Neonatal Acute Liver Failure

Sarah A. Taylor and Peter F. Whitington

Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, Chicago, IL

Neonatal acute liver failure (NALF) is a rare disease about which there is little published data; however, NALF is an extremely important condition as it is distinct from acute liver failure seen in older children and adults. First, unlike acute liver failure in older patients, NALF can be diagnosed in an infant with cirrhosis. This is due to the fetal-neonatal continuum of liver disease, or the principle that neonatal liver failure may be the result of a liver disease that began in utero. Further differences exist in the mechanism of disease, diagnostic principles, and the common etiologies of NALF when compared with pediatric and adult acute liver failure. This review will address many of the distinguishing features of NALF and focus on the most common etiologies of NALF, including gestational alloimmune liver disease (GALD), the most common cause of NALF. Additionally, this review will provide insight into the pathogenesis, diagnosis, and treatment of this rare condition.

Liver Transplantation 22 677-685 2016 AASLD.
Received January 8, 2016; accepted February 24, 2016.

Writing a scientifically sound, evidence-based review of neonatal acute liver failure (NALF) is challenging for several reasons. Most importantly, there are few reliable published data upon which to base a review. This is partially the result of the rarity of the condition. It is considered to be very rare even though the actual incidence is completely unknown. Also, the way data have been collected and presented by age group does not include the narrowly defined neonatal group. Finally, there has been a rapid evolution of understanding over the last decade or so, which leaves older data inaccurate or suspect. A disease, gestational alloimmune liver disease (GALD), that had not been described a decade ago has emerged as the leading cause of NALF. Some of what we will present is based on published data (which is mainly experience-based) and much is based on our own experience. Our main purposes are to bring all of the experience related to NALF together in review and to present thoughts and concepts uniquely relevant to NALF.

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; CMV, cytomegalovirus; DGUOK, deoxyguanosine kinase; GALD, gestational alloimmune liver disease; HAMP, hepcidin; HH, hereditary hemochromatosis; HHV6, human herpes virus 6; HLH, hemophagocytic lymphohistiocytosis; HJV, hemojuvelin; HSV, herpes simplex virus; INR, international normalized ratio; IUGR, intrauterine growth restriction; IVIG, intravenous immunoglobulin; NALF, neonatal acute liver failure; NEC, necrotizing enterocolitis; NH, neonatal hemochromatosis; NK, natural killer; PALF, pediatric acute liver failure; PCR, polymerase chain reaction.

Address reprint requests to Sarah A. Taylor, M.D., Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University, 225 East Chicago Avenue, Box 65, Chicago, IL 60611. Telephone: 312-227-4337; E-mail: sataylor@luriechildrens.org

View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.24433

Concepts and Definitions

Thinking about NALF requires reorientation of thought from that applied to acute liver failure (ALF) in the older child and adult. This is because of the unique place in time occupied by the newborn in the cycle of life, which leaves it uniquely vulnerable in several important ways. Some definitions are in order for the reader to see the uniqueness of NALF in the spectrum of ALF. Neonatal means the following: of, relating to, or affecting the newborn, ie, the human infant during the first month after birth. Liver failure means the following: loss of vital liver function. ALF is defined as liver failure occurring within 8 weeks of onset of signs and symptoms of liver disease. Because birth is the earliest time at which signs and symptoms of liver failure can be observed, all neonatal liver failure is "acute" by definition.

The newborn is the direct extension of, or next developmental step after, intrauterine life. That liver disease may extend from the fetus into the newborn provides the potential for some NALF to have actually

begun in utero. The fetal-neonatal continuum of liver disease is the concept that some disease conditions that result in neonatal liver failure actually begin as fetal liver disease. Congenital cirrhosis means cirrhosis identified at or shortly after birth. The fetal-neonatal continuum of liver disease permits the possibility of cirrhosis in cases of NALF, which is an apparent paradox. ALF in general is defined as liver failure in the absence of preexisting liver disease and pathologically as acute injury without significant fibrosis. This has led to confusion in regard to thinking about congenital cirrhosis in the context of NALF. NALF can and absolutely does include newborns with cirrhosis, which is the consequence of liver disease in the fetus. Although perhaps not of immediate concern to the reader, the fetal-neonatal continuum of liver disease also permits the possibility of fetal liver failure, which would be defined as the loss of vital liver function in the fetus leading to fetal death and stillbirth.

The diagnosis of ALF has long depended upon disordered brain function (hepatic encephalopathy) as the defining feature of "liver failure." Moreover, progression of disordered brain function to coma and cerebral edema is established as a main determining factor in outcome of ALF. Because hepatic encephalopathy is difficult to detect or quantify in younger patients, the pediatric acute liver failure (PALF) study group removed it from the essential diagnostic criteria for entry into the PALF registry.[1] If hepatic encephalopathy is difficult to detect in young children, it is impossible in the newborn. So, the defining features of liver failure in NALF do not include hepatic encephalopathy. The PALF studies used coagulopathy (prothrombin time $\geq$ 20 seconds or international normalized ratio [INR] $\geq$ 2.0 after administration of parenteral vitamin K) as the primary defining feature of liver failure in young children where hepatic encephalopathy cannot be reliably determined. It is reasonable to apply this criterion to NALF except that the INR of the normal newborn extends up to 2.0 and the normal premature newborn may have an INR $\geq$ 2.0. So, abnormal coagulation as a defining feature of liver failure in NALF might best be reset to INR $\geq$ 3.0 to be on the safe side.

