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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)

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease that occurs in the setting of insulin resistance and increased adiposity. It has rapidly evolved into the most common liver disease seen in the pediatric population and is a management challenge for general pediatric practitioners, subspecialists and for health systems. In this guideline, the expert committee on NAFLD (ECON) reviewed and summarized the available literature, formulating recommendations to guide screening and clinical care of children with NAFLD.

Keywords

nonalcoholic fatty liver disease; children; treatment; recommendations

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease resulting from excessive fat accumulation in the liver. Due to its close association with obesity, it has become the most common liver disease in children in the United States. NAFLD can result in progressive fibrosis and lead to end-stage liver disease. Within the last decade, it has become one of the leading indications for liver transplantation in adults (1).

Best practices in management of pediatric NAFLD are not clearly defined. A guideline focused primarily on care of adults with NAFLD was released in 2011 (2). Recommendations addressing diagnosis of pediatric NAFLD were published in 2012 (3), however did not include screening, treatment and public health implications. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) commissioned the Expert Committee on NAFLD (ECON) to address this gap. The committee included specialists in general pediatrics, hepatology, gastroenterology, nutrition, cardiology, endocrinology, and pediatric obesity management.

The following recommendations are based on a formal review and analysis of the recently published world literature (Pubmed and EMBASE search through May 2015), guidelines from other societies when applicable, and the experience of the expert committee. These guidelines are intended for pediatricians, allied health professionals caring for children, pediatric gastroenterologists, hepatologists, endocrinologists and preventive cardiologists. They suggest preferred evidence-based approaches for the clinical care of children related to NAFLD but remain flexible and adjustable for individual patients and circumstances. In areas where insufficient evidence existed, the committee drew on the collective experience of the members to provide guidance.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to classify the quality of evidence and strength of recommendations (Table 1). The strength of recommendation in the GRADE system is classified as 1) strong or 2) weak. The quality of evidence for each recommendation is characterized as A) high B) moderate or C) low quality. The GRADE system assesses the quality of evidence available. Specifically, it evaluates the methodological limitations of studies, whether the results of

different studies are consistent or generalizable, and whether treatment approaches have been found to be effective (clinicalevidence.bmj.com). In this guideline, the term “children” includes 0–18 years.

NAFLD DEFINITION AND SUBGROUPS

Pediatric NAFLD is defined as chronic hepatic steatosis in children (≤ 18 years), which is not secondary to genetic/metabolic disorders, infections, use of steatogenic medications, ethanol consumption or malnutrition. In most children, NAFLD is associated with insulin resistance, central or generalized obesity, and dyslipidemia characterized by high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels.

Based on histology, NAFLD can be divided into nonalcoholic fatty liver (NAFL), which denotes bland steatosis, and nonalcoholic steatohepatitis (NASH), which is marked by steatosis plus lobular inflammation and hepatocellular injury (Table 2). A further characterization is presence of fibrosis, which may indicate a more severe phenotype even in the absence of NASH. In some children, a unique periportal pathologic pattern of injury exists that has been termed “portal predominant NASH.” The significance of the periportal pattern for future clinical events is unknown and it is rarely seen in adults. In this document, the terms for NAFLD phenotypes are defined in Table 2.

INCIDENCE AND PREVALENCE IN CHILDREN AND CLINICAL RISK FACTORS

At the time of the guideline development, there were no studies describing the incidence of NAFLD in children. Prevalence of NAFLD has been described both in the US and internationally. The prevalence varies by method of detection, which may include screening by ALT, imaging for steatosis, or confirmation by liver biopsy. In North American studies, NAFLD prevalence ranges from 0.7% in very young children aged 2–4 years (confirmed at autopsy), to 29–38% in obese children (by studies of ALT elevation as well as an autopsy study) (4–8). Moreover, the prevalence of NAFLD increased 2.7 fold from the late 1980’s to the current era (2007–2010), and at a more rapid rate than childhood obesity, based on analysis of ALT elevation in serial NHANES cohorts (7).

Prevalence varies by race/ethnicity. US studies have revealed a 4-fold increased risk of hepatic steatosis in Hispanic, compared to non-Hispanic adolescents (11–22 years old) (8). White and Asian children also have high prevalence, compared to African-American children (5). The prevalence also differs by gender, with most studies showing higher percentages in male compared to female children (5, 9, 10). Prevalence is higher in obese children compared to normal weight, although not all children with NAFLD are obese (5).

Several comorbidities have been associated with increased prevalence and/or severity of pediatric NAFLD, although the pathophysiology of these associations remains incompletely understood. Obstructive sleep apnea (OSA) was associated with the presence of NASH in 2 pediatric studies, independently of BMI and standard metabolic risk factors (11, 12). It is not known whether OSA treatment ameliorates NASH. Among children newly diagnosed with

type 2 diabetes mellitus (T2DM), elevated ALT is more frequent in Hispanic children compared to African American children (13). In addition, pediatric patients with panhypopituitarism appear to have increased risk of NAFLD, NASH, and even cirrhosis (14, 15), similar to the increased prevalence (77%) and severity of NAFLD reported among adults with hypopituitarism (16).

In summary, NAFLD is highly prevalent in children, with a greater risk in certain subpopulations; obese children; male children; Caucasian, Asian and Hispanic children; and those with pre-diabetes, diabetes, OSA and panhypopituitarism.

NATURAL HISTORY OF NAFLD IN CHILDREN

Two small retrospective studies reported results of repeat liver biopsies done for clinical indications in children receiving usual clinical care for NAFLD. The first study showed that fibrosis remained stable or resolved in 11 of 18 patients after an average of 28 months (17). Worsening fibrosis was reported in 4 out of 5 patients reviewed in a retrospective study at a mean time frame of 41 months (18).

The natural history of pediatric NAFLD in the setting of lifestyle counseling was represented by the placebo arm of the TONIC trial, a 2 year randomized control trial designed to compare vitamin E, metformin and placebo with liver biopsies at baseline and at 2 year follow up (19). All 3 arms received nutrition and physical activity (lifestyle) advice. In the placebo cohort, 28% had resolution of NASH, 40% improved fibrosis, 40% improved steatosis and 43% improved lobular inflammation. Progression of disease was seen in 25%. The mean change in ALT from baseline to week 96 was −35 (−57 to −14).

Longitudinal studies in adults demonstrate that patients with NAFLD have increased mortality compared to matched control populations (20). The increased mortality in adults is secondary to cardiovascular disease (CVD), cirrhosis, and hepatocellular carcinoma. In adults, fibrosis stage at baseline is the most predictive feature of future liver disease related mortality (21). Pediatric NAFLD may be more severe compared to NAFLD identified in adulthood (22). Limited data suggest that children diagnosed with NAFLD have increased morbidity and mortality in adulthood (18).

Although limited, the pediatric data on the natural history of pediatric NAFLD support some conclusions. Fifteen percent of children with NAFLD have stage 3 fibrosis or higher at diagnosis (23) and disease in children appears to be more severe compared to adults (22). Given that pediatric disease is by definition early onset disease, it may represent an aggressive phenotype of the disease. Reports show that a few children have rapid progression to clinical events from NAFLD (death, transplant, diabetes, CVD). Because such clinical events from pediatric NAFLD typically do not occur under the age of 21 years, studies determining clinical outcomes from pediatric NAFLD will require long-term follow up into adulthood. Extrapolation from adult natural history studies may not be sufficient because today’s children are more likely to experience early onset of obesity, increased severity of obesity and exposure in utero to maternal obesity and insulin resistance compared to children of prior decades (24).

