Metabolic Liver Disease in Children

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The aim of this article is to provide essential information for hepatologists, who primarily care for adults, regarding liver-based inborn errors of metabolism with particular reference to those that may be treatable with liver transplantation and to provide adequate references for more in-depth study should one of these disease states be encountered.


Inborn errors of metabolism are caused by single enzyme defects that result in abnormalities in the synthesis or catabolism of proteins, carbohydrates, or fats. Most are due to a defect in an enzyme or transport protein that alters a metabolic pathway. This group of diseases differs from what is called metabolic disease in the adult or more accurately metabolic syndrome, which includes visceral obesity, elevated triglycerides, elevated fasting blood sugar, high blood pressure, and a decrease in high-density lipoprotein cholesterol levels.

This group of diseases can be divided into (1) diseases that lead to structural liver damage with liver failure or cirrhosis, with or without injury to other tissues, such as alpha-1-antitrypsin deficiency (A1ATD) and cystic fibrosis (CF), and (2) diseases due to a metabolic defect expressed solely or predominantly in the liver but leading to injury to other organ systems. Examples of such diseases include the urea cycle disorders and hyperoxaluria.

Although individually rare, when considered together, liver-based metabolic diseases represent approximately 10% of pediatric liver transplants and, in some centers, are the second most common indication for liver transplant after biliary atresia. It is probable that many data sets [including the United Network for Organ Sharing (UNOS) registry] underestimate the incidence of transplantation for metabolic liver disease for several reasons. Diagnosis in the acute situation may be problematic [for example, Wilson disease (WD)]; investigation prior to transplantation may be inadequate; and historically, the defect may have been unrecognized, or definitive diagnostic tests were not available (for example, the progressive intrahepatic cholestasis syndromes).

Abbreviations: A1ATD, alpha-1-antitrypsin deficiency; AGT, alanine:glyoxylate aminotransferase; AL, argininaemia; ALT, alanine aminotransferase; AS, argininosuccinic aciduria; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BCAA, branched-chain amino acids; BCKD, branched-chain alpha-keto acid dehydrogenase complex; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export protein; CESD, cholesterol ester storage disease; CF, cystic fibrosis; CPT, cystic fibrosis transmembrane conductance regulator; CN, Crigler-Najjar; CoA, coenzyme A; CPS, carbamyl phosphate synthetase; CTX, cerebrotendinous xanthomatosis; DNA, deoxyribonucleic acid; EPP, erythropoietic protoporphyria; ER, endoplasmic reticulum; FEV1, forced expiratory volume in 1 second; FIC1, familial intrahepatic cholestasis type 1; G6P, glucose 6-phosphate; G6Pase, glucose 6-phosphatase; GAL, galactose-1-phosphate uridyl transferase; GGT, gamma-glutamyltransferase; GSD, glycogen storage disease; HCC, hepatocellular carcinoma; HFH, homozgyous familial hypercholesterolemia; HFI, hereditary fructose intolerance; INR, international normalized ratio; LDL, low-density lipoprotein; LT, liver transplantation; MDR3, multidrug resistance P-glycoprotein 3; MELD, Model for End-Stage Liver Disease; MESSAGExMELD Exceptional Case Study Group; MMA, methylmalonic aciduria; MSUD, maple syrup urine disease; NH, neonatal hemochromatosis; NPC, Niemann-Pick type C; NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexendione; OPTN, Organ Procurement and Transplantation Network; OTC, ornithine transcarbamylase; PA, propionic acidemia; PELD, Pediatric End-Stage Liver Disease; PFIC, progressive familial intrahepatic cholestasis; RBB, regional review board; TII, tyrosinemia type I; UCDA, ursodeoxycholic acid; UDP, uridine diphosphate; UGT1A1, uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1; UNOS, United Network for Organ Sharing; WD, Wilson disease.

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The following sections discuss the important single gene defect diseases encountered in experienced pediatric liver transplant centers and include most of the conditions for which liver transplantation (LT) is demonstrable benefit. However, because of space limitations, the discussion is not exhaustive, and LT has very infrequently been undertaken in other metabolic conditions. One notable area not discussed is hematological conditions with a molecular basis, which include the hemophlias, hypercoagulable disorders, and defects of complement inactivation, which lead to recurrent hemolytic uremia syndrome.

**A1ATD**

A1ATD is well known to adult physicians as a cause of chronic obstructive airway disease due to deficiency of the circulating protease inhibitor α1 antitrypsin. In pediatric populations, this condition is one of the more common causes of neonatal cholestasis, chronic liver disease, and liver failure.

A1ATD is an autosomal recessive disorder, with an incidence in the Caucasian population of approximately 1:1600 to 1:2000 live births, and results from a single gene defect. The most common disease-causing alleles are PiZ (Glu342Lys) and PiS (Glu264Val), which result in levels of circulating α1 antitrypsin of 15% and 60% of normal, respectively. However, only the PiZ phenotype has been definitively demonstrated to cause liver disease in childhood. The heterozygous state is not a cause of liver disease per se, but it may act as a modifying factor, exacerabing the risk or progression, in other liver diseases such as hepatitis C virus, nonalcoholic fatty liver disease, and cryptogenic cirrhosis.

The epidemiology of A1ATD has been well studied, and according to Swedish studies, 11% of patients with the PiZ phenotype develop evidence of neonatal cholestasis. Of these, approximately 25% progress to early liver failure, 25% go onto cirrhosis and chronic liver disease, and the remainder will eventually normalize liver function and avoid the complications of chronic liver disease. An additional 6% present with clinical features of liver disease later in infancy or childhood without a history of neonatal jaundice, and according to later publications from the same authors, an estimated 10% of adults with PiZ may develop cirrhosis.

The mechanism of liver disease has not been fully elucidated; however, studies have shown that there is decreased export of mutant Z α1 antitrypsin molecules from hepatocytes. Because of abnormal protein folding, the Z protein has a propensity to polymerize within the endoplasmic reticulum (ER) of the hepatocyte, where its accumulation is revealed as the characteristic periodic acid Schiff–positive granules seen on light microscopy. The accumulation of Z protein in the ER appears to trigger mechanisms that lead to liver disease as yet to be fully elucidated. Proposed mechanisms include altered bile acid metabolism, hepatotoxic drugs, elevated levels of cytokines, biliary obstruction, vitamin deficiencies, essential fatty acid deficiency, and bacterial toxins. Studies have shown that the lack of CFTR alters ductular chloride secretion, which results in viscous biliary secretions with subsequent biliary obstruction that leads to focal biliary fibrosis and ultimately cirrhosis. However, not all patients develop liver disease, and this has increased the search for modifier genes.

Depending on the report, 20%-50% of CF patients develop liver disease, which ranges in severity from asymptomatic derangement of liver function tests to focal biliary fibrosis to cirrhosis with portal hypertension and chronic liver failure. Features of advanced clinical liver disease are most prominent in adolescents and young adults with CF; however, the overall incidence is only 4%-10% of all CF patients. Management focuses on the complications of cholestasis and portal hypertension. Treatment with ursodeoxycholic acid (UCDA) has demonstrated improved bile flow and improved aminotransferases but does not appear to stop the progression of fibrosis. The use of beta-blockers is limited by the potential for bronchoconstriction. Surgical portosystemic shunts have been performed when endoscopic variceal obliteration has been inappropriate or ineffective, but encephalopathy has been reported.

