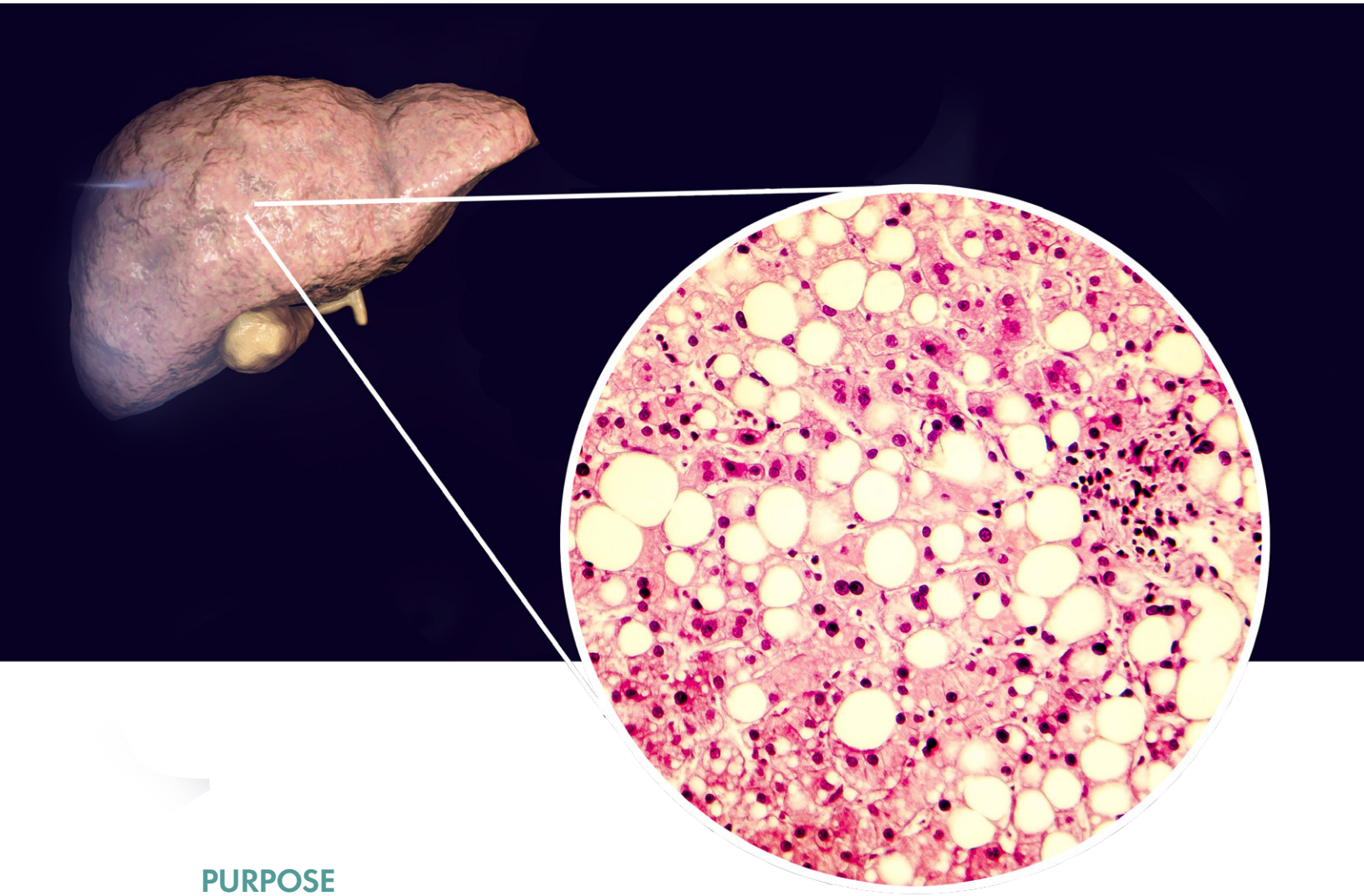
Clinical Practice Guideline Summary: Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children[1]



PURPOSE

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease resulting from excessive fat accumulation in the liver. Because of its close association with obesity, it has become the most common liver disease in children in the United States. While guidelines on adult NAFLD management[2] and pediatric NAFLD diagnosis[3] exist, best practices for management of pediatric NAFLD are needed. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) commissioned the Expert Committee on NAFLD to develop guidelines[1] to inform clinical care decisions. These recommendations are based on a formal review of recently published world literature, guidelines from other societies and the experience of the expert committee. They suggest preferred evidence-based approaches but remain flexible and adjustable for individual patients and circumstances.