SCREENING FOR NAFLD IN CHILDREN

Similar to other chronic liver diseases, NAFLD is often asymptomatic. Historically, NAFLD was frequently identified incidentally due to blood liver biochemistries or abdominal imaging, such as ultrasound or computed tomography (CT), ordered for other indications. Screening for NAFLD is appropriate because it can be detected prior to the onset of irreversible, end-stage liver disease. Identification of children with NAFLD is important because effective treatment is available (weight management through lifestyle improvements). While more challenging to implement than prescribing a medication, lifestyle intervention can be effective at reversing NAFLD and even NASH, particularly if initiated early in the course of disease, before advanced fibrosis has developed.

Screening Tests

The currently recommended screening test, alanine aminotransferase (ALT), is an inexpensive, universally available blood test. ALT is minimally invasive and has an acceptable sensitivity. The assay is standardized between facilities; however the reporting of normal values is not. Several studies have evaluated upper limits of normal in children. In the US, gender-specific biologically based cutoffs have been determined from nationally representative data and have been validated in a fairly diverse cohort (25). These cutoffs are 22 mg/dl for girls and 26 mg/dl for boys. A Canadian study found the upper limit of normal for ALT to be 30 mg/dl in children 1–12 years of age, and 24 mg/dl in those between 13–19 years (26). For the diagnosis of NAFLD, the use of two times the gender-specific ALT (ALT ≥50 for boys and ≥44 for girls) in overweight and obese children age ≥ 10 has a sensitivity of 88% and a specificity of 26% (27). NASH is more common in children with ALT ≥ 80 U/L compared to those with ALT < 80 U/L (41% compared to 21% respectively) (27).

Aspartate aminotransferase (AST) and (gamma glutamyl transferase) GGT have not been independently tested as screening tools for NAFLD in children. In the context of elevated ALT, higher AST and higher GGT are associated with worse histology (27). However elevated AST or GGT in the context of normal ALT may represent a condition other than NAFLD.

Imaging has also been utilized as a screening tool for NAFLD. Clinically available, routine ultrasonography performs poorly for the detection of steatosis in children because of its low sensitivity and specificity particularly in children who have lower degrees of steatosis (i.e. involving <33% of hepatocytes) (28). In addition, ultrasound is inaccurate for quantification of steatosis in children with NAFLD. More precise ultrasound methodology has been developed (29); however, it is not widely available. The limitations of ALT and ultrasonography as screening tools for NAFLD can lead to inconsistencies, as patients with NAFLD can have an ALT<40 U/L in the context of ultrasonography that suggests the presence of steatosis and vice versa (27). Magnetic resonance imaging and spectroscopy (MRI and MRS) have been validated and shown to be accurate for detection and quantification of hepatic steatosis in both adults and children (30, 31). Clinical applications for MRI and MRS-based measurement of hepatic steatosis are rapidly becoming available in pediatric centers. At this time, MR-based methods are not used widely for screening because of cost, lack of availability and lack of validated cutoffs to determine NAFLD. This area is

rapidly developing however, and some pediatric centers are already using MR in clinical practice for the quantification of steatosis. Hepatic steatosis is sometimes also identified by CT scans, often performed for other clinical indications. Combined adult and pediatric data show that CT detects steatosis with a sensitivity of 46–72% and specificity 88–95% but is not typically performed as a screening test for NAFLD due to concerns about radiation exposure (32). When hepatic steatosis is incidentally identified by imaging studies performed for other clinical indications, further diagnostic work-up to determine the cause of steatosis is needed (see Diagnosis section).

The relative cost-effectiveness of these various screening modalities (ALT vs. imaging) has not been studied. ALT is significantly less expensive compared to imaging modalities and therefore is preferred as the first-line screening test for NAFLD, despite its limitations.

At-Risk Populations to Screen

Overweight and obese children are at increased risk for NAFLD. Risk increases in the setting of cardio-metabolic risk factors, including insulin resistance, pre-diabetes, diabetes, dyslipidemia, central adiposity, as well as in certain races and ethnicities as discussed above. Non-overweight children with these cardiometabolic risk factors are also at risk for NAFLD. Genetic predisposition strongly affects the risk of NAFLD development and the overweight siblings and overweight parents of patients with NAFLD are at high risk of NAFLD (33). Siblings who are ≥ 10 years old and have a BMI ≥ 85th percentile are at high risk of NAFLD.

The optimal age to screen for NAFLD and the need for repeat screening are undetermined because of the lack of pediatric studies on incidence and natural history. A cross sectional, autopsy-based study revealed a large prevalence difference between children age 5–9 years and children 10–15 years (5). A limitation of this study was relatively few subjects within the mid-ages and the cross-sectional nature. Certain groups, such as Hispanics, may be at risk for earlier onset disease (34).

Recommendations

1 Selected children should be screened for NAFLD. Strength – 1, Evidence – B

- **a.** Screening should be considered beginning between ages 9–11 years for all obese children (BMI ≥95th percentile) and for overweight children (BMI ≥85th and < 94th percentile) with additional risk factors (central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH). Strength - 1, Evidence – B
- **b.** Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH or hypopituitarism. Strength - 2, Evidence – B
- **c.** Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, Hispanic ethnicity,

insulin resistance, pre-diabetes, diabetes, dyslipidemia). Strength - 2, Evidence - C.

2 Currently, the best screening test for NAFLD in children is ALT, however it has substantial limitations. Strength – 1, Evidence - B

- **a.** Interpretation of ALT should be based upon gender specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) and not individual laboratory upper limits of normal. Strength – 1, Evidence - A
- **b.** Persistently (> 3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis. Strength 1, Evidence – C
- **c.** ALT of >80 U/L warrants increased clinical concern and timely evaluation, as the likelihood of significant liver disease is higher. Strength - 2, Evidence - C
- **d.** Clinically available routine ultrasound is not recommended as a screening test for NAFLD in children due to inadequate sensitivity and specificity. Strength – 1, Evidence – B

3 Follow-up screening for NAFLD is recommended. Strength - 2, Evidence – C

- **a.** When the initial screening test is normal, consider repeating ALT every 2–3 years if risk factors remain unchanged. Strength – 2, Evidence - C
- **b.** Consider repeating screening sooner if clinical risk factors of NAFLD increase in number or severity. Examples include excessive weight gain or development of other medical problems that increase risk of NAFLD, such as type 2 diabetes or obstructive sleep apnea. Strength – 2, Evidence - C

DIAGNOSIS OF PEDIATRIC NAFLD

Initial Evaluation

NAFLD is a diagnosis of exclusion requiring presence of hepatic steatosis and exclusion of other causes of hepatic steatosis besides NAFLD (Table 3). Importantly, an obese or overweight child with chronically elevated liver enzymes should not be assumed to have NAFLD. Evaluating the cause of chronically elevated liver enzymes to establish a diagnosis is of NAFLD is very important because it excludes other hepatic conditions which may require specific treatments distinct from treatment of NAFLD. This cost-effectivness of this approach is unknown but consequences of missing another liver disease requiring alternate treatment can be significant and serious. , Until a test is developed specifically for NAFLD, it remains a diagnosis of exclusion.

The utility of non-invasive tools for the diagnosis of NAFLD has been assessed against the currently accepted clinical reference, which is hepatic histology. A review of the literature suggests that to date surrogate markers and scores developed to predict steatosis (e.g.

"NAFLD liver fat score," "fatty liver index," "hepatic steatosis index," and the "pediatric prediction score") are not accurate enough or sufficiently validated to be clinically useful (35). Other scores have also been shown to be inadequate in predicting the presence of steatosis (36) or remain to be validated (37).