Indications for transplantation are synthetic liver
failure and unmanageable portal hypertension with recurrent variceal hemorrhaging or intractable ascites. It has been recommended that LT should be considered before the deterioration of lung function.\textsuperscript{24} The best outcomes are seen in patients without severe lung involvement, and pulmonary status may improve post-liver transplant.\textsuperscript{24,34–36} Optimal timing for transplantation should be influenced by several factors, such as pulmonary status, nutritional status, and cardiac function. Patients who have well-preserved pulmonary function have waitlist mortalities predicted by the severity of their liver disease (MELD/PELD score in the United States); however, those patients who have lung involvement should be considered for extra priority so that they can receive an isolated liver transplant before pulmonary deterioration would necessitate a combined liver-lung transplant.\textsuperscript{37}

Outcome data indicate that the 1-year patient survival rate following LT is 75%-100%.\textsuperscript{34,35,38} Based on OPTN data as of November 15, 2007, patient survival is 95% and 78% at 1 and 5 years, respectively. Graft survival is reported to be 83% and 75% at 1 and 5 years, respectively. Late mortality is generally related to the progression of pulmonary disease.

**FAMILIAL INTRAHEPATIC CHOLESTASIS SYNDROMES**

These diseases are autosomal recessive syndromes due to defects in hepatocytic canalicular membrane transport mechanisms. They share the potential to cause hepatocellular cholestasis, which may progress to cirrhosis and liver failure before adulthood. Defects in 3 genes encoding canalicular proteins have been well characterized to date.\textsuperscript{39} The clinical phenotypes vary in severity, and disease names can subsequently be confusing. We will therefore discuss each condition according to the gene product affected, namely, familial intrahepatic cholestasis type 1 (FIC1), bile salt export protein (BSEP), and multidrug resistance P-glycoprotein 3 (MDR3). The characteristic feature of the first 2 conditions described in this group is a low level of serum gamma-glutamyltransferase (GGT) throughout the progression of the disease. Genetic mutation analysis is commonly required in order to distinguish the 2 conditions. Phenotypically similar liver disorders may also result from congenital defects in bile acid synthesis, and these will be discussed later. The third condition, MDR3 deficiency, has appropriately elevated GGT levels when liver disease is manifested. Mild mutations and heterozygosity for these conditions have been implicated in the etiology of certain cases of intrahepatic cholestasis of pregnancy.\textsuperscript{40,41}

**FIC1 Deficiency [Progressive Familial Intrahepatic Cholestasis Type 1 (PFIC1), Byler Disease, Greenland Cholestasis, Benign Recurrent Intrahepatic Cholestasis (BRIC), and Tygstrup Syndrome]**

Originally described in the descendents of an Amish patriarch, Joseph Byler, the first of these conditions is due to a genetic mutation in the \textit{FIC1} (\textit{ATP8B1}) gene. Phenotypes of FIC1 deficiency include a spectrum ranging from severe, with intractable pruritus, jaundice, failure to thrive, hepatosplenomegaly, and progression to liver failure in childhood (PFIC1), to benign, with intermittent pruritus with or without jaundice (BRIC).\textsuperscript{42–46} Genotype/phenotype correlations have been demonstrated, the more disruptive mutations being associated with PFIC1, whereas BRIC patients tend to have proportionally more missense mutations.\textsuperscript{47} FIC1 is expressed in the canalicular membrane of hepatocytes and on cholangiocytes and apices of enteric epithelia.\textsuperscript{48,51} FIC1 is also expressed in extrahepatic tissues, mainly in the intestine and pancreas but also in many other tissues.\textsuperscript{52} The function of the gene product, a class 1 ATPase, has not been fully elucidated; however, altered function of the protein is associated with diminished activity of the farnesoid-X receptor, which is known to directly activate BSEP.\textsuperscript{53,54}

The result of mutations in \textit{FIC1} is poor biliary excretion of bile acids with elevated serum levels. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and conjugated bilirubin levels are elevated, but GGT remains in or below the normal range even with severe liver injury. Appearances on liver biopsies from patients with PFIC1 vary in the presence of portal tract inflammation and fibrosis. However, the presence of coarse granular bile within the canaliculi and the paucity of canalicular microvilli have been consistently noted on electron microscopy.\textsuperscript{44}

Treatment with cholestyramine, UCDA, and various forms of biliary diversion has been effective in some, but not all, cases. Indications for liver transplant include end-stage liver disease, although commonly the decision is made prior to this occurring because intractable pruritus may impair sleep, appetite, and concentration to such an extent that quality of life for these children becomes intolerable. LT corrects the biliary abnormality in bile acid excretion; however, chronic secretory diarrhea seen in some patients with PFIC1 may be exacerbated following LT.\textsuperscript{55} Prior to transplant, the excretion of bile acid and the absorption in the intestine are balanced. However, post-transplant, there is normal biliary excretion of bile acids by the transplanted graft, but the intestine remains FIC1-deficient. The increased bile acids in the intestine can then lead to intractable diarrhea.\textsuperscript{52,56}

**BSEP Deficiency (PFIC2 and BRIC2)**

BSEP deficiency has a spectrum of clinical phenotypes similar to FIC1 deficiency, although chronic diarrhea is not a feature. The disease is caused by mutations in a liver-specific adenosine triphosphate (ATP)–binding cassette transporter gene (\textit{ABCB11}). The product of this gene is BSEP, which is the principal canalicular transporter of bile acids into bile, and its expression is almost entirely confined to the hepatocyte canalicular membrane. Severity of the disease has been correlated with the degree of BSEP expression.\textsuperscript{57}

Circulating bile acids levels are significantly elevated,
leading to the prominent features of severe and often intractable pruritus and cholestasis. AST and ALT levels are elevated with the onset of cholestasis, but GGT remains low. Liver biopsies for PFIC2 demonstrate inflammation, giant cell transformation, and lobular and portal fibrosis; however, bile duct proliferation is generally not seen. Bile has been characterized as amorphous or filamentous compared to the coarse granular bile of PFIC1.43,44 Several cases of hepatocellular carcinoma (HCC) have been described in young children with severe forms of BSEP deficiency.58 It is recommended that patients be monitored regularly with α-fetoprotein levels and ultrasonography. Mild and intermittent cases of BSEP deficiency, termed BRIC2, have been described with no or very slow progression of fibrosis.

Treatment with external biliary diversion may be effective in some patients, leading to partial or complete clearing of cholestasis and pruritus, but in the more severe cases, the liver disease progresses inexorably. Chronic liver failure, HCC, and severe pruritus constitute indications for LT in early childhood. An initially effective biliary diversion may have diminishing effectiveness as the patient ages, and some patients come to LT later in adolescence.

**MDR3 Deficiency (PFIC3)**

PFIC3 is caused by mutations in the class III multidrug resistance P-glycoprotein gene MDR3 (ABCB4), which is responsible for canalicular phospholipid transport.

Clinical features include pruritus and jaundice, although the age at onset varies from 1 month to 20 years or more. Liver disease is associated with elevation of aminotransferases and bilirubin but, unlike the previous conditions, is associated with elevated GGT levels.45 The liver biopsy in PFIC3 demonstrates extensive bile duct proliferation and perportal fibrosis.43 At the milder end of the clinical spectrum, mutations in MDR3 have also been associated with recurrent cholesterol cholelithiasis and gall bladder disease; characteristic features include recurrence following cholecystectomy and prevention of recurrence by UCDA therapy.59

Successful LT has been well documented for familial intrahepatic cholestasis syndromes with patient survival of 70%-90%.39,60-64 LT has also been shown to improve growth velocity and bone mineralization in PFIC patients.39

**DISORDERS OF BILE ACID SYNTHESIS**

Nine distinct inborn errors of bile acid synthesis have been identified to date and as a group have been estimated to be the cause of 2% of persistent cholestasis in infants.65 These disorders can be attributed to deficiencies of a single enzyme in the biosynthesis pathway of bile acids or to a significant disruption of peroxisomal function. De novo bile acid synthesis starting with cholesterol occurs through a series of enzymatic steps within the cytosol, mitochondria (sterol nucleus modification), and peroxisome (side chain shortening) of the hepatocyte. A disruption involving any one of these steps can result in the accumulation of toxic bile acid metabolites.66

Figure 1 shows a simplified schema of the synthesis of the 2 principal primary bile acids in humans. The best characterized defects in bile acid synthesis are identified. 3β-Hydroxysteroid Δ5-oxidoreductase deficiency and 3β-hydroxy-Δ7-C27-steroid dehydrogenase deficiency cause neonatal cholestasis with progression to chronic liver disease if untreated.

