Evaluating Primary Care Providers' Responses to Serum Alanine Aminotransferase Elevations

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Elevations in serum ALT levels—even when mild and intermittent—can signal serious liver disease. These investigators examine whether clinicians at one VA medical center are recognizing the danger and taking appropriate action.

Measurement of a patient's serum alanine aminotransferase (ALT) level is the most sensitive laboratory test for hepatocellular injury.[1,2] Consequently, ALT measurements are routinely performed to assess liver function in patients with symptoms suggestive of hepatobiliary tract disease and to identify liver inflammation in asymptomatic patients.[3–5] Less recognized, however, is the fact that even mild, intermittent elevations in serum ALT levels can indicate potentially life threatening liver problems.

Such elevations may be caused by an ongoing inflammatory reaction in the liver, which can lead, ultimately, to liver cirrhosis and hepatocellular carcinoma. This process has been well described in the context of chronic hepatitis C virus (HCV) infection.[6,7] Other potential causes of subtle ALT elevations include chronic hepatitis B virus (HBV) infection, chronic alcohol use, use of medications with hepatotoxic effects, chronic exposure to other hepatotoxins, autoimmune hepatitis, Wilson disease, alpha-1-antitrypsin deficiency, and celiac disease. Recently, subtly increased serum ALT levels have been observed in patients with nonalcoholic fatty liver disease (NAFLD), which encompasses a wide range of conditions involving the accumulation of fat in hepatocytes.[8,9] Early recognition of NAFLD may become increasingly important in the United States as the rapidly advancing obesity epidemic continues to boost the number of patients with metabolic syndrome,[10,11] the most common cause of NAFLD.[12,13]

In light of these facts, it is clear that any serum ALT measurement above normal limits should be taken seriously and should prompt an investigation to determine the etiology. A casual, ongoing review of patient records at the Samuel S. Stratton VA Medical Center (Stratton VAMC), however, began to raise concerns about inadequate primary care follow-up of serum ALT elevations at this facility. This review suggested that primary care providers (PCPs) frequently were performing incomplete workups for ALT elevations, if at all. Furthermore, it appeared that PCPs rarely—if ever—considered NAFLD, secondary to metabolic syndrome, as a potential cause of serum ALT elevations.

To investigate the matter further, we conducted a formal review of the medical records of 500 Stratton VAMC patients who had documented ALT elevations in 2001. We sought to determine whether, over the two years that followed, these patients' PCPs had performed an appropriate workup and arrived at a diagnosis (or diagnoses) to explain the elevation. Additionally, we attempted to ascertain whether the PCPs had recognized cases in which patients were likely to have NAFLD secondary to metabolic syndrome.

DEFINING THE APPROPRIATE WORKUP

When a patient's serum ALT level is found to be elevated and there is no previously diagnosed condition to explain such an elevation, the PCP's first step should be to elucidate a thorough patient history, including risk factors for common diseases affecting the liver and assessment of alcohol intake, illicit drug use, and use of potentially hepatotoxic medications (Table 1). A comprehensive physical examination should follow, including measurement of body mass index (BMI) or waist circumference.

Initial laboratory testing should include HCV antibodies, HBV surface

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antigen (HBsAG) and HBV core antibody (HBcAB), and studies of iron metabolism (to evaluate for hemochromatosis and iron overload). It is also helpful, especially if the patient is found to be overweight (BMI greater than 25) or obese (BMI greater than 30), to obtain a fasting glucose or hemoglobin A_{1c} (HbA_{1c}) level and a lipid profile in order to investigate the possibility of metabolic syndrome–related NAFLD.

Patients who test positive for HCV antibodies require further testing for the presence of HCV RNA (through the polymerase chain reaction method) to determine whether there is active, chronic infection. Those who test positive for HBsAG should receive further HBV serologic testing, including HBV DNA. In addition, it is generally recommended that patients who have tested positive for either HCV or HBV be offered HIV testing, since the diseases are transmitted through similar routes and coinfection is common.

An imaging study of the liver—preferably ultrasound—should complete the workup. This helps establish or rule out hepatomegaly, steatosis, or a biliary etiology.