Similar to the issues noted under screening, clinically available ultrasound technology is not accurate for the diagnosis of hepatic steatosis because of its low sensitivity and specificity (28, 38). Although ultrasound is widely available and can exclude hepatic masses, cysts, or gallbladder pathology, a normal hepatic ultrasound cannot exclude the presence of NAFLD and therefore is not useful for diagnosis or follow-up. CT though reasonably sensitive and specific for hepatic steatosis is not recommended for diagnosis due to radiation risk. When available, MRI and MRS are highly accurate for estimating steatosis (31, 39, 40). Further studies are needed in children to identify and validate cutoffs that have diagnostic accuracy for NAFLD.

Assessment of Steatosis Severity

It is currently not known whether the severity of steatosis in children with NAFLD predicts short- or long-term clinical outcomes. Non–invasive techniques for quantifying the degree of steatosis include investigative ultrasonography techniques and MR-based technologies but these are not widely available. (31, 41). Steatosis involving greater than 5% of hepatocytes or liver tissue by weight is considered abnormal (42, 43). The validated NAFLD Activity Score (NAS) is a semi-quantitative assessment of NAFLD histopathology frequently utilized in clinical trials and research (44, 45). The NAS uses a semi-quantitative scale of 0–3 to assess steatosis seen on histology (< 5% of hepatocytes, 5–33%, 34–66% and >67%).

Diagnosing Steatohepatitis and Determining NASH Severity

NASH is defined as the presence of hepatic steatosis with necroinflammation and hepatocellular injury with or without fibrosis (45). Identification of fibrosis in children with NASH and NAFLD is important because these phenotypes are expected to be more likely to progress to cirrhosis (46). Clinical parameters, such as the degree of obesity or the severity of metabolic dysregulation (47), as well as non-invasive markers of hepatocellular injury (e.g. keratin 18) do not adequately distinguish patients with NAFL from those with NASH (48–55). ALT is not sensitive enough to predict with certainty the NAFLD phenotype or severity; however NASH is more common in children with ALT ≥ 80 U/L compared to those with ALT < 80 U/L (41% compared to 21% respectively) (27).

Liver biopsy is the current standard to define the presence and severity of NAFLD, including the presence of NASH, and to eliminate alternative and/or concurrent diagnoses. Liver biopsy has inherent limitations for staging NAFLD because of the non-uniformity of disease throughout the liver in reference to the small sample of liver obtained. Adequate sample length (≥ 2 cm) and width decreases the risk of misclassification, but does not eliminate it. The NAFLD activity score (NAS) is a research tool for semi-quantitatively rating features of the histology and its use was not intended to include the confirmation of a clinical diagnosis (56).

Liver biopsy is generally safe in children (57–60), including those who are overweight or obese (61), as it is associated with a low risk of complications. Children who are extremely obese (BMI ≥ 120% of the 95th percentile or BMI > 35 kg/m^2, whichever is lower) may present special challenges due to difficulty assessing the position of the liver and increased depth of the subcutaneous adipose tissue layer, and may warrant referral to interventional radiology. The optimal timing of liver biopsy to confirm the diagnosis of NAFLD and to follow-up on its progression has not been established. Currently, clinical practice varies widely. Proceeding to liver biopsy should be a shared decision with the child's caregiver made after discussion of the benefits and risks. Benefits of liver biopsy include identifying those with more severe or progressive disease so that they can pursue more intensive treatment if office based lifestyle counseling fails. More intensive weight-management options may include referrals to multidisciplinary intensive lifestyle interventions or even surgical weight loss in a severely obese adolescent who meets additional clinical criteria. Importantly, liver biopsy differentiates other chronic liver diseases, such as autoimmune hepatitis, which can be challenging to exclude non-invasively.

Assessment of Fibrosis

Fibrosis in the setting of NAFLD is currently determined by liver histology and staged using a semi-quantitative scale of 0–4 (56). Children with NAFLD may have fibrosis without NASH. In general, clinical signs and symptoms of advanced fibrosis and cirrhosis may include fatigue, splenomegaly, low platelets, AST/ALT ratio > 1, spider angiomata and palmar erythema. Decompensated cirrhosis can also present with abnormal bruising, variceal bleeding, ascites, jaundice, pruritus and encephalopathy. However, overt signs and symptoms of advanced fibrosis or cirrhosis are very uncommon in children with NAFLD and NASH. Limited data suggest that clinical markers, such as higher BMI and increased waist circumference, are associated with the presence of fibrosis in patients with NAFLD/NASH (62, 63). In a predominantly adult population, the NAFLD fibrosis score predicts the presence of fibrosis with moderate accuracy (64). The Pediatric NAFLD fibrosis score is less accurate; however these results remain to be validated (65). Limited data suggest that the combined Pediatric NAFLD Fibrosis Index (PNFI) and Enhanced Liver Fibrosis (ELF) scores are accurate in estimating fibrosis in children with NAFLD; however, the PNFI alone and the Pediatric NAFLD fibrosis score are less accurate (65–67). The accuracy of currently marketed fibrosis biomarker tests in children, as well as markers such as AST to platelet ratio and hyaluronic acid (and their optimal cutoffs), remain to be determined (68–72). In a predominantly Hispanic cohort of children presenting to an outpatient gastroenterology clinic for suspected fatty liver disease, an ALT ≥ 80 was associated with advanced fibrosis (bridging or cirrhosis) with a sensitivity of 76% and specificity of 59% (27).

In terms of imaging modalities for the assessment of fibrosis, acoustic radiation force impact (ARFI), Transient Elastography (TE) and Magnetic Resonance Elastography (MREl) have predominantly been assessed in adults and are becoming more widely available at many centers. However, the pediatric literature is characterized by small sample size, and particularly small numbers of patients with clinically significant fibrosis (≥2).TE has been shown to have an ROC of 0.79–1.0 for predicting clinically significant fibrosis (73–75). MRE detects clinically significant fibrosis with an ROC of 0.92 and is scanner and reader

independent (76). These technologies would benefit from further validation studies to determine optimal cut-points and ability to longitudinally track fibrosis in children.

Recommendations

4 When evaluating a child suspected to have NAFLD, it is recommended to exclude alternative etiologies for elevated ALT and/or hepatic steatosis and investigate the presence of co-existing chronic liver diseases. (Figure 1). Strength – 1, Evidence – A

5 Liver biopsy should be considered for the assessment of NAFLD in children who have increased risk of NASH and/or advanced fibrosis. Potential clinical signs of increased risk of fibrosis in children with NASH may 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. Strength – 1, Evidence – B

6 The use of ultrasound is not recommended for the determination or quantification of steatosis due to poor sensitivity and specificity. Ultrasound may be useful for assessing other causes of liver disease such as masses, gallbladder disease, changes associated with portal hypertension etc. Strength – 1, Evidence – B

7 The use of CT is not recommended for determination or quantification of steatosis due to radiation risk. Strength -1, Evidence – B.

TREATMENT OF NAFLD IN CHILDREN

In the review of treatment of pediatric NAFLD, 42 clinical trials performed in children with NAFLD were identified. Limitations of the studies included a lack of standardization in the diagnostic criteria used, non-randomization or lack of adequate control groups, insufficient treatment (e.g. lifestyle intervention of very short duration or sub-therapeutic medication dose), inconsistent or inadequately defined outcomes, and varying approaches to data analysis. Conducting treatment trials for NAFLD in children remains challenging because of the lack of validated non-invasive biomarkers and insufficient knowledge of the natural history of the disease. High quality treatment studies require histologic assessment of liver outcomes or, at minimum, a quantitative non-invasive measurement of liver fat and/or fibrosis and a biochemical measurement of liver inflammation (ALT). Substantial ALT decrease (if elevated at entry) or normalization may also be an acceptable surrogate in NAFLD treatment trials, particularly in early phase studies, but is less accurate than histology or imaging.