Sterol 27-hydroxylase (also known as CYP27A) is a mitochondrial enzyme, a deficiency of which causes cerebrotendinous xanthomatosis. Progressive neurologic dysfunction, premature atherosclerosis, and cataracts characterize this condition. Large deposits of cholesterol and cholestanol are found in virtually every tissue, particularly the Achilles tendons, brain, and lungs. Liver disease is not generally a feature of this condition, but a self-limiting neonatal cholestasis may occur before the onset of the characteristic signs.67

Defects of peroxisomal bile acid synthesis are gener-
Hepatic presentations
The definition of hepatic presentations requires the exclusion of neurological symptoms by a detailed clinical neurological examination at the time of diagnosis.
- **H1 (acute hepatic Wilson disease):** Acutely occurring jaundice in a previously apparently healthy subject due to a hepatitis-like illness, Coomb’s negative hemolytic disease, or a combination of both. It may progress to liver failure necessitating emergency liver transplantation.
- **H2 (chronic hepatic Wilson disease):** Any type of chronic liver disease with or without symptoms. It may lead to or even present as decompensated cirrhosis.

Neurologic Presentations
Patients in whom neurological and/or psychiatric symptoms are present at diagnosis.
- **N1:** Associated with symptomatic liver disease.
- **N2:** Not associated with symptomatic liver disease.
- **NX:** Presence or absence of liver disease not investigated.

Other Presentations
- **O:** Patients that do not fall into any of the above categories.

TABLE 1. Classification of Clinical Presentations of Wilson Disease According to the 8th International Conference on Wilson Disease and Menkes Disease in 2001

<table>
<thead>
<tr>
<th>Presentations</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>The definition of hepatic presentations requires the exclusion of neurological symptoms by a detailed clinical neurological examination at the time of diagnosis.</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Patients in whom neurological and/or psychiatric symptoms are present at diagnosis.</td>
</tr>
<tr>
<td>Other</td>
<td>Patients that do not fall into any of the above categories.</td>
</tr>
</tbody>
</table>

WD

In 1912, Dr. S.A. Kinnier Wilson described 4 patients with a profound movement disorder and cirrhosis of the liver. The molecular basis of WD is now well understood, with mutations in the gene ATP7B being responsible for the failure of biliary excretion and incorporation of copper into ceruloplasmin. The ATP7B gene encodes for an ATP-dependent copper transporter with 8 transmembrane domains, which is active in the trans-Golgi. Defects in the WD protein lead to accumulation of copper in the liver and subsequently in the brain, cornea, kidney, and other tissues.

WD disease may present clinically in a number of ways, and the common phenotypes have been codified as shown in Table 1.

Pediatric presentations of WD are typically hepatic, including asymptomatic disease detected on routine physical examination, chronic hepatitis, cirrhosis, and fulminant hepatic failure. Another important presentation results from screening the premorbid sibling of an affected individual. Neurological presentations are predominantly seen in adults but can occur in adolescents and feature a progressive movement disorder with dysarthria, dysphagia, apraxia, and tremor. Neurological presentations also include psychiatric manifestations in approximately one-third of patients. These manifestations may include diminished performance at work or school, depression, mood swings, and frank psychosis.

WD has been described in all ethnic groups and has an overall estimated incidence of 1 in 30,000-50,000 births, but in some ethnic groups, the incidence may be much higher, particularly in Sardinia, where 10-12 new cases are reported per year. Olivarez et al. used a mutational analysis approach to estimate the incidence in Caucasians in the United States as 1 in 55,000. There have been >200 mutations described, and although some mutations are more common in a particular ethnic or geographical population, there is no “common” mutation akin to Δ508 in CF.

Although commonly the diagnosis is straightforward with the presence of Kayser-Fleischer rings, a low serum ceruloplasmin level, increased urinary excretion of copper, and elevated liver copper on biopsy, not all cases are so obvious. A diagnosis of WD is unlikely to occur without clinical suspicion and appropriately directed investigation. All standard tests used to secure a diagnosis of WD have their drawbacks, and results of these tests may misdirect the diagnosis either away from a true diagnosis of WD, such as a normal level of ceruloplasmin and absence of Kayser-Fleischer rings, or toward WD because of a high liver copper level when in...
recently, this has been updated with another 20 years of experience.82-85 Patient survival rates following LT are reported to be in the range of 73%-88% from single-center studies.82,84-89 Based on OPTN data as of November 15, 2007, patient survival rates are 89% and 84.4% at 12 and 60 months, respectively.

### TABLE 2. King’s College Wilson Disease Prognostic Index

<table>
<thead>
<tr>
<th>Score</th>
<th>Bilirubin (μmol/L)</th>
<th>INR</th>
<th>AST (IU/L)</th>
<th>Platelets ($\times 10^9$/L)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0-100</td>
<td>0-1.2</td>
<td>0-100</td>
<td>0-6.7</td>
<td>&gt;45</td>
</tr>
<tr>
<td>1</td>
<td>101-150</td>
<td>1.3-1.6</td>
<td>101-150</td>
<td>6.8-8.3</td>
<td>34-44</td>
</tr>
<tr>
<td>2</td>
<td>151-200</td>
<td>1.7-1.9</td>
<td>151-300</td>
<td>8.4-10.3</td>
<td>25-33</td>
</tr>
<tr>
<td>3</td>
<td>201-300</td>
<td>2.0-2.4</td>
<td>301-400</td>
<td>10.4-15.3</td>
<td>21-24</td>
</tr>
<tr>
<td>4</td>
<td>&gt;300</td>
<td>&gt;2.5</td>
<td>&gt;401</td>
<td>&gt;15.4</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

**NOTE:** The information for this table was taken from Merle et al.76 A score ≥ 11 has a positive predictive value of 92% and a negative predictive value of 97% for death or the need for liver transplant.

**Abbreviation:** INR, international normalized ratio.

fact the patient has another cause for cholestasis such as sclerosing cholangitis. Because the diagnosis can be so challenging, an expert panel developed a diagnostic scoring system that has come to be known as the Leipzig criteria.74,75 Only the demonstration of 2 disease-causing mutations in ATP7B can absolutely secure the diagnosis, but in a recent study, only about 60% of patients demonstrated mutations on both chromosomes, and 15% had no identifiable mutations; this reemphasizes the need for very careful diagnostic workup of suspected cases of WD.76

Chelation therapy with d-penicillamine, trientine, or ammonium tetrathiomolybdate, with or without zinc salts, introduced in a timely manner has been shown to be effective in preventing progression of WD and in many cases may lead to resolution of symptoms.77 However, medical treatment cannot be expected to reverse decompensated cirrhosis, fulminant liver failure, or established neurological injury.71,78,79 Choice of medical therapy is provider-dependent and has not been comparatively analyzed.

LT before the onset of extrahepatic features of WD cures the metabolic defect. However, medical therapy is highly effective, and therefore only those patients who have progressive liver disease despite chelation therapy should be considered for transplantation. To aid in the determination of which patients require LT, the group at King’s College Hospital examined their experience, from which they devised a prognostic index.80 More recently, this has been updated with another 20 years of data, so the current King’s WD score is calculated as shown in Table 2.76 Petrasek et al.81 suggested that this scoring system may also be useful for evaluating adults with decompensated chronic liver disease due to WD.

