



Roadmap for evaluation of abnormal liver chemistries

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Clinicians often struggle with the dilemma of how and when to approach a patient with unexplained elevated liver test results. Since this topic was last addressed in 2002, we lack data on the efficacy of evaluation of asymptomatic patients with minimally abnormal liver tests (1). Ever-changing and local lab driven dissimilar ranges for the upper limit of normal (ULN) liver tests contribute to the clinician resorting to use observation of the asymptomatic individual's minimally elevated liver chemistries. Dr. Kwo and colleagues have addressed these gaps in this update of guidelines for the evaluation of abnormal liver chemistries (2). A close look at consultations for abnormal liver tests reveals several points of interest.

Outpatient gastroenterology referrals and inpatient consultations for abnormal liver chemistries are common, with a reported frequency in the range of 5–27% (Table 1). Abnormal liver chemistry referral are third in frequency following the more common GI referrals of abdominal pain and gastrointestinal bleeding and encompasses divergent patient populations in various medical facilities such as Veteran Affairs, community, academic and inner city hospitals (3–8). This article provides important evidence in support of assessing risk for individuals with even minor elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) because of increased liver related mortality risks of 1.21- to 11.2-fold are identified (2,9,10). In a systematic review and meta-analysis by Kunutsor *et al.* (11), it was concluded that there is positive independent associations of baseline levels of gamma glutamyltransferase (GGT) and alkaline phosphatase (ALP) with all-cause mortality. Although many other studies have paradoxically shown that extremely lower baseline

ALT levels predict long-term all-cause mortality among adults (12,13). This discrepancy in the results of these studies could be due to their retrospective nature and other confounding factors such as presence of undiagnosed liver diseases and loss of muscle mass associated with aging.

Time brings clarity to terms such as liver function tests (LFT), primary biliary cirrhosis (PBC), prior to onset of cirrhosis and “normal” ALT. The term LFT for AST and ALT should be phased out and liver chemistries or liver tests should be used. This article emphasizes that liver-derived ALT and AST represent injury rather than function and the spectrum of primary (non-suppurative) biliary disease or PBC should be designated as primary biliary cholangitis.

There is a broad-based desire for better defining, generalizing and unifying the current multiple definitions of normal range for serum ALT among laboratory specialists. This issue has implications as many studies have shown that in patients who have liver disease with normal and near-normal ALT levels carry some risk of disease progression. Previous studies have also grouped patients according to variable ULN cut-offs. This article and its cited references remind us of factors such as age, gender, race, diurnal variation, body mass index (BMI), smoking, alcohol consumption, exercise, and unrecognized presence of underlying liver disease may account for currently variable ranges to ALT normal lab values. Data are discussed and a proposal is made to replace current local lab ULN ranges for ALT with lower normal limit ranges of 29 to 33 IU/L for males and 19 to 25 IU/L for females. If ULN for ALT in men and women is considered to be 33 and 25 IU/L respectively, then many individuals with historically normal transaminases will be considered to have elevated

Table 1 Summary of studies reporting frequency of referral for abnormal liver tests

Author, year	Patient type	Study length (months)	Total number of GI consultations	Number of GI consultations for abnormal LFT (%)
Pancotto, 1981 (3)	Inpatient	12	902	144 (18.0)
Bohra, 2003 (4)	Inpatient	5	242	24 (10.0)
Cai, 2003 (5)	Inpatient	12	1,080 (in 1988)	289 (26.8)
	Inpatient	12	1,267 (in 1998)	203 (16.0)
Day, 2010 (6)	Inpatient	23	278	35 (12.6)
Saha, 2011 (7)	Clinic, pregnant	36	406	36 (8.9)
Zambrana-García, 2016 (8)	Clinic	4	138	7 (5.0)

GI, gastrointestinal; LFT, liver function tests.

levels and many of these individuals will need further hepatological work-up. Clarity in defining the appropriate range of normal ALT and AST with availability of larger datasets is now possible. These datasets will refine, redefine and confirm this proposal of universally accepted ULN values with confidence. The guidelines go farther than those in the past to recommend evaluation of patients with $<2\times$ ULN of ALT as “borderline elevation” with distinct assessment recommendations. It begins with the category of $<2\times$ ULN compared with previous recommendations starting at $<5\times$ ULN. With advent of obesity epidemic, another addition to Kwo *et al.* article’s *Figure 1* on algorithm for evaluation of AST and/or ALT could be to change the word “assess” to “identify and initiate” weight loss strategies. Given what we have learned from asymptomatic Hepatitis C infected individuals, the time and tools to evaluate this lower threshold for abnormality has arrived. Using the first encounter with the patient as an opportunity to educate them in behavior and lifestyle modification will involve them in seeking to improve the abnormal test results in the 3–6 months follow-up.

Another important issue on which authors could have commented on was low levels of transaminases in patients with end stage renal disease (ESRD) on hemodialysis (HD) which occurs due to hemodilution and pyridoxine deficiency. It has also been shown that hemodialysis decreases hepatitis C viral load and influences production of hepatocyte growth factor and alpha interferon, and accelerates lymphocyte activation. In these patients, the degree of transaminitis does not correlate to liver injury. Therefore, a minimal transaminase elevation in patients on hemodialysis should prompt the physicians to perform liver injury evaluation. However, these findings have not been

verified in large scale studies and reporting authors did not consider loss of muscle mass in chronic dialysis patients due to nitrogen imbalance (14).

This article follows a trend seen in other guidelines and opens with a table guideline of key recommendations, so that the reader may rapidly review pertinent points for each individual case. Of note, all of these recommendations should be considered with discretion and individualized when faced with a patient referred for deranged liver tests, as they are strongly recommended but with very low level of supportive evidence. Clearly, in the absence of appropriate and high quality evidences, these are “Practice-based practice guidelines” which are generated from accumulation of knowledge gained by clinical practice over decades. Undoubtedly, additional further high quality data will be published in literature because of recognized vacuum of studies and we might expect modification of these guidelines in the near future. The final recommendation demands astute recognition of a patient in need. Emphasis on early recognition of signs of liver failure as unexplained prolongation of prothrombin time, new onset hepatic encephalopathy, with abnormal liver enzymes should trigger liver transplantation evaluation in the appropriate setting. This is emphasized in this publication with inclusion in evaluation schemes for moderate, severe and massive LFT elevations.

One might be tempted to consider using this publication as a side step to ask for a consult. There is no match for the wealth of knowledge and clinical acumen that sifts through this broad reaching topic to bring insight into the ranking of possible diagnoses and timely management recommendations.

These guidelines are strengthened by consensus of

the three seasoned hepatologists and the review of other gastroenterologists. This commentary puts forth that it is a current roadmap with strong recommendations yet very low evidential support level. It reveals that there is more work before us to do to address our lack of understanding on this topic.

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