Treatment Population

All children with NAFLD should be offered lifestyle intervention counseling if overweight or obese. It is unknown how to prioritize which children with NAFLD should receive more intensive treatment. Due to the lack of natural history data, it is also unknown if children with NAFL have a lower risk of developing NASH or fibrosis in the future, as is generally the case in adults with NAFL. For the same reason, it is unknown whether or to what degree

children with NASH are more likely to have progressive fibrosis or increased risk of CVD. NAFLD progression may be linear or wax and wane with environmental changes, growth changes or weight loss. Given the uncertainty, most treatment trials for pediatric NAFLD have included a wide range of disease severity.

Goals of Treatment

The most commonly accepted goal of treatment is regression of NAFLD, defined as decrease in steatosis, inflammation and/or fibrosis. A second accepted goal is resolution of NASH. The durability of these histologic changes in children is unknown. Decrease in ALT is commonly used as a surrogate marker of improvement in histology of NAFLD, as there is some evidence to support its use in pediatric clinical trials (19, 77). While an ALT at a single time-point has poor correlation to phenotype, a decrease in ALT of 10 U/L over 96 weeks is associated with 1.28 relative odds of improvement in histology and 1.37 relative odds of resolution of NASH (77). In studies of NAFLD detected in adulthood, presence of fibrosis was more predictive of clinical outcome compared presence of NASH(46, 78). Both NAFL and NASH have been shown to progress in stage of fibrosis (79). Until natural history studies are completed in children, these data are the best information available and can help inform current practice.

Ultrasound is not able to reliably detect changes in steatosis and therefore does not have a role in assessing steatosis longitudinally. Likewise, CT and MRI/MRS modalities have not been adequately studied in children with NAFLD as surrogate markers for NAFLD or NASH improvement. Liver biopsy remains the clinical standard for determining improvement in liver histology after treatment, but frequency and timing of a follow-up biopsy must be weighed against the risks of the procedure.

An additional and overarching goal of treatment for patients with NAFLD is to decrease excess adiposity in order to improve dyslipidemia, insulin resistance, high blood pressure and central adiposity, all of which are closely associated with NAFLD, as well as with T2DM and CVD risk. In children, the NAFLD comorbidities (diabetes, CVD, and hypertension) are important considerations of treatment in order to improve future clinical outcomes.

Recommendations

8 Pending the development of more accurate biomarkers to non-invasively assess improvement in NAFLD, sustained decrease in ALT from baseline may be used as a surrogate marker of response to treatment, particularly for durations of ≤ 1 year. Strength – 2, Evidence – C

9 Assessment of change in fibrosis over time is reasonable as a treatment outcome in children over longer time periods (≥ 2 years) and currently requires a liver biopsy for staging. Strength – 2, Evidence – C

Treatment of Pediatric NAFLD with Lifestyle Changes

At this time, dietary improvements and increasing physical activity (lifestyle modifications) are the primary treatment for pediatric NAFLD because of its strong association with excess

weight gain and obesity. Seventeen lifestyle intervention studies were identified in the literature search but these were very heterogeneous in design, including varying duration (1 month to 1 year), entry criteria, outcome measures and lifestyle approaches. Nonetheless, there were a number of non-randomized, uncontrolled cohorts that together demonstrate a trend of improvement in non-invasive markers of NAFLD (ALT and steatosis) with combined lifestyle and exercise (80–96). Multidisciplinary clinics designed to treat obesity have also reported improved liver enzymes and histology in children with NAFLD (81, 97, 98). Multidisciplinary lifestyle approaches of moderate to high intensity (>25 contact hours over 6 months) have been shown to be most effective in pediatric weight management (99). However in these studies, there was not sufficient evidence to determine whether or to what degree BMI improvement or weight loss is required for improvement in NAFLD in children; however, in adult studies weight loss of ≥ 10% of baseline weight was associated with ≥ 90% resolution of NASH.

The available data do not support a specific diet over others for the treatment of NAFLD (e.g. low glycemic index versus low fat). Two large randomized controlled trials (RCT) have demonstrated that reduction of sugar-sweetened beverages decreases adiposity in children (100, 101) and may benefit overweight and obese children with NAFLD. A RCT also supports both aerobic and resistance exercise as beneficial for reducing hepatic fat in children. Aerobic exercise intervention was compared to resistance exercise and no exercise in obese boys and the results suggested significant reduction in hepatic fat as measured by MRS in both exercise groups (82). Few children had NAFLD at baseline, but among those that did, there was a promising response to exercise with both hepatic fat reduction and improvement in total and visceral fat. There are clear comprehensive health benefits to a healthier diet and increasing physical activity (102) and these remain the first line approach to treatment of NAFLD in children (Figure 2).

Recommendation

10 Lifestyle modifications to improve diet and increase physical activity are recommended as the first-line treatment for all children with NAFLD. Strength – 1, Evidence - B

11 Avoidance of sugar-sweetened beverages is recommended as a strategy to decrease adiposity. Strength – 1, Evidence – A

12 Increasing moderate to high intensity physical activity and limiting screen time activities to < 2 hours per day is recommended for all children including those with NAFLD. Strength – 1, Evidence – B

Medications and Supplements

A number of medications and supplements have been considered for use in pediatric NAFLD. Multiple clinical trials or cohort studies have focused on metformin (19, 103–106) or vitamin E (19, 107–110) as potential treatments for NAFLD. Metformin plus lifestyle counseling or vitamin E plus lifestyle counseling were each tested against placebo plus lifestyle counseling in a large, multicenter, 3 arm RCT; the TONIC trial (19). Sustained ALT reduction was the primary endpoint and change in histology the secondary endpoint in this

study, which included 173 children aged 8–17 years. Although the primary outcome of sustained reduction of ALT was not different between either drug and placebo, vitamin E treatment was associated with statistically significant improvements in histology, as shown by a lower NAFLD activity score (via improvement in ballooning) and greater resolution of NASH. The latter was shown in a smaller subset of participants who had biopsy-confirmed NASH. Concerns about the safety of high dose vitamin E have been raised in adults, following meta-analyses of clinical trials, which have indicated an increased mortality with vitamin E, as well as increased adverse cardiovascular events and prostate cancer (111, 112). Interestingly, other meta-analyses have not had similar results (113). Although no significantly greater risk of adverse events were noted in the children receiving high dose vitamin E in the TONIC trial over a two year period, the long term benefits and risks remain unknown.

The TONIC study found that metformin administered at 500 mg twice daily dose in combination with lifestyle counseling was not different than placebo in terms of NAS score or ALT improvement (19). However, there was also no significant decrease in homeostatic model assessment-insulin resistance (HOMA-IR) in the metformin group. It remains unknown whether improvement in insulin sensitivity in children with NAFLD would lead to improvement in NAFLD or whether certain subsets of patients with NAFLD could benefit from metformin when given at typical clinical doses.

