# Nonalcoholic Fatty Liver Disease

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# **Educational Gap**

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in the United States, affecting approximately 10% of all children, and clinicians should be aware of how to address this challenging diagnosis.

Objectives After reading this article, readers should be able to:

- Define the spectrum of nonalcoholic fatty liver disease (NAFLD) and understand the natural history of the disease.
- 2. Know the clinical features of NAFLD and recognize those at risk for the disease.
- Understand the general approach to the screening and diagnosis of NAFLD and the limitations of commonly used laboratory and imaging techniques.
- 4. Understand the broad differential diagnosis of NAFLD.
- 5. Know the most effective means of preventing and treating NAFLD.

#### DEFINITION

Nonalcoholic fatty liver disease (NAFLD) describes two distinct conditions that occur, by definition, in the absence of significant alcohol intake. The first is steatosis, which is defined as excess fat accumulation within hepatocytes. Histologically, the steatosis is often macrovesicular, meaning large droplets, and can be found in more than 5% of hepatocytes. The second condition, nonalcoholic steatohepatitis (NASH), is characterized by the additional histopathologic features of hepatic inflammation or fibrosis. Over time, NASH may progress to cirrhosis, which later may be associated with hepatocellular carcinoma.

### **EPIDEMIOLOGY**

NAFLD was first described in the pediatric population nearly 3 decades ago and has since emerged as the most common cause of liver disease in the developed world. Prevalence estimates vary, but the most accurate data are based on liver histopathology. The only pediatric study to generate prevalence data using histopathology is the Study of Child and Adolescent Liver Epidemiology (SCALE)

AUTHOR DISCLOSURE Drs Fusillo and Rudolph have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device. trial, a landmark autopsy study in San Diego, California, that examined liver histology from 742 children who died of unnatural causes. (I) After adjusting for age, gender, race, and ethnicity, the prevalence of NAFLD in San Diego was estimated to be 9.6% among *all* children. In obese children, the prevalence of NAFLD was 38%. Increasing age, weight, male gender, and Hispanic ethnicity were each independently predictive of NAFLD.

Many studies have used surrogate markers such as serum alanine aminotransferase (ALT) and ultrasonography to establish NAFLD prevalence, with estimates ranging widely based on the study population. Using ALT as a disease surrogate, a recent large cross-sectional study by Welsh et al using National Health and Examination Survey data demonstrated that the prevalence of NAFLD in adolescents has increased from 3.9% between 1988 and 1994 to 10.7% from 2007 to 2010. (2) In this cohort, nearly 30% of obese girls and 50% of obese boys had elevated ALT values. Overall, available data suggest that NAFLD may affect as many as 10% of children in the United States.

#### **RISK FACTORS AND ASSOCIATIONS**

#### Obesity

Obesity is the most significant risk factor for the development of NAFLD. Numerous studies have demonstrated a direct correlation between NAFLD and body mass index (BMI), with higher disease burdens in heavier patients. In the SCALE trial, for example, NAFLD was absent in underweight children but present in 5% of normal-weight children, 16% of overweight children, and 38% of obese children. As these data indicate, it is important to recognize that NAFLD may also occur in normal-weight children, albeit less frequently than in overweight and obese children.

#### Insulin Resistance and the Metabolic Syndrome

Insulin resistance is clearly associated with NAFLD. Multiple studies have shown elevated fasting insulin levels and reduced insulin sensitivity in children with NAFLD, and the severity of hyperinsulinemia may correlate with the degree of steatosis or NASH. The presence of NAFLD not only increases the risk of developing type 2 diabetes but may worsen glycemic control in children with diabetes and contribute to the development and progression of chronic diabetic complications.

The metabolic syndrome is a cluster of conditions that, when co-occurring, confer risk for developing heart disease, diabetes, and stroke. NAFLD has been strongly associated with several features of the metabolic syndrome, including obesity, dyslipidemia, and hypertension. There is such overlap between these entities, in fact, that many consider NAFLD to be the hepatic manifestation of the metabolic syndrome. However, not all patients with metabolic syndrome have NAFLD.