When these studies fail to reveal a plausible cause for the ALT elevation, it is appropriate to consider other, less common liver diseases (such as autoimmune hepatitis and Wilson disease) and to obtain a gastroenterology consultation for possible liver biopsy. Patients who are diagnosed with a treatable condition (such as HCV, HBV, hemochromatosis, or autoimmune hepatitis) should be referred to gastroenterology or an appropriate specialty clinic for treatment.

Table 1. Medications known to cause elevations in serum alanine aminotransferase levels

- Acetaminophen
- Alpha-methyldopa
- Amoxicillin-clavulanic acid
- Amiodarone
- Carbamazepine
- Dantrolene
- Diltiazem
- Disulfiram
- Fluconazole
- Glipizide
- Glyburide
- Heparin
- 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins")
- Isoniazid
- Ketoconazole
- Labetalol
- Metformin
- Nicotinic acid
- Nitrofurantoin
- Nonsteroidal anti-inflammatory drugs
- Pioglitazone
- Phenylbutazone
- Phenytoin
- Prednisone
- Rosiglitazone
- Propylthiouracil
- Protease inhibitors
- Sulfonamides
- Trazodone
- Valproic acid
- Zafirlukast

STUDY DESIGN AND METHODS

An initial search showed that, between January 2001 and December 2001, 2,315 patients at the Stratton VAMC had one or more serum ALT level above the normal range (25 to 65 U/L) documented in their records by PCPs. Of these patients, we selected the first 500, alphabetically according to last name, for our chart audit. The protocol was approved by the medical center's Institutional Review Board and Research and Development Committee.

In order to exclude any patients whose ALT elevation might be explained by a previously diagnosed condition, we reviewed diagnosis lists and provider notes in the charts. For those whose ALT elevation could not be attributed to a previously diagnosed condition identified in the chart, we assessed the workup, diagnoses, and follow-up documented in the chart by the PCP.

We collected information on patient history (including questions about alcohol use); diagnoses; BMI and other relevant physical examination findings; medications; relevant diagnostic tests, such as blood chemistries, complete blood cell count, tests for HBV and HCV, copper studies, iron studies, antinuclear antibody assays, and imaging studies; and any assessment for NAFLD. We also checked to see if patients were referred to gastroenterology and if a liver biopsy was performed. We used a checklist to collect these data, and we included all relevant data recorded in the charts from January 1, 2001 through December 31, 2003 in order to provide for adequate follow-up time subsequent to the detection of elevated ALT levels.

In assessing whether PCPs appropriately identified patients with likely metabolic syndrome, we used criteria based on those established by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults—known commonly as the Adult Treatment Panel (ATP) III (Table 2).[14] Because measurements of patients' waist circumference were not available, however, we used a BMI of 30 or greater as a surrogate marker of abdominal obe-

Table 2. Criteria for identifying the metabolic syndrome, as established by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults[14]

Definitive metabolic syndrome
- Frank type 2 diabetes

Likely metabolic syndrome (at least three of the following)
- Abdominal obesity: waist circumference > 40 in for men or > 37 in for women[a]
- Triglyceride level > 150 mg/dL (fasting value)
- High-density lipoprotein cholesterol level < 40 mg/dL for men or < 50 mg/dL for women
- Blood pressure > 130/85 mm Hg
- Glucose intolerance: fasting glucose > 120 mg/dL or hemoglobin A_{1c} level > 6.6%

[a]In the present study, waist circumference measurements were not available, and a body mass index of 30 or greater was used as a surrogate marker of abdominal obesity.

