The Continuing Challenge of "Indeterminate" Acute Liver Failure in Children

One of the most challenging problems in pediatric hepatology is the child who presents with acute liver failure (ALF). The barriers to determining a specific diagnosis are multiple and daunting. There is a very limited time frame for completing an evaluation before liver transplantation. Many diagnostic tests for specific causes do not have high sensitivity or specificity and are not standardized across institutions that care for these patients. Liver biopsy is often not possible because of coagulopathy, and transjugular biopsy is often insufficient for a diagnosis.[1] Even adequate tissue sampling often does not yield a specific diagnosis, especially in the presence of massive necrosis and parenchymal collapse.[2] Finally, even after an exhaustive workup is completed, there will still be a significant proportion of cases with an "indeterminate" diagnosis. Currently, no specific cause is defined in approximately half of pediatric patients with ALF.[3]

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Specific diagnosis has clinical importance because certain causes of ALF have a better prognosis in many cases without transplantation (acetaminophen toxicity), may respond to specific medical therapy (autoimmune hepatitis), may represent a contraindication for transplant (mitochondrial disorders affecting other organ systems), or may have implications for genetic testing/screening in family members (Wilson disease). In this issue of *The Journal*, Narkewicz et al[4] in the Pediatric Acute Liver Failure Study Group take an important first step in addressing this issue by undertaking an honest and comprehensive evaluation of diagnostic practices for pediatric patients with indeterminate ALF across the centers in their consortium.

The authors reviewed data from 703 pediatric patients entered into their database at 20 centers in the United States, Canada, and Great Britain from 1999 to 2008. The study focused on the diagnostic evaluation performed in the patients with indeterminate ALF (47% of the total) in 4 categories: drug exposure, including acetaminophen, autoimmune hepatitis (AIH), metabolic diseases, and infectious causes. Evaluation of the cause of ALF and assignment of a final diagnosis were at the discretion of the attending physician at each center during the hospital course. The results were somewhat surprising for tertiary care centers specializing in pediatric liver disease. Although a drug history was obtained in 99%, a toxicology screen and an acetaminophen level were obtained in only 36% and 38%, respectively. No testing for common metabolic diseases was done in 54%. No testing for autoimmune markers was performed in 21%. Testing for hepatitis B, hepatitis C, and Epstein-Barr virus was done in 80%, 86%, and 68%, respectively. In comparison to the patients with a specific diagnosis, the indeterminate group was younger, had a higher total bilirubin at presentation, and had a significantly higher transplantation rate within 3 weeks of presentation, even when the subgroup with acetaminophen poisoning was excluded from analysis. This underscores the urgency for a complete evaluation in the indeterminate group.

Closer inspection of these results does provide a reasonable explanation for omission of testing in some instances. For example, in the case of acetaminophen, levels obtained greater than 24 hours after acute dosing or in cases of long-term dosing are often not helpful in establishing hepatotoxicity with Rumack-Matthew nomography. Perceptions of the age distribution of certain metabolic diseases probably explain the higher screening rates for fatty acid oxidation defects in younger patients and for measurement of ceruloplasmin and urine copper for Wilson disease in older patients. Also, as the authors point out, perceptions of typical clinical presentations for some diseases, such as neonatal iron storage disease, influence decisions to screen. Evaluations were equally complete or incomplete regardless of rapidity of ALF progression, although testing may have been more complete in patients perceived as being more ill. Finally, blood volume considerations for infants probably impacted on decisions for specific testing in this age group.

Ultimately, through more extensive analysis of registry data and prospective trials in a multicenter setting, such as the Pediatric Acute Liver Failure consortium, guidelines may be developed to standardize the evaluation of the pediatric patient with ALF. Algorithms that stratify and prioritize testing in the context of age, degree and rate of deterioration of liver function, and that specify the use of specific tests that demonstrate the greatest sensitivity and specificity in the setting of ALF are needed. Such guidelines should not focus solely on testing but take into account the clinical features of the diseases being considered as well. New biomarkers with greater reliability and rapid turnaround for the diagnosis of specific liver diseases that can result in ALF are needed. For example, urine drug screens do not include every possible hepatotoxin, especially many common medications and environmental toxins.[5] Ceruloplasmin levels are of little value in the setting of ALF because of Wilson disease;

AIH	Autoimmune hepatitis
ALF	Acute liver failure

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however, when combined with alkaline phosphatase/total bilirubin and aspartate aminotransferase/alanine aminotransferase ratios, a high sensitivity and specificity may be possible.[6]

In the realm of new diagnostic biomarkers, there has been much enthusiasm for the measurement of serum 3-(cystein-S-yl) acetaminophen protein adducts produced by binding of the reactive metabolite NAPQI to cysteinyl sulfhydryl groups on proteins. Measurement of these adducts shows promise for providing greater diagnostic accuracy for acetaminophen hepatotoxicity in the setting of ALF, because the elimination half-life of adducts appears to be greater than that of the parent compound.[7] However, at present, there is not sufficient evidence for the measurement of these adducts alone to prove a causal relationship between acetaminophen ingestion and hepatic injury or provide utility in the clinical setting, because levels of these adducts parallel, but do not precede, markers for liver injury.[8] A small but significant percentage of patients with ALF with a known cause other than acetaminophen toxicity also have these adducts.[9] In these cases, it is also possible that acetaminophen may act as a negative disease modifier. Also, better markers for the diagnosis of fatty acid oxidation defects, such as the use of esterified carnitine concentrations in bile as predictive of a poor prognosis in ALF, as well as a possible marker for this group of disorders, will improve diagnosis and management of a subset of patients with ALF.[10,11] More reliable diagnostic tools are also needed to diagnose ALF because of AIH. A recent study demonstrated the presence of autoantibodies associated with non-AIH diagnoses, including drug-induced and viral causes, in ALF in children.[12] Until new and specific biomarkers are developed and validated for clinical use, the tests that are available should be optimized. However, even with improved diagnostic accuracy for the diseases that we know can cause ALF, a significant proportion of cases will remain with unknown causes. Innovative clinical research in a multicenter setting to identify new hepatotropic viral agents, metabolic disorders, environmental toxins, as well as other potential causes of pediatric ALF, is urgently needed.

The clinical entity of indeterminate ALF in children may be analogous to another diagnostic challenge in pediatric hepatology, the infant with idiopathic neonatal cholestasis. Over the past 2 decades, as new specific causes for neonatal cholestasis have been discovered and diagnostic methods have improved, the proportion with "idiopathic" disease has continually grown smaller. Undoubtedly, the same will be true for indeterminate ALF, and multicenter research consortia, such as the Pediatric Acute Liver Failure group, will play a key role in this advancement. Given the relatively rare occurrence of pediatric ALF, continued funding for multicenter studies is essential for future progress. However, as the report in this issue of *The Journal* makes clear, new tests will only achieve optimal utility if they are judiciously applied in a uniform and evidence-based manner. The Pediatric Acute Liver Failure group is to be commended for taking the important first step of identifying and reporting their experience in this area as a guide for the future. ■

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