#### Age and Environment

The prevalence of NAFLD increases throughout childhood. In the SCALE trial, for example, NAFLD was identified in 0.2% of children between 2 and 4 years of age and in 17.3% of children between the ages of 15 and 19 years. This trend may be at least partially explained by obesity because BMI increases with age in children. (3)

Environmental changes may also contribute to the high prevalence of NAFLD. In the previously cited study by Welsh et al, the prevalence of NAFLD more than doubled over the past 20 years, even after controlling for other modifiable risks such as BMI, suggesting that other factors may be responsible. (2)

#### Gender and Ethnicity

NAFLD is approximately 40% more common in boys than girls and is also more prevalent among certain ethnicities, with the highest rates seen in Hispanic and Asian children (12% to 14% and 10%, respectively). Slightly lower rates are seen among Caucasians (7% to 9%). Despite higher rates of obesity and diabetes, African American children have substantially lower rates of NAFLD (2% to 6%). Recent advances suggest that these prevalence differences may be explained by genetic polymorphisms. The specific genes implicated in NAFLD are discussed in further detail later in this article.

#### Cardiovascular Disease

Multiple studies have found increases in carotid intima media thickness in children with NAFLD, and adults with NAFLD are more likely to die from cardiovascular disease than from liver complications. It is unclear, however, whether these cardiovascular changes are due to NAFLD itself or associated risk factors such as abdominal obesity, insulin resistance, and dyslipidemia. Although strongly associated, causation has yet to be determined.

#### **Obstructive Sleep Apnea**

Obstructive sleep apnea (OSA) is common in children, also associated with obesity, and an independent risk factor for the metabolic syndrome. Studies in adults and children have established an association between OSA and NAFLD, with an improvement in serum ALT and ultrasonographically documented steatosis following OSA treatment. A recent cross-sectional study of 65 children demonstrated that the presence and severity of OSA correlates with NASH and fibrosis on liver biopsy, even after controlling for BMI, abdominal adiposity, metabolic syndrome, and insulin resistance. (4)

#### Quality of Life

Several large studies have found that children and adults with NAFLD report significantly lower quality of life and mental health scores than the general population. However, just as with cardiovascular disease, causality is unclear, and impairments could be due to related comorbidities such as obesity or diabetes mellitus. One recent study comparing children with NAFLD to obese children without the disease found no significant difference in overall quality of life, although those with NAFLD reported significantly worse scores on specific psychosocial indices, including depression and body-esteem, as compared to controls. (5)

## PATHOGENESIS

The pathogenesis of NAFLD is not well understood. Historically, the development of NAFLD and NASH has been explained via the "two-hit hypothesis." According to this theory, the first "hit" is the accumulation of fat within hepatocytes or insulin resistance. This, in turn, makes the liver more susceptible to additional injury (ie, the development of NASH and fibrosis) via a yet-to-be-identified second "hit." Of note, this theory is largely speculative and remains unproven.

Alternatively, recent literature has pointed to a host of other possible etiologic pathways, including diets high in simple sugars or changes to the intestinal microbiome. Certain genes, as discussed in the next section, are also clearly associated with disease states, although their precise pathogenic role to date is unknown. Ultimately, much research is needed to elucidate a detailed etiologic pathway.

#### **Genetic Factors**

NAFLD may exhibit familial clustering, and several familial aggregation studies conducted over the past decade have demonstrated a significant genetic contribution to overall disease risk. Recent studies have identified several single-nucleotide polymorphisms that help explain the differing disease burden among races. Most notably, the I148M variant of the patatin-like phospholipase 3 (*PNPLA3*) gene is strongly associated with increased hepatic steatosis, NASH, and fibro-sis. *PNPLA3* encodes the protein adiponutrin, which is involved in lipid regulation. In some study cohorts, nearly 50% of Hispanics carry a *PNPLA3* mutation. One *PNPLA3* polymorphism found predominantly in African Americans, S453I, is associated with *decreased* hepatic steatosis.

These single-nucleotide polymorphisms and others provide a potential explanation for differing disease prevalence among various ethnic groups. How these genes specifically contribute to disease pathogenesis, however, remains largely unknown. Currently, genetic testing is not routinely used in clinical practice.

#### **CLINICAL FEATURES**

NAFLD is an insidious disease; most affected children are asymptomatic. Some patients report nonspecific complaints, including vague right upper quadrant abdominal pain, fatigue, or malaise. Physical examination may reveal increased waist circumference or cutaneous striae and up to 50% of affected children may have acanthosis nigricans, a marker for hyperinsulinemia. Hepatomegaly is often not present on examination or difficult to appreciate but may be seen on imaging studies in 40% to 50% of those who have NAFLD. Splenomegaly, when present, should raise suspicion for portal hypertension and advanced hepatic disease.

