

# Clinical spectrum of paediatric liver diseases in Singapore

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**ABSTRACT** A wide spectrum of disorders can affect the liver. This spectrum of acute and chronic liver diseases in children differs among populations from various parts of the world because of inherent differences in genetic and environmental factors. This review article provides a concise overview of important paediatric liver disorders prevalent in Singapore and discusses the epidemiology and outcomes of these conditions specific to our local context.

*Keywords:* cholestasis, hepatitis, liver disease, paediatrics

## INTRODUCTION

The liver is the largest intra-abdominal organ that performs a myriad of key metabolic functions and processes in the body. It plays a vital role in carbohydrate, lipid and protein metabolism and synthesis; bilirubin and bile acid transport; and drug metabolism and detoxification. These functions, in turn, affect other physiologic processes in the other systems, including the haematologic, endocrine, skeletal, immunologic and central nervous system.<sup>(1)</sup> Hence, a wide spectrum of disorders can affect the liver, and the complications arising from fulminant or decompensated liver disease are often severe and multisystemic.

The aetiologies of acute and chronic liver disease in children differ in various parts of the world, most likely owing to inherent differences in genetic and environmental factors. For example, viral hepatitis is still considered more prevalent in Asian populations, whereas certain genetic conditions such as alpha-1 antitrypsin deficiency or cystic fibrosis-associated liver disease are more likely to be diagnosed in Western populations. By contrast, biliary atresia (BA), the aetiology of which is still unclear, affects patients worldwide, but has a seemingly higher incidence in Asian countries such as Japan and Taiwan.<sup>(2)</sup>

Through this review article, we aim to provide a concise overview of the paediatric liver diseases that are prevalent in Singapore, with specific emphasis on the local data on epidemiology, management and outcomes.

## LIVER DISORDERS PRESENTING IN INFANCY

### Anatomic/Structural disorders

#### *Biliary atresia*

BA is a fibro-obliterative disease of the extrahepatic and intrahepatic bile ducts, presenting typically with cholestasis and acholic stools in early infancy. The incidence of BA appears to be higher in Asia, and Taiwan and Japan have reported incidences of 1 in 5,000 and 10,000 live births, respectively.<sup>(2,3)</sup> In comparison, the incidence rates in the United Kingdom and Europe range from 1 in 15,000 to 1 in 20,000 live births.<sup>(4,5)</sup> In

Singapore, around three to five new cases of BA are diagnosed annually, which equates to an estimated incidence of 1 in 10,000 live births. Although BA is considered a rare condition, it is the leading cause of chronic liver disease in childhood and is the most common indication for liver transplantation in children.<sup>(6)</sup> The cause of BA remains unknown, although there appear to be two distinct phenotypes: a syndromic form with prenatal onset and association with other congenital anomalies (most notably cardiac and splenic malformations) accounts for 10%–20% of cases, and an acquired form of isolated BA represents 80%–90% of cases. BA with splenic malformation is exceedingly rare in Singapore, with no such cases reported in our local series.<sup>(7)</sup> Although the cause of BA remains unknown, it is likely to be multifactorial, with an interplay of a combination of genetic, infective/viral, pro-inflammatory and toxic factors.<sup>(2)</sup>

Diagnosis is suspected based on typical findings of conjugated hyperbilirubinaemia associated with pale or acholic stool in a young infant. On ultrasonography, the gallbladder (GB) is absent, contracted and/or dysplastic even after a four-hour fast, and the triangular cord sign (hyperechogenic liver hilum) may be present. The GB ghost triad, consisting of GB <1.9 cm, lack of smooth/complete echogenic mucosal lining with an indistinct wall and irregular/lobular contour, was demonstrated in 30 out of 31 babies with BA in a study conducted in Singapore by Tan Kendrick et al, and was found to be an accurate sign for the diagnosis of BA.<sup>(8)</sup> A hepatobiliary iminodiacetic acid (HIDA) scan is a radioisotope excretion study that typically shows good hepatic uptake but absent excretion into the intestines within 24 hours. Unfortunately, the finding of absent radioisotope excretion on HIDA scan is not specific for BA. Liver histology shows evidence of extrahepatic biliary obstruction by varying degrees of portal tract fibrosis, ductular proliferation and cholestasis with bile plugs.<sup>(2)</sup> Operative cholangiogram performed at the time of surgery is considered the gold standard for the diagnosis of BA.