When patients present with fulminant failure or when medical treatment fails, liver transplant has proved to be a valuable treatment. There are reports that neurological abnormalities improve or recover after transplantation, and some authors have advocated considering neurological manifestations as indicators for liver transplant, although this concept remains controversial.82-85 Patient survival rates following LT are reported to be in the range of 73%-88% from single-center studies.82,84-86 Based on OPTN data as of November 15, 2007, patient survival rates are 89% and 84.4% at 12 and 60 months, respectively.

### NEONATAL HEMOCHROMATOSIS (NH)

NH or neonatal iron-storage disease is so named because of the large amount of stainable iron found in the liver, pancreas, endocrine glands, and other tissues of affected infants. It is the cause of severe and often fatal neonatal liver disease. No specific defect of iron metabolism has been identified, unlike adult onset hemochromatosis.90,91 Infants present acutely with liver failure in the perinatal period and demonstrate massively elevated ferritin levels, elevated iron saturation (>98%), hypoalbuminemia, hypoglycemia, hyperbilirubinemia, and coagulopathy. Age at onset has been reported to range from 0 to 31 days after birth.92-94 The onset of liver damage appears to begin prior to birth, and the disease is maternally transmitted. The diagnosis is confirmed by the demonstration of extrahepatic siderosis either by magnetic resonance imaging spectroscopy for iron in the heart, pancreas, and endocrine glands or by histological examination of a biopsy from the inner lip or cheek showing siderosis of acinar salivary glands.

Studies by Whittington et al. show that NH may be the result of a transplacental immune interaction directed at the fetal liver, and more accurate nomenclature might be congenital alloimmune hepatitis.95 On the basis of this proposed mechanism of liver injury, 4 patients received treatment with double-volume exchange transfusion and intravenous immunoglobulin administration. Two patients recovered, and 2 went on to liver transplant.96 In addition, mothers who have had previous infants with NH have been treated during subsequent pregnancies with intravenous immunoglobulin administered weekly from 18 weeks of gestation. This treatment has prevented or decreased the severity of NH in subsequent offspring.97,98

Treatment of the sick NH infant with a “cocktail” of antioxidants has been advocated on the basis of the hypothesis of oxidative injury due to iron overload, which appears not to be the case. The cocktail used includes deferoxamine, vitamin E, N-acetylcysteine, selenium, and prostaglandin-E1; however, studies have not been able to validate the efficacy of this approach and suggest that LT may be the treatment of choice.94,99

Transplantation in this group of patients has been reported, although the numbers are small.100,101 One
of the larger studies looked at 19 patients with NH: 12 (63%) patients died, and of the 7 patients who survived, 5 underwent LT and were alive after a median follow-up of 5.6 years.\textsuperscript{94}

CARBOHYDRATE METABOLISM

Hereditary Fructose Intolerance (HFI)
Fructose is metabolized in the liver by 3 enzymes: fructokinase, aldolase B, and triokinase. HFI is caused by aldolase B deficiency, which blocks metabolism of fructose-1-phosphate into dihydroxyacetone phosphate and D-glyceraldehyde. Accumulation of fructose-1-phosphate can cause hypoglycemia due to the inhibition of glycogen phosphorylase and the inability to condense glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. In addition, excess amounts of fructose-1-phosphate can lead to ATP depletion, which is thought to lead to impaired protein synthesis and, ultimately, liver and renal dysfunction.\textsuperscript{102}

Patients with HFI are asymptomatic until fructose, sucrose, or sorbitol is introduced into the diet. The initial presentation is usually after weaning or when fruits and vegetables are started. Presentation can include hypoglycemia after ingesting fructose, nausea, vomiting, abdominal pain, and lethargy. Patients who remain undiagnosed can develop failure to thrive, liver disease, and renal tubular dysfunction. Beyond infancy, these patients develop a dramatic aversion to sweet foods and instinctively self-impose a fructose-free diet.\textsuperscript{102} Lack of dental caries is characteristic of patients with HFI.\textsuperscript{103} Transplantation has been reported for this condition; however, it can be managed medically with restriction of fructose, sucrose, and sorbitol intake and should not require transplantation.

Galactosemia
The conversion of galactose to glucose is mediated by a series of 4 enzymes. Classical galactosemia is caused by a deficiency in the galactose-1-phosphate uridylyl transferase (GALT) gene. Several different alleles have been identified; the most common mutation is Q188R, which occurs in 70% of patients.\textsuperscript{104} GALT deficiency blocks the metabolism of galactose-1-phosphate to uridine diphosphate (UDP) galactose. The buildup of galactose-1-phosphate further disrupts glucose metabolism and leads to the symptoms described below. Most infants in the United States with galactosemia are now detected with neonatal screening.\textsuperscript{105} Vomiting, diarrhea, lethargy, and hypotonia can present within hours of milk ingestion. Continued galactose ingestion leads to hemolysis, jaundice, liver disease, lactic acidosis, and renal tubular acidosis. Acute presentations in the neonatal period are frequently related to \textit{Escherichia coli} sepsis.\textsuperscript{106} Failure to thrive, hepatomegaly, splenomegaly, cirrhosis, and cataracts characterize the more chronic course.

A report by Otto et al.\textsuperscript{107} describes a patient with galactosemia who developed HCC and subsequently received a liver transplant. Post-transplantation, a normal diet was instituted, and no galactose was detected in the serum. Although transplantation has been reported for this condition, it should be managed medically with a galactose-free diet and should not require transplantation. Despite aggressive management, long-term complications occur frequently and can include mental retardation and ovarian dysfunction in females.\textsuperscript{108}

GLYCOGEN STORAGE DISEASE (GSD)
Inherited defects in enzymes that regulate glycogen synthesis or catabolism, primarily in the liver and/or muscle, are responsible for this group of diseases. In theory, all of the hepatic glycogenoses are correctable by LT; however, indications for LT are limited to those patients with chronic liver failure, hepatic tumors, or unmanageable metabolic dysfunction. The hepatic GSDs include types I, III, IV, VI, and IX; however, the last 2 conditions tend to be mild and are not generally considered for LT. Glycogen metabolism is illustrated in Fig. 2.

GSD Type I
Glucose 6-phosphatase (G6Pase) deficiency is a defect in free glucose production. The enzymatic domain of G6Pase is expressed at the inner surface of the ER membrane. Glucose 6-phosphate (G6P), generated in the cytosol by glycolytic and gluconeogenic pathways,
requires active transfer into the lumen of the ER by a specific G6P transporter. Deficiency of the catalytic enzyme G6Pase produces GSD Ia, and a deficiency of G6P transporter is responsible for GSD type Ib.109 The metabolic consequences of GSD Ia and GSD Ib are similar, with the exception of neutropenia seen in type Ib. Diagnosis is increasingly made by molecular genetic studies; the more traditional approach of measuring enzyme activity on liver biopsy has been diminishing because of the fact that cases of GSD Ib were commonly missed unless activity was measured on both fresh and frozen tissue. Freezing a liver specimen disrupts the ER membrane, exposing the catalytic activity of G6Pase if present, and thus in a case of GSD Ib in which only frozen tissue is assayed, G6Pase activity will be normal.

The usual clinical presentation of GSD type I is an infant of a few months of age with recurrent fasting hypoglycemia, protuberant abdomen, and growth retardation. The first symptoms often are not apparent until weaning, especially in infants who are breast-fed on demand. The characteristic “doll’s” facies ascribed to this condition is due to excessive subcutaneous fat deposition in the cheeks. The protuberant abdomen is due to massive hepatomegaly, without splenomegaly. Biochemical features of GSD I include fasting ketotic hypoglycemia with elevated plasma lactate, urate, and triglycerides.110 Additionally, because GSD 1b patients have neutropenia, they may present with infection or inflammatory bowel disease.

