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# Pediatric cholestatic liver disease: Successful transition of care

## ABSTRACT

With recent medical advances, more patients with childhood-onset liver disease and more pediatric liver transplant recipients are surviving into adulthood, generating distinctive challenges to adult primary care providers. Young adults with pediatric liver disease are a unique cohort of patients with different evaluation and monitoring strategies, treatment, complications, and comorbidities. This creates a critical need for successful transition of these patients into adult care, with incorporation of a formal transitional model and multidisciplinary team.

## KEY POINTS

The causes of cholestasis in children are different from those in adults, with genetic inherited causes more common in childhood.

Cholestasis in children can be caused by biliary tract obstruction such as in biliary atresia or defects in forming and excreting bile acids and other components of bile.

With the growing number of people with childhood-onset liver disease surviving into adulthood, it is important for internists to be aware of unique problems and challenges in continuing management of this population.

In addition to medical comorbidities, these patients may also have impaired psychosocial functioning and quality of life.

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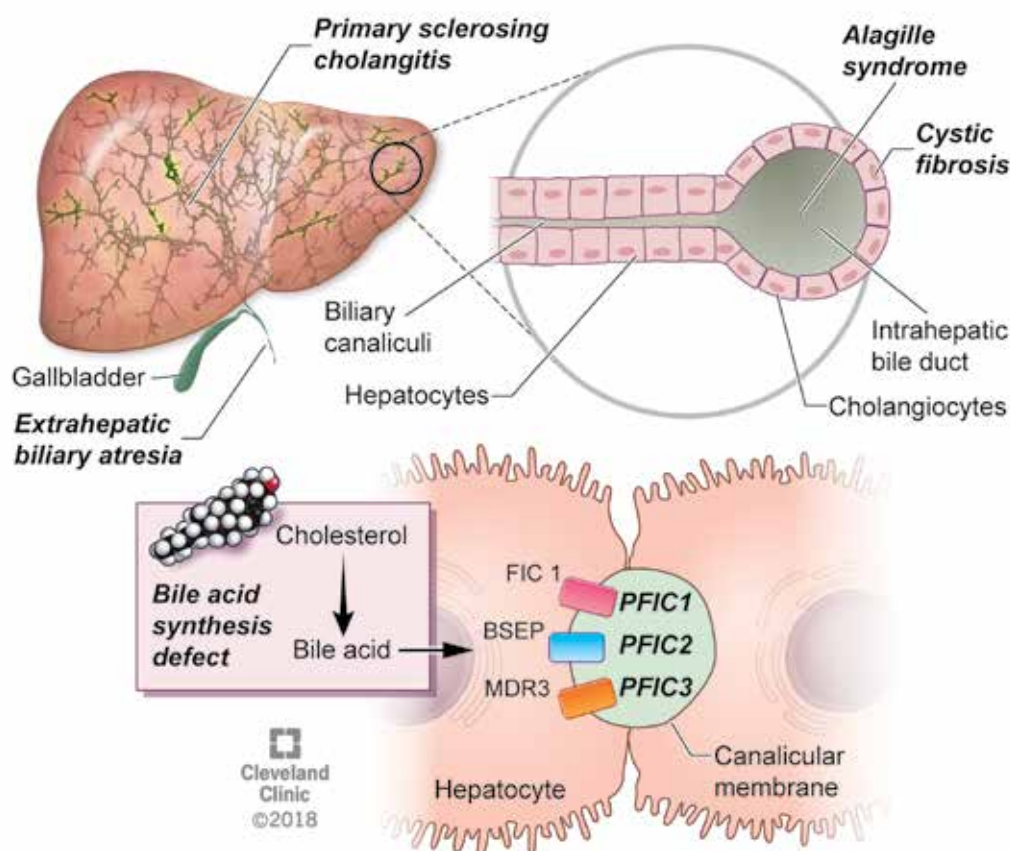
**T**HANKS TO ADVANCES in medical science and our understanding of inherited and acquired liver disease, many more children with acquired or congenital liver disease survive into adulthood than they did 2 decades ago. Improvements in immunosuppression and surgery have increased the chances of pediatric liver transplant recipients reaching adulthood, with a survival rate of 75% at 15 to 20 years.<sup>1</sup>

The causes of cholestasis in children are different from those in adults (**Figure 1**). Pediatric cholestasis is caused either by genetic defects that affect the process of synthesis, processing, or secreting bile, or by mechanical obstruction of the biliary tract, the classic example being biliary atresia.