Serum ALT may be mildly to significantly elevated and is a helpful initial screening test (see Diagnosis section). In the absence of cirrhosis, serum bilirubin, albumin, and the International Normalized Ratio should be within normal parameters. Serum alkaline phosphatase may be elevated. Gamma-glutamyl transpeptidase may also be elevated and is directly correlated with the degree of fibrosis. Ultrasonography, if obtained, generally demonstrates increased hepatic echogenicity consistent with fatty infiltration. Additional radiologic findings in NAFLD are discussed in the Imaging section. Practitioners also should assess for signs and symptoms of the metabolic syndrome such as hypertension, diabetes mellitus or insulin resistance, OSA, and dyslipidemia.

#### Natural History

As previously stated, steatosis may progress to NASH and ultimately cirrhosis. Although few longitudinal data exist in the pediatric literature to support this concept, adult data are more robust. In one pediatric study following 66 NAFLD patients for up to 20 years, four children showed progression from steatosis to NASH on serial liver biopsies. (6) In addition, children with NAFLD had a nearly 14-fold higher risk of mortality or need for liver transplantation than the general population of the same age and gender.

The precise number of children with NAFLD who have simple steatosis, NASH, or cirrhosis is unknown. It is clear, however, that some patients with simple steatosis do not develop progressive liver disease but rather live with chronic hepatic steatosis. Conversely, many of those with NASH progress rapidly to advanced liver disease. In short, it is currently impossible to identify those patients at highest risk for disease progression. Risk stratification measures are sorely needed.

Although the frequency and time course of disease progression remains unclear, the severity of liver involvement at the time of diagnosis may be predictive. Given that 5% to 10% of patients present with advanced fibrosis upon initial pathologic assessment, a staggering number of children are at high risk for long-term complications. Further, adult studies have implicated NAFLD-related cirrhosis as a risk factor for developing hepatocellular carcinoma.

## DIAGNOSIS

Professional society recommendations for NAFLD screening are conflicting. In 2007, The American Academy of Pediatrics (AAP) recommended biannual liver tests for obese (BMI >95th percentile) children and overweight (BMI >85th percentile) children with additional risk factors. (7) More recently, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended obtaining ultrasonography and screening liver tests in all obese children. (8) Joint guidelines released 1 month later by the American Gastroenterological Association (AGA), the American Association for the Study of Liver Diseases (AASLD), and the American College of Gastroenterology (ACG) did not make a formal recommendation for screening of overweight/obese children for NAFLD due to a "paucity of evidence." (9) Although no clear consensus exists, we believe it is reasonable to obtain liver function tests in overweight or obese children.

In general, NAFLD should be suspected in overweight or obese children with elevated ALT values or suggestive ultrasonographic findings. Serum ALT is a readily available, inexpensive disease marker that, when elevated, is often two to three times the upper limit of normal. However, ALT is neither sensitive nor specific for NAFLD; values often fluctuate and may even be normal in patients with simple steatosis, NASH, or cirrhosis. Furthermore, the precise ALT threshold for the diagnosis of liver disease varies between institutions and is a topic of some controversy. The Screening ALT for Elevation in Today's Youth (SAFETY) study demonstrated that an upper ALT threshold of 53 U/L (0.89  $\mu$ kat/L) had a sensitivity of detecting NAFLD of only 36% in girls and 32% in boys. To detect liver disease more reliably, the authors suggested using a lower ALT threshold of 22 U/L (0.37  $\mu$ kat/L) in girls and 25 U/L (0.42  $\mu$ kat/L) in boys. This threshold increased the sensitivity of identifying NAFLD to 80% in boys and 92% in girls, with a specificity of 79% and 85%, respectively. (10)

Liver biopsy is currently considered the gold standard for diagnosing NAFLD. Histologic samples can distinguish

simple steatosis from NASH, determine the severity of hepatic fibrosis, and eliminate competing diagnoses. However, liver biopsy is invasive, relatively expensive, and associated with a risk for significant but uncommon morbidities. Furthermore, percutaneous liver biopsy captures only a tiny portion of the overall liver mass ( $\sim I/50,000$ <sup>th</sup>), and because NAFLD lesions can be unevenly distributed, sampling errors are unavoidable. Liver biopsy is also an impractical population-level screening test.