Table 3. Classification of 500 patients with elevated serum ALT[a] levels documented during 2001 who were selected for chart audit

Patient group	No. (%) of patients	Mean (SD) elevated serum ALT level	Range of elevated serum ALT levels
Group A (positive HCV[b] antibodies)	129 (26%)	152 (155) U/L	67–593 U/L
Group B (negative or unknown HCV antibodies)	320 (64%)	101 (56) U/L	68–248 U/L
Excluded due to conditions with secondary liver effects	30 (6%)	129 (124) U/L	68–745 U/L
Excluded due to lack of data	21 (4%)	97 (47) U/L	66–147 U/L

[a]ALT = alanine aminotransferase. [b]HCV = hepatitis C virus.

sity (though this practice has not been validated). The lipid levels collected, when available, included serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides. Additionally, we collected all available fasting serum glucose or HbA_{1c} levels. In assessing alcohol use, we defined excessive use as greater than 210 g/wk for men or greater than 140 g/wk for women.[15]

STUDY PATIENTS

After reviewing the charts of 500 patients with at least one serum ALT level above the normal range of 25 to 65 U/L, we excluded 51 patients (Table 3). Of these, 30 had previously diagnosed conditions with known secondary effects on the liver that could have accounted for the ALT elevation. These 30 patients had a mean (SD) elevated serum ALT level of 129 (124) U/L. Fourteen of these patients had various cancers, including lung and renal cancer, with evidence of metastatic disease to the liver; nine had acute illnesses, such as severe sepsis or pneumonia; four had choledocholithiasis; two had acute pancreatitis; and one was believed to have acute drug-induced liver failure.

The other 21 patients excluded were all enrolled in drug rehabilitation programs. For this reason, we did not have access to their provider notes. These patients had a mean (SD) elevated serum ALT level of 97 (47) U/L.

The remaining 449 patients included in the study were divided into two groups based on the results of HCV antibody testing. Group A consisted of the 129 patients who tested positive for HCV antibodies, and Group B consisted of the 320 who either tested negative or were not tested for HCV antibodies (thus, their HCV antibody status was unknown).

We felt it would be useful to divide the study patients into these two groups because the increased prevalence of HCV among veterans makes it probable that undiagnosed chronic infection would account for a substantial number of the ALT elevations in this population. By separating out those whose ALT elevations most likely resulted from HCV infection (Group A), we could focus on how well PCPs evaluated other possible causes of ALT eleva-

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tion in Group B. Since not all patients in Group A would have active HCV infection, and since multiple comorbidities could exist in these patients, however, we looked at the entire spectrum of evaluations performed in Group A as well.

PRIMARY CARE WORKUPS

Group A

The 129 patients in Group A had a mean (SD) age of 52 (13.2) years, and 124 (96%) of them were male. The group had a mean (SD) elevated serum ALT level of 152 (155) U/L.

We found documentation of HCV RNA testing in the records of 80 (62%) of the Group A patients—of whom 75 tested positive, confirming active, chronic HCV infection (Figure 1). Among the patients with confirmed active infection, 52 (69%) had the HCV genotype established.

Ninety-six (74%) of the 129 Group A patients had records indicating that they were tested for coinfection with HBV. The majority of these patients, however, received an incomplete HBV evaluation, as they were tested only for HBcAB and not for HBsAG. Only 37 patients (28% of the total group) received both HBV tests, and active infection was confirmed in seven of these patients (5% of the total group).

An additional seven patients (5%) were tested for HIV coinfection—all of whom tested positive. The rarity with which HIV evaluation was performed in Group A was mainly attributable to patients' refusal to undergo testing. No Group A patients were found to be coinfected with all three viruses (HCV, HBV, and HIV).

Records indicated that 29 Group A patients (22%) had iron studies performed. Results were normal for all patients tested. No patients were tested for Wilson disease or autoimmune hepatitis.

