novo* infection in children after LT. Further studies are needed to determine the impact of the new drugs on these patient groups.

Based on current knowledge of the human immunodeficiency virus (HIV) and hepatitis C virus (HCV), immunomodulators and combination treatments targeting several steps in HBV replication will likely be required to achieve a functional cure for HBV. Preclinical studies are applying this strategy in animal models[68], and clinical trials are investigating combinations of several antiviral drugs or immune boosters with antiviral agents. This new approach using combination therapies will need to be individualized, but many patients may be eligible.

In summary, strategies to eliminate HBV in paediatric liver transplant recipients include HBV immunization both pre- and post-LT. Early detection of HBV infections, especially of escape mutants, which lead to vaccine failure in recipients, and of cccDNA in the livers of positive anti-HBc donors, should be evaluated *via* molecular and viral genetic analysis in the liver tissues of both the donors and recipients. Patients with vaccine failure or DNH should promptly undergo antiviral therapy. **Figure 2** shows the proposed strategies to eliminate HBV in children post-LT.

## HEPATITIS C VIRUS

HCV infections are a global health problem, with an estimated 71 million people being chronically infected in 2016 and 400000 deaths annually worldwide[69]. Therefore, in 2016, the World Health Organization (WHO) set the goal of eliminating HCV by 2030. There has been significant progress towards this goal in screening policies, improving access to care, and reducing the costs of direct-acting antivirals (DAAs). Compared with adult patients, little attention has been paid to diagnosis, therapy, and prevention for children and adolescents. One reason is that prior to 2017, no DAAs were licensed for use in patients under 18 years old, and evidence was lacking to support paediatric management guidelines and policies. The majority of national HCV policies do not include explicit recommendations for HCV testing and treatment in children and



**Figure 2** Proposed strategies to prevent *de novo* hepatitis B infection[41-48,52,53]. LT: Liver transplantation; HBV: Hepatitis B virus; anti-HBc: Hepatitis B core antibody; anti-HBs: Hepatitis B surface antibody.

adolescents[70]

### Transmission route and natural history

In 2018, the global prevalence of HCV viraemia in populations under 18 years old was 0.13%, with an overall burden of 3.3 million cases[71]. The true HCV infection prevalence in paediatric populations is unknown due to a lack of universal screening strategies. Perinatal transmission is a major cause of recognized HCV infections in children, with transmission rates of 5% from HCV-infected mothers and 10% from HCV-HIV-coinfected mothers[72,73]. Moreover, the opioid epidemic is associated with an expanding ongoing risk of HCV transmission from mothers to children[74]. In the United States, nearly 29000 HCV-infected women gave birth annually from 2011-2014 [75]. Moreover, the transmission risk increases with higher maternal HCV viral loads, HIV coinfections, longer labour durations, amniocentesis or foetal-scalp monitoring, and prolonged membrane rupture[72,76-78]. Several studies from developed countries have reported increased injection drug use as a risk factor of HCV and HIV infections among adolescents[79,80]. Sexual transmission of HCV is also a major factor in men who have sex with men, including those infected with HIV or those who have received a pre-exposure prophylaxis for HIV[81,82].

After vertical HCV transmission, 25%-40% of patients spontaneously clear the infection within the first 4 years of life[83]. Approximately half of infants born with HCV will develop chronic disease that may lead to cirrhosis and hepatocellular carcinoma in late childhood[84]. The natural history of paediatric HCV differs from that of HCV acquired in adulthood. Host factors (*e.g.*, rs12979860 mutation in the *IL28B* gene[85], natural killer cell cytolytic functions[86]) and viral factors (*e.g.*, HCV genotype)[87] are associated with spontaneous clearance of HCV infections. Children with chronic HCV infections are mostly asymptomatic, with mild degrees of hepatitis and fibrosis during childhood and higher rates of spontaneous HCV clearance. Therefore, it is uncommon for children and adolescents to develop HCV-associated end-stage liver disease or hepatocellular carcinoma (HCC)[88]. Comorbidities, including haematological disease with iron overload, obesity, alcohol use, and concomitant viral infections (*e.g.*, HBV or HCV), are associated with accelerated liver fibrosis and cirrhosis development[89]. HCV-related extrahepatic manifestations are less common in paediatric patients than in adult patients[90]. In general, HCV

infections in children and adolescents are related to poor life quality and reduced cognitive functioning[84].