Histology of the liver shows swollen hepatocytes with apparent cell wall thickening caused by peripheral displacement of organelles by the stored glycogen. The excessive cytoplasmic glycogen stains with periodic acid Schiff and is readily digested by diastase. Microvesicular fat is almost invariably seen in the biopsy, but there is little in the way of inflammatory activity or fibrosis.

The goal of therapy is to prevent hypoglycemia and thus limit additional metabolic abnormalities. Management consists of frequent feedings, which in infants often includes continuous nighttime nasogastric feedings. Uncooked cornstarch ingested every few hours in older patients has been shown to release glucose slowly and steadily and allows avoidance of hypoglycemia. In patients with GSD 1b, neutropenia and its consequences can be managed with granulocyte-stimulating factor.111,112 Chronic fibrotic liver disease is not a consequence of GSD 1, but poor metabolic control frequently leads to the development of hepatic adenoma in adolescents and adults, which can undergo malignant transformation. Patients should be surveyed annually with ultrasound because of the increased risk of malignancy. If a lesion is detected, serial imaging should be obtained to assess for change in size, number of lesions, and margin effacement. Alpha-fetoprotein and carcinoembryonic antigen should also be routinely monitored.113,114 Although the kidney does not participate significantly in systemic glucose homeostasis, G6Pase is expressed in renal tissues, and renal dysfunction ranging from hyperfiltration to chronic renal failure can be encountered in older patients.

Liver transplant provides correction of the systemic metabolic defect. Indications for LT in patients with GSD I include inability to control metabolic disturbances with medical management, hepatic adenoma, or HCC.113,115 Because of the overall rarity of patients with GSD I that develop hepatic adenoma, there are no specific recommendations regarding when to transplant. However, there is limited literature that suggests that orthotopic liver transplantation is warranted when there are multiple adenomas or when malignant transformation is suspected.116,117 Faivre et al.118 reported an improvement in quality of life and catch-up growth post–liver transplant; however, renal dysfunction is not impacted. Based on OPTN data as of November 15, 2007, patient survival is 84% and 80% at 12 and 60 months, respectively.

GSD Type III

GSD III is due to a mutation in the gene encoding glycogen debrancher enzyme. The phenotype is generally milder than GSD I, but symptomatic hypoglycemia does occur. Management is primarily dietary, and GSD III has no indication for LT in childhood. However, cirrhosis can occur in adults with this condition. Liver tumors are seen in GSD III only in association with fibrotic liver disease. Most patients with GSD III have liver and muscle involvement.113 Muscle weakness is absent or minimal in childhood but can become debilitating in adults. There is currently no effective treatment, and this includes LT, for the myopathy or cardiomyopathy related to GSD type III.

GSD Type IV

This condition presents with infantile cirrhosis with or without cardiac and neurological involvement. GSD IV is caused by a mutation in the gene encoding glycogen branching enzyme. Abnormal unbranched glycogen accumulates in the liver, heart, muscle, skin, intestine, brain, and peripheral nervous system. Chronic liver disease is manifested as hepatosplenomegaly, portal hypertension, and failure to thrive. LT is an effective treatment for progressive liver failure, although it is indicated only when no other organ systems are affected. Unfortunately, cardiac or neurological features may also become apparent after successful transplantation.119,120

MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS

Mitochondrial respiratory chain disorders are caused by one or more defects of inner membrane respiratory chain enzymes. These enzymes are involved in the transport of electrons from glucose and fatty acid metabolism to oxygen. NADH-CoQ oxidoreductase (complex I), succinate dehydrogenase (complex II), coenzyme Q–cytochrome c oxidoreductase (complex III), cytochrome c oxidase (complex IV), and ATP synthase (complex V) may be individually or multiply deficient.121
These 5 complexes are made up of at least 89 polypeptides, most of which are coded for by nuclear genes, although 13 are encoded in mitochondrial deoxyribonucleic acid (DNA). In addition, mitochondrial DNA depletion and mutations in mitochondrial ribonucleic acid genes can result in defects of the respiratory chain complexes. Because of the fundamental importance of oxidative phosphorylation to cell function, these defects are, by necessity, partial: a complete deficiency is incompatible with life. Heteroplasmy refers to the fact that there may be different populations of mitochondria within a cell, between cells, and between tissues, only one of which may be defective. The clinical phenotype is determined by the relative preponderance of the defective mitochondria in any given tissue. Almost any organ system can be affected by a mitochondrial cytopathy, but commonly tissues with high-energy demands, such as brain, muscle, and liver tissues, are most affected.122

LT has been reported for presumed mitochondrial respiratory chain disorders but should be considered only if the disease appears to be confined to the liver.123-125 Even in patients with apparent isolated liver involvement, metabolic derangement in other body systems may become apparent months or even years later. Sokal et al.121 reported on LT in 11 patients; 6 died post-transplant, 3 of whom developed neurological disease post-transplant.

Additionally, children who develop fulminant liver failure while receiving the anticonvulsant sodium valproate appear to have mitochondrial dysfunction and may have the features of Alpers’ syndrome (psychomotor retardation, intractable epilepsy, and liver failure in infants and young children). Experience has dictated that such patients are rarely if ever suitable candidates for LT because a neurological death post-transplant is seemingly inevitable.126,127

**TYROSINEMIA TYPE I (TTI)**

TTI is an autosomal recessive disorder with an incidence of 1:100,000 to 1:120,000. It is due to a defect in fumaryl acetoacetate hydrolase, the last enzyme in the tyrosine catabolism pathway, which results in accumulation of metabolites such as fumarylacetoacetate and maleylacetoacetate.128 One of the byproducts of these metabolites is succinyl acetone, the presence of which is a diagnostic marker for tyrosinemia (Fig. 3). Apoptosis of hepatocytes and apoptosis of renal tubular epithelial cells are characteristic features of this disease, and the apoptotic signal in this disease seems to be initiated by fumarylacetoacetate.129 Fumarylacetoacetate and maleylacetoacetate are alkylating agents that cause damage to DNA, which results in a predisposition to HCC.

Presentation of tyrosinemia can include acute liver failure, chronic liver disease, HCC, renal tubular dysfunction, and episodic porphyria-like neurological episodes caused by succinyl acetone inhibiting the metabolism of δ-aminolevulinic acid.130 In a study by Mitchell et al.,131 42% of patients had neurological crises that began at a mean age of 1 year. Episodes included severe pain with extensor hypertonia, vomiting or paralytic ileus, muscle weakness, and self-mutilation.

Historical treatment of TTI dictated LT. The medical management of TTI has changed considerably with the introduction of 2-(2-nitro-4-trifluoromethylbenzol)-1,3-cyclohexendiome (NTBC) in 1992. NTBC blocks the sec-
The urea cycle. Abbreviation: ATP, adenosine triphosphate.

Figure 4. The urea cycle. Abbreviation: ATP, adenosine triphosphate.

ond step in tyrosine degradation, thus preventing formation of the alkylating metabolites.(Fig. 3).

In a study by Mohan et al., prior to the introduction of NTBC, 35% of patients with TTI received LT. After NTBC treatment was introduced, the number of patients who have required LT has decreased to 12%. Currently, the indication for transplantation includes treatment failure or development of HCC. Holme and Lindstedt reported that only 10% of the patients did not respond clinically to NTBC treatment. In half of these patients, successful LT was performed.

One-year survival rates following LT are reported to be 88%-100%. Despite successful liver transplant, kidney cells accumulate succinyl acetone, which is excreted in the urine and predisposes to renal disease. Based on OPTN data as of November 15, 2007, patient survival is 92.5% at both 12 and 60 months post-transplant.