With the growing number of adult patients with pediatric-onset liver disease, internists and adult hepatologists need to be aware of these liver diseases and develop expertise to manage this challenging group of patients. Moreover, young adults with pediatric-onset chronic liver disease pose distinct challenges such as pregnancy, adherence to medical regimens, and psychosocial changes in life.

These patients need a “transition of care” rather than a “transfer of care.” Transition of care is a multifaceted process that takes the medical, educational, and psychosocial needs of the patient into consideration before switching their care to adult care physicians, whereas transfer of care is simply an administrative process of change to adult care without previous knowledge of the patients.<sup>2</sup>

In this article, we discuss relatively common types of inherited childhood-onset cho-



BSEP = bile salt export pump; FIC 1 = familial intrahepatic cholestasis protein 1; MDR3 = multidrug resistance protein 3; PFIC = progressive familial intrahepatic cholestasis

**Figure 1.** Cholestasis in children can be caused by biliary tract obstruction such as in biliary atresia (top) or defects in forming and excreting bile acids and other components of bile (bottom).

lestatic disease and their implications and management in adulthood (Table 1). Other acquired or rare cholestatic diseases are beyond the scope of this article.

## ■ BILIARY ATRESIA

Biliary atresia is a progressive inflammatory fibrosclerosing cholangiopathy of unknown cause. Its prevalence varies with geographic location, ranging from 1 in 6,000 to 1 in 19,000, with the highest prevalence in Taiwan.<sup>3</sup>

Biliary atresia usually presents within the first few weeks of life, with progressive cholestasis leading to failure to thrive and to fat-soluble vitamin deficiency. Approximately 20% of patients have congenital splenic, gastrointestinal, genitourinary, cardiac, and venous malformations.<sup>4,5</sup> Untreated, biliary

atresia progresses to end-stage liver disease and death within 2 years.

The first-line treatment for biliary atresia is to establish biliary outflow with the Kasai procedure (hepatic portoenterostomy), in which a jejunal limb is anastomosed in a Roux-en-Y with the liver. The outcomes of the Kasai procedure depend on the timing of surgery, so timely diagnosis of biliary atresia is crucial. When the Kasai procedure is performed within 60 days of birth, biliary flow is achieved in up to 70% of patients; but if performed after 90 days, biliary flow is achieved in fewer than 25%.<sup>6</sup>

Long-term outcomes of biliary atresia in patients with their native liver have been reported in a few studies.

In a French study,<sup>7</sup> 743 patients with biliary atresia underwent the Kasai procedure at a median age of 60 days. Survival rates were

TABLE 1

## Implications of some childhood-onset liver diseases in adulthood

Liver disease	Implications in adulthood	Screening strategies in adulthood
<b>Biliary atresia</b>	<p>Progressive liver fibrosis, cirrhosis</p> <p>Portal hypertension with variceal hemorrhage</p> <p>Cholangitis</p> <p>Hepatopulmonary syndrome and portopulmonary hypertension</p> <p>Hepatocellular carcinoma</p> <p>Possible need for liver transplant</p>	<p>Periodic monitoring of liver function depending on severity of liver disease</p> <p>Screening for esophageal varices with upper endoscopy at least annually; primary prophylaxis can be considered with beta-blockers and endoscopic variceal ligation to prevent variceal bleeding</p> <p>Adequate treatment of cholangitis with oral or intravenous antibiotics depending on the severity of presentation; role of prophylaxis is unclear</p> <p>Screening for hepatopulmonary syndrome and portopulmonary hypertension with agitated saline echocardiography in appropriate clinical setting</p> <p>Ultrasonography of the abdomen and alpha-fetoprotein every 6 months or annually to screen for hepatocellular carcinoma</p>
<b>Alagille syndrome</b>	<p>No new onset of cardiac or liver disease with liver transplant being rare in adulthood</p> <p>Hepatocellular carcinoma</p> <p>Onset of renal manifestations such as hypertension or renal artery stenosis</p> <p>Neurovascular accidents such as stroke or intracranial hemorrhage</p> <p>Pregnancy complicated by severity of cardiac or liver disease</p>	<p>Annual ultrasonography and alpha-fetoprotein to screen for hepatocellular carcinoma</p> <p>Renal ultrasonography with Doppler to screen for renal vascular anomalies</p> <p>Magnetic resonance angiography every 5 years and before any major intervention to screen for intracranial vascular abnormalities</p> <p>Screening for any cardiac disease before conception</p> <p>Genetic counseling should be considered before conception</p>
<b>Progressive familial intrahepatic cholestasis (PFIC)</b>	<p>Adult-onset cholestasis</p> <p>Gallstones</p> <p>Hepatocellular carcinoma</p> <p>Intractable diarrhea</p> <p>Intrahepatic cholestasis of pregnancy</p> <p>Benign recurrent intrahepatic cholestasis</p>	<p>Management of extrahepatic manifestations, especially in PFIC 1</p> <p>Periodic assessment of liver function for low gamma-glutamyl transferase cholestasis after liver transplant in patients with PFIC 2</p> <p>Annual ultrasonography and alpha-fetoprotein to screen for hepatocellular carcinoma, cholangiocarcinoma and pancreatic adenocarcinoma in patients with PFIC 2</p>

