MASH IN FOCUS

Current Developments in the Management of Metabolic Dysfunction-Associated Steatohepatitis

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Highlights From the Recent AASLD Guidance on MASLD/MASH in Children

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G&H Why was there a need to develop separate practice guidance for pediatric metabolic dysfunction-associated steatotic liver disease?

SX In 2023, when the American Association for the Study of Liver Diseases (AASLD) initiated revision of its clinical practice guidance for metabolic dysfunction-associated steatotic liver disease (MASLD), it had intended to include a brief pediatric segment. When the committee reviewed the pediatric literature, it became clear to us that there were several significant epidemiologic and clinical differences in children with MASLD; therefore, many of the recommendations that were being gathered for the treatment of adults did not apply as well to children. Ultimately, the AASLD decided to commission a separate pediatric-focused practice statement to provide evidence-based guidance on how to evaluate and manage MASLD, including metabolic dysfunction-associated steatohepatitis (MASH), in children.

G&H How was the pediatric practice statement developed?

SX The AASLD invited a committee of experts in pediatric MASLD, which included board-certified hepatologists and gastroenterologists with expertise in the area, as well as additional multidisciplinary experts in the field, including a pediatric pathologist and pediatric endocrinologist. Several of the doctors had additional training and certification in obesity medicine. We were then tasked with conducting a comprehensive literature search to identify all possible pediatric studies through March 2024 related to epidemiology, natural history, pathophysiology, screening, evaluation, treatment, and outcomes of pediatric MASLD. We used the highest available evidence level—randomized clinical trials, large observational cohort studies, systematic reviews, and meta-analyses—to develop evidence-based clinical practice statements. If high-level evidence was not available, we relied on expert consensus. We also identified critical gaps and unmet needs in the field. The practice statement was published in *Hepatology* at the end of last year.

G&H According to the AASLD guidance, which children should undergo screening for MASLD?

SX Owing to the high prevalence of MASLD in children and the clear association with early morbidity and mortality risk, the practice statement recommends screening children starting at age 10 years who are overweight (defined in pediatrics as a body mass index [BMI] of the 85th percentile or higher) with cardiometabolic risk (including insulin resistance, prediabetes, diabetes, lipid abnormalities, and hypertension). Additionally, children with obesity (BMI ≥95th percentile) should be screened, regardless of whether they have cardiometabolic risk factors, because there is a strong association of obesity with MASLD. Starting screening at age 10 years also aligns with the American Academy of Pediatrics recommendation to screen children with overweight and obesity for cardiometabolic risk starting at that age. Recent studies have also identified a high prevalence of MASLD in younger children with obesity, so selective screening in

younger ages can also be considered in the presence of cardiometabolic risk factors or strong family history of MASH; however, universal screening of children younger than 10 years is not recommended.

G&H What screening methods are recommended for pediatric patients, and what pediatric-specific thresholds should be followed?

SX This is one of the key differences between adult and pediatric patients with MASLD/MASH. The currently available screening methods to detect clinically significant MASH that are used in adults, such as vibration-controlled elastography and blood tests used to identify a higher risk of fibrosis, have significant limitations in children. Therefore, we relied on the evidence we currently have, which is that serum alanine aminotransferase (ALT) levels are the most validated and optimal screening method for MASLD and MASH in children. The practice statement recommends using the 95th percentile for the upper limit of normal, which is greater than 22 U/L for females and greater than 26 U/L for males. In children less than 10 years of age, a higher cutoff of greater than 30 U/L is generally recommended based on population-based studies of normal values in healthy children. ALT has very reasonable sensitivity and specificity of around 80% to 85%, is low cost, and is widely available, so we continue to recommend it for MASLD and MASH screening in children. Higher levels of ALT increase specificity for MASLD and MASH, but lower sensitivity.

G&H What tools are recommended for diagnosing MASLD or MASH in pediatric patients?