UREA CYCLE DISORDERS

The urea cycle is a series of biochemical reactions by which ammonia is detoxified and converted to the excretory product, urea. Only hepatocytes express all of the enzymes necessary for urea production. Defects result in an accumulation of nitrogenous waste, especially ammonia, which is highly neurotoxic. Human disease has been described as due to a deficiency of each of the enzymes, as shown in Fig. 4. The disease names for the first 2 defects describe the enzyme deficiency, that is, carbamyl phosphate synthetase (CPS) deficiency and ornithine transcarbamylase (OTC) deficiency. The remaining 3 disorders are known by the characteristic metabolite detected in affected individuals, namely, citrullinemia, argininosuccinic aciduria (AS), and argininemia (AL).

The clinical presentations of CPS, OTC, AS, and AL deficiencies are virtually the same, although there is great variability in severity within and between the diseases. The clinical picture may be of severe neonatal hyperammonemia, which can be lethal or may appear any time thereafter with varying degrees of severity. As a rule, AS and AL deficiencies tend to be milder diseases than CPS and OTC deficiencies because both citrulline and arginosuccinate can serve as an excretable waste product. Variability within conditions is primarily related to mutation(s) present (and hence enzyme activity). CPS, AS, and AL deficiencies are autosomal recessive conditions, and OTC deficiency is X-linked. This does not, however, mean that heterozygous females, with a single OTC gene mutation, are necessarily unaffected. In some heterozygous females, because of lyonization, the mutant allele may be activated in sufficient hepatocytes to cause a variable degree of hyperammonemia. The clinical features associated with arginase deficiency are markedly different from the other urea cycle disorder. Although hyperammonemia may be present, it is usually mild, and spastic quadriplegia, psychomotor retardation, hyperactivity, and growth failure are the more striking manifestations.

Urea cycle disorders are the primary causes of hyperammonemia in the neonatal period, but other organic acidemias can also present with severe hyperammonemia, and careful clinical and biochemical assessment is critical. An elevated ammonia level (>200 μmol/L) can lead to cerebral edema, with irreversible neurologic compromise reported at levels > 300 μmol/L. Acute signs include anorexia, hypothermia, lethargy, irritability, vomiting, hyperventilation, and seizures. Medical treatment during the acute presentation is based initially on reducing blood ammonia levels by (1) limiting protein breakdown by discontinuing protein intake and supplying sufficient glucose intravenously to limit catabolism, (2) providing biochemical alternatives for nitrogen excretion (intravenous and oral sodium benzoate and phenylacetate are used for this pur-
pose), and (3) direct removal of ammonia with high-flow hemodialysis.

Long-term management includes dietary protein restrictions. Oral sodium benzoate and phenylacetate (phenylbutyrate is more palatable and converts to phenylacetate \textit{in vivo}) are usually required. In the first 4 conditions, the defects block synthesis of arginine, and this in the face of an overall protein-restricted diet will lead to arginine deficiency. Supplementation is therefore essential, and in AS and AL deficiency, additional arginine will facilitate increased production of citrulline and arginosuccinate, respectively, thus contributing to nitrogen excretion. In CPS and OTC deficiency, citrulline supplementation can be substituted for arginine administration. Despite intensive treatment, patients can suffer recurrent hyperammonemia events, notably during intercurrent illness.

Patients who have had recurrent elevated serum ammonia levels can have devastating neurological sequelae. For the best neurological outcomes, early diagnosis and aggressive management are essential. LT provides replacement of the deficient enzyme, and plasma ammonia levels normalize within 24 hours of transplantation. LT is indicated in patients with recurrent or poorly controlled hyperammonemia but needs to be undertaken before severe, irreversible neurological injury occurs. LT cannot correct existing neurological injury; however, Whittington et al. reported improved quality of life post-transplant, in addition to decreased cost of care. Based on OPTN data as of November 15, 2007, patient survival rates are 93.8% and 90% at 12 and 60 months, respectively.

**DISORDERS OF BRANCHED-CHAIN AMINO ACIDS (BCAA)**

**Maple Syrup Urine Disease (MSUD)**

MSUD is caused by mutations in any of the 4 genes that encode the components of the branched-chain alpha-keto acid dehydrogenase complex (BCKD), which catalyzes the catabolism of BCAA, leucine, isoleucine, and valine (Fig. 5). The keto acids of BCAA are present in the urine and produce the characteristic maple syrup odor of the urine. Untreated MSUD may lead to severe neurological injury and death.

The clinical phenotype is dependent on the degree of residual enzyme activity. Classical MSUD, seen in infants with less than 2% BCKD activity, causes an increase in BCAA from birth. By 2 days of age, if MSUD is untreated, infants can develop ketonuria, irritability, lethargy, and dystonia. Of note is the absence of significant hyperammonemia. By 4 days of age, neurological sequelae progress, and infants may develop apnea, seizures, and cerebral edema. Emergency treatment includes removal of neurotoxins by dialysis. Initiation of treatment before 72 hours of age greatly reduces morbidity and mortality and the cost of medical care. Long-term management includes dietary restriction of BCAA and aggressive management of episodic metabolic decompensation.

**Methylmalonic Aciduria (MMA) and Propionic Acidemia (PA)**

MMA is caused by a deficiency of methylmalonyl–coenzyme A (CoA) mutase, which is a catalyst for the conversion of methylmalonyl-CoA to succinyl-CoA (Fig. 5). Vitamin B12 is a cofactor for methylmalonyl-CoA mutase, and therefore defects in cobalamin metabolism can also produce MMA, but the clinical features usually are milder and respond to B12 supplementation.
PA is caused by a mutation in the genes encoding propionyl-CoA carboxylase. The deficiency of propionyl-CoA blocks the conversion of propionyl-CoA (Fig. 5), which is formed by the catabolism of isoleucine, valine, methionine, threonine, and odd-chain fatty acids, to methylmalonyl-CoA.156

Clinical presentations for MMA and PA are very similar. Onset is typically in the neonatal period, after feeds containing protein have been started. Severe ketoadidosis, hyperuricemia, neutropenia, vomiting, lethargy, hyperammonemia, seizures, and coma can all be seen. If not recognized and treated promptly, these patients progress to severe brain damage and death. Patients who present in the neonatal period have a poor prognosis.151,156 Immediate treatment is based on removal of toxic metabolites with dialysis.157 Longer term treatment is with dietary protein restriction and essential amino acid supplementation.

Metabolic decompensation can occur when patients have intercurrent illnesses. Episodes of metabolic decompensation may be associated with basal ganglia stroke, which results in severe motor disabilities including a dystonic movement disorder.156,158 In addition, there is a high risk of cardiomyopathy, which can lead to acute cardiac failure and pancreatitis.159 Patients with MMA are at risk of developing a progressive tubular interstitial nephritis progressing to end-stage renal failure in adolescents. There is also a late-onset form that tends to have a milder course, less frequent and severe decompensation episodes, and decreased neurological sequelae.158

Indication for LT includes severe forms of PA and MMA that experience frequent metabolic decompensations despite optimal dietary management.160-162 Neurological deterioration post-transplantation has been documented.159,163-168 Neurological manifestations have included weakness, muscle spasms, dystonia, and metabolic stroke. LT corrects only the enzyme defect in the liver, and thus elevated levels of methylmalonate can still exist in other organ systems, particularly the central nervous system and the kidneys.159,164 These patients continue to excrete urinary metabolites, and some have demonstrated a metabolic acidosis at times of physiological stress. LT for MMA will not alter the progressive renal deterioration, and the decision to transplant should include consideration of combined liver and kidney transplantation.165,169

Currently, the criteria for LT in MMA are not well defined. The decision to undergo LT is complex and should balance the benefits of decreased episodes of metabolic decompensation and improved protein tolerance with the potential for neurological and renal deterioration.167 Clearly, LT is not curative in MMA, but it may improve the severity of the disease.