### **Diagnostic testing**

Several current international guidelines recommend anti-HCV testing (with a confirmatory nucleic acid assay for a positive result) for all pregnant women, especially those in high-risk groups, including those with past or current injection drug use, incarceration history, unregulated tattoos/piercings, receipt of contaminated blood products, or exposure in HCV-endemic areas[91-93]. HCV RNA can be found in breast milk and colostrum, but breastfeeding does not increase HCV transmission rates except in HCV-HIV coinfecting mothers[94]. All children born to HCV-infected mothers should be tested for HCV infection before 18 mo of age. Because anti-HCV antibodies passed from mothers can persist until 18 mo of age, HCV infection in children younger than 18 mo can be diagnosed by detecting HCV RNA. High-risk adolescents, including those who with histories of injection drug use and men who have sex with men, should be tested for HCV infection[95].

The asymptomatic nature of HCV infection and the high cost of diagnostic screening are the important barriers to detecting and treating HCV-infected patients [96]. Thus, a simple, cost-effective diagnostic method for routine HCV screening especially for low- to middle- income countries is needed. The core antigen of HCV (HCV Ag) is an alternative for screening and diagnosis. This test can be used as a supplemental marker after anti-HCV testing to reduce the requirement of further confirmatory HCV RNA assays[97]. Point-of-care tests of viraemia are related with improvement in access to testing [98].

### **Treatment DAAs in HCV infection before/after LT**

Advancement of oral DAA therapies has resulted in a paradigm shift in treating HCV, with cure rates of > 90% and few adverse effects. DAAs with pan genotypic activity are recommended as preferred regimens for all treatment-naïve and treatment-experienced HCV patients, regardless of age, sex, stage of liver fibrosis, or HIV coinfection[93,99,100]. Conversely, pegylated-interferon-based regimens are no longer recommended. DAA treatment with an approved regimen is recommended for all children and adolescents ≥ 3 years old with HCV infection, regardless of disease severity[101,102]. Early antiviral treatment should be administered to reduce morbidity and mortality if extrahepatic manifestations occur (*e.g.*, glomerulonephritis and cryoglobulinemia).

Adolescents aged 12-17 years who are treatment-naïve or -experienced, without cirrhosis or with compensated cirrhosis (Child-Pugh A) should be treated according to the recommendations for adult patients. For pangenotypic HCV, two DAA regimens are recommended: sofosbuvir (400 mg)/velpatasvir (100 mg) once daily for 8-12 wk, achieving a 95% sustained virological response (SVR)-12 rate (97/102; 1 virological failure) with mild-to-moderate adverse events[103]; a fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) once daily for 8 wk, achieving a 100% SVR-12 rate with a good safety profile[104]. Although the clinical trial for glecaprevir /pibrentasvir included only adolescents with HCV genotypes 1-4, this drug was approved by the Food and Drug Administration (FDA) for adults with all genotypes. In 2019, the FDA approved treating genotype-specific HCV with sofosbuvir (400 mg)/ledipasvir (90 mg) for 12 wk in adolescents aged 12-17 years or weighing at least 35 kg with genotypes 1, 4, 5, or 6, without cirrhosis or with compensated cirrhosis[105, 106].

Children aged 3-11 years who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated cirrhosis (Child-Pugh A) with any HCV genotypes should be treated with the FDA-approved regimens of a fixed-dose combination of sofosbuvir (200 mg)/velpatasvir (50 mg) for those aged > 6 years weighing ≥ 17 kg and sofosbuvir (150 mg)/velpatasvir (37.5 mg) for 12 wk[103] in those with weighing < 17 kg. One trial found that for children aged 3-11 years, the fixed-dose combination of glecaprevir (250 mg)/pibrentasvir (100 mg) for those weighing 30-44 kg, glecaprevir (200 mg)/pibrentasvir (80 mg) for those weighing 20-29 kg, and glecaprevir (150 mg)/pibrentasvir (60 mg) for those weighing 12-19 kg for 8-16 wk achieved a 96% SVR-12 rate, without drug-related severe adverse events[107]. However, this formulation is not yet FDA approved.

Overall, DAA-experienced children and adolescent patients with HCV are rare in clinical practice (Table 3). Because data for these populations are limited, DAA-experienced paediatric patients with HCV infections should be treated using the guidelines for adult patients.