57.1% at 2 years, 37.9% at 5 years, 32.4% at 10 years, and 28.5% at 15 years. In other studies,<sup>4-9</sup> the 20-year transplant-free survival rate ranged from 23% to 46%. Therefore, at least one-third of children with biliary atresia survive to adulthood with their native liver.

### Implications of biliary atresia in adulthood

Although the Kasai procedure improves biliary outflow, up to 70% of patients develop complications of biliary atresia such as progressive fibrosis, cirrhosis, portal hypertension, cholangitis, and hepatocellular carcinoma, even after a successful Kasai procedure.<sup>10</sup>

**Portal hypertension** with evidence of splenomegaly, thrombocytopenia, or ascites is found in two-thirds of long-term survivors of biliary atresia with a native liver, with variceal hemorrhage occurring in 30%.<sup>11</sup> Therefore, patients with biliary atresia who have evidence of portal hypertension should be screened for varices with upper endoscopy on an annual basis. Management of variceal hemorrhage in these patients includes the use of octreotide, antibiotics, variceal ligation, and sclerotherapy; primary prophylaxis can be achieved with beta-blockers and endoscopic variceal ligation.<sup>12</sup>

**Cholangitis** is frequent, occurring in 40% to 60% of biliary atresia patients after the Kasai procedure, and about one-fourth of these patients have multiple episodes.<sup>13</sup> The number of episodes of cholangitis negatively affects transplant-free survival.<sup>14</sup> Patients with cholangitis should be adequately treated with oral or intravenous antibiotics depending on the severity of presentation. The role of prophylaxis with antibiotics remains unclear.<sup>15</sup>

**Pulmonary complications** such as hepatopulmonary syndrome and portopulmonary hypertension can also occur in biliary atresia patients with a native liver. It is important for physicians to be aware of these complications and to screen for them, for example, with agitated saline echocardiography for hepatopulmonary syndrome and with echocardiography for portopulmonary hypertension. Timely screening is crucial, as the outcome of liver transplant depends on the severity at the time of transplant in these conditions, especially portopulmonary hypertension.

**Hepatocellular carcinoma** has been rarely reported in children with biliary atresia,<sup>16</sup> so well-defined guidelines for screening in young adults with biliary atresia are lacking. Most centers recommend screening with ultrasonography of the abdomen and alpha-fetoprotein measurement every 6 months or annually starting soon after the Kasai procedure, since hepatocellular carcinoma has been reported in children as young as age 2.<sup>16</sup>

**Transplant.** Adult hepatologists are faced with the challenging task of deciding when it is time for transplant, balancing the long-term complications of biliary atresia with the risk of long-term immunosuppression after trans-

plant. In addition, young adults with these complications may have preserved synthetic function, resulting in low Model for End-Stage Liver Disease (MELD) scores, which may complicate the process of listing for transplant.

**Neurocognitive deficits** are reported in children with biliary atresia,<sup>17</sup> but young adults with biliary atresia generally have reasonable cognitive function and prospects for education and employment.

