Nonalcoholic fatty liver disease in children and adolescents

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INTRODUCTION

Obesity is associated with a clinical spectrum of liver abnormalities collectively known as nonalcoholic fatty liver disease (NAFLD) [1,2], the most common cause of liver disease in children [3-5]. The abnormalities include steatosis (increased liver fat without inflammation) and nonalcoholic steatohepatitis (NASH; increased liver fat with inflammation and hepatocellular injury) (picture 1). The natural history of NASH in children is not well described, but in some cases, it may lead to fibrosis, cirrhosis, and ultimately liver failure [6-8].

The clinical presentation, evaluation, and management of NAFLD in children and adolescents are discussed below. Evaluation and management of other obesity-related comorbidities and the pathogenesis of NAFLD are discussed separately. (See "Overview of the health consequences of obesity in children and adolescents" and "Pathogenesis of nonalcoholic fatty liver disease".)

DEFINITIONS

NAFLD represents a spectrum of fatty liver disease that occurs in the absence of secondary causes of hepatic steatosis, such as alcohol consumption, hepatitis C, parenteral nutrition, steatogenic medication (eg, valproate), lipodystrophy, or inborn errors of metabolism [9].

NAFLD is subdivided into three categories, defined by histologic findings (table 1) [10]:

- **Nonalcoholic fatty liver (NAFL)** – Fatty liver (>5 percent hepatic steatosis) **without** hepatocellular injury
- **Nonalcoholic steatohepatitis (NASH)** – Fatty liver **with** inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without fibrosis
- **NASH cirrhosis** – Cirrhosis with current or previous histologic evidence of NASH or NAFL

EPIDEMIOLOGY

Prevalence and demographics — The estimated population prevalence of NAFLD is most often based upon indirect evidence of a fatty liver, either using evidence of hepatic steatosis from imaging or elevations in serum aminotransferase levels. Definitive diagnosis of NAFLD requires liver biopsy, which is not feasible in population-based cohorts, outside of autopsy studies. There is a modest male predominance in the studies that used biochemistry to diagnose NAFLD but not in studies using ultrasound. Patients are typically diagnosed after nine years of age, in part because clinical practice guidelines recommend that screening begin around age 9 to 10 years. However, case reports describe steatosis developing earlier, including in utero [11], and cirrhosis developing as early as eight years [10,12].

Estimates of NAFLD prevalence vary by method of ascertainment, as well as the population studied (ie, referral, community, ethnic group), as illustrated by the following reports:

- **Histology** – Since NAFLD can only be reliably diagnosed with histology, the best estimate of prevalence in an unselected population comes from autopsies. In an autopsy study of 742 children and adolescents in San Diego County, the prevalence of fatty liver was 9.6 percent overall and 38 percent in children with obesity [13]. Histologic steatohepatitis was seen in 23 percent of the subjects with fatty liver, or 3 percent of the population overall. The prevalence of fatty liver was strongly associated with race/ethnicity, independent of obesity: Hispanic youth had a fivefold increase in risk for fatty liver as compared with Black youth, after adjustment for body mass index (BMI). White youth had intermediate levels of risk. Because this study used histologic measures of fatty liver in an unselected population, it is the best representation of the prevalence of fatty liver disease among children and adolescents in the United States. Another autopsy study conducted in New York City confirmed the relatively low rates of NAFLD and steatohepatitis among Black children and adolescents compared with Hispanic or White children and adolescents [14]. However, this study found comparable rates of NAFLD among Hispanic and non-Hispanic

White individuals, which may be due to a higher proportion of Caribbean-Hispanic ancestry and lower proportion of Mexican/Central American Hispanic ethnicity compared with the San Diego County region. Caribbean-Hispanic ancestry is associated with a higher percentage of African and/or European genetic admixture that could be protective against NAFLD [15].

- **Aminotransferase elevations** – Serum aminotransferase elevations provide an indirect estimate of the prevalence of NAFLD in a population but have limited sensitivity and specificity [16]. Typically, the prevalence of NAFLD is underestimated using aminotransferase elevations, but this depends in part on the alanine aminotransferase (ALT) threshold employed in the study.

  In a large population-based study in the United States, 10 percent of adolescents with obesity had elevations of serum ALT >30 units/L and 1 percent had ALT >60 units/L [17]. In another large population-based study, 11 percent of all children had ALT above the biologically derived upper limit of normal (ULN; >25.8 units/L for boys and >22.1 units/L girls) [18]. A meta-analysis estimated the prevalence of NAFLD by abnormal ALT to be 7 percent in the general population (9 studies) and 13.7 percent in children with obesity (14 studies) [5].

- **Ultrasound** – Ultrasound also provides an indirect estimate of NAFLD, with poor sensitivity and specificity [19]. In a meta-analysis, the prevalence of hepatic steatosis was 7.6 percent in the general population (10 studies) and 41.3 percent in children with obesity (34 studies) [5].

Risk factors and comorbidities — NAFLD is strongly associated with obesity in all age groups [1,2]. It is also closely associated with elements of metabolic syndrome (abdominal fat distribution, insulin resistance, diabetes, dyslipidemia, and hypertension [20-23]), and with polycystic ovary syndrome and obstructive sleep apnea, independent of the degree of obesity [9,24-26]. Therefore, children with NAFLD should be carefully evaluated for these comorbidities (table 2) and receive counseling regarding healthy lifestyle to help reduce the risk of cardiovascular disease and type 2 diabetes mellitus. (See 'Natural history' below.)

Occasionally, NAFLD occurs in individuals without obesity, often accompanied by insulin resistance and dyslipidemia, or in lipodystrophy syndromes [27]. Several single-nucleotide polymorphisms have been associated with increased risk of NAFLD, and among lean children, genetic risk factors may be a stronger predictor of liver fat than cardiometabolic markers [28,29].

Other risk factors for NAFLD include maternal obesity during gestation [30], panhypopituitarism [31], sarcopenia or lower muscle mass [32,33], and Hispanic ethnicity. (See 'Prevalence and demographics' above.)

Natural history — The natural history of pediatric NAFLD is illustrated by a study of 122 children with biopsy-confirmed NAFLD who were enrolled in the placebo arm of clinical trials and received standard-of-care lifestyle counseling [34]. After a median of 1.6 years follow-up, repeat liver biopsy revealed:

- Borderline and definite NASH at baseline – Resolved to no NASH in 29 percent
- NAFLD or borderline NASH at baseline – Progressed to definite NASH in 18 percent
- Complete resolution of NAFLD – Occurred in 2.4 percent (3 of 122 children, all of whom had NAFLD but not NASH at baseline)
- Fibrosis – Improved in 34 percent and progressed in 23 percent

Clinical characteristics associated with disease progression/fibrosis worsening included baseline adolescent age, ALT, as well as total and low-density lipoprotein (LDL) cholesterol levels. Longitudinal predictors of disease progression were a rising ALT, gamma-glutamyl transpeptidase (GGTP), and hemoglobin A1c as well as the development of type 2 diabetes. These factors may help guide escalation to more intensive interventions and decisions regarding repeat liver biopsy (see 'Follow-up' below). Overall, 7 percent of the cohort developed incident type 2 diabetes within two years, at a cumulative incidence rate nearly 300-fold the rate of the general pediatric population.