**Table 3 Recommended direct-acting antiviral regimens for children who are naïve to or experienced with direct-acting antiviral therapy [101,102]**

Age	Genotype	No cirrhosis/ cirrhosis	Recommended regimens of DAAs	Duration (wk)
12-17 yr	Pan-genotypes	No cirrhosis	Sofosbuvir 400 mg/ velpatasvir 100 mg	12
		Compensated cirrhosis (Child-Pugh A)	Glecaprevir 300 mg/pibrentasvir 120 mg	8-12
12-17 yr or BW ≥ 35 kg	1, 4, 5, 6	No cirrhosis	Sofosbuvir 400 mg/ledipasvir 90 mg	12
		Compensated cirrhosis (Child-Pugh A)	Sofosbuvir 200 mg/velpatasvir 50 mg (BW ≥ 17 kg)	
3-11 yr	Pan-genotypes	No cirrhosis	Sofosbuvir 150 mg/velpatasvir 37.5 mg (BW < 17 kg)	12
		Compensated cirrhosis (Child-Pugh A)	Glecaprevir 250 mg/pibrentasvir 100 mg (BW 30-44 kg); Glecaprevir 200 mg/pibrentasvir 80 mg (BW 20-29 kg); Glecaprevir 150 mg/pibrentasvir 60 mg (BW 12-19 kg)	12; 8-16; 8-16; 8-16;

BW: Body weight.

### LT in paediatric patients in the DAA era

Children and adolescents with chronic HCV infections rarely require LT for complications from liver cirrhosis or HCC; recurrent HCV after LT is also clinically rare. In a retrospective study of the United Network of Organ Sharing database, Gupta *et al*[108] found that 120 paediatric patients received transplants for chronic HCV infections in 1994-2010. One-year and 3-year survival rates were 97% and 89%, respectively, in patients with post-paediatric end-stage liver diseases. Pre-LT recipient factors, good surgical technique, and effective treatment for HCV infections are associated with good prognostic outcomes in paediatric patients after LT[108]. Patients who achieve an SVR have less mortality than do those without SVR after treatment. Treatment has better effects on disease outcomes if it is started before cirrhosis[109]. To prevent long-term liver disease and HCV spread, antiviral therapy should be available in childhood.

LT for HCV-related diseases has decreased in the era of DAA treatment. Treating patients before LT reduces the chance of graft dysfunction after LT and may stabilize or improve liver function. SVR before LT may lead to the delisting of some patients [110]. Patients with decompensated (Child-Pugh B or C) cirrhosis who have model for end-stage liver disease (MELD) scores of < 20 without HCC and are awaiting LT should be treated with DAAs before LT. The recommended regimen is sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin 1000-1200 mg/day for 12 wk or sofosbuvir (400 mg)/velpatasvir (100 mg) for 24 wk in those with contraindications for ribavirin. Patients with MELD scores > 20 should undergo transplantation first and treated for HCV infection after LT if the waiting time is < 6 mo[111,112].

### Future treatment

**Vaccines:** Despite the high curative rate of HCV infections by DAAs, high-risk populations remain at risk of reinfection, even after successful treatment. Preventing new HCV infections is vital and may result in the WHO's 2030 global elimination goal. A prophylactic HCV vaccine might also help to achieve this goal by preventing transmission. Nevertheless, no vaccine for preventing HCV infections has been approved to date.

A recent phase 1-2, randomized, double-blind, placebo-controlled trial by Page *et al* [113] enrolled adults aged 18-45 years who had injected drugs within 90 d. These adults received either an intramuscular injection of a recombinant chimpanzee adenovirus type-3 vector-priming vaccination (ChAd3-NSmut vaccine) on day 0 and a recombinant modified vaccine (Ankara, MVA-NSmut vaccine) booster on day 56 (vaccine group) or a saline placebo on days 0 and 56. Despite inducing HCV-specific T-cell responses and lowering peak HCV RNA levels, the vaccine failed to prevent chronic HCV infection compared with placebo[113]. The innate variability of HCV enveloped proteins and the limited knowledge of HCV protein structures are barriers to developing an HCV vaccine. Future work should determine the optimal HCV epitopes to target vaccine development.