Mechanisms of Liver Failure in NALF

Conceptually, NALF begins at a different liver starting point than ALF or PALF in general. In those 2 conditions, the starting point is a developed and functioning liver to which an insult is applied, resulting in liver failure; whereas, in NALF the insult may have been applied in fetal life before the liver has developed and had a chance to function normally. Although some cases of NALF can be explained by the same mechanisms applied to ALF, many cannot.

Acute hepatic necrosis is the most common mechanism of ALF. It may be due to viral infection, toxins, or another etiology, but the basic principle of ALF is that something has caused the death of enough hepatocytes to cause organ failure. Often the insult (etiology) can be determined, but in PALF many cases are left unexplained leading to so-called "indeterminate PALF."[1] An emerging concept of "immune dysregulation" leading to aberrant natural killer (NK) cell function and cytokine-related liver necrosis has assumed a prominent place in theories related to indeterminate PALF. The etiology of acute hepatic necrosis in cases of NALF is almost always viral infection, though not with the typical hepatitis viruses (hepatitis A, hepatitis B, and hepatitis E viruses) that often cause ALF. The newborn has limited immune defense against ordinary viral infection. As a result, viruses that have the capacity to infect the liver and do it injury may regularly and without immune rebuttal produce acute hepatic necrosis in the newborn. Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome) is associated with hepatic necrosis in NALF and is in fact the prototype for the immune dysregulation theory in PALF. Hypoxic/ischemic injury is sometimes seen as a cause of acute hepatic necrosis in NALF. The newborn liver is relatively refractory to hypoxic injury. As a result, neonatal asphyxia is primarily associated with brain injury and sometimes with acute kidney injury, but almost never with liver failure. Ischemia (circulatory failure) is more often associated with liver failure, but never in the absence of other major organ dysfunction. Patients with severe congenital heart disease and in particular cardiomyopathy may show prominent liver dysfunction.

Hepatic replacement is rarely cited as a cause for ALF, though metastatic cancer may in fact produce liver failure in adults. Replacement of hepatic parenchyma with nonfunctioning tissue is an occasional cause of NALF, massive hepatic hemangioma being the most prominent etiology. Congenital leukemia, neuroblastoma, and nephroblastoma are also cited. Hepatoblastoma typically presents after the newborn period. Down's syndrome (trisomy 21) is occasionally associated with NALF and is almost always

accompanied by myelodysplastic syndrome and massive amounts of hepatic myelopoesis. The simple mass effect of myelopoetic elements in the liver may cause the liver failure in this condition.

Failure of hepatocyte organelle function is rarely cited as a cause for ALF although it may contribute to toxic liver injury, as in acetaminophen injury. In PALF, it is relatively more commonly cited. Patients with Alper's disease, an autosomal recessive mitochondrial disease due to mitochondrial DNA polymerase gamma mutations, may be pushed into liver failure by administration of the antiseizure medication valproic acid, as this drug's metabolism is largely mitochondrial. Mitochondrial cytopathy is a relatively common cause of PALF in the less than 1-year age group and potentially a cause of NALF.

Failure of hepatic parenchymal development is never cited as a cause of ALF or PALF. However, it is likely a common underlying mechanism in NALF. Although it may potentially result from some primary genetic cause (ie, not yet described mutations in genes related to hepatocyte development), most cases of NALF-related failure of parenchymal development are secondary to immune injury to developing hepatocytes in GALD. This will be discussed in detail below.