Another study found that NAFLD in children and young adults is associated with excess mortality due to cardiovascular or liver disease or cancer compared with the general population [35].

CLINICAL PRESENTATION

Most patients with NAFLD are asymptomatic [1]. A minority of children may complain of right upper quadrant pain or nonspecific symptoms such as abdominal discomfort and fatigue [36,37]. Other symptoms that have been reported in patients with NAFLD, such as regurgitation, bloating, and musculoskeletal pain, are unlikely to be due to the NAFLD itself. Instead, these symptoms may be related to other obesity-associated comorbidities such as gastroesophageal reflux disease, constipation, functional abdominal pain, or slipped capital femoral epiphysis [38]. Children and adolescents with NAFLD rarely have signs of end-stage liver disease (such as

palmar erythema, spider angiomata, muscle wasting, jaundice, or encephalopathy) because historically, the disease has rarely progressed to decompensated cirrhosis during childhood.

On examination, acanthosis nigricans is common, reflecting the association between NAFLD and insulin resistance/type 2 diabetes. Hepatomegaly and/or splenomegaly may be present but may be difficult to ascertain on physical examination if significant abdominal adiposity is present.

Laboratory abnormalities typically include elevations in liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), alkaline phosphatase, and gamma-glutamyl transpeptidase (GGTP) [1,4,12,39,40]. These abnormalities may resolve or improve in children with overweight or obesity who are able to reach a healthier weight and body composition through lifestyle or other measures [39,41]. Though less common, serum aminotransferase concentrations can also be normal in children with NAFLD [42]. Aminotransferase concentrations may also decline in the setting of cirrhosis. In patients with NAFLD, GGTP may be normal or elevated. However, **isolated** elevations of GGTP may suggest an alternate diagnosis, such as primary sclerosing cholangitis, excess alcohol intake, or a side effect of a medication (eg, antiepileptic medications).

SCREENING

Serum ALT (recommended) — Screening for NAFLD consists of measuring serum alanine aminotransferase (ALT), as recommended in a guideline from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and summarized in the algorithm (algorithm 1) [9]:

- **Indications** – Screen all children with obesity (body mass index [BMI] ≥95 percentile); screen overweight children (BMI ≥85 percentile) if other risk factors are present (eg, signs of insulin resistance or a family history of NAFLD). Begin screening for NAFLD between 9 and 11 years. Screening can be considered at a younger age if there are strong risk factors for NAFLD. (See 'Risk factors and comorbidities' above.)

- **ALT interpretation** – For serum ALT interpretation, we suggest using the following upper limit of normal (ULN):

  - Adolescents 12 to 17 years:

    - Girls – 22 units/L
    - Boys – 26 units/L

- Children 1 to <12 years – 30 units/L

Note that these values are substantially lower than the upper limits reported in most pediatric hospital laboratories.

The cutoffs for adolescents represent the 97th percentiles for a healthy lean population, as determined from the National Health and Nutrition Examination Survey for adolescents 12 to 17 years old [43]. Use of these thresholds is supported by a separate study from Germany, which reported comparable upper limits of normal, although somewhat higher thresholds in younger children and a transient rise peripubertally [44]. For younger children, our suggestion for an upper limit ALT threshold (30 units/L) is derived from the CALIPER study [45].

- **Next steps** – Subsequent steps depend upon the degree and duration of ALT elevation:

  - For those with normal ALT results, repeat screening in one to three years (or sooner in children with increasing obesity or other risk factors), while providing counseling to promote a healthy body weight.

  - For those with moderate ALT elevations (ALT >ULN, but <80 units/L), repeat the measurement of serum ALT within a few months. If ALT remains elevated, intensify counseling on diet and exercise to achieve weight loss.

  - For those with ALT that is persistently >2 × ULN (ie, >44 units/L for adolescent girls, 52 units/L for boys) for three or more months, refer to a gastroenterologist for a full evaluation, as described below.

  - For patients with elevated ALT and symptoms of an acute infection (fever, vomiting, diarrhea, pharyngitis, etc), measure ALT again two to four weeks after resolution of the illness to verify if the ALT elevation persists, before initiating further evaluation. Similarly, for asymptomatic patients with more marked acute liver enzyme elevations (>10 × ULN), repeat the test two weeks later rather than initiating a more extensive evaluation. Many viral illnesses, including influenza, Epstein-Barr virus, cytomegalovirus, influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and others, can be associated with mild to marked liver enzyme elevations, and some of these infections can be asymptomatic.

  - Other indications for further evaluation include ALT elevations >80 units/L (on two occasions); signs or symptoms of acute liver disease, or red flags for advanced liver disease, as described below. (See 'Indications' below.)

The timing and pace of the evaluation should also be influenced by the presence of other clinical risk factors, such as the degree of obesity, signs of insulin resistance, ethnicity (eg, Hispanic children have higher risk [46]), comorbidities such as type 2 diabetes or obstructive sleep apnea, or clinical symptoms or signs of more advanced liver disease [47].

- **Limitations** – Although serum ALT is recommended as the primary screening test for NAFLD, it has variable sensitivity and specificity for detecting clinically significant NAFLD, depending on the threshold used. In one study of children with overweight and obesity, ALT >2 × ULN had a sensitivity of 88 percent and specificity of 26 percent for detecting NAFLD [16]. ALT >80 units/L had a sensitivity of 57 percent and specificity of 71 percent. Accordingly, a normal or mildly elevated ALT does not rule out NAFLD. As an example, in a large study of children and adolescents with suspected NAFLD who underwent liver biopsy, fibrosis was seen in 12 percent of those with normal ALT and in 54 percent on those with mildly elevated ALT (defined as ALT 26 to 50 units/L in boys and 23 to 44 units/L in girls) [48]. Advanced fibrosis (bridging fibrosis or cirrhosis) was seen in none of the children with normal ALT, 9 percent of those with mildly elevated ALT, and 15 percent of those with significantly elevated ALT (defined as ALT ≥50 units/L in boys and ≥44 units/L in girls). Thus, biochemical tests are only moderately helpful in predicting the presence or severity of NAFLD.

Ultrasonography — Imaging is **not** recommended as a screening test for NAFLD in clinical practice. Although ultrasound can detect the presence of fatty liver, indicated by increased echogenicity, the sensitivity and specificity for detecting clinically significant NAFLD is poor [9,49,50]. However, some imaging modalities may be helpful for assessing severity of liver disease [9,19]. (See 'Imaging' below.)

FURTHER EVALUATION

Indications — Indications for further evaluation are (algorithm 1) [9]:

- Alanine aminotransferase (ALT) >2 × upper limit of normal (ULN), ie, >44 units/L for girls or >52 units/L for boys, for more than three months [16].
- ALT >80 units/L on at least two occasions and in the absence of symptoms of acute infection.
- Signs or symptoms suggesting acute liver disease, including right upper quadrant tenderness, jaundice, or dark urine (bilirubinuria).

- Red flags for advanced liver disease, including gastrointestinal bleeding, jaundice, splenomegaly, firm liver edge, enlarged left lobe, encephalopathy manifesting as chronic fatigue and/or declining school performance, low platelets or white blood cell count, elevated direct bilirubin, or elevated international normalized ratio. These findings are uncommon in the context of pediatric NAFLD.