Therefore, NAFLD is often considered a diagnosis of exclusion, and many physicians screen children with suspected NAFLD for other causes of liver disease. The differential diagnosis is broad and includes various genetic, metabolic, nutritional, pharmacologic, infectious, and systemic causes. Conditions that may cause hepatic steatosis are listed in the Table, although other liver disorders may also cause an elevated ALT value in the absence of steatosis. A thorough history and physical examination are critical, as is thoughtful testing for other causes of liver disease. However, as noted previously, guidelines for testing vary, and there is no single, accepted testing algorithm for patients with elevated ALT values. The AAP, for example, does not make specific testing recommendations for children with prolonged ALT elevations. (7) Instead, subspecialist referral is suggested. According to the ESPGHAN consensus statement, children younger than 10 years of age should undergo extensive laboratory testing to exclude other forms of liver disease. (8) The same is recommended in older (>10 years of age), low-risk children after a 3- to 6-month trial period of lifestyle modification and weight loss. Conversely, joint guidelines from the AGA, AASLD, and ACG only recommend laboratory testing to exclude diseases other than NAFLD in "very young" or nonobese children. (9)

In our practice and in many centers, additional screening for infectious causes (hepatitis B and C), autoimmune hepatitis, and  $\alpha$ -I antitrypsin deficiency are performed in children of any age. Tests for cystic fibrosis or other inheritable metabolic diseases should be strongly considered in very young children (ie, <3 years) and, to a lesser extent, for those younger than 10 years of age. Muscular disorders may also present with elevated aminotransferase values and measurement of creatine phosphokinase may, therefore, be considered during initial testing. In such cases, the clinician should pay attention to the serum aspartate aminotransferase, which is often higher than the ALT. Finally, elevated serum aminotransferase values are found in many patients with newly diagnosed celiac disease. Evaluation of tissue and total serum transglutaminase immunoglobulin (Ig)A, therefore, may be appropriate for any child consuming a gluten-containing diet.

# TABLE. Causes of Hepatic Steatosis in Children(8,11)

GENETIC/METABOLIC	NUTRITIONAL	SYSTEMIC
$\alpha$ 1-antitrypsin deficiency	Anorexia nervosa	Acute fatty liver of pregnancy
Alper's syndrome	Cachexia	Autoimmune hepatitis
Alström syndrome	Obesity	Celiac disease
Bardet-Biedl syndrome	Rapid weight loss	Cystic fibrosis
Bile acid synthesis defects	Starvation	Diabetes type 1
Cantú syndrome	Total parenteral nutrition	Hepatitis C
Cholesterol ester storage disease		Hypothalamopituitary disorders
Cohen syndrome	Pharmacologic	Inflammatory bowel disease
Congenital disorders of glycosylation	Calcium-channel blockers	Nephrotic syndrome
Cystic fibrosis	Cocaine	Polycystic ovarian syndrome
Dorfman-Chanarin syndrome	Coralgil	Reye syndrome
Dysbetalipoproteinemia	Estrogens	Systemic lupus erythematosus
Fatty acid oxidation defects	Glucocorticoids	Thyroid disorders
Familial hyperlipoproteinemia	Highly active antiretroviral therapy	
Fructosemia	L-asparaginase	
Galactosemia	3,4-Methylenedioxymethamphetamine (Ecstasy)	
Glycogen storage disease	Methotrexate	
Homocystinuria	Perhexiline	
Lipodystrophies	Tamoxifen	
Porphyria cutanea tarda	Toxins (alcohol, pesticides, others)	
Prader-Willi syndrome	Valproate	
Shwachman Diamond syndrome	Vitamin A toxicity	
Turner syndrome		
Tyrosinemia type I		
Weber-Christian syndrome		
Wilson disease		

Wilson disease and autoimmune hepatitis warrant particular consideration because both conditions can have a waxing and waning course and can be fatal if the diagnosis is missed or treatment is delayed. However, both also are relatively rare and can be difficult to diagnose. Results of laboratory tests should be interpreted cautiously. Ceruloplasmin, which is routinely measured to screen for Wilson disease, is typically low in disease states. However, ceruloplasmin values vary with age, are normally low in infants, and can be falsely positive or negative. Abnormal serum ceruloplasmin concentrations should prompt a 24-hour urine copper quantification, slit-lamp examination (for Kayser-Fleischer rings), liver biopsy, and genetic testing. All of these evaluations should be performed in consultation with a specialist. With regard to autoimmune hepatitis, antibodies are falsely positive in a substantial number of patients with NAFLD. Any diagnostic uncertainty should prompt the clinician to refer the child to a specialist. A suggested approach for testing children with suspected NAFLD is outlined in the Figure.