Specific Disease Etiologies in NALF

There are few relevant articles in the world literature to which the reader might go to gain further insight regarding the etiology of NALF. Durand et al.[2] present a 14-year single-center retrospective review of 80 infants ($\leq$1 year of age) who presented with ALF, as defined by a prothrombin time $>$ 17 seconds and factor V concentration of $<$ 50%. They classified their patients by causation as metabolic disorders (34 patients; 42.5%); neonatal hemochromatosis (NH; 13 patients; 16.2%); undetermined cause (13 patients; 16.2%); acute viral hepatitis (12 patients; 15.0%); and miscellaneous (8 patients; 10.0%). Most of the patients in this series do not represent NALF: the median age at onset of liver failure in this series was $>$ 3 months. Work by Sundaram et al.[3] presents prospectively acquired data from 148 infants $\leq$ 90 days of age enrolled into the PALF study. Importantly, the study places their data into 5 diagnostic groups: metabolic diseases; NH; viral infections; other etiologies; and indeterminate. The "indeterminate" diagnosis was assigned to 56 (37.8%) of patients. It should be pointed out that this diagnosis does not imply that a specific diagnosis could not be determined, only that it was not. The data are not clear as to whether these patients had acute hepatic necrosis as is seen in "indeterminate PALF" in older pediatric patients. Most of the members of the next largest group, metabolic diseases, do not typically produce NALF. However, mitochondrial disease (the sum of "respiratory chain defect" plus "mitochondrial disorder" in their study) comprised 8 (5.4%) patients and 17 of the patients in the study by Durand et al.,[2] and certainly mitochondrial disease should be included prominently among potential NALF etiologies. The other diseases typically present after 30 days of age, although galactosemia may rarely present as NALF. The 2 largest groups that would be expected to produce liver failure in the $\leq$ 30-day age group are NH (20 patients, 13.5%) and viral infections (24 patients, 16.2%), both of which also appear as prominent etiologies in the study by Durand et al.[2] The review by Jackson and Roberts[4] is interesting as it presents the construct of neonatal liver failure (in their definition, liver failure at $\leq$ 60 days of age) being due to acute necrosis or chronic liver disease (ie, the extension of fetal liver disease). This construct is flawed by the fact that in 2001 no cause of fetal liver disease was known and thus the fetal origin of "chronic" liver disease in the newborn could only be inferred. However, viral infections and metabolic disease figured prominently in the acute liver disease category and NH in the chronic liver disease category. Thus, when all of these data are considered, the big players in NALF appear to be few. They are discussed in some detail and with a modern update below in the order of importance in NALF.

GALD is by far the most common cause of NALF (in our experience 60%-90% of patients). Some background and definitions are necessary at this point. NH is by definition neonatal liver disease in association with siderosis of various extrahepatic tissues in a pattern similar to that seen in hereditary hemochromatosis (HH).[5,6] NH is the most common single-disease etiology reported in both series by Durand et al.[2] and Sundaram et al.[3] of PALF in young infants. However, NH is not a disease; rather it is a phenotype of severe fetal liver disease from any cause.[7] Clinical observations and study of livers from NH patients have led to the acknowledgment that the fetal liver disease causing NH is most often the result of gestational alloimmunity,[8,9] a condition now called GALD. It can be assumed that the NH cases in the aforementioned series were in actuality GALD-NH cases.

Because GALD always presents in the newborn, typically at birth, it can further be assumed that these were cases of NALF. Thus, GALD appears to be the single most common disease causing NALF. Importantly, GALD and NH are not synonyms. GALD is a cause of NH, and NH is a symptom of GALD. NH proven to be due to GALD can be referred to as GALD-NH. NH cases in which no other cause can be identified are assumed to be due to GALD and can be referred to as either NH or GALD. However, GALD can produce severe fetal liver injury and even fetal death in the absence of extrahepatic siderosis.[10] These cases should be referred to simply as GALD.

Iron overload and tissue siderosis are defining features of NH.[6] In GALD-NH, they result from impaired feedback control of maternofetal iron flux because of low fetal liver hepcidin expression.[11] This creates an environment of iron overload in which tissues with normal iron uptake mechanisms accumulate excess iron. The tissues most commonly affected with siderosis are pancreatic acinar cells, myocardium, thyroid follicular epithelium, adrenal cortex, and mucosal glands of oronasopharynx and respiratory tree. Notably, reticuloendothelial cells including Kupffer cells and those in the spleen do not accumulate iron. Because of the similarity in distribution of tissue siderosis, NH was once thought to be a member of the HH family of genetic disorders and retains its place there in the Online Mendelian Inheritance in Man catalogue (OMIM 231100). HH types 1 and 2 are characterized by accumulation of excess body iron. In HH type 1, homozygous C282Y mutations in the HFE gene result in a modest increase in the fraction of dietary iron absorbed and the development of iron overload over many years. In HH type 2 (2a due to homozygous hemojuvelin [HJV] gene mutations and 2b to hepcidin [HAMP] gene mutations), so-called juvenile hemochromatosis, iron overload occurs at a much more rapid rate because of the central importance of hepcidin and hemojuvulin in regulation of iron homeostasis. Importantly, disordered iron homeostasis in these conditions leads to iron overload, and iron toxicity leads to organ injury and dysfunction. In contrast, in NH fetal liver dysfunction leads to disordered iron homeostasis and iron overload. In HH, iron overload precedes and is a prerequisite for liver disease, whereas in NH liver disease precedes and is a prerequisite for iron overload. It is unnecessary to do genetic testing for HH of parents or child in the setting of NH.