History — Patients with NAFLD typically have no symptoms of liver disease. Their symptoms, if any, usually are secondary to complications of obesity (eg, knee/groin pain due to slipped capital femoral epiphysis, intermittent right upper quadrant abdominal pain secondary to gallstones, regurgitation due to gastroesophageal reflux disease, or headaches secondary to increased intracranial pressure). (See "Overview of the health consequences of obesity in children and adolescents".)

In addition, it is particularly important to identify signs and symptoms of the following comorbid conditions, each of which may contribute to the development or worsen severity of fatty liver:

- Hypothyroidism – Symptoms may include cold intolerance and recent weight gain. In children whose epiphyses have not fused, an important sign is declining height velocity. (See "Acquired hypothyroidism in childhood and adolescence".)

- Obstructive sleep apnea – Suggested by persistent snoring, pauses in breathing, nocturnal enuresis, and early morning fatigue or headaches. (See "Evaluation of suspected obstructive sleep apnea in children".)

- Type 2 diabetes – Symptoms may include polyuria, polydipsia, or unexplained weight loss, although many patients are asymptomatic. (See "Epidemiology, presentation, and diagnosis of type 2 diabetes mellitus in children and adolescents".)

- Depression/anxiety – Mental health issues are prevalent in this population and may affect the patient's ability to implement the recommended lifestyle interventions [51].

- Alcohol and drugs – Evaluate specifically for alcohol use and the possibility of hepatotoxic drugs (especially anticonvulsant medications and certain antimicrobials). (See "Drug-induced liver injury".)

- Family history – Evaluate the family history for autoimmune conditions, NAFLD, Wilson disease, cryptogenic cirrhosis, or liver transplantation.

Physical examination — The physical examination is focused on identifying the following (table 3):

- Signs of comorbid conditions, especially those that promote fat deposition in the liver (eg, hypothyroidism, insulin resistance, lipodystrophy, panhypopituitarism, or lysosomal acid lipase deficiency).
- Risk factors for advanced NAFLD (abdominal fat distribution, acanthosis nigricans) or signs of advanced NAFLD (splenomegaly).
- Signs suggesting end-stage liver disease (eg, jaundice, palmar erythema, edema, spider angiomata, or asterixis). End-stage liver disease is rare in pediatric patients with NAFLD.
- Systolic and diastolic blood pressure, measured with an appropriately sized cuff. Hypertension is a common comorbidity of obesity and NAFLD.

Laboratory evaluation

Routine laboratory testing

- Complete blood count (CBC) with differential
- ALT, aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transpeptidase (GGTP), total and direct bilirubin, albumin
- Hemoglobin A1c and/or fasting glucose
- Fasting lipid panel (triglycerides, total cholesterol, high-density lipoprotein and low-density lipoprotein [LDL] cholesterol)

Testing for additional comorbid conditions — Children and adolescents with NAFLD should be screened for other comorbidities associated with overweight and obesity, including dyslipidemia, hypertension, type 2 diabetes, renal impairment, and obstructive sleep apnea (table 2). Screening and management is the same as for other children with obesity. However, screening is particularly important in children with NAFLD, due to the clustering of these comorbidities among children with obesity. (See "Clinical evaluation of the child or adolescent with obesity", section on 'Initial management'.)

An increased prevalence of chronic kidney disease has been associated with NAFLD in children and adults [52,53]. We therefore additionally screen our pediatric patients with NAFLD yearly with serum blood urea nitrogen, serum creatinine, and urine albumin-to-creatinine ratio calculations to detect early injury and allow early intervention [54]. This is particularly relevant for children who have concomitant conditions associated with higher risk of developing chronic kidney disease, including severe obesity, hypertension, and type 2 diabetes.

Although several studies have suggested a risk of decreased bone mineral density in children with NAFLD, in particular those with NASH, the degree of reduction is mild and of unclear clinical significance [55]. Therefore, we do not recommend routine dual-energy x-ray absorptiometry (DXA) screening for osteopenia.

Tests to exclude other liver diseases — The differential diagnosis of moderate aminotransferase elevations with evidence of fatty liver on imaging is outlined in the table (table 4). The yield of screening for these disorders is low; in a cohort of 900 children referred for suspected NAFLD, only 2 percent were diagnosed with another disorder that caused or contributed to the liver disease [56]. Nonetheless, testing is still recommended because some of these disorders require specific treatment, including celiac disease, autoimmune hepatitis, hemochromatosis, viral hepatitis and Wilson disease.

For patients with persistent elevations in ALT >2 × ULN, we suggest the following tests (algorithm 1):

- **Viral hepatitis** – Anti-hepatitis C antibodies, hepatitis B surface antigen, anti-hepatitis A antibodies, and tests for other chronic viral infections if indicated by the history.
- **Celiac disease** – Tissue transglutaminase and total immunoglobulin A (IgA). (See "Epidemiology, pathogenesis, and clinical manifestations of celiac disease in children", section on 'Non-gastrointestinal manifestations'.)
- **Hypothyroidism** – Thyrotropin and free thyroxine.
- **Autoimmune hepatitis** – Anti-nuclear antibodies (ANA), anti-liver/kidney microsomal antibodies, and anti-smooth muscle antibodies, and a total protein and IgG level. Of note, positive serum autoimmune antibodies are seen in approximately 20 percent of children and adults with NAFLD [57-59]. Therefore, low-positive titers (eg, ANA 1:40) do not exclude the diagnosis of NAFLD, but patients with high-positive titers should be further evaluated for the possibility of autoimmune hepatitis [10]. High globulins or increased total protein-to-albumin ratio also support the possibility of autoimmune hepatitis. (See "Overview of autoimmune hepatitis".)
- **Wilson disease** – The minimum screen for Wilson disease is to measure serum ceruloplasmin levels. In addition, for patients with signs or symptoms that increase suspicion for this disorder (eg, low ceruloplasmin, marked elevations in AST and ALT, especially with elevated AST:ALT ratio, or neurologic or psychiatric symptoms), include a 24-hour urine collection for copper excretion. If performing a liver biopsy, a hepatic tissue

concentration of copper can be quantified. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history".)

- **Alpha-1 antitrypsin deficiency** – Screen for this disorder by measuring serum alpha-1 antitrypsin levels, or "PI" typing/phenotype. PI phenotypes associated with liver disease are ZZ or SZ. Heterozygotes (MZ or MS) do not have overt alpha-1 antitrypsin-related liver disease, but the genotype may contribute to the severity of their NAFLD [60,61]. (See "Extrapulmonary manifestations of alpha-1 antitrypsin deficiency", section on 'Hepatic disease'.)

- **Other genetic liver diseases** – For selected patients, such as those with early onset of liver disease (eg, preschool age), evidence of fatty liver in the context of a lean phenotype, significant dyslipidemia, or other atypical features, we also screen for the following conditions:

  - **Lysosomal acid lipase deficiency** (cholesteryl ester storage disease; MIM #278000) – Screen for this disorder in any patient with hepatosplenomegaly, prepubertal evidence of advanced liver fibrosis or cirrhosis, xanthelasma, or family history of unexplained hepatic dysfunction or early onset cardiovascular disease [62-67]. Patients with lysosomal acid lipase deficiency tend to have greater elevations of serum LDL compared with patients with NAFLD and develop premature atherosclerosis [62]. Due to the fatty liver, some patients with this condition are misdiagnosed as having another storage disease (Gaucher or Niemann-Pick) or NAFLD.