The Kasai portoenterostomy (KP) is a surgical procedure that aims to re-establish bile flow and alleviate biliary obstruction. Substantial observational evidence shows that earlier diagnosis

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and surgical intervention result in better outcomes in terms of preservation of native liver function.<sup>(3,9,10)</sup> However, various international studies have reported jaundice clearance rates of 40%–60% at six months after KP,<sup>(11,12)</sup> and progressive biliary fibrosis and cirrhosis still occur in the majority of cases. Retrospective local single-institution data comprising 72 patients over a 27-year period reported an overall six-month jaundice clearance rate of 55.6%.<sup>(13)</sup> Post-KP corticosteroids have been used in some centres as an adjuvant therapy,<sup>(14)</sup> which may reduce the ongoing inflammation that contributes to the progressive biliary fibrosis; however, the benefit of post-KP corticosteroids remains controversial, and hence, this practice has not been universally adopted.<sup>(12)</sup>

Cholangitis is a frequent complication in BA, with an incidence of 64.3%, which exerts a significant burden on healthcare and financial resources.<sup>(15)</sup> In a study published in 2014, Lee et al found that patients with BA in Singapore experienced an average of 3.6 episodes of cholangitis, and the average length of hospital stay per episode was 15 days, amounting to an estimated cost of S\$8986.61.<sup>(15)</sup> Despite the use of extended courses of prophylactic perioperative antibiotics together with the addition of post-KP corticosteroids, Goh et al were unable to demonstrate a reduction in cholangitis rates in the first two years after KP in their cohort of patients with BA (1.44 vs. 1.85 episodes per patient-year,  $p = 0.13$ ).<sup>(16)</sup>

Even after 'successful' KP, children with BA will have some degree of hepatic fibrosis or cirrhosis. Disease progression and eventual development of complications associated with portal hypertension and liver decompensation occur in two-thirds of patients. In Singapore, a 72% survival rate has been observed in patients with their native livers at two years after KP and a 46% survival rate has been observed at five years after KP.<sup>(7)</sup> BA remains the most common indication for liver transplantation among children in Singapore.<sup>(17)</sup>

### **Choledochal malformation**

Choledochal malformation is characterised by inherent dilatation of a part of or the entire biliary tree, and can be categorised into distinct anatomic subtypes. Type I, which describes the classical cystic or fusiform dilatation of the common bile duct, is the most common type, accounting for 85% of the cases. Choledochal malformations are reported to be more common in Asians than in Western populations, and a marked female predominance has been observed.<sup>(18)</sup> The pathogenesis is postulated to be related to an abnormal pancreatobiliary junction that promotes the reflux of activated pancreatic enzymes into the proximal bile ducts, leading to damage and weakening of the biliary wall and resultant dilatation. By contrast, intrahepatic ductal dilatations in types IV and V are more probably the result of disruption to embryonic ductal plate remodelling.

Choledochal malformations may present in infants and children with obstructive jaundice, cholangitis, abdominal mass and/or pancreatitis, but can present late into adulthood. Choledochal cysts may sometimes be identified prenatally on routine antenatal scans. For extrahepatic choledochal

malformations, surgical resection of the dilated extrahepatic bile duct and reconstruction with a Roux-en-Y hepaticojejunostomy is the standard approach. Complete cyst excision has shown favourable outcomes, based on a local study reported by Joseph et al.<sup>(19)</sup> Liver transplantation is a viable option for patients who develop complications from Caroli's disease.