Vitamin E, as a treatment for biopsy-confirmed NAFLD, has also been tested in a smaller RCT in combination with lifestyle counseling and vitamin C; the two antioxidants taken together were, however, not superior to lifestyle intervention alone (109). High rates of vitamin D insufficiency have been identified in pediatric NAFLD (114–116), but there are no trials in children evaluating vitamin D supplementation as a treatment for NAFLD. In a small study of ursodeoxycholic acid in children, diet alone compared to ursodeoxycholic acid plus diet or ursodeoxycholic acid without diet did not show any benefit of the drug (117). This concurs with adult data that do not support its use in NAFLD (118).

Both docosahexaenoic acid (DHA) and fish oil have been considered for treatment of NAFLD. A small RCT testing 6 month supplementation with either 250mg or 500mg DHA versus placebo for pediatric NAFLD found no improvement in ALT (119). An adult study suggests that fish oil worsens NASH (120). Probiotics (Lactobacillus GG and VSL #3) have been tested in two small studies of short duration (2–4 months); however, both studies were limited by the use of sonographic outcome measures (121, 122). ALT improved significantly in one study compared to placebo and this could represent an area for future research.

In summary, no medication or supplement has been shown to be of significant value for the management of NAFLD in children.

Recommendations

13 No currently available medications or supplements are recommended to treat NAFLD because none have been proven to benefit the majority of NAFLD patients. Strength - 2, Evidence – C

Weight Loss Surgery as a treatment for NAFLD or NASH in Children

Bariatric or weight loss surgery (WLS) can lead to clinically meaningful weight loss in severely obese adolescents (minimum BMI ≥ 35 kg/m^2) with average BMI reductions of approximately 30% at 1 year postoperatively after both roux-en-y gastric bypass and vertical sleeve gastrectomy in a large multicenter adolescent cohort (123). At three years post-surgery, an average 28% weight reduction was maintained in the cohort. This reduction in BMI is typically associated with substantial improvement and even resolution of many obesity-related comorbid conditions, including dyslipidemia, high blood pressure, insulin resistance, diabetes and sleep apnea at one to two years post-operatively (124, 125). Because these conditions are often associated with the presence of NAFLD and because studies in adults undergoing bariatric surgery have suggested a high degree (up to 89%) of NASH resolution one to two years post-operatively (126), severe NASH has been proposed as a criterion for WLS in several published adolescent bariatric surgery guidelines (127).

There is paucity of data on the natural history of NAFLD and NASH in adolescents undergoing WLS. There are only four WLS outcome studies in this population that have included an assessment of NAFLD status at baseline (128–132), and among those only one included histological evaluation of NAFLD (130). In terms of outcome post WLS, only one study provided data on the progression of the liver disease. This study did not include histological outcomes but instead followed the change in ALT and AST in 81 adolescents undergoing roux-en-y gastric bypass over a 2-year period (132). Mean ALT and AST improved significantly at 1 and 2 years (mean decrease of nearly 50%); however, no data on ALT/AST change were provided for the adolescent group undergoing conventional care (controls), therefore it is unknown if this intervention was superior to lifestyle intervention. It should be noted that similar to adult cohorts, the proportion of patients with severe NASH among adolescents undergoing WLS tend to be low (130). It is unclear if this is related to selection/referral bias or due to potential biological differences among the more severely obese. Therefore, the generalizability of the overall positive NAFLD outcomes reported among adults undergoing bariatric surgery to children with histologically advanced or fibrotic NASH is limited.

Recommendation

14 Bariatric surgery is not recommended as a specific therapy for NAFLD given lack of outcome data in adolescents. Bariatric surgery may be considered for selected adolescents with BMI ≥ 35 kg/m^2, who have non-cirrhotic NAFLD and other serious comorbidities (e.g. T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with WLS. Strength - 1, Evidence - B

CARDIOVASCULAR DISEASE RISK IN THE SETTING OF NAFLD IN CHILDREN

Longitudinal studies in adults demonstrate an independent increase in CVD associated with markers of NAFLD (133–136). This risk (ranging from 1.23 to 4.82 increase in odds of events or disease) appears to be independent of classical risk factors such as BMI, obesity or

other components of the metabolic syndrome (136). In several adult studies, CVD has been found to be the leading cause of mortality in patients with biopsy proven NAFLD (20, 137). To date, there are no studies reporting the effect of NAFLD diagnosed in childhood on the risk of CVD in adulthood. However, abundant evidence demonstrates that CVD risk factors, and specifically dyslipidemia, are commonly associated with NAFLD in children (138, 139). The most common pattern of dyslipidemia is high triglycerides and low HDL, typical of the insulin resistant state. Studies evaluating surrogate markers of atherosclerosis and autopsy findings of atherosclerosis confirm that children with NAFLD frequently have early atherosclerosis (140–144).

There are no studies in the pediatric population using lipid-lowering drugs as a treatment for NAFLD. The effect of lipid lowering medications on NAFLD histology is also unknown. In adults, statins are recommended as safe for treating dyslipidemia in the setting of NAFLD; however, they are not used as a treatment for NAFLD (2). A few studies in children have evaluated the response of plasma lipids to treatments of NAFLD. In a 2-year trial testing the effect of DHA supplementation versus placebo for treating NAFLD in children, triglycerides improved in the DHA group compared to placebo (145). In the TONIC trial, resolution of NASH was associated with improvement in LDL and non-HDL cholesterol but not with improvement in triglycerides (19, 146). Finally a small pilot study of a low-fructose diet demonstrated improved levels of oxidized LDL, a marker of CVD risk in children with NAFLD (96).

Despite the lack of pediatric data specifically on NAFLD, there is evidence to support the approach to CVD risk reduction in children. The ‘Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report’ delineates current practice recommendations for screening and treating children (147). At the time of this document, universal screening with a lipid panel is recommended for all children age 9–11 years (147). For ages 2–8 years, a lipid panel is recommended if risk factors exist or if there is a family history of dyslipidemia or of CVD. Management algorithms are detailed in the Summary Report and are useful when evaluating dyslipidemia in children with NAFLD.

Children with NAFLD are at increased risk of hypertension compared to obese children without NAFLD, a risk that persists over time (23, 139). Guidelines exist on monitoring and treating hypertension in overweight children that are applicable to children with NAFLD (148).

Recommendations

15 Children with NAFLD should be screened for dyslipidemia at diagnosis and periodically as indicated by current lipid guidelines for children. Strength – 1, Evidence – B

16 It is recommended to monitor blood pressure in children with NAFLD. Strength – 1, Evidence – B

PRE-DIABETES AND DIABETES IN THE SETTING OF NAFLD

Limited pediatric data exist on the prevalence of pre-diabetes or T2DM in subjects with NAFLD. A retrospective analysis of a pediatric cohort with T2DM revealed the prevalence of elevated serum aminotransferases to be 48%, with 60% of these elevations being two or more times above the upper limit of normal (149). Recent cross-sectional and longitudinal studies have described an association between NAFLD and glucose dysregulation(150). In a cohort of 677 children with biopsy confirmed NAFLD, pre-diabetes and diabetes were associated with significantly higher odds of having NASH (OR 1.8 and 2.6, respectively) (151). Assessment of a relatively large multiethnic cohort of obese adolescents revealed that the prevalence of pre-diabetes and metabolic syndrome increases significantly with increases in hepatic fat content measured with MRI (152).

Studies also indicate that hepatic steatosis is related to metabolic parameters in the longitudinal setting. A cohort of 76 obese children showed that both glucose (fasting and 2-h blood glucose and AUC 2-h blood glucose) and insulin sensitivity (WBISI) indices at a mean follow-up of 1.9 years are significantly correlated with baseline hepatic fat content (150). More importantly, during the follow-up, a significant improvement of β-cell function in subjects with low compared with high liver fat content occurred. These relevant correlations were further confirmed by the multiple, stepwise, linear regression analysis showing an independent relationship between baseline hepatic fat and longitudinal metabolic parameter (2-h blood glucose and WBISI) even after adjusting for confounding factors (age, sex, ethnicity, BMI z-score, change in BMI z-score, and duration of follow-up).