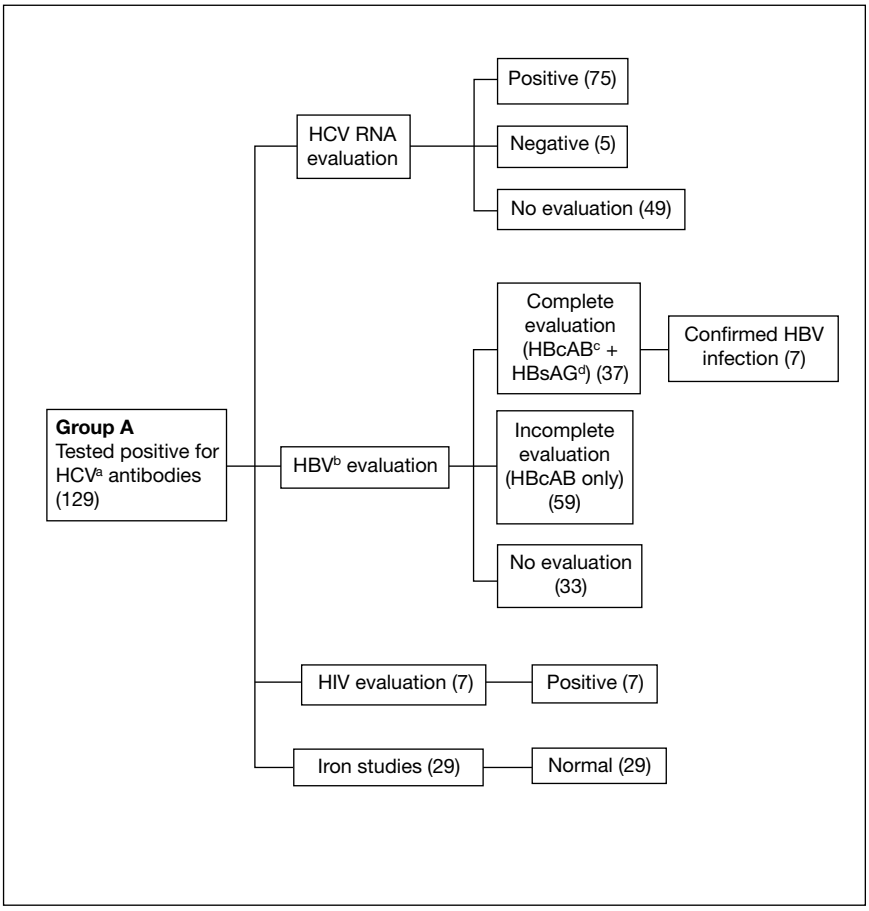

Figure 1. Diagnostic laboratory workup in the 129 study patients who tested positive for HCV antibodies (Group A). No patients were tested for Wilson disease or autoimmune hepatitis. [a]HCV = hepatitis C virus. [b]HBV = hepatitis B virus. [c]HBcAB = HBV core antibody. [d]HBsAG = HBV surface antigen.

Provider notes suggested that alcohol use was considered a likely contributor to ALT elevation in 59 (46%) of the Group A patients. None of these patients' records, however, contained quantification of daily or weekly alcohol consumption.

Group A patients had a mean (SD) BMI of 28.6 (6.1), and 45 patients had a BMI of over 30. Using the modified ATP III criteria, we found evidence indicating likely metabolic syndrome in 27 patients (21%), and another 19 (15%) had documented type 2 diabetes. As such, NAFLD was possible in a substantial number of Group A patients—yet none had records suggesting that primary care providers had considered the condition as a potential cause of ALT elevation.

We found documentation of liver imaging with either ultrasound or computerized tomography (CT) for 53 Group A patients (41%). A total of 43 patients (33%) had documentation of referral for gastroenterology consultation, 35 of whom had a percutaneous liver biopsy and five of whom refused liver biopsy.

Overall, based on our records review, only 19 (15%) of the patients in Group A received a complete labora-

tory workup (HCV antibodies, HCV RNA, HBcAB, HBsAG, and iron studies), and only 10 (8%) had a complete laboratory workup plus a liver imaging study. In many Group A patients, especially the five who tested negative and the 49 who were never tested for HCV RNA, further workup for other possible causes of elevated ALT was indicated. Yet records do not show that other causes were aggressively pursued, and the possibility of NAFLD appears not to have been entertained by any PCPs.

Group B

The 320 patients in Group B had a mean (SD) age of 58.3 (13.2) years. As in Group A, the vast majority (305, or 95%) were male. The mean (SD) elevated serum ALT level for the group was 101 (56) U/L.