### **Metabolic liver disorders**

Depending on the specific individual disease, metabolic liver disorders could present at birth with hydrops fetalis, in infancy with cholestasis or acute liver failure, or later in childhood with acute liver failure, chronic liver disease, and/or isolated organomegaly. The diagnosis of such metabolic conditions has been expedited in recent times with the availability of rapid gene sequencing panels. Many of these conditions are inherited in an autosomal recessive pattern, and parental consanguinity is a recognised risk factor.

Fortunately, metabolic liver disorders are relatively rare in Singapore. For example, galactosaemia, tyrosinaemia and alpha-1-antitrypsin deficiency, which are important causes of acute or chronic liver failure in the West, are uncommon locally. Having said that, if a young child or infant presents with acute liver failure, the possibility of an underlying metabolic disease should be considered. According to data from Western countries, metabolic disease as a cause of acute liver failure was identified in 15% of children presenting below the age of three years and in 7% of children presenting at 3–18 years.<sup>(20)</sup> In our own local study, a metabolic cause was identified in 38.9% of children presenting with acute liver failure under 12 months of age.<sup>(21)</sup>

A detailed review of the full spectrum of metabolic disorders is beyond the scope of this article. However, two metabolic disorders of local importance are summarised here.

### **Citrin deficiency**

Citrin deficiency, or citrullinaemia type 2, is an autosomal recessive disorder caused by mutations in SLC25A13 gene located on chromosome 7q21. This condition has a high prevalence in East Asian races, with carrier frequencies of 1:112 in Koreans, 1:69 in Japanese and 1:48 in Southern Chinese individuals.<sup>(22,23)</sup> A carrier frequency of 1 in 41 has been reported for citrin deficiency in Singapore.<sup>(24)</sup> Citrin is a mitochondrial aspartate-glutamate carrier associated with the urea cycle, which is expressed mostly in the liver. Mutation in the gene causes disruption in a diverse range of metabolic pathways, including the urea cycle, aerobic glycolysis, gluconeogenesis (with resultant hypoglycaemia) and, possibly, fatty acid synthesis. Accumulation of nicotinamide adenine dinucleotide in hepatocyte cytosol also inhibits galactose metabolism, resulting in galactosuria and secondary galactosaemia. Citrin deficiency can present in three distinct age-dependent phenotypes, namely neonatal intrahepatic cholestasis of citrin deficiency (NICCD), failure to thrive and dyslipidaemia caused by citrin deficiency in older children, and recurrent hyperammonaemia and neuropsychiatric symptoms in adults with citrullinaemia type II (CTLN2).<sup>(23)</sup>

In NICCD, in particular, infants present with early-onset neonatal hepatitis with cholestasis, hypoglycaemia and hypergalactosaemia. Typical biochemical features include hyperammonaemia; hypoalbuminaemia; and increased plasma levels of citrulline, tyrosine, threonine, arginine and methionine. In East Asian races, the presence of positive urinary reducing substance may be more indicative of NICCD rather than classic galactosaemia (secondary to reduced galactose-1-phosphate uridyl transferase activity), which is more prevalent in Western populations.<sup>(25)</sup> Initial management involves supplementation with lactose-free formula with medium-chain triglyceride and fat-soluble vitamins. The hepatitis appears to resolve spontaneously in most cases, usually within the first year of life, although in rare circumstances, it can progress to liver failure necessitating transplantation. In infants with resolved NICCD, features of CTLN2 may develop in later years; hence, ongoing health surveillance into adulthood is essential.

### **Glycogen storage disease**

Glycogen storage diseases (GSD) are due to defects of glycogen synthesis or breakdown with resultant abnormal storage and mobilisation of glycogen. They have a number of subtypes, each with a specific enzyme defect. The liver and/or muscle may be affected. GSD type Ia/b and type III are most commonly encountered locally, but GSD type IV, VI and IX, which are less common, can also involve the liver, with varying severity of liver dysfunction, hepatomegaly, hypoglycaemia, hyperlipidaemia and lactic acidemia. Dietary management to prevent hypoglycaemia is the mainstay of treatment. Surveillance for hepatic adenomas is important, as patients are at a risk of malignant transformation. Certain subtypes such as GSD type IV and IXb/c may be associated with more severe liver dysfunction that can progress to cirrhosis and portal hypertension.<sup>(26)</sup> Liver transplantation is indicated for progressive liver failure, symptomatic multiple hepatic adenomas, hepatocellular carcinoma or failure to achieve metabolic control. Successful long-term outcome with improvement in metabolic control in GSD type 1 has been documented following liver transplantation in Singapore.<sup>(27)</sup>