    Lysosomal acid lipase deficiency can be diagnosed using an enzyme-based biochemical test [68]. A list of laboratories that perform this test can be accessed through the Genetic Testing Registry website. Treatment with sebelipase alfa leads to improved aminotransferases, hepatic steatosis, and lipid profiles, and the drug is now approved for use in the United States and several other countries [69-74].

    A fulminant infantile form, which is known as Wolman disease, is characterized by hepatosplenomegaly, hepatic fibrosis, failure to thrive, and adrenal calcifications or insufficiency. (See "Causes of primary adrenal insufficiency in children", section on 'Defects in cholesterol biochemistry'.)

  - **Abeta/hypobetalipoproteinemia** (MIM #615558, #605019) – These disorders are suggested by the findings of low triglycerides and undetectable or low LDL on a lipid profile; other laboratory findings include low fat-soluble vitamin levels (due to fat malabsorption) [75]. Abetalipoproteinemia (MIM #200100) typically presents in infancy with more severe symptoms including steatorrhea, failure to thrive, and

progressive neurologic complications; this would be an unlikely cause of fatty liver in an older child with obesity. If the results of these tests are concerning for these conditions, lipoprotein electrophoresis or genetic testing can be used to confirm the diagnosis. A list of laboratories that perform these tests can be accessed through the Genetic Testing Registry website. (See "Low LDL-cholesterol: Etiologies and approach to evaluation".)

- **Lipodystrophy** (MIM #608594, #151660, #269700) – When lipodystrophy is suspected, based on physical examination findings of abnormal fat distribution and fatty liver in the context of a lean body habitus, insulin resistance and dyslipidemia, refer to genetics for further work-up. (See "Lipodystrophic syndromes".)

A general approach to evaluating a patient with abnormal liver biochemistries is presented separately. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Imaging

- **Ultrasound** – We suggest performing liver ultrasound as part of the full evaluation in a child with chronically elevated liver enzymes. The purpose is to evaluate for liver or biliary abnormalities, particularly if the history and physical examination suggest the presence of gallbladder disease or complications such as portal hypertension (eg, splenomegaly). The purpose is not to screen for NAFLD or to quantify hepatic steatosis, because ultrasound has poor sensitivity and specificity for detecting clinically significant NAFLD [9,49,50].

- **Magnetic resonance imaging (MRI)** – MRI provides a more accurate quantitative measure of steatosis than ultrasound [76-78]. However, similar to ultrasonography, it is not useful for screening for clinically important NAFLD, because the severity of hepatic steatosis does not correlate with clinical features of advanced NAFLD (eg, presence of steatohepatitis, fibrosis, etc) [37,49,79,80].

- **Methods to assess fibrosis severity** – Ultrasound-based elastography or magnetic resonance elastography show some promise in determining which patients have significant fibrosis [81-86] but have important limitations precluding widespread implementation:

  - Transient elastography (eg, FibroScan) is a point-of-care ultrasonographic test used to noninvasively assess the severity of hepatic steatosis (Controlled Attenuation Parameter [CAP] score) and liver stiffness (in kPa) [87,88]; however, pediatric thresholds for detecting NAFLD have not yet been adequately validated.

- Ultrasound-based shear wave elastography correlates with significant fibrosis in pediatric patients with NAFLD, but this modality also has high technical failure rates in patients with obesity [84].

- Magnetic resonance elastography, a noninvasive approach to evaluate liver stiffness, can detect advanced fibrosis (overall accuracy 89 to 90 percent; negative predictive value of 95 to 96 percent; positive predictive value of 29 to 30 percent) [81,89]. However, the technique is not able to discriminate well between no fibrosis versus mild fibrosis and its ability to detect inflammation has not been established [90]. Further, high cost, lack of widespread availability, and need for further validation of appropriate cutoff values render it inappropriate for routine screening of NAFLD [81].

These tools may also be useful noninvasive measures to follow disease progression [85] but require further validation in longitudinal cohort of children with NAFLD to determine optimum thresholds for detecting progression in fibrosis, as well as optimal populations, as some of the techniques have higher failure rates as severity of obesity worsens. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Radiographic examinations'.)

Liver biopsy

- **Indications** – Indications for liver biopsy in patients with suspected NAFLD have not been established, and practice varies.

  Arguments in favor of performing a liver biopsy are that it is the only means to definitively confirm the diagnosis of NAFLD and the most accurate approach to assess severity, particularly the presence and extent of inflammation and fibrosis [4,9]. If the liver biopsy identifies advanced NAFLD, more intensive weight loss interventions and close monitoring are warranted. In particular, for severely obese adolescents, the presence of advanced NAFLD may prompt consideration of weight loss surgery (see "Surgical management of severe obesity in adolescents"). Furthermore, the liver biopsy occasionally identifies a cause of liver disease other than NAFLD, such as autoimmune hepatitis.

  Arguments against liver biopsy are that it is invasive and the results most often confirm the presence of NAFLD and do not inform management, because there is no approved treatment for NAFLD other than weight loss interventions. For patients with more severe NAFLD, the results might lead to intensifying weight management interventions and closer follow-up.

Therefore, the decision about whether to perform a liver biopsy should be made on a case-by-case basis, after discussion of the benefits and risks with the patient and their family. In our practice, we generally suggest a liver biopsy for patients with the following features:

- Clinical features that are associated with more severe or progressive liver disease, such as ALT persistently >80 units/L or splenomegaly, thrombocytopenia, or increased liver stiffness by elastography, particularly in patients with prediabetes or diabetes or significant dyslipidemia.
- Patients with severe obesity who are candidates for weight loss surgery but are undecided about whether to proceed.
- Patients with features that suggest an alternate cause of the liver disease for which liver biopsy would be useful or essential to confirm the diagnosis (such as autoimmune hepatitis).

(See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Role of liver biopsy'.)

- **Interpretation of results** – If biopsy is performed, typical histologic features of NAFLD include steatosis, often with lobular or portal inflammation or ballooning degeneration of hepatocytes; fibrosis indicates advanced disease (picture 1) (see "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Histologic findings'). Cirrhosis is rare in pediatric NAFLD. Compared with older adolescents or adults, children in the early phases of puberty often display unique histopathologic features of NAFLD, including portal inflammation and portal fibrosis in the absence of hepatocellular ballooning; this histologic pattern has been called "type 2" NAFLD, while the pattern typically seen in adults has been called "type 1" NAFLD (table 1) [10,91,92].

DIAGNOSIS

NAFLD should be suspected in a child with typical clinical features (obesity and persistent mild to moderate elevations of serum alanine aminotransferase [ALT], typically one to six times the upper limit of normal [ULN], generally ALT 30 to 250 units/L). A provisional diagnosis of NAFLD can be made by excluding other causes of liver disease through a focused history, physical examination, and laboratory evaluation. The timing and extent of the evaluation depends upon the degree of ALT elevation and whether any atypical features are present.

A definitive diagnosis of NAFLD can only be made by liver biopsy, but this is not always necessary for clinical management. (See 'Liver biopsy' above.)

MANAGEMENT

Weight loss — Weight management is the only established treatment for NAFLD and is the primary treatment recommendation in guidelines from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition and the American Gastroenterological Association [9,10] Small nonrandomized studies in children have shown improvement in liver histology or aminotransferase activity after weight loss [4,39,93-95].