## HEPATITIS E VIRUS

Hepatitis E virus (HEV) was first discovered in the 1980s and normally manifests as an acute self-limited condition[114], though chronic HEV infection courses were recognized in 2008 in organ-transplant recipients[115]. HEV infection seroprevalence varies from 0.3%-75.6% depending on the area and diagnostic method[116-121]. HEV is transmitted mainly *via* the faecal-oral route, but mother-to-child[122], liver graft-to-recipient and plasma-derived-product transmission[123,124] have been reported. One study reported HEV transmission *via* liver graft[125], and several cases of HEV infections transmitted by blood transfusion have been reported. These findings have led to universal HEV-RNA testing in blood donors in many countries[123,124,126,127]. To detect HEV infection in immunocompetent children, primary testing with anti-HEV IgG and IgM is reasonable, and HEV RNA in stool and serum samples should be assessed in highly suspected cases that yielded negative results by serological methods[128]. However, serum HEV RNA analysis is preferable in immunocompromised patients, as they cannot mount an antibody response[129]. HEV infection has clinical impacts in immunocompromised hosts, especially in those needing organ transplantation. Moreover, HEV infections can be asymptomatic pre-existing chronic liver diseases or solid organ transplantation[130-133], or liver-associated morbidity due to progressive fibrosis and cirrhosis may be present[134]. Additionally, these conditions increase the risk of graft rejection[132]. In 2014, the European Association for the Study of the Liver proposed a well-organized stepwise plan for managing HEV infections in both adults and children after organ transplantation[128]. Once HEV infection is detected in children after LT, immunosuppression should be reduced when possible, and these children should be followed up within 3 mo. HEV-RNA clearance may occur in one-third of these patients. If chronic HEV infection persists, antiviral therapy with ribavirin (15 mg/kg/d) should be administered for at least 3 mo[135], and HEV clearance should be monitored monthly *via* PCR. Three promising recombinant vaccines against HEV with high efficacy have been developed[136] and can maintain seroprotection for > 4.5 years[137,138]. Many studies and case reports of HEV-infected children after LT have resulted from this increased awareness. Table 4 shows the results of previous studies[130-133,139,140] and HEV infection data for children after LT in our centre (unpublished data).

Strategies to eliminate HEV infection include prevention by implementing hygienic measures and thoroughly cooking food, screening plasma-derived products from immunocompromised patients and, developing an HEV vaccine. Early detection and effective treatment with antiviral agents in infected patients are also crucial.

### **Future: How to eliminate HEV after LT**

**Diagnostic testing for HEV infection:** As chronic HEV infections in children after LT lead to progressive hepatitis and liver fibrosis, suspected cases should be tested. As serologic testing is insufficient to detect HEV infections in immunosuppressed patients, HEV infections should be diagnosed based on HEV-RNA detection in specimens. Protzer *et al*[141] reported molecular detection of HEV in liver-biopsied tissues from four liver-transplanted patients, whereas serology only detected two (Mikrogen assay). Prost *et al*[142] compared HEV-RNA detection in clinical liver-biopsy tissues between *in situ* testing and qPCR from paraffin-embedded liver tissues and found that qPCR was more effective. Additionally, Ankavay *et al*[143] found that detecting the open reading frame 2 (ORF2) protein of HEV *via* immunohistochemistry of liver tissues can be used as a rapid histopathological method to diagnose HEV infections. The sensitivity and specificity of this technique were the same as those of tissue PCR for HEV RNA. The ORF2 clone 1E6 antibody yielded the highest diagnostic accuracy and was more sensitive for HEV serotypes 1 and 3 in the livers of both immunocompromised and immunocompetent patients[143]. Detecting HEV in liver tissues may be more reliable and may correlate directly with liver inflammation and damage in the immunocompromised. Regardless, a limitation of ORF2 clone 1E6 staining is that it is less sensitive for HEV genotypes 2 and 4. A cost-effective method of detecting HEV infection with high efficacy is still needed. Table 5 summarizes the HEV detection methods and their diagnostic value[144,145].

**Antiviral therapy for HEV infection:** In addition to ribavirin, other medications used in HEV-infected adults include pegylated interferon- $\alpha$  and add-on effects of sofosbuvir with ribavirin[128,146]. Recent data show that interferon  $\lambda$ 1-3 inhibits HEV replication in an *in vitro* culture system and may be effective for treating HEV infections[147]. Another proposed medication is zinc salt. In a human hepatoma cell study, zinc salt dose-dependently inhibited replication of HEV genotypes 1 and 3[148]. In fact, zinc