CRIGLER-NAJJAR (CN) SYNDROME

CN syndrome is the result of defective bilirubin-UDP-glucuronosyltransferase activity due to mutations in the gene uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1). This results in unconjugated hyperbilirubinemia, which untreated can lead to kernicterus. This is a condition of severe neural injury associated with deep yellow staining of the basal ganglia, cerebellum, and bulbar nuclei. Manifestations include ataxia, athetosis, seizures, dysarthria, mental slowing, and lethargy.170,171 Two phenotypes are recognized: CN1 and CN2. CN2 is responsive to phenobarbital, which induces residual enzyme activity and thus controls jaundice. CN1 is unresponsive to enzyme induction. A third condition, Gilbert syndrome, is due to a prolonged TATA box in the 5-prime promoter region of UGT1A, which produces entirely benign mild recurrent unconjugated jaundice usually apparent from puberty onward. No treatment is needed for Gilbert syndrome.

Treatment for CN1 includes exchange transfusions to acutely reduce unconjugated bilirubin levels; the neonatal brain is at particular risk for kernicterus. Once serum bilirubin concentrations are acceptable, phototherapy is usually adequate to maintain them below critical levels. Phototherapy with blue/green light (optimally around a wavelength of 450 nm) detoxifies unconjugated bilirubin in the skin to colorless excretable products.172 In infants, treatment may be required for 12 hours a day, but as the child gets older, phototherapy becomes less effective because of changes in the thickness and pigmentation of the skin and because of a reduction in the body’s surface-to-volume ratio. Treatment with tin-protoporphyrin or zinc-mesoporphyrin may decrease the hours of phototherapy required per day.173 However, spending most of the day under phototherapy can severely affect quality of life.

At present, LT is the only definitive treatment for CN1.171,174 Timing of transplantation should be based on neurological injury and performed in young patients.170,171,174-176 Most patients have received a standard orthotopic liver transplant, but this condition does not require complete hepatic replacement, and the native liver functions normally in all respects other than bilirubin conjugation; therefore, both orthotopic auxiliary LT177,178 and hepatocyte transplantation179 have been undertaken successfully. Based on OPTN data as of November 15, 2007, patient survival is 91.7% at 12 months post-transplant.

PRIMARY HYPEROXALURIA

Primary hyperoxaluria type 1 results from a deficiency of the peroxisomal enzyme alanine:glyoxylate amino-transferase (AGT).180,181 The metabolic defect leads to excessive oxalate production, which injures the kidneys and accumulates in other tissues of the body. Renal damage results from deposition of calcium oxalate within the renal tubules or in the urinary tract as calculi. Onset and progression are highly variable, ranging from a severe neonatal presentation with rapid progression to renal failure to adults with calculi and essentially preserved renal function.182 Severity of clinical disease is related to a spectrum of residual enzyme activity. Some patients respond to pharmacological
doses of pyridoxine. As renal function deteriorates, oxalate accumulates in other tissues; of particular importance is cardiac deposition, which leads to arrhythmias, heart block, and death. Extradrenal accumulation progresses rapidly once patients require dialysis because current forms of dialysis remove oxalate very inefficiently.

AGT is expressed in hepatocytes, and therefore LT acts as enzyme replacement therapy. Urinary excretion of glycocollate normalizes after LT, but oxaluria continues for a considerable time because of systemic accumulation of oxalate. Isolated renal transplantation in individuals with large systemic oxalate accumulations tends to result in rapid injury to the allograft from oxalate deposition, except perhaps in those pyridoxine-sensitive cases. As a rule, combined liver and kidney transplantation is required for long-term survival. Preemptive LT prior to significant renal dysfunction has been advocated, but decision making is complicated by the variable progression of this disease. Survival following LT with or without renal transplantation for patients with primary hyperoxaluria type 1 on the basis of OPTN data as of November 15, 2007 is 89.2% and 71% at 12 and 60 months, respectively.

FAMILIAL HYPERCHOLESTEROLEMIA
Homoygous familial hypercholesterolemia (HFH) is a rare disorder with an incidence of 1 per million that leads to childhood coronary artery disease, myocardial infarction, and death before the age of 20. HFH is due to a mutation in the gene for the low-density lipoprotein (LDL) receptor. LDL receptor may be absent or, when present, cannot bind to LDL. Patients have plasma cholesterol levels > 500 mg/dL and often > 1000 mg/dL. Drug therapy is ineffective in this condition. Seventy percent of the body’s LDL receptors are located in the liver; thus, liver transplant is the only option for treating HFH. LT should be performed before coronary artery disease develops. Case reports have reported successful liver transplants with normalization of cholesterol levels and prevention of cardiac sequelae. Combined cardiac and liver transplantation has also been undertaken for this condition.

NIEMANN-PICK TYPE C (NPC)
Although named because of phenotypic similarities to Niemann-Pick types A and B, NPC is due not to a deficiency of sphingomyelinase but to 1 of 2 defects in intracellular cholesterol transport. Ninety-five percent of NPC is due to mutations in the NPC1 gene, with the remaining 5% due to mutations in the NPC2 gene. The majority of patients with NPC (45%–65%) have neonatal jaundice. A study from Denver describes 27% of patients initially diagnosed with idiopathic neonatal hepatitis as having NPC. However, only approximately 10% of subjects progress to hepatic failure. Within the group of patients with abnormal aminotransferases, 80% had fibrosis on liver biopsy, and 20% had normal hepatic architecture. Splenomegaly due to lipid storage is seen in 90% of cases as the disease progresses. Later, usually during childhood or adolescence, progressive neurodegeneration is seen with ataxia, loss of speech, seizures, and characteristic vertical supranuclear ophthalmoplegia and eventually spasticity, dementia, and death.

In an infant, a clinical or histological diagnosis of idiopathic neonatal hepatitis should prompt examination of bone marrow for foamy cells (lipid-laden macrophages) or “sea-blue” histiocytes. Although they are frequently present on careful examination of the liver biopsy, their absence does not exclude the diagnosis. Electron microscopy of the skin, rectal neurons, liver, or brain may show polymorphous cytoplasmic bodies. The diagnosis of NPC is confirmed by biochemical testing that demonstrates impaired cholesterol esterification and positive filipin staining in cultured fibroblasts.

Liver function tests may normalize, but other patients demonstrate persistent aminotransferase elevation associated with chronic fibrotic liver disease. Subsequently, HCC has been described in these patients. LT cures the liver disease; however, the neurological progression is unaffected, and therefore LT is not generally recommended. Patients with NPC who have received a liver transplant have gone on to develop splenomegaly and the characteristic devastating neurodegenerative course.

CHOLESTERYL ESTER STORAGE DISEASE/ WOLMAN DISEASE
A deficiency of lysosomal enzyme acid lipase can result in 1 of 2 disorders, both with significant hepatic involvement. Wolman disease is a lethal condition that presents with vomiting, diarrhea, hepatosplenomegaly, and severe failure to thrive in early infancy. Adrenal glands are usually calcified and may be massively enlarged. These patients tend to die from nutritional failure by 2-3 months of age. A recent case report suggests that stem cell transplantation may effect a cure for this condition.

Cholesteryl ester storage disease [cholesteryl ester storage disease (CESD)] is a milder disorder usually detected later in childhood. Patients with CESD present with hepatosplenomegaly and hyperlipidemia. CESD may be confused with GSD 1 because of the commonality of hepatosplenomegaly and elevated lipid levels; however, recurrent hypoglycemia and lactic acidosis, common in GSD 1, are not seen in CESD.