Given the high prevalence of NAFLD, the limitations of liver biopsy, and questions regarding the appropriate evaluation, alternate noninvasive diagnostic modalities are critically needed for accurate diagnosis and risk stratification. Numerous biomarkers have been studied for noninvasive diagnosis of NAFLD, but none are yet sufficiently accurate Figure. Suggested algorithm for testing children with suspected NAFLD. ALT=alanine aminotransferase; NAFLD=nonalcoholic fatty liver disease; INR=International Normalized Ratio; PN=parenteral nutrition; US=ultrasonography; GGT=gamma glutamyl transferase; HBsAg=hepatitis B surface antigen; HCV Ab=hepatitis C virus antibody; A1A= $\alpha$ -1 antitrypsin; IgA=immunoglobulin A; tTG=tissue transglutaminase; CPK=creatine phosphokinase; ANA=antinuclear antibody; Ab=antibody



for independent use. Active research is currently underway to identify appropriate serum markers, imaging tests, and biomarker panels. Although primarily experimental in children and not yet sufficiently accurate for widespread use, many of these tests show promise for noninvasive diagnosis of NAFLD and identification of fibrosis.

#### Imaging

Liver ultrasonography is one of the most frequently used imaging modalities that is often obtained as an initial screening test in those with suspected NAFLD. On these images, hepatic steatosis appears as diffuse increased liver echogenicity. Liver ultrasonography is an attractive screening test because of its wide availability, low cost, and absence of radiation. Several studies have demonstrated a strong correlation between ultrasonography and liver biopsy findings, concluding that this imaging technique is useful for the quantification of steatosis. However, ultrasonography is unreliable in detecting mild steatosis (approximately <30% fat infiltration); normal findings do not definitively rule out NAFLD. Ultrasonography is also operator- and interpreterdependent, with suboptimal intra- and interobserver agreement. Its accuracy can also be limited in morbidly obese patients. Finally, ultrasonography is relatively nonspecific and cannot differentiate simple steatosis from NASH. Nonetheless, when combined with an elevated serum ALT in the proper clinical setting, ultrasonographic findings may be highly suggestive of NAFLD.

Hepatic steatosis is identified on nonenhanced computed tomography scan as decreased attenuation of the liver parenchyma. This modality has greater specificity than ultrasonography in detecting hepatic steatosis but should not be routinely obtained in children due to radiation exposure. Magnetic resonance imaging (MRI) can provide a reliable quantitative measure of hepatic fat infiltration, although relatively few studies have been conducted in the pediatric population. MRI detects the difference in resonance between water and fat protons, identifying steatosis as an increased signal or proton density attributed to fat. It can detect as little as 3% steatosis and is subject to less variability, making it a far more sensitive test than ultrasonography. However, MRI is limited by high costs, lengthy scan times, and the frequent need for sedation in younger children.

MR spectroscopy (MRS) is the most accurate imaging modality for the detection and quantification of steatosis. Using liver biopsy as comparison, adult studies have estimated the sensitivity and specificity of diagnosing steatosis by MRS to be 73% to 100% and 92% to 97%, respectively. However, MRS has the same limitations as MRI and requires specific equipment that is often available only at specialized centers, further limiting its widespread use.

Elastography, a technique approved by the United States Food and Drug Administration for adults and currently under investigation in children, sends an impulse through the liver that creates tissue vibration (shear waves) that is measured by ultrasonography or MRI. The shear waves correlate with tissue elasticity, which is used as a surrogate for fibrosis. This modality, therefore, is a noninvasive but direct means by which to detect hepatic fibrosis. Transient elastography is probably the most commonly used elastography modality in the United States and has demonstrated reasonable sensitivity and specificity in detecting hepatic fibrosis. Another elastography study, acoustic radiation force imaging, is integrated into the conventional ultrasonography system and can be conducted during standard liver imaging. Preliminary data have shown transient elastography and acoustic radiation force imaging to be effective in ruling out fibrosis and in detecting cirrhosis but they may have suboptimal accuracy at discriminating intermediate fibrosis scores. Although promising and increasingly available in the United States, large pediatric studies are needed to validate the widespread use of these modalities outside of a research setting.