Of the Group B patients, 209 (65%) tested negative for HCV antibody, while the other 111 (35%) had no documentation of HCV antibody testing (Figure 2). A total of 145 patients (45%) were tested for HBV infection, 45 of whom received both HBcAB and HBsAG testing. Active infection was confirmed in one patient (0.3% of the total group).

No patients in Group B had documentation of HIV testing. Iron studies were performed for 36 (11%) of the Group B patients, two of whom tested positive for hemochromatosis (0.6% of the total group). Eighteen patients (6%) had documentation of testing for autoimmune hepatitis. In one of these patients, the diagnosis was supported by positive serology (antinuclear and smooth muscle antibodies) and confirmed through liver biopsy. No patients in Group B had records indicating that they were tested for Wilson disease.

Provider notes suggested that PCPs considered the possible role of alcohol use in the ALT elevation for 125 (39%) of the Group B patients and determined this factor to be a likely contributor in 24 patients (8%). Although aminotransferase levels tended to be higher, overall, in the 24 patients in whom alcohol use was considered a likely contributor to ALT elevation, compared with the rest of Group B, only seven of these patients had the ratio of aspartate aminotransferase/ALT levels of greater than 2 that typically is observed in alcoholic liver disease.[16] As in Group A, patients' records did not quantify daily or weekly alcohol use.

A total of 181 Group B patients (58%) had a BMI of at least 30. Of these patients, 85 (47%) had type 2 diabetes. Overall, 192 Group B patients (62%) met the modified ATP III criteria for metabolic syndrome. As in Group A, however, PCPs appear not to have considered NAFLD as a possible cause of ALT elevation. In the 39 cases in which liver imaging confirmed fatty liver, the PCP seems not to have recognized its relationship to insulin resistance.

CT or ultrasound of the liver was performed for 81 Group B patients (25%). Only 18 patients (6%) were referred for gastroenterology consultation, and 12 of these underwent percutaneous liver biopsy.