DEFINITIONS

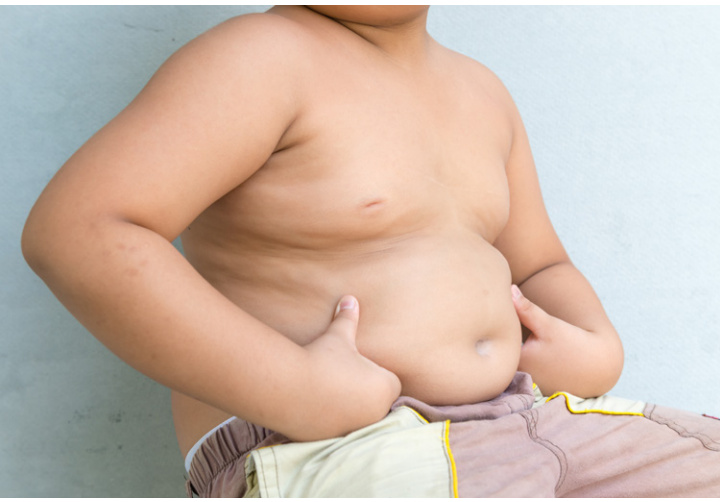
TABLE 1. *NAFLD definitions and phenotypes in children (18 years or younger).*

Phenotypes	Definitions
NAFLD	Inclusive term referring to the full spectrum of disease Indicates fatty infiltration of the liver in the absence of significant alcohol, genetic/metabolic disorders, malnutrition or medications that cause steatosis Fatty infiltration is typically defined as fat >5% of the liver by imaging, direct quantification, or histologic examination
NAFL	Steatosis without specific changes to suggest steatohepatitis, with or without fibrosis
Pediatric Nonalcoholic Steatohepatitis (NASH)	Hepatic steatosis with inflammation, with or without ballooning injury to hepatocytes and fibrosis Zone 3 (venule) centered injury pattern or confluent pattern typically with ballooning Portal predominant (zone 1) centered injury pattern often without ballooning
NAFLD with fibrosis	NAFL or NASH with periportal, portal, or sinusoidal or bridging fibrosis
NAFLD with cirrhosis	Cirrhosis in the setting of NAFLD

SCREENING

- Screening for NAFLD should be considered beginning between ages 9-11 for all obese children (BMI≥95th percentile) and for overweight children (BMI≥85th and <94th percentile) with additional risk factors: central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/nonalcoholic steatohepatitis (NASH).
- Consider screening in younger patients with risk factors (severe obesity, family history of NAFLD/NASH or hypopituitarism) and in sibling/parents of children with NAFLD with risk factors (obesity, Hispanic ethnicity, insulin resistance, prediabetes or diabetes, dyslipidemia).
- Screen using alanine aminotransferase (ALT) based upon sex-specific upper limits of normal (ULN) in children (22 U/L for girls and 26 U/L for boys) and not individual laboratory upper limits of normal. Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis.
- ALT of >80 U/L warrants clinical concern and timely evaluation, as the likelihood of significant liver disease is higher.
- When the initial screening test is normal and risk factors remain unchanged, consider repeating ALT screening every 2-3 years. Consider repeating screening sooner if clinical risk factors increase in number or severity.
- Clinically available routine ultrasound is not recommended as a screening test for NAFLD in children because of inadequate sensitivity and specificity. See Figure 1 for a suggested assessment algorithm.

FIGURE 1 *Assessment Algorithm*



DIAGNOSIS

- When evaluating suspected NAFLD, exclude alternative etiologies for elevated ALT in the context of hepatic steatosis and investigate the presence of coexisting chronic liver diseases (Table 2).

- In children at increased risk of NASH and/or advanced fibrosis, consider liver biopsy for the assessment of NAFLD. Potential clinical signs of increased fibrosis risk in children with NASH include higher ALT (>80 U/L), splenomegaly, and AST/ALT >1. Known clinical risk factors for NASH and advanced fibrosis include panhypopituitarism and type 2 diabetes.

- Neither ultrasound nor CT are recommended for the determination or quantification of steatosis because of poor sensitivity and specificity, and radiation risk, respectively.