- **Diet and exercise** – The main approach is lifestyle modification, with emphasis on dietary changes to achieve weight loss. No particular diet has been clearly shown to be superior to any other in the treatment of NAFLD, although avoidance of sugar-sweetened beverages is often recommended [9]. One open-label, randomized trial in a cohort of 40 adolescent males, predominantly Hispanic (95 percent), reported that a diet with low free sugars for eight weeks resulted in greater reduction in hepatic fat compared with usual diet (adjusted mean difference -6.23 percent, 95% CI -9.45 to -3.02) [96]. It is possible that these effects were mediated, in part, by weight loss since the subjects on the low-sugar diet lost more weight during the study compared with those consuming their usual diet (mean between-group difference -2 kg, 95% CI -3.3 to -0.8 kg). Notably, this differential weight loss in the intervention group occurred despite the fact that the intervention diet only restricted free sugar intake to <3 percent of daily caloric intake but did not restrict total energy intake (in kcal), which did not decrease significantly during the eight-week period in the intervention group. Because the prescribed foods were given to the household during the study, these findings may not be generalizable to other populations treated with dietary counseling alone.

  Weight loss and/or weight maintenance in younger children are difficult to achieve, but tend to be enhanced by family-based and patient-centered approaches and more intensive interventions. These strategies are discussed separately. (See "Prevention and management of childhood obesity in the primary care setting".)

  Physical activity is also crucial for the management of NAFLD and reversal of sarcopenia. Similarly to dietary changes, no type of exercise has been found to be superior in this context. In one study, physical activity improved NAFLD (as measured by alanine aminotransferase [ALT] elevations), independent of weight loss [97]. Patients should be advised to limit their screen time to no more than two hours per day.

- **Surgery** – Weight loss surgery may be appropriate in selected adolescents with severe obesity [10]. Surgically induced weight loss improves NAFLD in adults, and observational evidence suggests that this is also true for adolescents. (See "Management of nonalcoholic fatty liver disease in adults", section on 'Bariatric surgery' and "Surgical management of severe obesity in adolescents", section on 'Comorbidity improvement'.)

Medications that target weight loss and may have indirect benefits on NAFLD are discussed in the next section.

Pharmacotherapy

- **Medications that target weight loss** – Medications that target weight loss are increasingly available and may have indirect benefits on NAFLD. Medications approved for weight loss in adolescents and adults include semaglutide and liraglutide (glucagon-like peptide 1 receptor [GLP-1] agonists) and orlistat. These have not been studied as specific treatments for NAFLD in youth, though GLP-1 agonists have shown benefit in studies in adults with NAFLD. GLP-1 agonists are also approved for treatment of type 2 diabetes in youth. The evidence and other considerations are discussed separately. (See "Management of nonalcoholic fatty liver disease in adults", section on 'Potential pharmacologic therapies' and "Prevention and management of childhood obesity in the primary care setting", section on 'Pharmacotherapy'.)

- **Medications that target NAFLD –** A few medications have been evaluated for treatment of NAFLD, but none of these are recommended for routine treatment of NAFLD [9]. Pharmacologic approaches that have been investigated in children include vitamin E, metformin, cysteamine bitartrate, and losartan [98]. In clinical trials, none of these have shown a convincing advantage over lifestyle intervention alone [99,100].

  - **Vitamin E** – The primary consideration for pharmacologic treatment is vitamin E. Limited evidence suggests that vitamin E has beneficial effects on some serologic and histologic markers of NAFLD in some children. However, there are no data on long-term patient-related outcomes, and there are some concerns about long-term safety, based on indirect evidence from studies in adults [101]. In the absence of specific recommendations from guidelines [9,10], we suggest the following approach:

    - For patients who have not had liver biopsy or for those with steatosis alone (minimal inflammation), we suggest **against** treatment with vitamin E.

    - For patients with biopsy-proven steatohepatitis (with or without fibrosis) who are not improving with lifestyle intervention recommendations, we suggest that a

decision to treat with vitamin E be made on a case-by-case basis, after a discussion of the potential benefits and risks with the patient and family. It is particularly important for the patient and family to understand that lifestyle modification is the most essential component of treatment and should continue even if vitamin E is initiated as an adjunctive treatment. No medication or supplement, including vitamin E, has been proven to benefit the majority of patients with NAFLD.

- If treatment with vitamin E is undertaken, we suggest a dose of 800 units daily (typically given as 400 units twice daily for children <18 years). Patients should be monitored for response using serial measurements of ALT (every three months) and treatment continued only if there is evidence of response, with a significant sustained decline in ALT (eg, at least a 50 percent decline in ALT during the first three to six months). A repeat liver biopsy should be considered at the end of a two-year treatment cycle as this is the only way to assess histologic response to vitamin E. We do not recommend treating with vitamin E for more than two years, because long-term safety has not been evaluated in children or adults with NAFLD.

The main evidence supporting vitamin E treatment comes from a multicenter randomized trial that included 173 children and adolescents with biopsy-proven NAFLD [7]. This study found no benefit from vitamin E (800 units daily for two years) on the primary outcome of serum aminotransferase levels. However, in a subset of 121 children with steatohepatitis, the proportion with histologic resolution of steatohepatitis after 96 weeks of treatment was 58 percent ($p < 0.01$) for those treated with vitamin E, compared with 21 percent for those treated with placebo. No significant risks were noted during the two years of the trial. However, some studies in adults have linked high-dose vitamin E to higher risk of all-cause mortality, cardiovascular events, and prostate cancer. (See "Management of nonalcoholic fatty liver disease in adults", section on 'Patients with NASH but without diabetes' and "Vitamin intake and disease prevention", section on 'Vitamin E'.)

Another report suggests that vitamin E leads to significant reductions in ALT (>50 percent from baseline or normalization) in 38 percent of children with NASH in a "real world" setting [102].

- **Metformin** – Metformin is not effective for treatment of NAFLD and is not recommended for this purpose. In the multicenter trial described above, metformin (1000 mg daily) was no more effective than placebo for outcomes of ALT elevation or histologic features of NAFLD [7]. However, metformin is a first-line treatment for

adolescents with type 2 diabetes. (See "Management of type 2 diabetes mellitus in children and adolescents".)

- **Cysteamine bitartrate** – In a multicenter placebo-controlled randomized trial in 169 children with biopsy-confirmed steatohepatitis, treatment with cysteamine bitartrate delayed-release for one year resulted in significant reductions in serum aminotransferase levels and lobular inflammation but no overall reduction in histologic markers of NAFLD severity, compared with placebo [8].

- **Other** – Ursodeoxycholic acid, probiotic supplements, and omega-3 fatty acid supplements have not been shown to be effective for NAFLD in adults [9,10]. No robust clinical trials have evaluated these interventions in children.

Experience with the use of these and other drugs for NAFLD in adults is discussed separately. Clinical trials in adults with NAFLD have yielded some promising candidates, and approved pharmacotherapies for adults may emerge soon. (See "Management of nonalcoholic fatty liver disease in adults".)