#### TREATMENT

#### Nonpharmacologic Therapy

Weight loss is the only proven treatment for pediatric NAFLD. Multiple studies have shown that weight loss can normalize aminotransferase values and that substantial long-term benefit may be seen with as little as a 5% to 10% reduction in body weight. Weight loss, however, should be gradual because too rapid of a loss may acutely worsen liver disease. In young children, a reasonable approach is for a patient to nearly maintain his or her weight as height increases with age. Families should be engaged in the weight loss process; their involvement is critical for long-lasting lifestyle changes.

No recommendations have been published regarding the most efficacious nutritional modifications in children with NAFLD. A diet high in fructose or sucrose consumption may be associated with the development of NAFLD and, therefore, should be avoided. Restricting carbohydrate consumption in general may reduce hepatic steatosis, as might a low-glycemic index diet. Overall, a low-calorie, well-balanced diet in conjunction with moderate physical activity is probably the most efficacious approach to weight loss and resolution of steatosis. In addition to standard counseling, referral to a registered dietitian nutritionist should be considered, if available, for all overweight or obese patients with NAFLD. Referral to a social worker may also aid in addressing the psychosocial factors contributing to the child's obesity. Further studies are needed to better assess the degree of weight loss needed in children to induce meaningful histologic improvement and to standardize appropriate dietary therapy.

Bariatric surgery warrants mention as an effective weightloss option for morbidly obese individuals and has shown benefit for those with NAFLD. Short-term follow-up studies in adults after gastric bypass have demonstrated major improvements in liver histology and various obesity-related morbidities. However, long-term data are lacking and, as noted previously, rapid weight loss may acutely worsen liver disease. Furthermore, the age at which to perform bariatric surgery is also somewhat controversial. Although increasingly common, additional research is needed to assess the long-term risks and benefits of bariatric surgery for children and adolescents with NAFLD.

#### Pharmacologic Therapy

Pharmacologic therapy for NAFLD has been an area of substantial research in recent years, but no single treatment to date has proven convincingly effective in children. Metformin, an insulin sensitizer, has been studied in both children and adults with NAFLD but has been shown to be no more effective than lifestyle modification alone. The Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC) trial is a large multicenter, double-blind, randomized, placebo-controlled investigation comparing metformin (500 mg twice daily), vitamin E (400 IU twice daily), and placebo in children with NAFLD. (12) After 96 weeks, metformin was no better than placebo at achieving the primary outcome of ALT reduction. Thiazolidinediones such as rosiglitazone and pioglitazone are another class of insulin sensitizers that have been evaluated in adults with NAFLD. Although initial randomized, controlled trials have documented efficacy in lowering ALT and reducing hepatic steatosis, thiazolidinediones do not appear to decrease hepatic fibrosis. In addition, their use is limited in children due to adverse effects and the concern for long-term toxicities.

Because oxidative stress is believed to be a potential contributor to the development of NASH, various antioxidants have been studied as potential therapies. A pediatric randomized, controlled trial comparing vitamin E and vitamin C with placebo found that 2 years of antioxidant therapy did not improve NAFLD histology more than diet and exercise alone. (13) Similar results were found in the TONIC trial, where vitamin E was no better than placebo in decreasing aminotransferase values or improving NAFLD histology. (12) However, vitamin E did significantly improve hepatocellular ballooning on histology in a subgroup of children with NASH and led to a decrease in the NAFLD Activity Score, a histologic scoring system used in clinical trials to diagnose NASH. Due to the paucity of treatment options, many specialists start children with biopsy-proven NAFLD on vitamin E (400 IU twice daily) in addition to a standard weight-loss regimen.

Cysteamine, a medication that decreases lysosomal cysteine stores and is used in treating cystinosis, is believed to have additional antioxidant effects and has been shown in preliminary studies to reduce aminotransferase values in children with NAFLD. Additional studies are necessary to understand its precise mechanism of action and clinical utility in fatty liver disease.