### **Genetic disorders**

#### **Alagille syndrome**

Alagille syndrome is an autosomal dominant condition arising from mutations in either JAG1 (95% of cases) or NOTCH2 (5% of cases), with an estimated frequency of 1 in 30,000.<sup>(28)</sup> This syndrome is rare in Singapore, with a new case diagnosed every four to five years. Features include cholestasis with paucity of intralobular bile ducts on histology, cardiac disease (peripheral pulmonary stenosis), skeletal anomalies with butterfly thoracic vertebrae, posterior embryotoxon seen on slit-lamp examination of the eyes and characteristic facies (triangular face, prominent forehead, deep-set eyes, small-pointed chin). There is a lack of genotype-phenotype correlation in Alagille syndrome, and clinical manifestations may vary in affected members of the same family. Management of a child with Alagille syndrome involves alleviation of pruritus, monitoring and treatment of dyslipidaemia,

optimisation of nutrition and provision of fat-soluble vitamin supplementation. Liver transplantation is reserved mainly for advanced or decompensated cirrhosis or for patients with poor quality of life from intense/refractory pruritus. Genetic counselling and family screening are important, particularly to accurately assess the risk in further children.

### **Progressive familial intrahepatic cholestasis**

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic conditions that affect bile metabolism and transport. Four genes have been previously identified to be implicated in PFIC, namely FIC1 (PFIC1 or Byler's disease), ABCB11 (PFIC2), MDR3 (PFIC3) and TJP2 (PFIC4). More recently, mutations in NR1H4 and MYO5B that manifest as PFIC-phenotype have also been identified. All PFIC subtypes present with low gamma-glutamyl transferase cholestasis in infancy, with the exception of PFIC3. The diagnosis of PFIC is now aided by gene panels using next-generation sequencing technologies. Management involves the use of ursodeoxycholic acid, alleviation of pruritus with medications or surgical biliary diversion, and optimisation of nutrition. Liver transplantation is indicated for progressive liver disease, which will be curative for PFIC types 2, 3 and 4. In PFIC1, extrahepatic manifestations (diarrhoea, pancreatitis, sensorineural deafness), which are the hallmark of this subtype, may worsen after transplantation.<sup>(28)</sup>

Maralixibat is a novel, potent inhibitor of the apical sodium-dependent bile acid transporter/ileal bile acid transporter on the luminal surface of ileal enterocytes, which has shown early promise in alleviating pruritus as well as in improvement/normalisation of liver biochemistry in patients with PFIC.<sup>(29)</sup> Singapore is currently the only site from the Asia Pacific region that is participating in a worldwide, multicentre randomised-controlled phase 3 study to evaluate the efficacy and safety of Maralixibat in the treatment of patients with PFIC.<sup>(30)</sup>

### **Neonatal hepatitis in pre-term infants and multifactorial liver injury**

Pre-term infants are at a risk of developing cholestasis owing to immaturity of the hepatobiliary system, exacerbated by other events such as hypoxia, prolonged fasting, parenteral nutrition, drug toxicity and sepsis.<sup>(31)</sup> In a local study examining the causes of early-onset neonatal cholestasis before 14 days of life, secondary multifactorial liver injury was the most common cause. This liver dysfunction was observed to resolve typically within three months in all surviving infants with supportive management.<sup>(32)</sup>