Both of these conditions are autosomal recessive and are due to mutations in the lipase A gene. The severity of the phenotype is determined by the level of residual enzymatic activity. These disorders are characterized by progressive accumulation of triglycerides and cholesteryl esters in lysosomes in the tissues of affected persons. Histological examination of the liver demonstrates cholesteryl ester crystal deposition in Kupffer cells and damage to hepatic sinusoids. The diagnosis of CESD is confirmed by histochemical staining of liver biopsy specimens that demonstrates cholesteryl ester crystal deposition in Kupffer cells.
cells and to a lesser extent in hepatocytes, and the liver grossly has a characteristic orange color, which may immediately suggest the diagnosis.209

Currently, there are no specific treatments for CESD. Treatment with 3-hydroxy-3-methylglutaryl–CoA reductase inhibitors has been shown to lower very low density lipoprotein and LDL levels, and this may lower the risk of atherosclerotic heart disease; however, this does not prevent progressive hepatic damage. The indications for transplantation include cirrhosis and portal hypertension.210 There are limited case reports of patients receiving liver transplants for this condition.211-213 Long-term outcomes are not known, but anecdotal reports suggest good outcomes without neurological sequelae.

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

EPP is associated with a deficiency of ferrochelatase, which is the last enzyme in the heme biosynthesis pathway. EPP is a heterogeneous disease, with only 10% of EPP allele carriers being symptomatic and less than 2% developing progressive liver disease.214 An accumulation of protoporphyrin in liver, blood, skin, and other tissues characterizes EPP, with laboratory evidence of increased protoporphyrin in plasma, erythrocytes, and feces of most patients. The most common clinical manifestation is cutaneous photosensitivity, which usually presents early in childhood. The protoporphyrin molecule is excited by absorbing light energy and generates free radicals, which result in photosensitivity of all tis-

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### TABLE 3. MESSAGE Recommendations on MELD/PELD Exceptions for Metabolic Liver Disease

<table>
<thead>
<tr>
<th>Metabolic Disease</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson disease</td>
<td>MELD/PELD score is appropriate or meets status IA criteria.</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>Meets status IA criteria.</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>May need additional points for HCC or exception points if treatment with NTBC fails.</td>
</tr>
<tr>
<td>Glycogen storage diseases</td>
<td>Application to RRB is needed for a listing MELD/PELD score. Automatic exception is possible if HCC is present and fulfills current T2 criteria.</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>MELD/PELD score may be appropriate, but RRB is commonly involved if intractable pruritus is the indication for listing.</td>
</tr>
<tr>
<td>Biliary transport defects</td>
<td>Specific MESSAGE recommendations: Prior to end-stage renal disease: an initial MELD/PELD score plus 10% mortality equivalent, and every 3 months it will be increased by 10%. If the patient is more than 1 year of age, has end-stage renal disease, and is listed for combined liver-kidney transplant: an initial MELD/PELD score plus 15% mortality equivalent, and every 3 months it will be increased by 10%. If the patient is less than 1 year of age at time of listing for liver-kidney transplant: score of 40.</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>Addressed in current UNOS policy for listing of hyperammonemic conditions. PELD of 30 for 30 days, and if the patient is not transplanted in that time, he can be upgraded to status 1B.</td>
</tr>
<tr>
<td>Urea cycle defects</td>
<td>Apply to RRB for listing score.</td>
</tr>
<tr>
<td>Homozygous familial hypercholesterolemia</td>
<td>Apply to RRB for listing score.</td>
</tr>
<tr>
<td>Crigler-Najjar type I</td>
<td>Apply to RRB for listing score.</td>
</tr>
<tr>
<td>MSUD</td>
<td>Addressed in current UNOS policy for listing of hyperammonemic conditions (see urea cycle defects).</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Addressed in current UNOS policy for listing of hyperammonemic conditions (see urea cycle defects).</td>
</tr>
<tr>
<td>Proprionic acidemia</td>
<td>Addressed in current UNOS policy for listing of hyperammonemic conditions (see urea cycle defects).</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td>Specific MESSAGE recommendations: If FEV₁ &lt; 40% and the patient is listed for isolated liver: MELD/PELD plus 10% mortality equivalent, to be increased every 3 months by an additional 10%. If FEV₁ &lt; 40% and the patient is listed for liver-lung transplant: MELD/PELD score of 40 points.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>MELD/PELD score is appropriate.</td>
</tr>
<tr>
<td>Cholesterol ester storage disease</td>
<td>Should be assessed by RRB and metabolic expert.</td>
</tr>
<tr>
<td>Mitochondrial defects</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** The information for this table was taken from McDiarmid et al.,1 Horslen et al.,37 Meerman,224 and Samuel et al.225

**Abbreviations:** FEV₁, forced expiratory volume in 1 second; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MESSAGE, MELD Exceptional Case Study Group; MSUD, maple syrup urine disease; NTBC, 2-(2-nitro-4-trifluoromethylbenzol)-1,3-cyclohexendiome; PELD, Pediatric End-Stage Liver Disease; RRB, regional review board.
sues exposed to violet (405-nm) and green (546-nm) light.\textsuperscript{215} Liver injury is related to protoporphyrin accumulation in hepatocytes and biliary canaliculi.\textsuperscript{216-218} Cholestasis accelerates protoporphyrin accumulation, which in turn accelerates the progression of liver damage.\textsuperscript{219} A mouse model of EPP has shown that toxic bile is formed, causing bile duct damage contributing to biliary fibrosis.\textsuperscript{220} Therapy with hydrophilic bile acids has been used to decrease cholestasis and protoporphyrin levels.\textsuperscript{221-223} However, these treatments are effective only in the initial stages of liver disease in EPP. In addition, hemin infusion has been used to suppress erythropoiesis.\textsuperscript{224} In patients with advanced cholestatic liver disease, LT is the treatment of choice.\textsuperscript{221} However, LT does not eliminate the production of protoporphyrin by the bone marrow, and recurrence of liver disease is well described.\textsuperscript{225}

One unique complication of LT for EPP is the photoactivation of protoporphyrin by the operating room lights, which have caused tissue burns. Special filters should be placed on the operating room lights to decrease the incidence and severity of burns.\textsuperscript{163,215,219} McGuire et al.\textsuperscript{163} reported on a group of 20 patients who received a liver transplant for EPP. The overall patient and graft survival rates after transplantation were 85% at 1 year and 69% at 5 years. The recurrence rate was 65% of patients who survived longer than 2 months. Six grafts were lost to recurrent EPP disease. It has been suggested that bone marrow transplantation should be considered in patients who have recurrent disease after LT.\textsuperscript{163}

**CONCLUSION**

The conditions described in this review are mostly related to inherited single gene defects; however, phenotypically and biochemically, they are a disparate group of diseases. Although most of these conditions may be amenable to LT, the decision making is complicated not only by the variable phenotypes encountered and the potential for involvement of other organ systems but also by the fact that many of these diseases do not have liver injury and therefore will not have a meaningful MELD or PELD score on which to base transplant listing priority. For those conditions that have liver damage such as A1ATD, the MELD/PELD system appears to be appropriate, and for conditions that manifest hyperammonemia (primarily referring to the urea cycle disorders), there are specific UNOS policies that dictate listing priority. However, for most conditions, an application needs to be made to the local UNOS regional review board (RRB) for a listing score on a case-by-case basis. Variations in listing practices between RRBs have been a cause for concern. The MELD Exceptional Case Study Group has made recommendations with respect to metabolic liver disease to help guide the RRBs toward greater consistency across the United States, as shown in Table 3.\textsuperscript{1,37,226,227} The rarity and complexity of care needed dictate that such patients should be cared for in experienced centers.

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