**Pregnancy** with successful outcomes has been reported.<sup>8</sup>

## ■ ALAGILLE SYNDROME

Alagille syndrome is an autosomal-dominant multisystemic disease caused by mutations in the *JAG1* gene (accounting for > 95% of cases) and the *NOTCH2* gene, with highly variable expression.<sup>18</sup>

Extrahepatic manifestations include butterfly vertebral defects, facial dysmorphism (eg, deep-set and low-set eyes, with characteristic “triangular” facies), posterior embryotoxon (a congenital defect of the eye characterized by an opaque ring around the margin of the cornea), peripheral pulmonary stenosis, renal abnormalities, and vascular malformations.

Hepatic manifestations vary from asymptomatic laboratory abnormalities to progressive cholestasis starting in early infancy with intractable pruritus, xanthomas, failure to thrive, and end-stage liver disease requiring liver transplant in childhood in 15% to 20% of patients.<sup>19</sup>

## Implications of Alagille syndrome in adulthood

**Transplant.** Interestingly, the phenotype of hepatic disease is already established in childhood, with minimal or no progression in adulthood. Most children with minimal liver disease experience spontaneous resolution, whereas those with significant cholestasis might ultimately develop progressive liver fibrosis or cirrhosis requiring liver transplant in childhood. Only a small subset of children with minimal cholestasis progress to end-stage liver disease in late childhood or early adulthood.<sup>20</sup> Therefore, liver transplant for progressive liver disease from significant cholestasis

These patients need a ‘transition of care’ rather than a ‘transfer of care’



If untreated, biliary atresia progresses to end-stage liver disease and death within 2 years

almost always occurs in childhood, usually between ages 1 and 4.<sup>21</sup>

In a retrospective study comparing post-transplant outcomes in children with Alagille syndrome and biliary atresia, 1-year patient survival was excellent overall in children with Alagille syndrome, although slightly lower than in children with biliary atresia, most likely owing to extrahepatic morbidities of Alagille syndrome and especially the use of immunosuppression in those with renal disease.<sup>21</sup> Similarly, 1- and 5-year patient and graft survival outcomes of liver transplant in adults with Alagille syndrome were also excellent compared with those who received a liver transplant in childhood for Alagille syndrome or in adulthood for biliary atresia.<sup>22</sup>

**Hepatocellular carcinoma** has occurred in these patients in the absence of cirrhosis, which makes implementation of prognostic and surveillance strategies almost impossible to design for them. Annual ultrasonography with alpha-fetoprotein testing might be applicable in Alagille syndrome patients. However, deciding which patients should undergo this testing and when it should start will be challenging, given the paucity of data.

**Cardiovascular disease.** Cardiac phenotype is also mostly established in childhood, with the pulmonary vasculature being most commonly involved.<sup>19</sup> In contrast, renal and other vascular abnormalities can manifest in adulthood. Renal manifestations vary and include structural anomalies such as hyperechoic kidneys or renal cysts, which can manifest in childhood, and some abnormalities such as hypertension and renal artery stenosis that can manifest in adulthood.<sup>23,24</sup>

Vasculopathy is reported to involve the intracranial, renal, and intra-abdominal blood vessels.<sup>25</sup> Neurovascular accidents such as stroke and intracranial hemorrhage can occur at any age, with significant rates of morbidity and death.<sup>26</sup> Therefore, some experts recommend magnetic resonance angiography every 5 years and before any major intervention to prevent these devastating complications.<sup>20</sup>

**Pregnancy.** Successful pregnancies have been reported. Preexisting cardiac and hepatic disease can complicate pregnancy depending on the severity of the disease. Because of the autosomal-dominant pattern of inheritance,

infants have a 50% risk of the disease, so genetic counseling should be seriously considered before conception.<sup>27</sup> Prenatal diagnosis is possible, but the lack of genotype-phenotype correlation precludes its use in clinical practice.

## ■ PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of autosomal-recessive conditions associated with disruption of bile formation causing cholestatic liver disease in infants and young children. Three types have been described, depending on the genetic mutation in the hepatobiliary transport pathway:

- **PFIC 1** (Byler disease) is caused by impaired bile salt secretion due to mutations in the *ATP8B1* gene encoding for the familial intrahepatic cholestasis 1 (FIC 1) protein
- **PFIC 2** is caused by impaired bile salt secretion due to mutations in the *ABCB11* gene encoding for the bile salt export pump (BSEP) protein
- **PFIC 3** is caused by impaired biliary phospholipid secretion due to a defect in *ABCB4* encoding for multidrug resistance 3 (MDR3) protein.<sup>28</sup>

PFIC 1 and 2 manifest with low gamma-glutamyl transferase (GGT) cholestasis, whereas PFIC 3 presents with high GGT cholestasis.