Overall, only 22 patients in Group B (7%) appear to have received a full

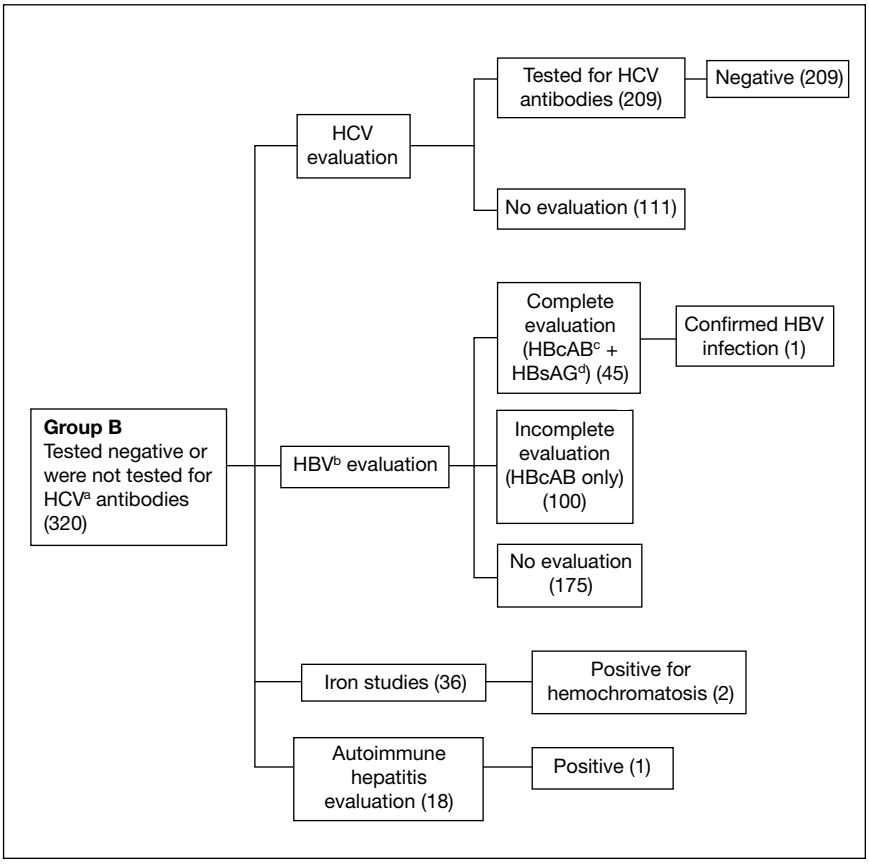

Figure 2. Diagnostic laboratory workup in the 302 study patients who either tested negative or were not tested for HCV antibodies (Group B). No patients were tested for HIV or Wilson disease. [a]HCV = hepatitis C virus. [b]HBV = hepatitis B virus. [c]HBcAB = HBV core antibody. [d]HBsAG = HBV surface antigen.