## **LIVER DISORDERS PRESENTING IN OLDER CHILDREN**

### **Viral hepatitis**

Hepatitis B virus (HBV) infection is the commonest viral hepatitis in Singapore. Although Singapore is in an endemic region for HBV infection, the HBV carriage rate is relatively low, at 5%–6%.<sup>(33)</sup> Chronic HBV infection is defined as having positive serum HBsAg for more than six months and is strongly associated with the risk of hepatocellular carcinoma (HCC), even in the paediatric age

group. Individuals infected perinatally are more likely to develop chronic HBV infection (90%) than those infected in adulthood (1%). A local study by Chan et al during the pre-vaccination era in the early 1980s showed a vertical transmission rate of 48% from HBsAg carrier mothers to their infants.<sup>(34)</sup> In a separate study by Quak et al, the prevalence of HBsAg carriers among infants in Singapore was 8.9%.<sup>(35)</sup> With the introduction of universal HBV vaccination for all newborns in Singapore since 1987 and the use of passive immunisation with HBV-immunoglobulin for infants born to HBeAg-positive mothers, vertical transmission rates have reduced tremendously, with protection rates of up to 90%–98% achieved.<sup>(36)</sup> Lee et al reported that the overall rate of failure of vaccine immunoprophylaxis in term infants delivered by HBV-carrier mothers in Singapore was low at 2.7%, with no difference in failure rates between monovalent and combination (monovalent plus combination '6-in-1') HBV vaccines.<sup>(37)</sup> Another similar local study reported adequate antibody response in preterm infants of HBV-carrier mothers using a three-to-four dose (depending on birth weight) HBV vaccination schedule.<sup>(38)</sup>

Chronic HBV infection in children is generally a mild disease, and is marked by four phases: (1) immune tolerant phase, characterised by normal liver enzymes, high HBV DNA levels, positive HBe and HBs antigens; (2) immune clearance phase, characterised by active liver inflammation with increased liver enzymes, decline in HBV DNA levels and seroconversion to anti-HBe antibodies; (3) inactive carrier phase, with low/undetectable HBV DNA levels, normal liver enzymes and positive anti-HBe antibody; and (4) reactivation phase, which occurs in 5% of anti-HBe-positive children, which leads to increase in HBV DNA levels and development of HBeAg-negative active hepatitis.

The main goals of therapy are to prevent disease progression and reduce the risk of cirrhosis and HCC. HBsAg clearance, however, is difficult to achieve with the current treatment options. Guidelines recommend that treatment should be considered in children with persistently elevated alanine transaminase (>1.5 times the upper limit of normal) for at least six months, and in those with high HBV DNA levels.<sup>(36)</sup> Drugs used for treatment of chronic HBV in children include interferon-alpha and nucleos(t)ide analogues such as lamivudine, entecavir, adefovir and tenofovir, each with specific minimum-age cut-offs. The challenges with HBV treatment option are the need for regular subcutaneous injections and the side effects associated with interferon-alpha, and an indefinite treatment duration and risk of antiviral resistance in relation to the use of nucleos(t)ide analogues. Locally, we have observed that spontaneous HBe seroconversion occurs in about 30% of children in the second decade of life, and we continue to maintain a relatively high threshold to initiate treatment for children with chronic HBV infection. Other viral hepatitis (hepatitis A, C and E) cases are relatively rarer among children in Singapore.

### Autoimmune liver disease

Paediatric autoimmune liver disease (AILD) can be classified into two types: classical autoimmune hepatitis (AIH) and the AIH-sclerosing cholangitis overlap syndrome (or autoimmune

sclerosing cholangitis, ASC).<sup>(39)</sup> These are progressive inflammatory liver disorders that are associated with positive auto-antibodies and raised immunoglobulin G. Two types of AIH are recognised: AIH type 1 with positive antinuclear antibody (ANA) and/or smooth muscle antibody, and AIH type 2 with positive anti-liver/kidney microsome (anti-LKM) and/or anti-liver cytosol type 1 antibodies. AIH-1 affects children and adults, whereas AIH-2 affects younger children and has a more fulminant presentation. ASC is significantly more common in children than in adults, and is usually characterised by concomitant features of AIH, sclerosing biliary disease on histology ('small-duct disease') and/or cholangiogram, and a strong association with inflammatory bowel disease. The prevalence of AIH in Singapore was reported to be 4 per 100,000 children.<sup>(40)</sup> Low et al described a series of 10 Singaporean children (six female) with AIH with a median age of five years, of whom seven had AIH-1 and three had ASC, and the majority were in biochemical remission.<sup>(41)</sup>