PFIC 1 and PFIC 2 usually cause cholestasis in early infancy, but PFIC 3 can cause cholestasis in late infancy, childhood, and even adulthood.

Because *ATP8B1* is expressed in other tissues, PFIC 1 is characterized by extrahepatic manifestations such as sensorineural hearing loss, growth failure, severe diarrhea, and pancreatic insufficiency.

## Implications of PFIC in adulthood

PFIC 1 and 2 (low-GGT cholestasis) are usually progressive and often lead to end-stage liver disease and cirrhosis before adulthood. Therefore, almost all patients with PFIC 1 and 2 undergo liver transplant or at least a biliary diversion procedure before reaching adulthood. Intractable pruritus is one of the most

challenging clinical manifestations in patients with PFIC.

First-line management is pharmacologic and includes ursodeoxycholic acid, antihistamines (eg, hydroxyzine), bile acid sequestrants (eg, cholestyramine, colestipol), naltrexone, and rifampin, but these have limited efficacy.<sup>10</sup>

Most patients, especially those with PFIC 1 and 2, undergo a biliary diversion procedure such as partial external biliary diversion (cholecystojejunocutaneostomy), ileal exclusion, or partial internal biliary diversion (cholecystojejunocolic anastomosis) to decrease enterohepatic circulation of bile salts. The efficacy of these procedures is very limited in patients with established cirrhosis. Excessive losses of bile can occur through the biliary stoma, leading to dehydration in patients with external biliary diversion. In patients who are not candidates for biliary diversion, endoscopic nasobiliary drainage of pancreatobiliary secretions could be achieved by placing a catheter in the common bile duct; this has been reported to be effective in relieving cholestasis in a few cases.<sup>29</sup>

Liver transplant is needed in patients with progressive liver disease and intractable pruritus despite medical management and biliary diversion. Unlike in biliary atresia, liver transplant is not curative in PFIC 1, due to extrahepatic manifestations: patients with PFIC 1 can still have intractable diarrhea and pancreatitis after liver transplant. More importantly, allograft steatohepatitis with further progression to cirrhosis can occur after liver transplant in patients with PFIC 1. Interestingly, biliary diversion has been reported to improve graft steatosis and diarrhea after liver transplant.<sup>30</sup>

Although graft survival after transplant is good in patients with PFIC 2, recurrence of low-GGT cholestasis has been reported and is believed to be due to the formation of anti-bile salt export pump (anti-BSEP) antibodies by the host immune system in response to exposure to new proteins from the transplant graft.<sup>31</sup>

**Cancer.** The risk of malignancy, especially hepatocellular carcinoma, is also increased in PFIC 2, affecting nearly 15% of patients. Therefore, standard hepatocellular carcinoma surveillance with ultrasonography or alpha-fetoprotein testing or both is recommended

in patients with PFIC 2. Cholangiocarcinoma and pancreatic adenocarcinoma have also been reported in patients with PFIC 2.<sup>20</sup>

Incomplete penetrance of mutations in *ATP8B1* and *ABCB11* can cause recurrent episodes of cholestasis and pruritus with asymptomatic periods between episodes, referred to as benign recurrent intrahepatic cholestasis. Prognosis is usually good, with no progression to cirrhosis.<sup>32</sup>

**Pregnancy.** In contrast to FIC 1 and BSEP deficiency, MDR3 defects lead to a wide phenotypic spectrum depending on the type of mutation. Heterozygous mutation is associated with increased risk of development of cholestasis during pregnancy, which typically presents with generalized pruritus in the third trimester and is associated with adverse fetal outcomes. Intrahepatic cholestasis of pregnancy is usually treated with ursodeoxycholic acid, with reported improvement in pruritus, liver function, and pregnancy outcomes.<sup>33</sup>

In adults, drug-induced liver injury and idiopathic cirrhosis have also been described with MDR3 defects. Intrahepatic lithiasis and cholesterol gallstones can also occur with MDR3 defects as a result of impaired secretion of biliary phospholipid.<sup>32</sup> Despite intrahepatic cholestasis of pregnancy, successful outcomes have been reported in women with PFIC.<sup>20</sup>