In the clinical setting, demonstration of extrahepatic siderosis is essential for diagnosis of NH and thus GALD-NH. This is accomplished by magnetic resonance imaging and/or oral mucosal biopsy.[6,12,13] Abnormal hepatic parenchymal siderosis is almost always seen in NH. However, it is a nonspecific finding in many newborn liver diseases and is not necessarily diagnostic of NH. Plasma iron indices reflect iron overload.[11] Plasma iron and transferrin saturation are typically high, whereas transferrin levels are normal to low. Serum ferritin levels are elevated to above 800 ng/mL in over 95% of patients, making this a sensitive marker of NH, but this is not specific for GALD-NH as it is observed in many neonatal liver diseases. It should be noted that a serum ferritin level above 7000 ng/mL is atypical for GALD-NH and suggests another etiology for liver disease.[14]

GALD is the prototype of fetal liver disease that extends into the newborn to produce liver failure. Evidence suggests that the alloimmune injury usually begins in midgestation.[15] Ongoing injury to developing hepatocytes during the second half of gestation results in failure to develop normal parenchyma, and the effort to develop parenchyma results in the proliferation of progenitor tubules and extensive parenchymal fibrosis.[16] The typical histopathology of GALD-NH reflects this dynamic: absence of normal hepatocytes; normal portal areas; numerous tubules in parenchyma; extensive parenchymal fibrosis; and multinucleate giant cells as the only remaining hepatocyte forms. The retention of membrane attack complex (complement C5b-9 complex) in remaining hepatocyte forms is taken as evidence of alloimmune injury.[8] This test has become useful in the diagnosis of GALD[14,17]; however, it remains a research tool and is not widely available for clinical use. Many patients will show regenerative nodules. Hepatic necrosis is never seen, in clear distinction from NALF due to perinatal infection. Clinical signs of portal hypertension often reflect the pathology, with a high frequency of ascites in the fetus and newborn. However, clinical observation has demonstrated that most newborns with GALD-NH maintain a patent ductus venosus, thus making splenomegaly uncommon.[18] This finding is not specific as it has been documented in other causes of NALF such as enterovirus infection,[19] but it explains the absence of splenomegaly in GALD and can provide supporting evidence for the diagnosis of GALD.

Most patients with GALD-NH show signs of fetal liver disease including intrauterine growth restriction and oligohydramnios. Some will have evidence of cirrhosis on prenatal ultrasound, such as ascites. Many

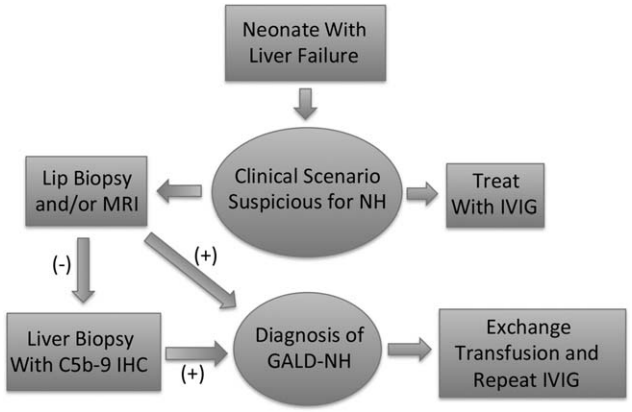

FIG. 1. Diagnostic and treatment algorithm for GALD-NH in NALF. Treatment with IVIG should be initiated upon clinical suspicion of GALD-NH while further diagnostic workup is ongoing. Liver biopsy staining with C5b-9 remains a research tool but has proven useful in diagnosis of GALD. Upon confirmation of GALD-NH, treatment with exchange transfusion and repeat IVIG should be performed.

are prematurely born. There is often a history of a maternal sibling lost to stillbirth or neonatal disease. These patients present with signs of liver failure, including hypoglycemia, bleeding, edema (anasarca, hydrops), and general sickness (culture negative sepsis). In a recent autopsy study, newborns dying in the first 3 days of life without a specific cause identified were found to have GALD.[20] An average INR above 4 reflects liver failure as do low serum albumin levels, typically below 2 g/dL. Aminotransferase levels are low, nearly always below 100 IU/L. It has been said that the low levels of aminotransferases reflect liver "burnout." That is not true. These livers are not burned out in that they can recover with medical therapy. The relatively low values probably reflect the failure to develop normal parenchyma.

GALD-NH is difficult to treat, as affected babies are sick and small, making liver transplant a difficult undertaking with poor reported outcomes. Historically, medical therapy has had even worse outcomes. However, directing treatment toward the alloimmune etiology has improved the success of medical therapy.[21] The treatment combines double volume exchange transfusion with high-dose intravenous immunoglobulin (IVIG) to remove offending antibodies and block their action including activation of complement. In the first report, 16 severe GALD-NH patients were treated: 12 survived intact with medical therapy alone. Subsequent experience with many more patients indicates a similar rate of survival with this therapy. A combined diagnostic and treatment algorithm for GALD-NH is provided in Fig. 1. If the clinical scenario is suspicious for GALD, treatment with IVIG should be instituted immediately while the diagnosis is pursued. After confirmation of the diagnosis, treatment should continue with exchange transfusion followed by repeat high-dose IVIG. Because the recovery period for these infants can take months, supportive care and avoidance of liver transplant if possible is indicated. It is exceedingly important to make a proper diagnosis in these patients because of the high rate of recurrence in the mother's subsequent pregnancies, which can be prevented by gestational treatment with high-dose IVIG.[22,23] Postmortem examination is an integral part of the diagnostic evaluation and should be performed in any infant in conditions that are suspect for GALD. With proper examination, a proper diagnosis can be made in nearly all patients.[14]