First-line management for both AIH and ASC is immunosuppressive treatment with prednisolone, and azathioprine is commonly added as a steroid-sparing agent. For patients who do not respond to first-line treatment, mycophenolate mofetil and calcineurin inhibitors may be used. Ursodeoxycholic acid is also added to the treatment for patients with ASC. Children with AIH who respond to immunosuppression have a good long-term prognosis. ASC is associated with worse outcome because of progression of bile duct disease that does not respond to immunosuppressive treatment.<sup>(39)</sup> Lee et al retrospectively reviewed children with primary sclerosing cholangitis and ASC in association with inflammatory bowel disease from Malaysia and Singapore, and reported that after a median follow-up period of 4.7 years, 75% of the children showed active persistent disease and 12.5% progressed to liver failure.<sup>(42)</sup> Progression to cirrhosis and end-stage liver failure is an indication of liver transplantation. Recurrence of AIH is a recognised complication after liver transplantation.

### Wilson disease

Wilson disease is caused by mutations in the ATP7B gene encoding a copper-transporting ATPase that is involved in copper excretion in the bile. Progressive accumulation of copper in the liver and other organs such as the central nervous system, cornea and kidneys leads to a wide range of clinical manifestations. Children present with liver diseases ranging from asymptomatic, incidental finding of abnormal liver biochemistry to acute hepatitis, hepatomegaly or acute liver failure. Neuropsychiatric symptoms usually develop later, from the second decade of life. Pathognomonic Kayser-Fleischer rings may be detected on slit-lamp examination but are usually more common in children with central nervous system involvement. Coombs-negative haemolytic anaemia has also been found to be associated with this condition. Diagnosis is suspected when serum caeruloplasmin is low and 24-hour urinary copper excretion is elevated at baseline and/or exceeds 25 µmol/24 hours after penicillamine challenge. Liver copper content on a biopsy tissue is not routinely measured because of lack of facility to perform this test in Singapore. Liver

histology may show increased copper deposition on rhodamine staining; however, this is neither a sensitive nor specific feature. In recent times, diagnosis of Wilson disease is preferably confirmed by mutation analysis of the ATP7B gene, which can also be used to screen asymptomatic family members.

Treatment is based on reduction of excess copper. This can be achieved by zinc salt, which acts by blocking intestinal absorption of copper, or copper-chelating agents such as D-penicillamine and trientine. Copper-chelating therapy could carry a risk of worsening of neurological symptoms. Avoidance of copper-rich food (shellfish, nuts, chocolate, mushrooms, organ meats) is advised until remission of disease is achieved.<sup>(43)</sup>

### Non-alcoholic fatty liver disease

In recent years, non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease, affecting a quarter of the global population, and has become one of the leading indications for liver transplantation in adults.<sup>(44)</sup> The prevalence of obesity in Asian countries has been increasing over the past three decades, and the current prevalence rates of NAFLD in China, Japan, India and Korea range between 25% and 40%.<sup>(45)</sup> Childhood obesity is seeing a similar trend, with increasing global prevalence in recent decades. The prevalence of overweight/obese children in Singapore is estimated to be 12.0% among primary school students and 10.5% among secondary school students.<sup>(46)</sup> Given its close association with obesity, it is expected that the incidence of NAFLD in children has correspondingly increased. Based on our personal experience, the volume of referral of new paediatric cases of NAFLD to the gastroenterology/liver clinics has been steadily increasing in the past two decades. In addition to sedentary lifestyle and dietary habits, other risk factors found to be associated with NAFLD include diabetes and insulin resistance, male sex and genetics factors such as PNPLA3 polymorphisms.<sup>(47)</sup>