## ■ OTHER CHILDHOOD-ONSET INHERITED CHOLESTATIC DISEASES

### Cystic fibrosis-associated liver disease

Nearly 40% of patients with cystic fibrosis develop liver disease.<sup>34</sup> Cystic fibrosis-associated liver disease encompasses a broad clinical spectrum including asymptomatic elevation of aminotransferases, neonatal cholestasis, hepatic steatosis, focal biliary cirrhosis, and multilobar cirrhosis. Cirrhosis and portal hypertension can occur in 5% to 10% of patients and is the third-leading cause of death in patients with cystic fibrosis.<sup>35</sup>

Risk factors for cystic fibrosis-associated liver disease include male sex, meconium ileus, and severe *CFTR* gene mutation (class I–III) with pancreatic insufficiency. Cystic fibrosis-related cirrhosis is more frequent in children and adolescents, whereas noncirrhotic portal hypertension and intrahepatic cholangiopa-

**Alagille syndrome tends to remain stable after childhood**

**PFIC 1 and 2  
(low-GGT  
cholestasis)  
usually progress  
and often lead  
to end-stage  
liver disease  
and cirrhosis  
before  
adulthood**

thies are more common in adults.<sup>36</sup>

Limited available studies support treatment with ursodeoxycholic acid in patients with cholestasis to delay the progression of liver disease, but the impact of this drug on long-term outcome is unknown.<sup>29</sup>

Most patients remain in compensated cirrhosis for many years before progressing to decompensated cirrhosis requiring liver transplant. Other indications for liver transplant include recurrent intractable variceal bleeding, hepatopulmonary syndrome, and portopulmonary hypertension. Combined liver and lung transplant may be considered in patients with advanced liver and lung disease. Outcomes after isolated liver or liver-lung transplant in cystic fibrosis patients have been comparable to those in patients with other liver diseases.<sup>37</sup>

## Defects in bile acid synthesis

Inherited defects of enzymes required for the synthesis of primary bile acids from cholesterol can cause cholestasis from impaired bile flow and production of hepatotoxic aberrant bile acids. The clinical presentation varies depending on the enzymatic defect and can range from liver disease of varying severity to neurologic manifestations. Idiopathic late-onset cholestasis and cirrhosis of unknown etiology have been reported in adults with bile acid synthesis defects.<sup>38,39</sup> Therefore, this diagnosis should be considered in cases of cryptogenic cirrhosis and other cholestatic features.

Treatment with primary bile acids (cholic acid) has been effective in most patients with defective bile acid synthesis.

## Primary sclerosing cholangitis

Primary sclerosing cholangitis is characterized by progressive obliteration of intrahepatic and extrahepatic bile ducts and is most commonly seen in patients with inflammatory bowel disease. Sclerosing cholangitis can also be secondary to other diseases in children such as immunodeficiency syndromes, Langerhans cell histiocytosis, cystic fibrosis, or sickle cell anemia.<sup>40</sup> Neonatal sclerosing cholangitis is a rare autosomal-recessive disease characterized by a severe form of cholangiopathy in neonates and young infants requiring transplant. It can be associated with Kabuki syndrome and neonatal ichthyosis-sclerosing cholangitis syndrome.

Treatment options are limited. Ursodeoxy-

cholic acid and oral vancomycin have variable efficacy. Liver transplant is needed in patients with decompensated cirrhosis. Patients with primary sclerosing cholangitis, especially adults, are at higher risk of developing cholangiocarcinoma, and therefore screening with ultrasonography or magnetic resonance imaging every 6 to 12 months is recommended.

The risk of preterm and cesarean deliveries may be elevated in women with primary sclerosing cholangitis, though data are limited.<sup>33</sup>

## ■ PEDIATRIC LIVER TRANSPLANT RECIPIENTS WHO SURVIVE INTO ADULTHOOD

### Adolescent rebellion poses risks

Outcomes of liver transplant in children and adolescents have improved tremendously in the past 2 decades with advances in surgical techniques, pre- and postoperative management, organ preservation, and immunosuppression. Now, most pediatric liver transplant recipients survive into adulthood, creating a unique challenge for internists and adult care hepatologists.<sup>41</sup>

In rebellious adolescents and young adults, risk-taking behavior, nonadherence to immunosuppressive medications, alcohol intake, and substance abuse increase the risk of graft rejection and loss. Current immunosuppressive drugs such as calcineurin inhibitors (tacrolimus, cyclosporine), mycophenolate mofetil, sirolimus, and corticosteroids have drastically decreased rejection rates in compliant patients.<sup>41</sup> Educating patients on the importance of taking their medications and avoiding alcohol and drug abuse is especially important for adolescents and young adults, as rates of nonadherence are high in these age groups.