Viral infection is considered a common cause of NALF (in our experience 20%-30% of patients). Viral infections involved in NALF are generally acquired at birth or thereafter and thus are rarely clinically evident at birth and typically present at a week or 2 of age. It is important to note that neonates with neonatal viral infections typically have had a normal intrauterine life and thus show no signs of fetal distress such as intrauterine growth restriction (IUGR). Premature infants are not immune to neonatally acquired infection and may be more susceptible to them because of a less mature immune system and lack of protective, transplacental maternal antibody. They generally have birth weights that are appropriate for gestational age. Diagnosis of viral infection is typically by polymerase chain reaction (PCR) of blood, nasal swab, or feces. This test should be performed in any newborn with NALF or suspected liver disease; finding a viral etiology precludes the need for broader and more expensive diagnostic testing. Perinatal viral infection produces NALF via acute hepatic necrosis. Thus, the aminotransferase levels are typically very high. The histopathology in postmortem specimens shows global necrosis often with collapse.

Herpes simplex virus (HSV) is now the most common viral agent associated with NALF. HSV infections are generally acquired by passage through the birth canal of mothers with active vaginal HSV infection, although the maternal infection may be asymptomatic. Mothers with a history of primary, vaginal HSV should be treated with special caution. If there is

any evidence of active infection, Caesarian section is the preferred method of birth. It is paramount to recognize HSV infection early because it has a high mortality rate without early initiation of treatment with acyclovir. Verma et al.[24] reported that of 11 patients of HSV-associated ALF, only 2 patients who received early parenteral acyclovir therapy survived. Neonates with HSV-associated NALF may have either disseminated HSV or HSV isolated to the liver. In either of these patients, neonates commonly lack the cutaneous findings associated with HSV such that a high index of suspicion is needed to make the diagnosis and initiate early treatment. If there is any concern for HSV-associated NALF, it is recommended to immediately start acyclovir treatment while awaiting PCR, biopsy, or culture. The liver histopathology in HSV-NALF shows, in addition to hemorrhagic necrosis, prominent viral inclusions. Among the other herpes viruses, human herpes virus 6 (HHV6) has also been associated with NALF,[2] even though HHV6 is generally considered to be a less malicious infection than HSV. Cytomegalovirus (CMV) is very rarely associated with NALF. More often it produces a chronic smoldering hepatitis with prominent cholestasis. CMV infection is the 1 major exception to the rule of infected infants showing no signs of intrauterine distress in that CMV may be transmitted transplacentally and can be acquired before birth, such that babies can be born with hepatic symptoms. The prognosis however is much better than for most other forms of neonatal viral hepatitis, in that the hepatic symptoms almost always regress spontaneously.

Agents that typically produce mild illness in adults may also produce NALF. Enterovirus infections are perhaps the most common. Recent diarrheal or respiratory illness in the mother should make enterovirus suspect. Although most perinatally acquired enterovirus infections are mild, some produce necrotizing enterocolitis (NEC) and NALF. In our experience, any baby with the combination of NEC and NALF should be considered to have an enterovirus infection. The outcome of such patients is poor. The postmortem liver histopathology in 3 patients showed global hepatic necrosis with no viable hepatocytes remaining. Although there is no FDA-approved therapy for enteroviral infection, there is anecdotal experience for using IVIG, and there is an experimental agent (pleconaril) that is sometimes available on a compassionate case basis. Within the enterovirus taxonomy lie the echoviruses, which have been associated with NALF, especially echovirus 11 in nursery outbreaks. Parvovirus B19 infection has been identified in patients with ALF and bone marrow failure, but not in NALF. Parvovirus B19 infections have been strongly associated with fetal anemia and nonimmune hydrops fetalis, which suggests the possibility of intrauterine infection with liver failure, although it is rarely if ever diagnosed in live born infants with liver failure. Adenoviruses have also rarely been reported to cause NALF.

HLH (hemophagocytic syndrome) is an unusual cause of NALF (in our experience $< 10\%$ of patients). HLH is a syndrome of excessive immune activation and is the most common malignant condition responsible for NALF. HLH may be either primary (gene mutations affecting the cytotoxic function of NK cells and T cells, in particular perforin) or secondary to viral infection. HLH was diagnosed in 4 of 148 patients in the series by Sundaram et al.[3] of PALF infants ≤ 90 days of age and 3 of 80 PALF patients in the series by Durand et al.[2] of infants ≤ 1 year of age. HLH may be underrepresented as a cause of NALF. Oncologists, who may not consider liver dysfunction to be an unusual feature of the disease, often manage these patients and perhaps do not report the liver failure. Features of HLH that should arouse suspicion are prominent hepatosplenomegaly and very high serum ferritin levels (typically 20-50,000 ng/mL). Diagnosis is based on fulfilling clinical criteria that include fever; splenomegaly; pancytopenia; hypertriglyceridemia and/or hypofibrinogenemia; elevated ferritin; low/absent NK cell activity; elevated soluble CD25 (soluble interleukin 2 receptor); and evidence of hemophagocytosis in bone marrow, spleen, lymph node, or liver. HLH is treated medically, typically with chemotherapy, and prognosis is guarded.