- Ultrasound may be useful for assessing other causes of liver disease (masses, gallbladder disease, changes associated with portal hypertension).

TABLE 2. *Differential diagnosis for pediatric hepatic steatosis*

Genetic/metabolic disorders	Medications	Dietary causes	Infections
Nonalcoholic fatty liver disease Fatty acid oxidation and mitochondrial disorders Citrin deficiency Wilson disease Uncontrolled diabetes Lipodystrophies Lysosomal acid lipase deficiency (LAL-D) Familial combined hyperlipidemia Abeta-/hypobetalipoproteinemia	Amiodarone Corticosteroids Methotrexate Certain antipsychotics Certain antidepressants *HAART Valproic acid	Protein-energy malnutrition (Kwashiorkor) Alcohol abuse Rapid surgical weight loss Parenteral nutrition	Hepatitis C (genotype 3)

*HAART = highly active antiretroviral therapy

TREATMENT

Goals of Treatment

- **Regression of NAFLD (steatosis, inflammation, fibrosis)**
- **Resolution of NASH**
- **Decrease excess adiposity**

Treatment Options

Lifestyle Changes (1st line treatment)	• Avoidance of sugar-sweetened beverages • Consumption of healthy, well-balanced diet • Moderate- high-intensity exercise daily • Less than 2 hours/day of screen time
Medications for NAFLD	• No currently available medications have been proved to benefit the majority of patients with NAFLD
Other Interventions	• Bariatric surgery can be considered in selected adolescents: BMI ≥35 kg/m^2, with noncirrhotic NAFLD and other serious comorbidities (type 2 diabetes, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with surgery

Assessment of Treatment

- Sustained decrease in ALT from baseline may be used as a surrogate marker of response to treatment, particularly for durations of ≤1 year.
- Over longer time periods (≥2 years) assessment of change in fibrosis as a treatment outcome is reasonable and requires a liver biopsy for staging.

ADDITIONAL DISEASE RISK IN CHILDREN WITH NAFLD

Cardiovascular Disease	• Screen for dyslipidemia at NAFLD diagnosis and periodically per current lipid guidelines[4] for children • Monitor blood pressure[5]
Prediabetes and Diabetes in NAFLD	• Screen for diabetes at diagnosis and annually using either fasting serum glucose level or glycosylated hemoglobin (HbA1c) level • A glucose tolerance test may be useful if the fasting glucose or HbA1c are in the prediabetic range

LONG-TERM CARE

- Children with NAFLD should be monitored at least annually for progression of disease and treatment.
- In overweight and obese children, when providing lifestyle counseling, more frequent visits are associated with better weight management outcomes.
- Consider a repeat liver biopsy 2-3 years after the first liver biopsy to assess progression of disease and to guide treatment, especially in patients with new or ongoing risk factors.
- Healthcare providers should counsel adolescents on the potential effects of binge drinking on increasing fibrosis progression.
- Families of children with NAFLD should be counseled on the risks of second-hand smoke exposure, and adolescents with NAFLD should be counseled against smoking and use of electronic nicotine delivery devices.
- Children with NAFLD should be routinely vaccinated against hepatitis A.
- Children with NAFLD should have prior receipt of hepatitis B vaccine verified and be immunized if no prior vaccination was received.
- Baseline liver enzyme levels should be obtained, and a baseline liver biopsy considered, in children with NAFLD before starting any medication known to be hepatotoxic. Enzyme monitoring should be guided by the baseline severity of the liver disease and the relative potential for hepatotoxicity of the medication.
- Providers should remain alert to psychosocial issues and screen children with NAFLD for these when indicated.

REFERENCES

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The membership of NASPGHAN consists of more than 2200 pediatric gastroenterologists, predominantly in 46 states, the District of Columbia, Puerto Rico, Mexico and 8 provinces in Canada. NASPGHAN strives to improve the care of infants, children and adolescents with digestive disorders by promoting advances in clinical care, research and education.

The **NASPGHAN Foundation** has a single goal: to improve the treatment and management of gastrointestinal, hepatobiliary, pancreatic and nutritional disorders in children. Through our work, we provide information and resources to parents, patients, and medical professionals dealing with these disorders.

The NASPGHAN Foundation Mission

The NASPGHAN Foundation funds and supports the research and education missions of NASPGHAN in order to enhance the health and well-being of children with gastrointestinal, liver, pancreas and nutritional disorders.

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