Although pregnancy is usually successful after liver transplant, it should be considered high-risk due to reported complications such as graft rejection, diabetes, preeclampsia, sepsis, prematurity, and low birth weight. Conception should be avoided for at least 1 year after transplant.<sup>42</sup> Appropriate counseling with regard to pregnancy and contraception is important.

There is no consensus on breastfeeding, but it is considered safe in women on low-dose calcineurin inhibitors.<sup>43</sup>

## Life is better with a new liver, but patients have special needs

Liver transplant is life-saving and improves quality of life. However, long-term pediatric liver transplant recipients face challenges such as strict adherence to medications and follow-up visits, avoiding exposure to infections, and fear of graft rejection.

Chronic liver disease in children leads to failure to thrive, growth failure, and even delayed puberty, which resolve in most patients after liver transplant before adulthood in the absence of other comorbidities.<sup>44</sup> However, these patients are reported to have lower psychosocial functioning and more psychiatric disorders such as anxiety or posttraumatic disorder.<sup>41,44</sup>

Therefore, a psychologist or other mental health professional should be part of the management team from the time of pretransplant assessment to identify mental health problems and the need for adjustments before liver transplant. Ongoing psychosocial assessment after liver transplant is equally important to identify risks such as drug or alcohol abuse, depression, posttraumatic stress disorder, and medication nonadherence, all of which can negatively affect posttransplant outcome.<sup>45</sup>

In addition, assessment of family functioning and structure is important for good long-term outcomes posttransplant; therefore, a social worker should also be a part of the transplant team. Psychosocial assessment tools can identify high-risk candidates who would benefit from earlier intervention to avoid any negative impact posttransplant.

Neurocognitive development can be delayed in children with chronic liver disease, and the delay may persist even after liver transplant, with reported impairments in intellectual ability, language, verbal, and visuospatial functioning skills.<sup>41</sup> In spite of this, a recent study found that more than half the study patients were employed at a median follow-up of 24 years from liver transplant and a median age of 27.<sup>46</sup>

Remarkably, pediatric liver transplant recipients have reported quality of life comparable to that in the general population,<sup>47</sup> and even better than in patients with other chronic illnesses.<sup>48</sup>

## Long-term medical comorbidities in pediatric liver transplant recipients

Favorable outcomes such as long-term survival and good quality of life in pediatric liver transplant recipients are lessened by late complications such as portal vein thrombosis or biliary strictures needing interventions, chronic graft rejection, adverse effects of immunosuppression, and recurrence of the disease.

Split-liver transplant—splitting a deceased-donor allograft to provide grafts for 2 recipients—has revolutionized liver transplant by increasing the donor pool and thereby decreasing waitlist mortality rates, especially in pediatric candidates. Despite this advantage, split-liver transplant is technically challenging and associated with increased perioperative complications compared with whole-liver transplant, especially in adult recipients. Recently, experienced centers have reported favorable outcomes with split-liver transplant comparable to those with whole-liver transplant; therefore, split-liver transplant should be considered after careful evaluation of donor organ and recipient clinical status.<sup>49</sup>

Old age in the recipient can also adversely affect liver transplant outcomes.<sup>50</sup>