SX With the recent nomenclature change from nonalcoholic fatty liver disease, a diagnosis of MASLD requires confirming that steatosis is present, and this holds true for both adults and children. There are two methods that can be used: imaging and biopsy. In addition, children should have at least 1 cardiometabolic risk factor. Magnetic resonance imaging–proton density fat fraction (MRI-PDFF), which is a method of quantifying fat in the liver, is the only validated imaging tool in children. However, it is not practical for point-of-care diagnosis because it is expensive and not widely available. Therefore, for imaging assessment, we rely on supportive imaging assessments such as ultrasonography. It is important to recognize, however, that ultrasound can miss steatosis, particularly at lower degrees, and can misclassify patients as having steatosis when, in fact, they may have a different cause of hepatitis. Therefore, ultrasound should be considered supportive but not diagnostic of MASLD. Controlled attenuation parameter, a measure of steatosis obtained during point-of-care vibration-controlled elastography, does not have accuracy for detecting or staging MASLD severity in children, particularly in those with overweight/obesity, and thus is not recommended for diagnosis. In routine clinical practice, ultrasound can be supportive of the diagnosis and rule out structural abnormalities in the liver or gallbladder disease, but if high accuracy is needed for diagnosis of liver steatosis, MRI-PDFF is the only validated imaging method in children. Biopsy is still also used in certain situations for confirming the diagnosis, such as when there is diagnostic uncertainty or concern for progressive liver disease.

> One of the points of emphasis in the guidance is that it is very important, whenever possible, to include multidisciplinary lifestyle management team members.

G&H Could you expand on when liver biopsy should be considered in pediatric patients?

SX In the pediatric field, we still rely on liver biopsy a lot more than our adult colleagues, who have more established and validated methods for detecting steatosis as well as MASH. Liver biopsy is necessary to evaluate for certain conditions, such as autoimmune hepatitis or drug-induced liver disease. It is also the only method currently available in children to confirm the diagnosis of MASH and stage severity because of the lack of reliable validated noninvasive methods. Even though there are currently no approved pharmacotherapies to treat MASH in children, knowing if a child has MASH or if they have significant or advanced fibrosis can guide treatment decisions to intensify obesity treatment (such as approved obesity pharmacotherapy or bariatric surgery) or help determine transition of care to an adult hepatologist as children enter adulthood. Thus, liver biopsy still remains an important diagnostic tool in children with pediatric MASLD.

G&H How can children with MASH be best managed according to the AASLD guidance, especially when initial lifestyle modification may not appear to be sufficient?

SX One of the points of emphasis in the guidance is that it is very important, whenever possible, to include multidisciplinary lifestyle management team members. Including the support of a registered dietitian, exercise specialist, and/or behavioral management specialist with pediatric obesity training can help children and their families identify specific actionable goals, implement them, and sustain them. This support can also help patients and families facing food insecurity, mental health conditions, and other challenges that may make it hard to change lifestyle habits.

Additionally, there are now approved pharmacotherapies to treat obesity in children, including glucagon-like peptide-1 (GLP-1) receptor agonists and phentermine/topiramate. These therapies are increasingly being offered to children when initial lifestyle modification alone is not sufficient to achieve significant improvements in metabolic comorbidities or weight status. There is a lot of excitement around GLP-1 receptor agonists for the treatment of obesity in children as well as adults, especially because these therapies seem to be very effective in treating a variety of cardiometabolic conditions, including MASH in adults. There is still a little hesitation about putting children on drugs that may be needed lifelong, as current data suggest that if these drugs are stopped, there is a high risk of regaining the weight that was lost. Thus, it is very important to include them in addition to lifestyle modification, not as the only treatment. Trials have suggested comparable weight loss outcomes in children as in adults, but more real-world data are going to be needed to see if the degree of weight loss in clinical practice is similar. In my own practice, I have seen that these medications can help slow the rate of weight gain and lead to cardiometabolic improvements, even if significant weight loss does not occur. Some patients lose more weight than others, and not every patient can tolerate the gastrointestinal side effects. As for pediatric MASH specifically, we do not have clinical trials yet to know how effective GLP-1 receptor agonists such as semaglutide (Wegovy, Novo Nordisk) will be for children with MASH. The pediatric guidance recommends considering GLP-1 receptor agonists and other approved antiobesity pharmacotherapies for the treatment of obesity in children with MASLD who meet the approved obesity indication, but these therapies are not approved for the treatment of MASH with fibrosis in children.