Other counseling — Children and adolescents with NAFLD should be counseled that alcohol consumption may exacerbate NAFLD. Thresholds for "safe" alcohol consumption in patients with NAFLD are unclear, but binge drinking or heavy alcohol use is associated with progressive disease in adults. Patients and families should also be counseled against smoking and secondhand smoke exposure [9]. The clinician should ensure that the patient has been immunized against hepatitis A and B by reviewing immunization records or performing serologic testing and providing immunization as needed. Because both obesity and liver disease are associated with higher risk of severe coronavirus disease 2019 (COVID-19) infection, COVID-19 vaccination should be especially encouraged for people with NAFLD. (See "Management of nonalcoholic fatty liver disease in adults", section on 'Risk factors' and "COVID-19: Vaccines".)

Follow-up — Weight management is most successful with frequent follow-up, support, and reinforcement of healthy habits. Body weight, body mass index (BMI), and lifestyle habits should be reviewed at each visit. New comorbid conditions can emerge over time, particularly if the obesity persists or worsens; therefore, screening should be done at minimum annually (table 2).

To monitor the NAFLD, most clinicians perform serial measurements of ALT every three to six months. In clinical trials, improvement in ALT of >50 percent or complete normalization of ALT are often used as surrogate markers of improvement or resolution, respectively, because these outcomes have been associated with histologic improvement in liver disease severity in several

studies [34]. However, changes in ALT should be interpreted in conjunction with the information obtained from the patient's history and physical examination.

A repeat liver biopsy can be considered two to three years after the initial biopsy, especially in patients with advanced stages of NAFLD (steatohepatitis or fibrosis) on the initial biopsy, or with new or ongoing risk factors, such as type 2 diabetes [9]. Repeat liver biopsy may also be useful to evaluate response following intensification of treatment, such as weight loss surgery, although practice varies.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nonalcoholic fatty liver disease" and "Society guideline links: Obesity in children" and "Society guideline links: Diabetes mellitus in children".)

SUMMARY AND RECOMMENDATIONS

- **Definitions** – Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of fatty liver disease that occurs in the absence of secondary causes of hepatic steatosis. NAFLD is subdivided into three categories, defined by histologic findings (table 1) (see 'Definitions' above):
  - **Nonalcoholic fatty liver (NAFL)** – Hepatic steatosis without hepatocellular injury
  - **Nonalcoholic steatohepatitis (NASH)** – Hepatic steatosis with inflammation and hepatocellular injury, such as ballooning of hepatocytes, with or without fibrosis
  - **NASH cirrhosis** – Cirrhosis with current or previous evidence of NASH or NAFL
- **Risk factors and clinical presentation** – NAFLD is strongly associated with obesity. Predictors of more advanced disease include markers of insulin resistance, prediabetes/diabetes, and Hispanic ethnicity. Most patients with NAFLD have no symptoms caused by the liver disease, although many have symptoms and signs of other obesity-related comorbidities (table 2). (See 'Epidemiology' above and 'Clinical presentation' above.)
- **Screening**

- **Indications** – Screening for NAFLD should be performed in all children with obesity (body mass index [BMI] ≥95th percentile), and for those who are overweight (BMI ≥85th percentile) if other risk factors are present (eg, signs of insulin resistance or a family history of NAFLD) (algorithm 1). Screening should be initiated between 9 and 11 years. (See 'Screening' above.)

- **Method** – Screening should consist of measurement of serum alanine aminotransferase (ALT). Most, but not all, children with NAFLD have mild elevations of ALT (typically one to six times the biologic upper limit of normal [ULN]), but disease severity is only weakly correlated with ALT elevation. Some children with NAFLD have more markedly elevated liver enzymes. Ultrasonography is not recommended for screening. (See 'Screening' above.)

- **Further evaluation** – Patients with suspected NAFLD and persistent elevations of serum ALT (>2 times the ULN for >3 months) should be further evaluated to exclude other causes of liver disease through a focused history, physical examination, and laboratory evaluation (algorithm 1). The timing and extent of the evaluation depends upon the degree of ALT elevation and whether any atypical features are present. (See 'Further evaluation' above.)

- **Diagnosis** – A provisional diagnosis of NAFLD can be made by excluding other causes of liver disease through a focused clinical evaluation (table 4). A definitive diagnosis of NAFLD can only be made by liver biopsy, but this is not always necessary for initial clinical management. However, histologic assessment of severity of disease can help guide therapeutic decisions such as whether to treat with vitamin E or to intensify weight management approaches, including considering weight loss medications or weight loss surgery for selected patients with more advanced disease. (See 'Liver biopsy' above and 'Diagnosis' above.)

- **Management**

  - **Weight loss** – For children and adolescents with NAFLD and obesity, we recommend interventions to reduce overweight and obesity (**Grade 1B**). The first-line approach in youth is counseling directed at improving diet and exercise habits. Weight loss surgery may be appropriate for selected adolescents with severe obesity, especially if liver biopsy shows evidence of advanced NAFLD. (See 'Weight loss' above.)

  - **Pharmacotherapy** – Medications that target weight loss, including semaglutide, are increasingly available and may have indirect benefits on NAFLD. A few other medications have been evaluated for treatment of NAFLD, but none of these are recommended for routine treatment of NAFLD. For patients with biopsy-proven

steatohepatitis (with or without fibrosis), a decision to treat with vitamin E should be made on a case-by-case basis, after a discussion of the potential benefits and risks with the patient and family. (See 'Pharmacotherapy' above.)

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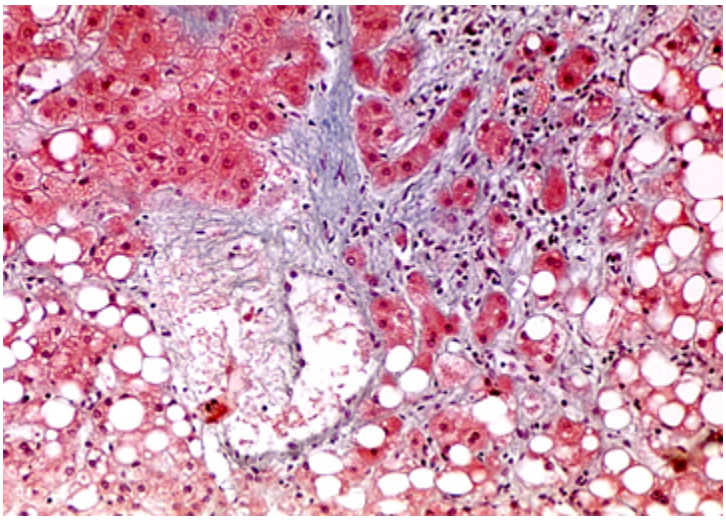
Topic 115661 Version 24.0

GRAPHICS

Nonalcoholic steatohepatitis liver biopsy



Liver biopsy showing steatosis, hepatocyte balloon degeneration, mixed acute and chronic inflammation, and pericellular fibrosis.

Courtesy of Marshall M. Kaplan, MD.

Graphic 59170 Version 1.0

Nonalcoholic fatty liver disease definitions and phenotypes

Phenotypes	Definitions
Nonalcoholic fatty liver disease (NAFLD)	Inclusive term referring to the full spectrum of disease
	Indicates fatty infiltration of the liver in the absence of significant alcohol, genetic diseases, or medications that cause steatosis
	Fatty infiltration is typically defined as fat >5% of the liver by imaging, direct quantification, or histologic estimation
Nonalcoholic fatty liver (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
Type 1	Venule (zone 3)-centered injury pattern or confluent pattern, typically with ballooning
Type 2	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

Other terms such as "presumed NAFLD" (also "clinical NAFLD" or "suspected NAFLD") are terms used in the literature with varying meanings. These terms are often used when a biopsy has not been performed to confirm the diagnosis.