**Table 4 Studies of children infected with hepatitis E virus after liver transplantation**

Ref.	Year	Country	Participants	Seroprevalence of HEV infection	Methods		Comments
					HEV IgM/G	HEV RNA	
1[130]	2012	Canada	Gr 1; N: 66 with normal LFT, aged 13.7 yr (1.8-25.5); Gr 2; N: 14 with transaminitis, aged 17.4 yr (5.9-19.8)	Gr 1: 10/66 (15%) with IgG +, none had IgM, HEV RNA +; Gr 2: 12/14 (86%) with IgG+; 9/12 (75%) with IgM+; 1/12 (0.8%) with HEV RNA +	Feldan Bio Inc, Saint-Augustin	Serum nested RT-qPCR	All in Gr 2 showed a trend toward chronic hepatitis and fibrosis; An 8-yr-old girl had chronic HEV infection (genotype 3) for > 10 yr and developed cirrhosis
2[131]	2012	Germany	N: 41 liver-transplanted children, aged 8.8 ± 4.2 yr	2/41 (4.9%) IgG +0/41 stool HEV RNA +	Mikrogen	Stool RT-qPCR	No case with chronic HEV infection
3[132]	2013	Germany	N: 22 liver-transplanted children, aged 6.7 yr (1.4-17.2)	1/22 (0.45%) IgG + by Wantai assay and HEV RNA + in serum	Wantai assay	Serum or stool PCR	10-year-old boy with HEV infection that had persistent transaminitis after 2-mo immunosuppressive reduction. Ribavirin 15 mg/kg/d was started for 6 mo. Normal LFT and undetectable serum and stool HEV RNA at day 42 of treatment.
4[139]	2014	Brazil	One liver-transplanted child: case report	HEV IgG/IgM and HEV RNA in serum and liver tissue at 6-10 yr after liver transplantation	Mikrogen	Liver and serum RT-PCR	A 4-yr-old girl with transaminitis from ACR at 6 yr after LT, had transaminitis off and on and HEV IgG/IgM and HEV RNA was detected 9-10 yr after LT. Chronic HEV infection was successful treatment with ribavirin for 10 mo.
5[133]	2015	France	84 liver-transplanted children, aged 12.3 yr	8/84 (8.3%) HEV IgG+	Wantai assay	Ceeram Tools <sup>®</sup> kit for HEV-RNA detection	None had HEV IgM/RNA +; No case of chronic infection
6[140]	2020	France	80 liver-transplanted children, aged 3.5 ± 4 yr	6/80 (8%) with HEV IgG+	Wantai assay	Ceeram Tools <sup>®</sup> kit for HEV-RNA detection	None had HEV IgM/RNA +; No case of chronic infection; 4/6 had undetectable HEV IgG after follow-up (3-42 mo)
7	2021	Thailand	30 liver-transplanted children with transaminitis, aged 1.2-17.6 yr	14/30 (45.2%) with HEV IgG+, 4 (13%) with HEV IgM+ and one case with HEV RNA in stool	Euroimmun kit	Stool PCR	All of them had persistence of HEV IgM from 5 to 44 mo and transaminitis from 4 to 30 mo before HEV testing. The previous treatment included graft rejection, <i>de novo</i> autoimmune hepatitis and CMV viremia.

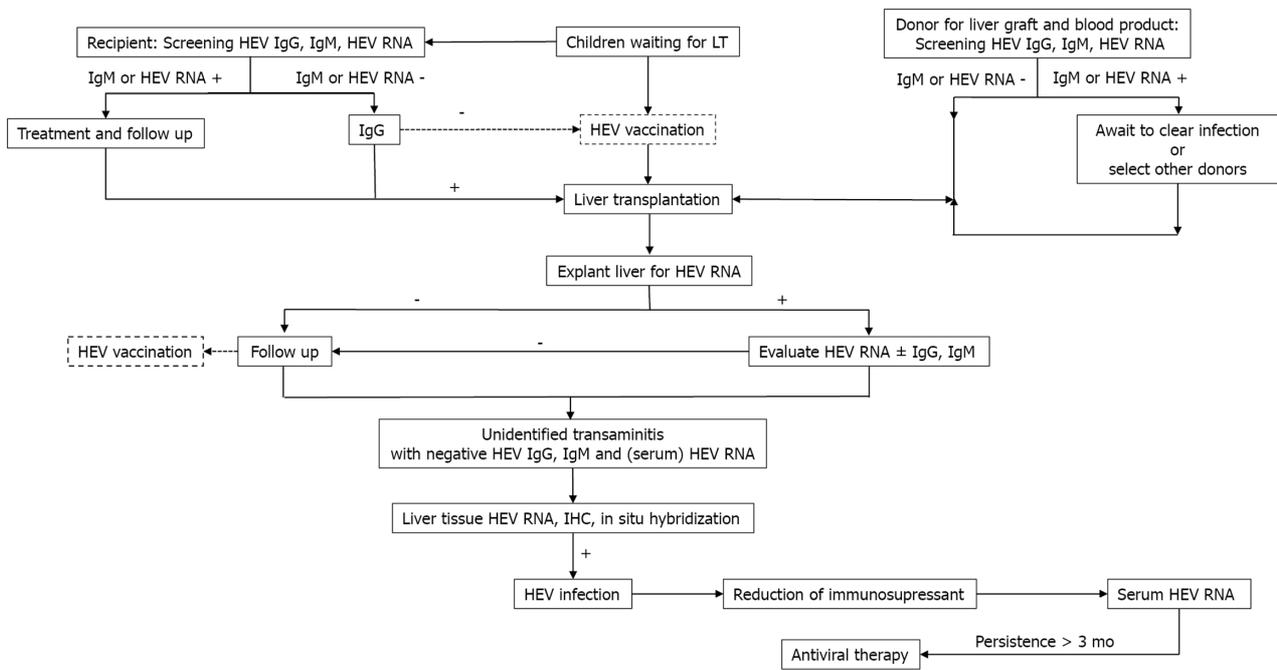
Ref: Reference; Gr: Group; RT-qPCR: Real-time polymerase chain reaction; HEV: Hepatitis E virus; ACR: Acute cellular rejection; MP: MP Biomedicals, formerly Genelabs Diagnostics, Singapore; Wantai assay: Wantai Biologic Pharmacy Enterprise, Beijing, China; LT: Liver transplantation; CMV: Cytomegalovirus.