Recommendation

17 It is recommended to screen children with NAFLD for diabetes at diagnosis and annually (or sooner if clinical suspicion arises) using either a fasting serum glucose level or a glycosylated hemoglobin (HbA1c) level. A glucose tolerance test may be useful if the fasting glucose or HbA1c are in the pre-diabetic range (Table 3). Strength – 1, Evidence - A

LONG TERM CARE FOR CHILDREN WITH NAFLD

Clinical Care

Clinical care and intensity of follow up may depend on the severity of the disease (more advanced NASH vs. NAFL), similar to other chronic liver diseases that occur in the same age range (autoimmune hepatitis, hepatitis B and C and primary sclerosing cholangitis). The optimal frequency of follow-up or laboratory/biopsy reassessment has not been studied in children with NAFLD; however, more frequent visits are known to be beneficial for nutrition and physical activity counseling in overweight and obese children (97, 153) and may contribute to success of NAFLD treatment as well (97, 153), as shown in adults (154). A decrease in ALT is commonly used as a surrogate marker of improvement in histology of NAFLD, and there is some evidence to support its use in pediatric clinical trials (19, 77). Importantly, in the individual patient, it does not always reliably correlate with improvement or worsening of disease. At this time, there are no non-invasive modalities adequately

validated for detecting progression or regression of fibrosis in children. Therefore, at this time liver biopsy remains the best available method for assessing change in fibrosis in children with NAFLD.

Recommendations

18 It is recommended to follow children with NAFLD on a yearly basis at a minimum to monitor for progression of disease and provide treatment. Strength 1, Evidence – C

19 When providing lifestyle counseling, more frequent visits (more contact hours with program staff) are associated with better weight management outcomes in overweight and obese children and therefore may also benefit overweight children with NAFLD/NASH. Strength 1, Evidence – B.

20 A repeat liver biopsy to assess progression of disease (particularly fibrosis) and to guide treatment is reasonable to consider 2–3 years following the first liver biopsy, especially in patients with new or ongoing risk factors, such as type 2 diabetes mellitus, NASH or fibrosis at diagnosis. Strength 2, Evidence – C

Exposures to Liver Toxins

Adolescence is a time of increased participation in high-risk behaviors with concurrent opportunities for establishing better health habits. Although emerging epidemiologic evidence suggests that light to moderate drinking may have a favorable effect on NAFLD (155), underage alcohol consumption is not recommended. A threshold effect may occur, with heavy, episodic drinking (e.g. “binge drinking”) in adults associated with an increased risk of fibrosis progression (156). Binge drinking is common amongst adolescents, with a potential negative impact in those affected by NAFLD. Prolonged cigarette smoking has been associated with advanced histologic severity of NAFLD in adults (157). A cross-sectional study of 355 American children revealed that second hand smoke exposure was associated with an increased prevalence of ultrasonographic evidence of hepatic steatosis (158).

Recommendations

21 In addition to standard counseling of adolescents, healthcare providers should counsel adolescents regarding the potential effects of increased fibrosis progression with binge drinking. Strength – 1, Evidence - B

22 Families of children with NAFLD should be counseled about risks of second hand smoke exposure and adolescents with NAFLD should be counseled against smoking and use of electronic nicotine delivery devices. Strength – 1, Evidence – B

Prevention of Hepatitis A and B

Children with chronic liver disease are at increased risk of morbidity and mortality if infected with Hepatitis A or B, vaccine-preventable diseases. While data specific to pediatric NAFLD are lacking, children with other chronic liver diseases seroconvert after 2 doses of

Hepatitis A vaccination (159, 160). The Red Book currently recommends that all children with liver diseases should receive Hepatitis A vaccine (161).

Universal vaccination for HB as infants began in 1991, so the vast majority of children and adolescents with NAFLD have been vaccinated. Children vaccinated for hepatitis B as infants frequently have low levels of hepatitis B surface antibody (anti-HBs) (162). Despite this, they usually have persistence of immune memory as demonstrated by Spradling et al (163) in which of those with no detectable hepatitis B surface antibody, 82% had immune protection. The Red Book recommends against routine postimmunization testing for anti-HBs unless the child falls into specific risk groups.

Recommendations

23 Children with NAFLD should be vaccinated routinely against hepatitis A. Strength – 1, Evidence – B

24 Children with NAFLD should have prior receipt of Hepatitis B vaccine verified and be immunized if no prior vaccination was received. Strength – 1, Evidence – A

Initiation and Monitoring of Potentially Hepatotoxic Medications

Children with NAFLD occasionally require medications for other conditions such as diabetes, infections, ADHD, psychiatric illness or other chronic illnesses. Certain medications commonly used for these conditions, are potentially hepatotoxic and require increased frequency of monitoring. A common example is the utilization of metformin for T2DMin patients who have both NAFLD and diabetes. Current recommendations are to evaluate transaminases before starting metformin and to check liver enzymes at the time of diagnosis of T2DM. However, evidence is lacking on how often to monitor liver enzymes after initiating therapy. Atypical antipsychotic drugs can also cause rapid and severe weight gain and emergence of cardiometabolic risk factors, as well as elevated liver enzymes in previously normal weight children. Liver enzymes therefore should be checked before starting atypical antipsychotics and are typically monitored during the course of therapy.

Recommendations

25 Baseline liver enzyme levels should be obtained in children with NAFLD before starting any medication known to be hepatotoxic. There is insufficient evidence to guide frequency of monitoring for enzyme elevation after initiation of potentially hepatotoxic medications and monitoring should be guided by the baseline severity of the liver disease and the relative potential for hepatotoxity of the medication. Strength – 1, Evidence – C

26 If potentially hepatotoxic drugs are being considered in patients with NAFLD, a baseline liver biopsy may be reasonable to consider for assessing the severity of liver disease prior to beginning the medication. Strength – 2, Evidence – C

Quality of Life

Because NAFLD is a chronic disease, it has the potential to affect more than just physical health in children. Quality of life is decreased among obese children with NAFLD compared to children obese without NAFLD (164). Indirect effects such as the emotional toll of worrying about a chronic liver disease may also be a contributor.

Recommendation

27 Providers should remain alert to psychosocial issues and screen children with NAFLD for these when indicated. Strength - 1, Evidence – B

CONCLUSIONS AND RESEARCH NEEDS

The emergence of NAFLD has been an important change in the landscape of pediatric liver disease. However, substantial gaps in knowledge remain and are research priorities. These gaps include:

- Delineating the natural history of pediatric NAFLD and identifying risk factors in childhood that predict progression versus regression and identify those at greater risk of adverse health outcomes.
- Non-invasive detection of NAFLD and NASH and quantification of steatosis, inflammation, hepatocellular injury and fibrosis. Longitudinal studies of imaging and biomarkers are needed to better determine their role in clinical care.
- Well-designed clinical trials to determine optimal treatment approaches, including the role of specific dietary interventions, type and duration of exercise, validation of pilot studies of promising therapies, as well as identification of novel medications, and role of weight loss surgery.
- Cost-effective strategies for screening, diagnosis and long-term follow-up, including frequency of visits, laboratory vs. biopsy reassessment

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What is known

- NAFLD is a highly prevalent liver disease in children.
- Guidance is needed for clinical care decisions for pediatric NAFLD.