From: Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: Recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017; 64:319. DOI: 10.1097/MPG.0000000000001482. Copyright © 2017 European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

Graphic 115653 Version 3.0

Additional assessment for weight-related comorbidities to be considered for selected children with obesity[1-5]

Condition	Tests	Reason	Note
Early atherosclerotic cardiovascular disease	Fasting lipid profile	Hyperlipidemia, hypertriglyceridemia, cardiovascular disease risk	▪ Children with obesity or other risk factors for early cardiovascular disease – Screen after 2 years of age. ▪ Children without obesity or other cardiovascular risk factors – Universal screening once between ages 9 and 11 years and once between ages 17 and 21 years. ▪ Refer to UpToDate content on dyslipidemia in children for interpretation and follow-up.
Hypertension	BP measurement	Multiple measurements are required to diagnose or exclude hypertension	Use appropriately sized cuffs and age-appropriate norms. Measure BP at all health care visits (and at least annually).
	24-hour ambulatory BP monitoring	Evaluate for "masked" hypertension; rule out "white coat" hypertension	Suggested if the diagnosis is unclear from random office measurements.
	CBC, metabolic panel, renin assay, urinalysis, renal ultrasound	Exclude other causes of hypertension	Suggested if hypertension is confirmed.
Metabolic dysfunction-associated steatotic liver disease (MASLD; formerly termed	Serum ALT		Initial screening with serum ALT for all children with obesity starting between 9 and

nonalcoholic fatty liver disease)			11 years of age. If normal, repeat at least every 2 to 3 years*.
	Evaluation for liver disease: ▪ Abdominal ultrasound to evaluate for anatomical abnormalities ▪ Screening laboratory tests¶; evaluation for viral hepatitis, autoimmune hepatitis, and endocrine disorders ▪ Exclude genetic disorders in selected patients	Determine cause of elevated transaminases	Perform this evaluation if ALT is >80 units/L, persistently elevated >2 times the ULN* for 6 months, or if other signs/symptoms of advanced liver disease are present.
	Liver biopsy	Determine cause of elevated transaminases, assess degree of hepatitis	Perform liver biopsy if ALT >2 times the ULN for >6 months. Imaging cannot accurately determine inflammation and fibrosis.
Type 2 diabetes mellitus or impaired glucose tolerance	Fasting glucose, HbA1c, or oral glucose tolerance test	Assess for insulin resistance and hyperglycemia	Perform in children ≥10 years old with overweight or obesity **and** 1 or more risk factors for type 2 diabetes[Δ]. ▪ Diabetes is diagnosed if fasting glucose ≥126 mg/dL or hemoglobin A1c ≥6.5% on 2 occasions. ▪ Prediabetes is diagnosed if fasting glucose

			100 to 125 mg/dL or hemoglobin A1c 5.7 to 6.4% on 2 occasions.
Sleep apnea	Polysomnogram (sleep study)	Evaluate sleep-related breathing disorders	Perform in patients who have obesity and symptoms suggesting obstructive sleep apnea◇.
Orthopedic disease	Hip radiographs	Evaluate for SCFE	Perform in patients with unexplained aching pain in hip, groin, thigh, or knee. Use frog-leg positioning for radiograph. Children with acute symptoms of SCFE should immediately stop all weightbearing activity (including walking) to prevent further displacement[3].
	Knee radiographs	Evaluate for genu varus (Blount disease) or valgus deformity	Perform in patients with genu varum (bow legs) or genu valgum (knock-knees).
Polycystic ovary syndrome	Total testosterone (or free testosterone) To evaluate for other causes of menstrual abnormalities: TSH, prolactin, DHEAS, 17-hydroxyprogesterone (early morning)	To confirm whether hyperandrogenemia is present and exclude other causes of hyperandrogenemia and/or abnormal menses	Perform in females with irregular menses or hirsutism. If laboratory testing is abnormal, additional workup is indicated.
Impaired kidney function	BUN, creatinine Urine for UACR	Evaluate for impaired kidney function and albuminuria	Perform in adolescents with severe obesity, hypertension, or type 2 diabetes§. UACR >30 mg/g is abnormal.
Precocious puberty	LH, FSH, testosterone or estradiol, DHEAS	Early onset of obesity	Physical examination often is sufficient to

			evaluate.
Pseudotumor cerebri	Funduscopic examination, lumbar puncture	Increased intracranial pressure suggested by papilledema and confirmed by lumbar puncture	Perform funduscopic examination in patients with frequent headaches.

BP: blood pressure; CBC: complete blood count; ALT: alanine aminotransferase; ULN: upper limit of normal; SCFE: slipped capital femoral epiphysis; TSH: thyroid-stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; BUN: blood urea nitrogen; UACR: urine albumin-to-creatinine ratio; LH: luteinizing hormone; FSH: follicle-stimulating hormone; GGTP: gamma-glutamyl transpeptidase.

* For interpretation of serum ALT, use the ULN of 22 units/L for females and 26 units/L for males, as determined from healthy lean children in the National Health and Nutrition Examination Survey (NHANES)[4]. Note that these values are substantially lower than the ULNs reported in most pediatric hospital laboratories.

¶ Screening laboratory tests for suspected metabolic dysfunction-associated fatty liver disease include a CBC with platelets, hemoglobin HbA1c, and lipid panel.

Δ Risk factors for type 2 diabetes include: family history of type 2 diabetes, high-risk race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander), signs of insulin resistance (eg, acanthosis nigricans), or conditions associated with diabetes (hypertension, dyslipidemia, polycystic ovary syndrome).

◇ Symptoms suggesting obstructive sleep apnea include persistent snoring (most nights, most sleeping positions), observed gasping or apneas, nocturnal enuresis, and morning headaches.

§ Screening for impaired kidney function is recommended for patients with type 2 diabetes[5]. UpToDate authors also suggest this screening for patients with other risk factors for developing chronic kidney disease, including severe obesity and hypertension.