Mitochondrial disorders are rare and unusual causes of NALF (in our experience $< 5\%$ of patients). This broad classification of gene-based diseases includes respiratory chain defects, errors in fatty acid oxidation, and mitochondrial DNA depletion syndromes. They are prominent causes of liver failure in young children,[2,3] but their place in NALF etiology is unknown. The mitochondrial DNA depletion disease due to deoxyguanosine kinase (DGUOK) mutations is certain to have a place because it has been reported to produce the NH phenotype. A suspicion for mitochondrial disease is raised by metabolic distress, such as hypoketotic hypoglycemia with lactic acidosis. The liver pathology in these patients typically shows microvesicular or mixed macrovesicular and microvesicular steatosis, reflective of the impairment of energy metabolism they share. These diseases are prototypic of liver failure due to failed organelle function. Necrosis is minimal. Suspected

TABLE 1. Presenting Clinical Findings in NALF Based on Etiology

	GALD-NH	Viral Infection	HLH	Mitochondrial Hepatopathy
Age at presentation	Usually at birth and almost always < 3 days	Typically 5-14 days	Variable, sometimes at birth	Variable, often first weeks to months of life
Premature birth	Most (70%-90%)	Usual population incidence	Uncommon	Uncommon
History of maternal sibling death	Common	Almost never	Uncommon	25% risk in full siblings
Oligohydramnios	Most (70%-90%)	Rare	Rare	Uncommon (polyhydramnios seen)
Intrauterine growth restriction	Most (70%-90%)	Rare	Rare	Possible (20%-30%)
Multiorgan involvement	Renal tubular dysplasia	Common in HSV especially brain	Bone marrow	Central nervous system and heart
Ascites	Common (40%-60%)	Rare	Uncommon	Uncommon
Patent ductus venosus	Most (70%-90%)	Never	Never	Never
Hepatomegaly	Uncommon (10%-20%)	Common	Common	Common
Splenomegaly	Uncommon (10%-20%)	Common though often mild	Common	Uncommon
Hypoglycemia	Usual	Common	Common	Usual
Coagulopathy	Profound (INR, 4-10)	Moderate to profound	Moderate to profound	Moderate to profound
Metabolic acidosis	No	No	No	Yes
Cholestasis	Not at birth; increasing afterward	Minimal at presentation	Moderate to severe	Moderate
ALT	Typically low or normal and almost always < 100 IU/L	Typically high and often > 1000 IU/L	Typically high and often > 1000 IU/L	Typically high and often 100-500 IU/L
Ferritin	Almost always > 800 ng/mL and < 7000	Often very high (>20,000 ng/mL)	Very high (>20,000 ng/mL)	Variable elevation
Alpha-fetoprotein	Almost always high (> 80,000 ng/mL in term neonate); typically > 300,000 ng/mL	Almost always normal (< 80,000 ng/mL in term neonate)	Almost always normal (< 80,000 ng/mL in term neonate)	Variable elevation
Lactate:pyruvate molar ratio and ketone body ratios	Normal	Normal	Normal	Abnormal

mitochondrial disease should lead to a tiered diagnostic algorithm that will often yield a specific diagnosis.[25]

Toxic metabolic hepatopathies are rare causes of NALF (in our experience < 1% of patients). Three autosomal recessive inherited diseases have the potential for producing NALF: hereditary tyrosinemia type 1, galactosemia, and hereditary fructose intolerance. In the series by Durand et al.[2] of 80 infants ≤ 1-year of age with ALF, 12 had hereditary tyrosinemia type 1, 2 had galactosemia, and 1 had hereditary fructose intolerance[2]; whereas in the series by Sundaram et al.[3] of 148 infants ≤ 90 days of age, 3 had hereditary tyrosinemia type 1, 12 had galactosemia, and none had hereditary fructose intolerance.[3] Thus, they are prevalent causes of PALF in infants, but the same cannot be said for NALF. Of the 3, only galactosemia regularly presents within the first month of life, after the onset of milk feeding. Most cases of galactosemia in the United States are diagnosed with newborn screening and never become clinically evident as liver failure. Hereditary fructose intolerance becomes evident after the onset of fructose or sucrose intake, which is typically when solid foods are introduced into the diet. However, use of some non-cow's milk infant formulas may cause it to present earlier. It is prudent to check the newborn screening results (for galactosemia), take a dietary history (for hereditary fructose intolerance), and collect urine for succinylacetone detection (for tyrosinemia type 1) when faced with a NALF case. Though the yield may be low, the cost is minimal, and all of these diseases are treatable.

Genetic cholestasis is a rare cause of NALF (in our experience < 1% of patients). The bile acid synthetic defect 5-beta-reductase deficiency is a reported cause of the NH phenotype. Cholestasis due to ABCB11 mutations (bile salt export pump disease) very rarely presents in the first month of life and even then typically with clinical cholestasis, not NALF. Still, these

diseases should be kept in mind when presented with a case of NALF with prominent cholestasis.