What is new

- The following recommendations are based on a formal review and analysis of the recently published world literature (Pubmed and EMBASE search through May 2015), guidelines from other societies when applicable, and the experience of the expert committee.
- Recommendations for clinical practice, including screening, diagnosis, treatment and public health considerations are covered in this pediatric guideline.

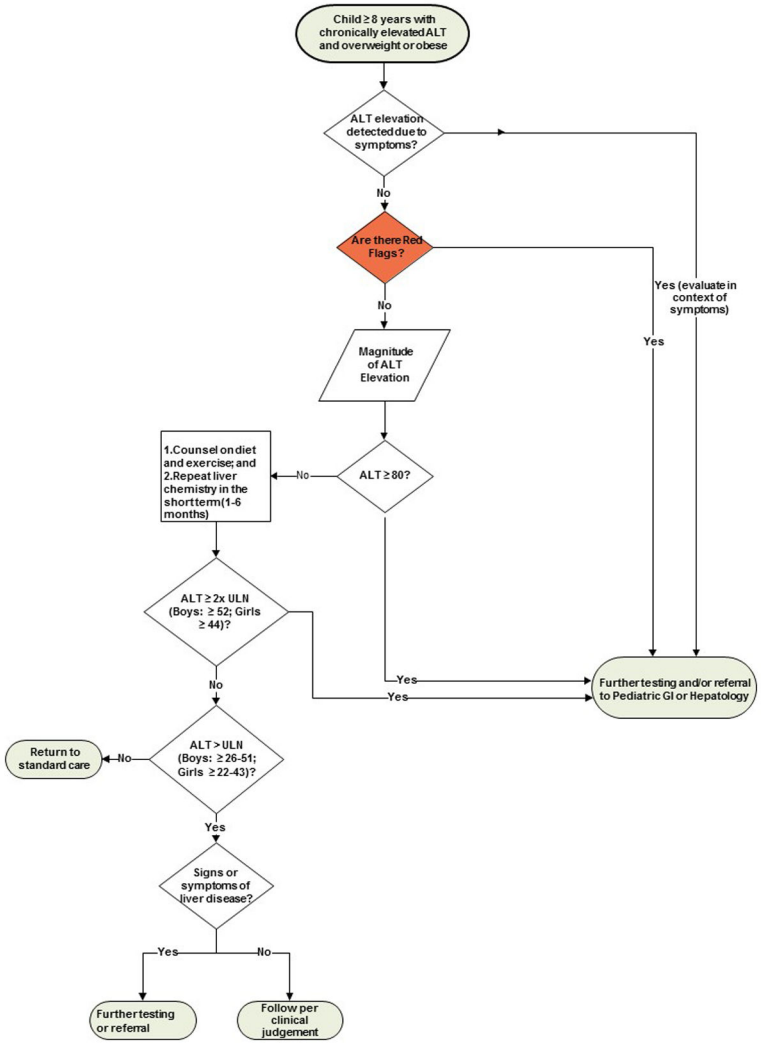

Figure 1.

An algorithm proposed by the ECON group. Further research is likely to alter the algorithm. The steps are suggested courses of action and should be interpreted within the clinical scenario of individual patients.

Additional testing for chronic liver diseases to consider:

- **Screening labs**: CBC with differential, AST, bilirubin (total, conjugated), alkaline phosphatase, GGT, INR, albumin, total protein, hemoglobin A1c
- **Exclude infections** (e.g. hepatitis A IgM, hepatitis B surface antigen, hepatitis C antibody, other chronic viral infections)
- **Exclude endocrine disorders** (TSH, free T4)
- **Exclude autoimmune causes of ALT elevation** (total IgA, total IgG and tissue transglutaminase antibody, anti-nuclear antibody, anti-smooth muscle antibody, anti-liver kidney microsomal antibody)

- **Exclude genetic causes of ALT** (ceruloplasmin and/or 24 hour urine copper, lysosomal acid lipase, alpha-1 antitrypsin phenotype)
- **Imaging:** Abdominal ultrasound to rule out anatomical abnormalities or assess features of portal hypertension, magnetic resonance imaging or spectroscopy to measure hepatic fat.
- **Liver biopsy** (histology, copper measurement, stain for microvesicular fat, assess fibrosis)

Red flags for advanced liver disease – chronic fatigue, GI bleeding, jaundice, splenomegaly, firm liver on exam, enlarged left lobe of the liver, low platelets, low white blood cell count, elevated direct bilirubin, elevated international normalized ratio (INR), long history of elevated liver enzymes (> 2 years).

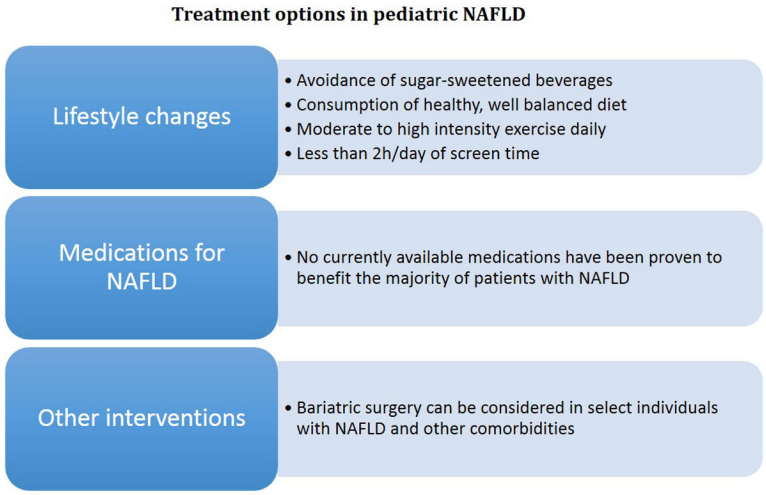

Figure 2.
Treatments for pediatric NAFLD

Table 1

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [4, 176]

	Criteria
Strength of recommendation	
Strong [1]	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient important outcomes and cost
Weak [2]	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption
Quality of evidence	
High [A]	Further research is unlikely to change confidence in the estimate of the clinical effect
Moderate [B]	Further research may change confidence in the estimate of the clinical effect
Low [C]	Further research is very likely to change confidence in the estimate of the clinical effect

Table 2

NAFLD Definitions and Phenotypes

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 diseases or medications that cause steatosis • Fatty infiltration is typically defined as fat > 5% of the liver by imaging, direct quantification or histologic estimation
NAFL	• Steatosis without specific changes to suggest steatohepatitis, with or without fibrosis
Pediatric NASH	• Hepatic steatosis with inflammation, with or without ballooning injury to hepatocytesand 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

Note: Other terms such as ‘presumed NAFLD’ (also ‘clinical NAFLD’ or ‘suspected NAFLD’) are terms used in the literature with varying meanings.

