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REPLY

Reply to letter to the editor in response to: Distinguishing autoimmune hepatitis from steatohepatitis in adolescents with obesity and positive screening alanine aminotransferase

Amber Hildreth[1,2] | **Jeffrey B. Schwimmer**[1,2]

[1]Department of Pediatrics, Division of Gastroenterology, Hepatology, and Nutrition, University of California San Diego School of Medicine, La Jolla, California, USA

[2]Department of Gastroenterology, Rady Children's Hospital, San Diego, California, USA

Correspondence
Jeffrey B. Schwimmer, Fatty Liver Clinic, Rady Children's Hospital San Diego and UC San Diego, 3020 Children's Way, MC 5030 San Diego, CA 92123, USA.
Email: jschwimmer@ucsd.edu

To the Editor,

We appreciate the opportunity to respond to the Letter to the Editor by Mandato et al. regarding our recent case series on autoimmune hepatitis (AIH) and nonalcoholic steatohepatitis (NASH).[1] We welcome the discussion and address key points raised by the authors.

Our manuscript's focus on AIH should not be mistaken for neglecting other etiologies. We stated that additional causes of elevated alanine aminotransferase (ALT) should be thoroughly evaluated as recommended in the 2017 North American Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines.[2] We highlighted AIH for diagnostic consideration because it is one of the more frequent alternative diagnoses encountered in children with suspected nonalcoholic fatty liver disease (NAFLD), particularly in the context of obesity and elevated ALT.[3] Notably, children with NAFLD may exhibit positive autoantibodies in the absence of AIH, and children with obesity and elevated ALT may have AIH with or without NAFLD. This reality creates the potential for missed or delayed diagnosis and necessitates exploration for AIH in such cases to prevent diagnostic oversight.

Mandato et al. state that "both transaminases and ultrasounds may cause unpredictable false positives and negatives". However, ALT is used as a screening test for NAFLD, not a diagnostic test. The challenges are (1) ALT is nonspecific and thus may uncover conditions other than NAFLD, and (2) there remains uncertainty about the optimal cutoff for ALT. In contrast, ultrasound is commonly used as a diagnostic test but has a performance characteristic of a screening test (sensitivity exceeds specificity). Combining ALT and ultrasound together does not address the broad differential diagnosis for elevated ALT or that ultrasound has a high rate of false positives for the diagnosis of hepatic steatosis. Our case series demonstrated the limitations of this approach, as each of the patients presented had elevated ALT and a positive ultrasound for steatosis, yet each one had different diagnoses. As the approach to NAFLD evolves toward affirmative diagnoses, there will be a growing dependence on imaging to detect steatosis. However, the use of clinical ultrasound is discouraged in both pediatric and adult guidelines due to its poor sensitivity, leading to an excessive number of false positives.[2,4]

The multisociety Delphi consensus group promotes an umbrella diagnosis of steatotic liver disease followed by the assignment of a cause to the etiology of steatosis.[4] For example, the presence of hepatic steatosis plus any cardiometabolic risk factor confers the diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD). This comes from a desire to make a positive diagnosis rather than a diagnosis of exclusion and includes a caveat to consider additional causes of steatosis, however, an evaluation for AIH specifically is not required to meet the diagnosis of MASLD and this

poses a potential risk of missing diagnoses. The international scoring system for AIH requires liver histology and thus does not negate the need for liver biopsy in this clinical setting. All three of our patients had the same AIH score of 3 points before liver biopsy and only separated diagnostically upon review of their histology. In summary, our cases reiterate the need for autoantibody testing in the evaluation of elevated liver chemistry, the inherent limitations of ultrasound as a measure of steatosis, and the need for liver histology when more than one diagnosis is being considered.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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