Simplified Differential Diagnosis of NALF

Four etiologies, GALD-NH, viral infection, HLH, and mitochondrial hepatopathy, comprise nearly all cases of NALF. The varying clinical features of these are presented in Table 1. Just a few variables reasonably clearly separate them: age at onset, evidence of fetal insult, presence of a patent ductus venosus, hepatomegaly, alanine aminotransferase (ALT) level, ferritin level, alpha-fetoprotein level, and persistent metabolic acidosis. By going through this simple checklist, one can rapidly decide on an approach to a definitive diagnosis as described above. An aberrant finding not typical of these diseases should lead in an alternate direction. For example, if a NALF patient were to have metabolic acidosis and the lactate level was high, mitochondrial disease should be considered. Likewise, genetic cholestasis might be considered in a NALF patient with significant cholestasis. The tendency, unfortunately, is to attempt to rule out every known cause of infant liver disease in these patients by exhaustive and expensive testing. Genetic diagnosis is not relevant in these patients because of the time it takes to get results back, and many diseases that are prominent causes of cholestatic disease, such as alpha-1-antitrypsin deficiency, just do not cause NALF. A well-thought parsimonious workup is far more useful.

Liver Transplantation in NALF

All liver transplantation in the neonate is performed for ALF, and thus the above-mentioned causes of NALF are the most commonly identified etiologies. "Indeterminate" NALF ranges from 16.2% to 37.8% in the studies by Durand et al.[2] and Sundaram et al.[3] and remains a prominent indication for liver transplant in the neonate. Many patients with "indeterminate" NALF are due to giant cell hepatitis, a nonspecific response to liver injury with characteristic multinucleated giant syncytial cells on histology that can result from an intrauterine or postnatal event, including infection or inborn error of metabolism. Although improved diagnostic techniques have increased the ability to make a precise diagnosis in NALF, giant cell hepatitis remains an important cause for liver transplantation in the neonate.

A complete investigation into the etiology of NALF is paramount as this influences the evaluation of the candidate as well as the timing of liver transplant (Table 1). Patients identified as having GALD with a significant coagulopathy but clinically stable should be observed, as liver injury from GALD can reverse over time with medical therapy and supportive care, thereby avoiding liver transplantation.[21,26] If necessary, however, liver transplant for infants with NH has been shown to have comparable outcomes to similar age-matched patients undergoing liver transplant for other etiologies of ALF.[27] Mitochondrial hepatopathy is important to identify in the neonate as the irreversible multisystem nature of some of these disorders introduces the need for caution when considering the patient for liver transplantation. Similarly, HLH is treated with chemotherapy, and a thorough investigation for this cause must be undertaken to avoid liver transplantation in an otherwise medically treatable disease or in one that is likely to recur.

Neonatal liver transplantation offers unique challenges that are worth mentioning. These patients are often critically ill with impaired respiratory, cardiac, and renal function. Encephalopathy cannot be easily evaluated in these patients and intracranial bleeding is common, portending poor outcome. Surgical considerations include the neonates' size and need for technical variant grafts. Most commonly, neonates will receive left-lateral segment grafts from infants and smaller children, although monosegment grafts have been used with some success. ABO-incompatible liver transplantation can be successfully performed in neonates and offers a means to overcome the lack of suitable organs for these challenging patients. Because neonates do not have prior sensitization to the major blood group antigens, they can successfully accept ABO-incompatible allografts without increased risk for patient or graft survival, biliary complications, vascular complications, or rejection.[28,29] Despite these challenges, liver transplantation in the neonate is successful with similar patient and graft survival when compared to older recipients[30] and should be considered in the appropriate candidate.

REFERENCES

1) Squires RH Jr, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, et al. Acute liver failure in children: the first 348