NAFLD is usually asymptomatic, and patients typically present as part of screening because of obesity or because of an incidental finding on liver biochemistry or abdominal imaging ordered for other indications. Even so, it has been shown that the NAFLD in children appears to be more severe than that in adults, with 15% of children having stage 3 fibrosis or higher at diagnosis.<sup>(48)</sup> Owing to an earlier onset, NAFLD in children may represent an aggressive phenotype of the disease compared with adult-onset NAFLD. Hence, screening for NAFLD in at-risk children (those with obesity, metabolic syndrome or a family history) is recommended, as detection before the onset of irreversible, end-stage liver disease is crucial. At the same time, before arriving at a diagnosis of NAFLD, clinicians should exclude other causes of hepatic fatty infiltration and/or elevated liver enzymes such as viral hepatitis, metabolic disorders, Wilson disease and use of hepatotoxic medications. Increasingly more paediatric centres are adopting the use of vibration-controlled transient elastography, a technique well-validated in adults with NAFLD, as a noninvasive tool to assess liver fibrosis.<sup>(49)</sup>

Management is centred on lifestyle modification to improve diet and increase physical activity, with weight loss as the main

goal. Asian data support a 7%–10% weight loss target, although there is evidence to suggest that NAFLD can improve with 3%–5% weight reduction.<sup>(45)</sup> With regard to pharmacologic therapy, there has been research interest in the use of various medication and supplements such as Vitamin E, metformin, ursodeoxycholic acid, docosahexaenoic acid and probiotics in the management of paediatric NAFLD. However, no medication or supplement has been shown to be of significant therapeutic value.<sup>(48)</sup> Bariatric surgery has been shown to improve obesity and diabetes as well as reduce hepatic steatosis and fibrosis in adults.<sup>(50)</sup> However, owing to limited data in paediatrics, bariatric surgery is not recommended as a specific therapy for NAFLD, although it may be considered for selected adolescents with BMI >35 kg/m<sup>2</sup> who have noncirrhotic NAFLD and other serious comorbidities such as diabetes or sleep apnoea that may improve with weight loss surgery.<sup>(48)</sup>

### Acute liver failure

Paediatric acute liver failure (PALF) is a rare but life-threatening condition characterised by hepatocellular necrosis and rapid deterioration in liver function in the absence of a pre-existing chronic liver disease.<sup>(51)</sup> The aetiology of PALF varies widely depending on the age of the child, and geographic and socioeconomic factors. Viral hepatitis A and B are reported to be the major causes of PALF in Asia, whereas indeterminate or seronegative hepatitis is the most common cause in Western populations.<sup>(52)</sup> Mortality rate without a liver transplant can be as high as 70%. Medical management of PALF is focused on supportive care, prevention and treatment of associated complications, investigation of the cause and provision of disease-specific treatment if a treatable cause is identified. Liver transplantation is a life-saving procedure in fulminant PALF in which spontaneous recovery does not occur despite medical therapy. In regions where shortage of size-matched deceased-donor organs remains a challenge, particularly in Asian countries such as Singapore, living-donor liver transplantation is an important and viable option, with comparatively favourable outcomes.<sup>(53,54)</sup>

A recent study in Singapore comprising 34 children with PALF found that the top three aetiologies were indeterminate (41.2%), metabolic disorders (26.5%) and infectious (26.5%).<sup>(21)</sup> In fact, no cases of hepatitis A or B infection causing PALF were observed. Spontaneous recovery was observed in 38.2% of the patients, and the overall mortality rate was 47.1%. Out of six patients who underwent living-donor liver transplantation, five (83.3%) survived at one year after transplantation.

## CONCLUSION

The liver is involved in many critical metabolic processes in the body. A single defect, mutation or impairment affecting any of these pathways can lead to significant downstream effects on liver function as well as other organ systems, giving rise to an extremely wide and varied spectrum of paediatric liver disease. The current technological advances in diagnostics and constant improvements in therapeutic options in paediatric hepatology

will allow us to maximise the long-term outcomes and quality of life of children with liver disease in Singapore.

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