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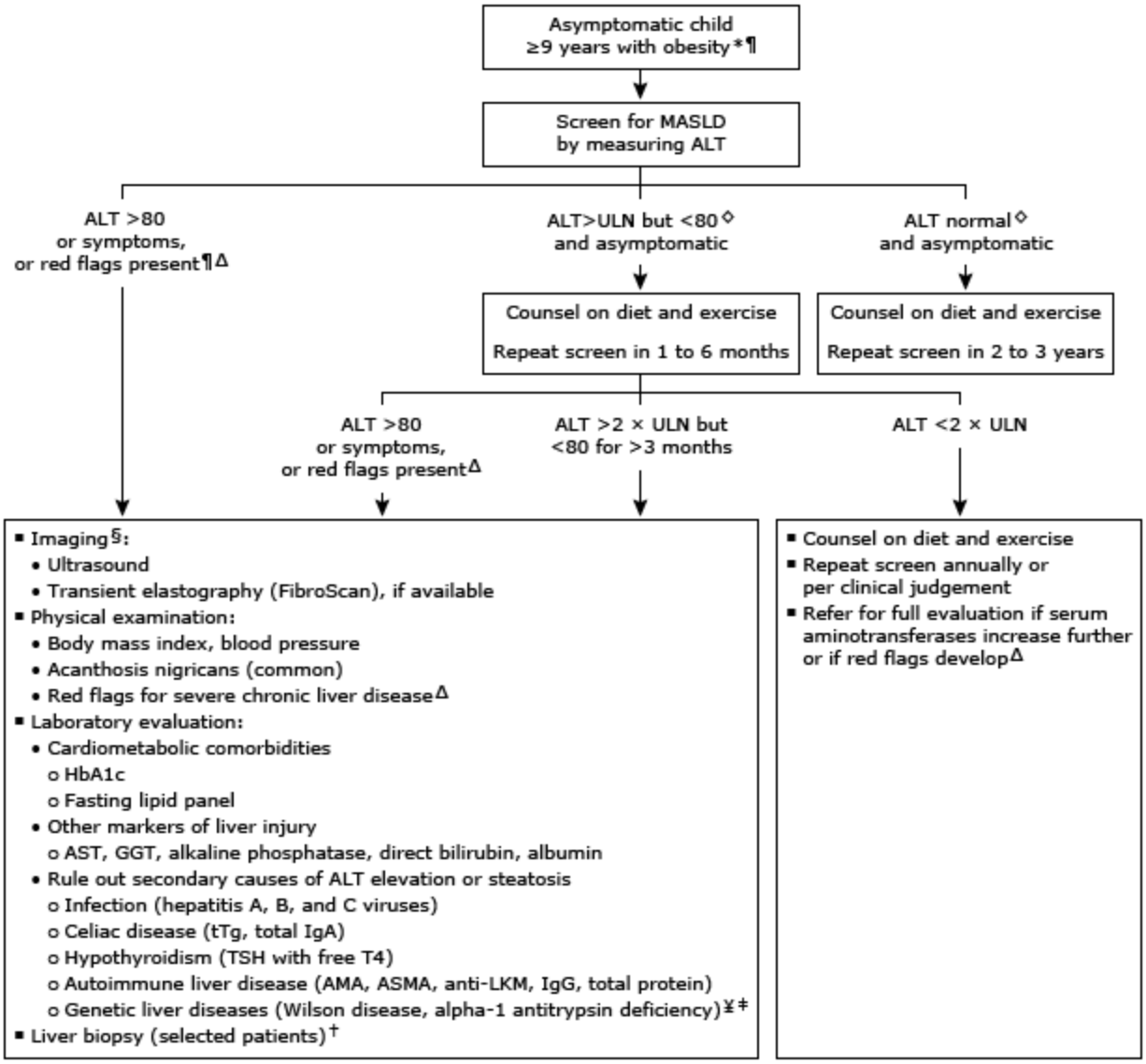
Graphic 65547 Version 29.0

Screening and evaluation for metabolic dysfunction-associated steatotic liver disease in children



ALT: alanine aminotransferase; AMA: antimitochondrial antibodies; anti-LKM: anti-liver-kidney microsomal antibodies type 1; ASMA: anti-smooth muscle antibodies; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; HbA1c: glycated hemoglobin; Ig: immunoglobulin; MASLD: metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MASH: metabolic dysfunction-associated steatohepatitis; T4: thyroxine; TSH: thyroid-stimulating hormone; tTg: tissue transglutaminase antibodies; ULN: upper limit of normal.

* Also screen children who are overweight (body mass index 85th to 95th percentile) if other risk factors are present, such as acanthosis nigricans (or other signs of insulin resistance) or a family history of MASLD or NAFLD. Younger children with overweight/obesity could also be screened if they have risk factors. NOTE: North American guidelines do not recommend obtaining imaging studies to screen all at-risk overweight and obese children for

MASLD/NAFLD[1]; however, European guidelines recommend obtaining both ALT and ultrasound in at-risk children[2].

¶ This algorithm applies to asymptomatic children. If ALT is elevated in the context of a recent viral infection, repeat the test in 2 to 4 weeks and proceed with further evaluation if it remains elevated.

Δ Red flags for advanced liver disease, such as chronic fatigue, gastrointestinal bleeding, jaundice, splenomegaly, firm liver edge, enlarged left lobe, low platelets, low white blood cells, elevated direct bilirubin, or elevated international normalized ratio.

◇ For children 12 to 17 years, we define the ULN for ALT as 22 unit/L for girls and 26 unit/L for boys; for children 1 to <12 years, the ULN is 30 unit/L as they are supported by large population studies[3-5].

§ The primary purpose of ultrasound is to evaluate for structural/anatomic causes of elevated liver enzymes (eg, gallbladder disease) or complications such as portal hypertension. It has poor sensitivity for detecting or quantifying hepatic steatosis. Vibration-controlled elastography (ie, FibroScan) provides information about steatosis and liver stiffness, but its utility for the diagnosis or monitoring of MASLD in children has not been established.

¥ Screening for Wilson disease consists of ceruloplasmin and/or 24-hour urine copper. Screening for alpha-1 antitrypsin deficiency is determination of the protease inhibitor phenotype. Protease inhibitor phenotypes associated with liver disease are ZZ or SZ.

‡ Screening for genetic liver diseases is performed for selected patients, depending on risk factors or signs/symptoms.

† Liver biopsy is considered the gold standard for diagnosis of MASH but may vary by practice setting. In our practice, we suggest liver biopsy for patients who have had ALT elevations >2 × ULN for 6 or more months or for those with ALT >80 unit/L, red flags for advanced liver disease[Δ], or features that suggest an alternate cause of the liver disease that requires biopsy for diagnosis.

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Graphic 117904 Version 5.0

Physical examination in a child or adolescent with suspected nonalcoholic fatty liver disease (NAFLD)

Finding	Implications
Findings associated with conditions that could lead to NAFLD	
Overweight (BMI ≥85th percentile) or obese (BMI >95th percentile)	
Goiter	Suggests hypothyroidism
Abnormal fat distribution	Suggests partial lipodystrophy
Papilledema, neurologic deficits, short stature, and/or severe obesity	Panhypopituitarism, eg, related to craniopharyngioma or its treatment
Xanthelasmata	Suggests lysosomal acid lipase deficiency
Findings associated with risk of advanced NAFLD	
Increased waist circumference	Abdominal obesity
Acanthosis nigricans	Insulin resistance, diabetes
Splenomegaly	Portal hypertension
Sarcopenia (muscle wasting)	Possible advanced liver disease

NAFLD: nonalcoholic fatty liver disease; BMI: body mass index.

Graphic 116583 Version 1.0

Differential diagnosis in a child with suspected nonalcoholic fatty liver disease[1]

Genetic/metabolic
Lysosomal acid lipase deficiency
Wilson disease
Fatty acid oxidation defects and other mitochondrial disorders
Partial/total lipodystrophy
Abetalipoproteinemia or hypobetalipoproteinemia
Immune-mediated
Celiac disease
Autoimmune hepatitis
Endocrine
Panhypopituitarism
Hypothyroidism
Uncontrolled diabetes
Infectious
Hepatitis C (genotype 3)
HIV-related lipodystrophy
Iatrogenic
Certain psychotropic medications
Corticosteroids
Other medications – Methotrexate, amiodarone
Rapid surgical weight loss
Parenteral nutrition

Reference:

1. *Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017; 64:319.*

Graphic 116582 Version 2.0

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