Table 3

Differential diagnosis for pediatric hepatic steatosis

Genetic/Metabolic disorders	Medications	Dietary causes	Infections
Nonalcoholic fatty liver disease	Amiodarone	Protein-energy malnutrition (Kwarshiorkor)	Hepatitis C (genotype 3)
Fatty acid oxidation and mitochondrial disorders	Corticosteroids	Alcohol abuse	
Citrin deficiency	Methotrexate	Rapid surgical weight loss	
Wilson's disease	Certain antipsychotics	Parenteral nutrition	
Uncontrolled diabetes	Certain antidepressants		
Lipodystrophies	HAART		
Lysosomal acid lipase deficiency	Valproic acid		
Familial Combined Hyperlipidemia			
Abeta-/ hypobeta-lipoproteinemia			

HAART: Highly Active Antiretroviral therapy

Table 4

Definitions of Prediabetes and Diabetes by the American Diabetes Association

	HgbA1c*	Fasting Glucose¥	2hr OGTT #	Random glucose
Prediabetes	5.7%–6.4%	100–125mg/dL (5.6–6.9mmol/L	140–199mg/dL (7.8–11.0 mmol/L)	
Diabetes	≥6.5%	≥126mg/dL (7.0 mmol/L)	≥200mg/dL (11.1 mmol/L)	≥200mg/dL (11.1 mmol/L)

*Lab using method that is NGSP certified & standardized to the DCCT assay

¥Fasting is defined as no caloric intake for at least 8 hours

#Test should be performed as described by the World Health Organization

Table 5

Summary of Recommendations

1	Selected children should be screened for NAFLD. **Strength – 1, Evidence – A**
	a. Screening should be considered beginning between ages 9–11 years for all obese children (BMI ≥95th percentile) and for overweight children (BMI ≥85th and < 94th percentile) with additional risk factors (central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH). **Strength - 1, Evidence – B**
	b. Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH or hypopituitarism. **Strength - 2, Evidence – B**
	c. Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD (obesity, Hispanic ethnicity, insulin resistance, pre-diabetes, diabetes, dyslipidemia). **Strength - 2 , Evidence - C.**
2	Currently, the best screening test for NAFLD in children is ALT, however it has substantial limitations. **Strength – 1, Evidence - B**
	a. Interpretation of ALT should be based upon gender specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) and not individual laboratory upper limits of normal**. Strength – 1, Evidence - A**
	b. Persistently (> 3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD or other causes of chronic hepatitis. **Strength 1, Evidence – C**
	c. ALT of >80 U/L warrants increased clinical concern and timely evaluation, as the likelihood of significant liver disease is higher. **Strength - 2, Evidence - C**
	d. Clinically available routine ultrasound is not recommended as a screening test for NAFLD in children due to inadequate sensitivity and specificity. **Strength – 1, Evidence – B**
3	Follow-up screening for NAFLD is recommended. **Strength - 2, Evidence – C**
	a. When the initial screening test is normal, consider repeating ALT every 2–3 years if risk factors remain unchanged. **Strength – 2, Evidence - C**
	b. Consider repeating screening sooner if clinical risk factors of NAFLD increase in number or severity. Examples include excessive weight gain or development of other medical problems that increase risk of NAFLD, such as type 2 diabetes or obstructive sleep apnea. **Strength – 2, Evidence - C**
4	When evaluating a child suspected to have NAFLD, it is recommended to exclude alternative etiologies for elevated ALT and/or hepatic steatosis and investigate the presence of co-existing chronic liver diseases. (Figure 1). **Strength – 1, Evidence – A**
5	Liver biopsy should be considered for the assessment of NAFLD in children who have increased risk of NASH and/or advanced fibrosis. Potential clinical signs of increased risk of fibrosis in children with NASH may 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. **Strength – 1, Evidence – B**
6	The use of ultrasound is not recommended for the determination or quantification of steatosis due to poor sensitivity and specificity. Ultrasound may be useful for assessing other causes of liver disease such as masses, gallbladder disease, changes associated with portal hypertension etc. **Strength – 1, Evidence – B**
7	The use of CT is not recommended for determination or quantification of steatosis due to radiation risk. **Strength -1, Evidence – B.**
8	Pending the development of more accurate biomarkers to non-invasively assess improvement in NAFLD, sustained decrease in ALT from baseline may be used as a surrogate marker of response to treatment, particularly for durations of ≤ 1 year. **Strength – 2, Evidence – C**
9	Assessment of change in fibrosis over time is reasonable as a treatment outcome in children over longer time periods (≥ 2 years) and currently requires a liver biopsy for assessment. **Strength – 2, Evidence – C**
10	Lifestyle modifications to improve diet and increase physical activity are recommended as the first-line treatment for all children with NAFLD. **Strength – 1, Evidence - B**
11	Avoidance of sugar-sweetened beverages is recommended as a strategy to decrease adiposity. **Strength – 1, Evidence - A**
12	Increasing moderate to high intensity physical activity and limiting screen time activities to < 2 hours per day is recommended for all children including those with NAFLD. **Strength – 1, Evidence - B**
13	No currently available medications or supplements are recommended to treat NAFLD because none have been proven to benefit the majority of NAFLD patients. **Strength - 2, Evidence – C**
14	Bariatric surgery is not recommended as a specific therapy for NAFLD given lack of outcome data in adolescents. Bariatric surgery may be considered for selected adolescents with BMI ≥ 35 kg/m^2, who have non-cirrhotic NAFLD and other serious comorbidities (e.g. T2DM, severe sleep apnea, idiopathic intracranial hypertension) that are likely to improve with WLS. **Strength - 1, Evidence - B**

15 Children with NAFLD should be screened for dyslipidemia at diagnosis and periodically as indicated by current lipid guidelines for children. **Strength – 1, Evidence - B**

16 It is recommended to monitor blood pressure in children with NAFLD. **Strength 1, Evidence - B**

17 It is recommended to screen children with NAFLD for diabetes at diagnosis and annually (or sooner if clinical suspicion arises) using either a fasting serum glucose level or a glycosylated hemoglobin (HbA1c) level. A glucose tolerance test may be useful if the fasting glucose or HbA1c are in the pre-diabetic range (Table 3). **Strength – 1, Evidence - A**

18 It is recommended to follow children with NAFLD on a yearly basis at a minimum to monitor for progression of disease and provide treatment. **Strength 1, Evidence - C**

19 When providing lifestyle counseling, more frequent visits (more contact hours with program staff) are associated with better weight management outcomes in overweight and obese children and therefore may also benefit overweight children with NAFLD/NASH. **Strength 1, Evidence B**.

20 A repeat liver biopsy to assess progression of disease (particularly fibrosis) and to guide treatment is reasonable to consider 2–3 years following the first liver biopsy, especially in patients with new or ongoing risk factors, such as type 2 diabetes mellitus, NASH or fibrosis at diagnosis. **Strength 2, Evidence C**

21 In addition to standard counseling of adolescents, healthcare providers should counsel adolescents regarding the potential effects of increased fibrosis progression with binge drinking. **Strength – 1, Evidence - B**

22 Families of children with NAFLD should be counseled about risks of second hand smoke exposure and adolescents with NAFLD should be counseled against smoking and use of electronic nicotine delivery devices. **Strength – 1, Evidence - B**

23 Children with NAFLD should be vaccinated routinely against hepatitis A**. Strength – 1, Evidence - B**

24 Children with NAFLD should have prior receipt of Hepatitis B vaccine verified and be immunized if no prior vaccination was received. **Strength – 1, Evidence – A**

25 Baseline liver enzyme levels should be obtained in children with NAFLD before starting any medication known to be hepatotoxic. There is insufficient evidence to guide frequency of monitoring for enzyme elevation after initiation of potentially hepatotoxic medications and monitoring should be guided by the baseline severity of the liver disease and the relative potential for hepatotoxity of the medication. **Strength – 1, Evidence – C**

26 If potentially hepatotoxic drugs are being considered in patients with NAFLD, a baseline liver biopsy may be reasonable to consider for assessing the severity of liver disease prior to beginning the medication. **Strength – 2, Evidence – C**

27 Providers should remain alert to psychosocial issues and screen children with NAFLD for these when indicated. **Strength - 1, Evidence – B**