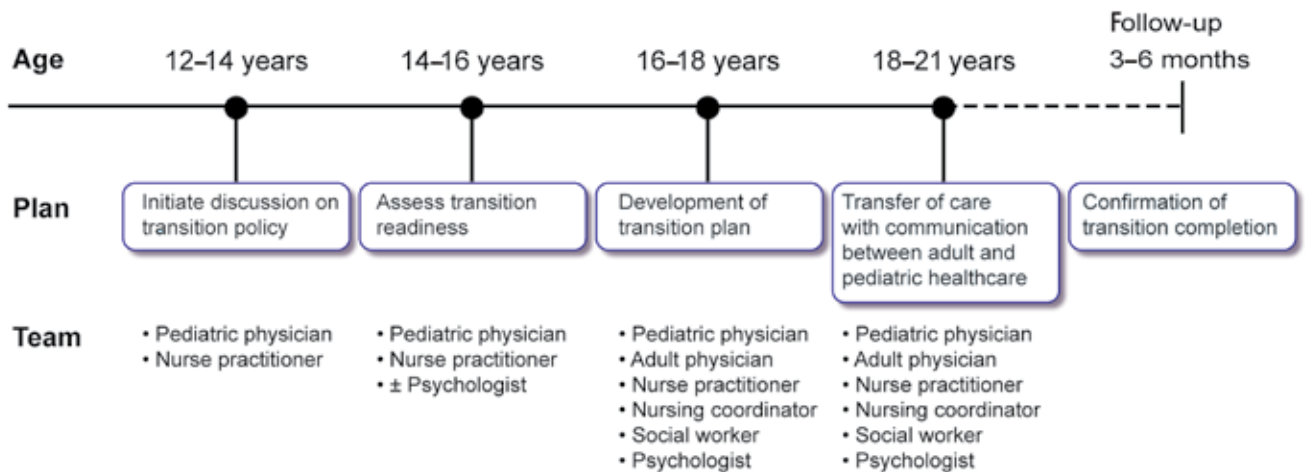
Interestingly, even in patients whose clinical course is unremarkable and biochemical values are normal, graft hepatitis or fibrosis of unknown cause with progression to cirrhosis has been described in the decade after transplant.<sup>41</sup>

Chronic rejection with eventual graft loss may be related to nonadherence in adolescents and can be reduced with use of an additional immunosuppressant such as sirolimus or mycophenolate. Chronic kidney disease can occur in about one-third of liver transplant recipients secondary to renal disease associated with primary disease (like Alagille syndrome), hepatorenal syndrome, and most importantly, use of calcineurin inhibitors.<sup>45</sup>

Components of the metabolic syndrome such as type 2 diabetes, obesity, nonalcoholic fatty liver disease, hypertension, and dyslipidemia are also seen in long-term pediatric liver transplant survivors. Internists are advised to screen for these comorbidities so that interventions can be applied early to improve long-term health outcomes and graft survival.

**About 15% of patients with PFIC 2 develop hepatocellular carcinoma**





**Figure 2.** Transitional model in childhood-onset cholestatic diseases.

About 40% of patients with cystic fibrosis develop liver disease

Of importance, multiple studies have shown a 2-fold increase in the rates of de novo malignancy in liver transplant recipients, including solid-organ and lymphoproliferative cancers, probably due to long-term immunosuppression. Posttransplant lymphoproliferative disorder occurs at lower rates than with other solid-organ transplants; its incidence is greatest in pediatric patients and in the first 12 to 18 months after transplant.<sup>51</sup>

## TRANSITION TO ADULT CARE

While the number of patients with childhood-onset liver disease and pediatric liver transplant recipients who survive into adulthood is increasing, there are no established guidelines or formal models for transitioning these patients into adult care. Consequently, studies on transitional process have examined various issues such as patient and parent frustration, poor medical knowledge among patients during transition, lack of parental facilitation, and inadequate knowledge on disease process among adult-care hepatologists.<sup>52-54</sup>

A position paper on transitional care from Europe has put forth important strategies.<sup>55</sup> A multidisciplinary team including a pediatric

provider, nurse practitioner, transplant coordinator, psychologist, social worker, and adult provider is vital for a successful transition. Key requirements for an adolescent patient include knowledge about the disease, demonstration of responsibility toward disease management, and self-management of healthcare needs such as scheduling appointments or insurance needs. This demanding task could be streamlined if pediatric liver transplant programs could adopt a formal transitional model (Figure 2). The transition could start as early as age 10 to 12, with gradual transfer of health management responsibilities from parents to adolescents from age 13 to 17.<sup>56</sup>

A prolonged period of transition up to age 25 is preferred in complicated cases. Distinctive consideration for transition should include those with neurocognitive developmental delay from underlying disease or hepatic encephalopathy before transplant. These patients need additional support and time to achieve independence in health management before transition.<sup>57</sup> Validated questionnaires are available to assess readiness to transition into adult care,<sup>58</sup> implying that the decision to transition should not be based solely on age. ■

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