**Table 5 Diagnostic tests for hepatitis E infection[144,145]**

Detection	Technique	Specimen
Virus or its components (direct method)	<b>HEV nucleic acid:</b> (1) RT-PCR; (2) Realtime RT-PCR; and (3) Loop-mediated isothermal amplification assay. <b>HEV RNA:</b> (1) <i>In situ</i> hybridization; (2) HEV viral protein (antigen); (3) EIA; and (4) IHC.	Serum, stool, bile, liver tissue
Host immune response (indirect method)	<b>Specific anti-HEV antibodies (IgM and IgG)</b> (sensitivity 72%-98% and specificity 78%-96%): (1) Indirect EIA; (2) Immunochromatographic assays; (3) Double-antigen sandwich-based EIAs; (4) $\mu$ capture EIAs for IgM anti-HEV; (5) Specific cellular immune response; and (6) ELISpot assays.	Serum, peripheral blood mononuclear cells

HEV: Hepatitis E virus; RT-PCR: Reverse transcription polymerase chain reaction; ELISpot: Enzyme-linked immune absorbent spot; EIA: Electroimmunoassay; IHC: Immunohistochemistry.

can directly decrease HEV replication by suppressing viral translation and processing of nonstructural proteins encoded by ORF1 and by inhibiting IFN- $\lambda$ 3 from binding to its receptor[149,150]. Moreover, zinc has an indirect effect by modulating host immune



**Figure 3** Proposed strategies to eliminate hepatitis E virus infection in children after liver transplants[127,128,130,135,141,142]. LT: Liver transplantation; HEV: Hepatitis E virus; IHC: Immunohistochemistry.

responses and is a cofactor in host cellular processes[150]. Hence, zinc is a promising drug for HEV therapy without serious adverse effects. Clinical and basic research are needed regarding the therapeutic benefits of zinc in HEV infections.

**Prevention with an HEV vaccine:** Since 2001, several vaccines based on virus-like particles have been developed[151], and there have been clinical trials on three vaccine candidates[136,137,152]. One is licensed in China, with 100% efficacy over 12 mo after 3 injections[137]. Moreover, the efficacy remained high at 86.8% after a 4.5-year follow-up[138]. However, these three vaccines mainly protect against genotypes 1 and 4 but cannot protect against genotype 3, which is the main genotype causing chronic HEV infections in patients after LT[153]. In 2019, an HEV vaccine was initiated and is progressing in clinical trials in the United States[153]. In general, an HEV vaccine will be a powerful weapon in public health for protecting against HEV infections (Figure 3).

## CONCLUSION

To eliminate viral hepatitis in paediatric liver-transplant recipients, multiple strategies must be integrated into clinical practice. Similar to the prevention of HAV infections, immunization is the mainstay of prevention against HBV infection in children with liver transplants. Regular monitoring of humoral immunity for HBV and HAV and revaccination programmes in cases with immunity loss are necessary. Antiviral therapy plays a major role in HBV and HCV infections. For HEV infection, molecular techniques for early detection in children with liver transplant with unidentified causes of hepatitis should be developed to guide proper management of HEV infection.

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