Given the potential role of intestinal bacterial overgrowth in the pathogenesis of fatty liver disease, altering the intestinal microbiota may help to prevent the development of steatohepatitis. Results of preliminary studies assessing the use of prebiotics and probiotics in liver disease are promising, and several studies are currently underway. Finally, several novel agents are currently in advanced clinical trials and could soon be approved for use in adults.

# Summary

- On the basis of strong research and consensus, nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in children and is soon to be the most common indication for liver transplantation in adults. Although the disease begins as simple steatosis, some patients may progress to nonalcoholic steatohepatitis (NASH) and cirrhosis, making early identification and treatment critical.
- The diagnosis of NAFLD can be challenging because patients are typically asymptomatic, with no major clinical symptoms of liver disease. Overweight and obese children are at the highest risk for disease. (1)(2)
- On the basis of moderate research and consensus, serum ALT is usually mildly elevated but is an imperfect test with a low sensitivity for detecting NAFLD at commonly used thresholds.
  (10) Liver biopsy is still considered the gold standard for diagnosis but is too invasive for population-level screening and is often used selectively. Novel, noninvasive diagnostic modalities and serum biomarkers are currently being studied but warrant further validation, especially in children.
- On the basis of moderate research and consensus, assessing serum liver tests in any overweight or obese child is reasonable. Liver disease should be suspected if the serum ALT is  $\geq$ 22 U/L (0.37  $\mu$ kat/L) in girls and  $\geq$ 25 U/L (0.42  $\mu$ kat/L) in boys. (10) Subspecialist referral should be considered for those with a normal BMI, persistent ALT elevation longer than 6 months, specific symptoms of advanced liver disease such as splenomegaly, or concerning laboratory findings on selected screening tests.
- On the basis of strong research evidence, weight loss is the most efficacious treatment for NAFLD.
- On the basis of some research and consensus, initiation of vitamin E therapy (400 IU BID) may be started, although its use probably should be restricted to those children with biopsy-proven disease. (12)
- On the basis of some research and consensus, novel elastography-based imaging modalities are being studied in children and several drugs show promise in treating NAFLD.

References for this article are at http://pedsinreview.aappublications.org/content/36/5/198.full.

# PIR Quiz

- 1. The highest risk of nonalcoholic fatty liver disease (NAFLD) is found in which of the following groups of children?
  - A. Underweight children.
  - B. Normal-weight children.
  - C. Overweight children.
  - D. Obese children.
  - E. Morbidly obese children.
- 2. Which of the following is most common in children with NAFLD?
  - A. Acanthosis nigricans.
  - B. Fatigue.
  - C. Hepatomegaly.
  - D. No symptoms.
  - E. Right upper quadrant abdominal pain.
- 3. An 8-year-old girl has a persistently mildly elevated alanine aminotransferase (ALT) and undergoes liver ultrasonography, which is read as normal. Approximately at what starting degree of fat infiltration (mild steatosis) can ultrasonography detect a fatty liver?
  - A. >15%.
  - B. >30%.
  - C. >45%.
  - D. >60%.
  - E. >75%.
- 4. A 14-year-old boy with an elevated ALT and increased echogenicity on liver ultrasonography undergoes liver biopsy and is confirmed to have nonalcoholic steatohepatitis In addition to weight loss, what other therapy is recommended?
  - A. Cysteamine.
  - B. Metformin.
  - C. Probiotics.
  - D. Vitamin C.
  - E. Vitamin E.
- 5. You are seeing a 15-year-old boy for follow-up. He has a body mass index of 88 and acanthosis nigricans. Laboratory testing documents an ALT of 33 U/L (0.55  $\mu$ kat/L) and elevated fasting insulin. There is no history of hepatotoxic medication use or substance abuse. What is the most appropriate first step in management?
  - A. Blood tests looking for a viral, autoimmune, or genetic cause for hepatitis.
  - B. Lifestyle modifications/weight loss.
  - C. Referral to a liver specialist.
  - D. Referral for liver biopsy.
  - E. Referral for liver ultrasonography.

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Steven Fusillo and Bryan Rudolph Pediatrics in Review 2015;36;198 DOI: 10.1542/pir.36-5-198

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Nonalcoholic Fatty Liver Disease Steven Fusillo and Bryan Rudolph *Pediatrics in Review* 2015;36;198 DOI: 10.1542/pir.36-5-198

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