G&H What is the role of bariatric surgery in the pediatric practice statement?

SX Bariatric surgery is well established as a treatment for severe obesity in children. Both single-center studies as well as multicenter observational cohort studies have shown that children with biopsy-confirmed MASLD/MASH (based on biopsies obtained at the time of surgery) have significant improvements in ALT with the majority (approximately 65%) achieving normalization after bariatric surgery. In a smaller subset of children who underwent repeat biopsies, 80% to 90% experienced resolution of their MASH after bariatric surgery. Thus, there are supportive data that bariatric surgery is an effective treatment for both MASLD and MASH in children. However, it is not known how well bariatric surgery works for children with more advanced fibrosis because the bariatric cohort studies to date have not typically included many children with more advanced fibrosis. That is starting to change now, as we have become more comfortable referring children with MASLD or MASH for bariatric surgery, so hopefully more data will become available in the future. Another gap is that it is not known how long the improvement lasts. There are no long-term follow-up studies to know whether improvement in MASH or MASLD persists 5 or 10 years after bariatric surgery. Although these research gaps need to be filled, bariatric surgery is a good treatment to consider, especially if an adolescent with severe obesity has numerous comorbid conditions, such as MASH, diabetes, and obstructive sleep apnea, for which bariatric surgery is also known to be very effective.

It is important to remember to screen children with MASLD/MASH for anxiety and depression because having those conditions can make it harder to implement lifestyle modifications.

G&H Would you like to highlight any other recommendations from the pediatric AASLD guidance?

SX It is important to remember to screen children with MASLD/MASH for anxiety and depression because having those conditions can make it harder to implement lifestyle modifications. There is also a higher prevalence of disordered eating among children with obesity and overweight, so it is important to screen eating habits before starting treatment, such as a GLP-1 receptor agonist for

obesity. It should also be noted that the guidance does not recommend any dietary supplements, including vitamin E, because of the lack of established evidence of efficacy for the treatment of MASH in children. After seeing information on the Internet, some families have inquired about using curcumin or fish oil, but the practice statement does not recommend them for the treatment of MASLD or MASH in children. There have been instances of drug-induced liver injury related to herbal supplements, so it is important to counsel families not to turn to such treatments.

G&H Are there any other key differences between the pediatric MASH recommendations vs the adult MASH recommendations?

SX The biggest take-home message I want practitioners who see both adults and children with possible MASLD to know is that Fibrosis-4 and Aspartate Aminotransferase–to-Platelet Ratio Index cutoffs do not work in children for detecting significant fibrosis. Additionally, the vibration-controlled transient elastography thresholds that have been developed and validated for adults with MASH to detect fibrosis have not been validated in children and should not be used as cutoffs in children. Although the adult guidance focuses heavily on using these tools in clinical practice for the detection of significant fibrosis, the cutoffs should not be applied to children.

G&H What are the future directions for pediatric MASH?

SX It would be helpful if the medications that are approved for use in adults with fibrotic MASH, such as semaglutide and resmetirom (Rezdiffra, Madrigal), could be studied in children with MASH. Children with MASH can develop progressive fibrosis, and emerging natural history data are showing that the onset of MASH during childhood can increase the risk of early mortality in young adulthood by up to 40-fold, with liver-related causes being the leading cause of death. Therefore, it would be very helpful to know to what degree children might benefit from these treatments and, ultimately, whether implementing them at younger ages would lead to better clinical outcomes and reduce mortality risk as these children become adults. More research is also needed in developing validated noninvasive biomarkers for the detection of MASH and fibrosis in children, as this would help us identify children who are likely to be at higher long-term risk and would accelerate the development of better treatments.

Disclosures

Dr Xanthakos has provided scientific consulting to Novo Nordisk and Madrigal related to the development of treatments for pediatric MASLD.

Suggested Reading

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