patients in the pediatric acute liver failure study group. J Pediatr 2006;148:652-658.
2) Durand P, Debray D, Mandel R, Baujard C, Branchereau S, Gauthier F, et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. J Pediatr 2001; 139:871-876.
3) Sundaram SS, Alonso EM, Narkewicz MR, Zhang S, Squires RH; for Pediatric Acute Liver Failure Study Group. Characterization and outcomes of young infants with acute liver failure. J Pediatr 2011;159:813-818.
4) Jackson R, Roberts EA. Identification of neonatal liver failure and perinatal hemochromatosis in Canada. Paediatr Child Health 2001;6:248-250.
5) Knisely AS, Mieli-Vergani G, Whitington PF. Neonatal hemochromatosis. Gastroenterol Clin North Am 2003;32:877-889.
6) Whitington PF. Fetal and infantile hemochromatosis. Hepatology 2006;43:654-660.
7) Zoller H, Knisely AS. Control of iron metabolism--lessons from neonatal hemochromatosis. J Hepatol 2012;56:1226-1229.
8) Pan X, Kelly S, Melin-Aldana H, Malladi P, Whitington PF. Novel mechanism of fetal hepatocyte injury in congenital alloimmune hepatitis involves the terminal complement cascade. Hepatology 2010;51:2061-2068.
9) Whitington PF. Gestational alloimmune liver disease and neonatal hemochromatosis. Semin Liver Dis 2012;32:325-332.
10) Whitington PF, Pan X, Kelly S, Melin-Aldana H, Malladi P. Gestational alloimmune liver disease in cases of fetal death. J Pediatr 2011;159:612-616.
11) Bonilla S, Prozialeck JD, Malladi P, Pan X, Yu S, Melin-Aldana H, Whitington PF. Neonatal iron overload and tissue siderosis due to gestational alloimmune liver disease. J Hepatol 2012;56: 1351-1355.
12) Knisely AS, O'Shea PA, Stocks JF, Dimmick JE. Oropharyngeal and upper respiratory tract mucosal-gland siderosis in neonatal hemochromatosis: an approach to biopsy diagnosis. J Pediatr 1988;113:871-874.
13) Udell IW, Barshes NR, Voloyiannis T, Lee TC, Karpen SJ, Carter BA, et al. Neonatal hemochromatosis: radiographical and histological signs. Liver Transpl 2005;11:998-1000.
14) Heissat S, Collardeau-Frachon S, Baruteau J, Dubruc E, Bouvier R, Fabre M, et al. Neonatal hemochromatosis: diagnostic workup based on a series of 56 cases of fetal death and neonatal liver failure. J Pediatr 2015;166:66-73.
15) Bonilla SF, Melin-Aldana H, Whitington PF. Relationship of proximal renal tubular dysgenesis and fetal liver injury in neonatal hemochromatosis. Pediatr Res 2010;67:188-193.
16) Asai A, Malladi S, Misch J, Pan X, Malladi P, Diehl AM, Whitington PF. Elaboration of tubules with active hedgehog drives parenchymal fibrogenesis in gestational alloimmune liver disease. Hum Pathol 2015;46:84-93.
17) Debray FG, de Halleux V, Guidi O, Detrembleur N, Gaillez S, Rausin L, et al. Neonatal liver cirrhosis without iron overload caused by gestational alloimmune liver disease. Pediatrics 2012; 129:e1076-1079.
18) Tsai A, Paltiel HJ, Sena LM, Kim HB, Fishman SJ, Alomari AI. Neonatal hemochromatosis and patent ductus venosus: clinical course and diagnostic pitfalls. Pediatr Radiol 2009;39:823-827.
19) Sharma R, Crowley J, Squires R, Bond G, Sindhi R, Mazariegos G, Soltys K. Neonatal acute liver failure complicated by patent ductus venosus: diagnosis and management. Liver Transpl 2013; 19:1049-1052.
20) Melin-Aldana H, Park C, Pan X, Fritsch M, Malladi P, Whitington P. Gestational autoimmune liver disease in newborns with an indeterminate cause of death following a complete autopsy. J Neonatal Perinatal Med 2015;8:23-31.
21) Rand EB, Karpen SJ, Kelly S, Mack CL, Malatack JJ, Sokol RJ, Whitington PF. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. J Pediatr 2009;155:566-571.
22) Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet 2004;364:1690-1698.
23) Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high-dose intravenous immunoglobulin. Pediatrics 2008;121:e1615-1621.
24) Verma A, Dhawan A, Zuckerman M, Hadzic N, Baker AJ, Mieli-Vergani G. Neonatal herpes simplex virus infection presenting as acute liver failure: prevalent role of herpes simplex virus type I. J Pediatr Gastroenterol Nutr 2006;42:282-286.
25) Molleston JP, Sokol RJ, Karnsakul W, Miethke A, Horslen S, Magee JC, et al.; for Childhood Liver Disease Research Education Network (ChiLDREN). Evaluation of the child with suspected mitochondrial liver disease. J Pediatr Gastroenterol Nutr 2013;57:269-276.
26) Ekong UD, Melin-Aldana H, Whitington PF. Regression of severe fibrotic liver disease in 2 children with neonatal hemochromatosis. J Pediatr Gastroenterol Nutr 2008;46:329-333.
27) Sheflin-Findling S, Annunziato RA, Chu J, Arvelakis A, Mahon D, Arnon R. Liver transplantation for neonatal hemochromatosis: analysis of the UNOS database. Pediatr Transplant 2015;19: 164-169.
28) Sundaram SS, Alonso EM, Whitington PF. Liver transplantation in neonates. Liver Transpl 2003;9:783-788.
29) Gelas T, McKiernan PJ, Kelly DA, Mayer DA, Mirza DF, Sharif K. ABO-incompatible pediatric liver transplantation in very small recipients: Birmingham's experience. Pediatr Transplant 2011;15:706-711.
30) Sundaram SS, Alonso EM, Anand R; for Study of Pediatric Liver Transplantation Research Group. Outcomes after liver transplantation in young infants. J Pediatr Gastroenterol Nutr 2008;47:486-492.