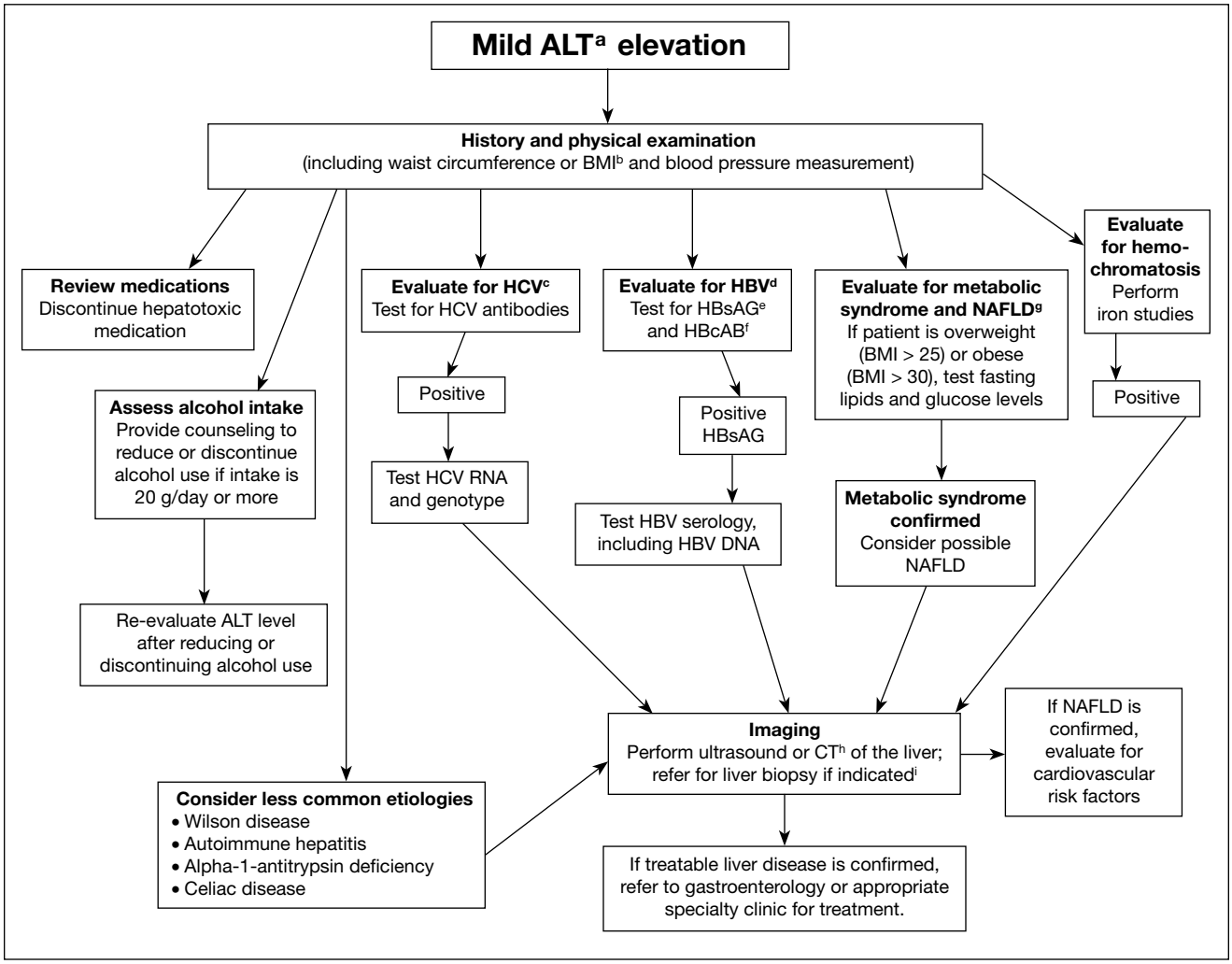

Figure 3. Suggested initial diagnostic algorithm for a patient with mild ALT elevation. Even if one component of the workup yields a possible cause of the abnormality, other components should be completed to make sure any comorbidities are identified. [a]ALT = alanine aminotransferase. [b]BMI = body mass index. [c]HCV = hepatitis C virus. [d]HBV = hepatitis B virus. [e]HBsAG = HBV surface antigen. [f]HBcAB = HBV core antibody. [g]NAFLD = nonalcoholic fatty liver disease. [h]CT = computed tomography. [i]When diagnosis is unclear or disease stage needs to be defined.

laboratory workup (HCV antibodies, HCV RNA, HBcAB, HBsAG, and iron studies), and none had a complete laboratory workup plus a liver imaging study. Although not complete, the workup could be considered acceptable in six Group B patients, in that it included an imaging study and it resulted in a diagnosis that could have explained the ALT elevation (autoimmune hepatitis in one patient, steatosis in two, chronic HBV infection in one, and hemochromatosis in two). In 92 Group B patients (29%), on the other hand, there were insufficient data on chart review to even speculate about the cause of the ALT elevation. Because some patients were not evaluated for chronic HCV or HBV, it is quite possible that chronic viral hepatitis could have been the unrecognized cause of ALT elevation.

ADDRESSING THE GAPS

At the Stratton VAMC, serum ALT measurement has been included in a panel of blood chemistries that is used frequently by PCPs to screen for liver diseases. This was the case for at least two years prior to 2001, the year selected for our review. Nevertheless, this formal review confirmed our earlier observations that PCPs at this facility often investigate serum

ALT elevations inadequately. Thus, it is likely that many patients with potentially progressive liver disease are not diagnosed accurately or treated promptly—a possibility that is especially concerning for patients with HCV.

Additionally, it appears that PCPs may not be aware of the connection between metabolic syndrome and NAFLD and, as a result, may be missing opportunities to treat associated cardiovascular disease in patients with NAFLD resulting from this syndrome. Although no patients in our study were tested for Wilson disease, and very few were tested for autoimmune hepatitis, this may have been appropriate given the age and characteristics of our study population. Evaluation for these conditions may be performed more commonly by gastroenterologists than by PCPs.

Our study suggests that PCPs may be inclined to disregard mild ALT elevations, especially when repeated testing yields results within the normal range. Subtle ALT elevations often can fluctuate back into the normal range, despite ongoing disease in the liver, however. As such, the finding of a normal serum ALT level following an elevated level does not render the elevated measurement clinically insignificant. Even in such cases, clinicians should investigate the cause of the elevation, considering the entire spectrum of hepatocellular diseases.[3–5,17]

Evaluating for HCV

Our data indicate that, despite ongoing VA efforts to raise awareness of the increased prevalence of chronic HVC infection among veterans and the resulting need for heightened vigilance and screening in this population,[18] many PCPs do not fully appreciate the sensitivity of the serum ALT level in signaling possible HCV infection. In fact, significant liver pathology has been noted in patients with HCV who have only minimally elevated—or even normal—serum ALT levels.[6,7] Chronic HCV can progress slowly and silently for years before the patient develops symptoms and signs of liver damage.

Thus, any elevation of ALT, no matter how subtle, should prompt PCPs to consider HCV—particularly when the patient history includes HCV risk factors. In our study, however, one quarter of the patients had no record of HCV screening over the three year period covered in the chart audit. Even more alarming was the finding that only 62% of the patients who tested positive for HCV antibodies had documented testing for HVC RNA—the essential next step in confirming active infection.

Considering the role of alcohol

Another troubling finding in our study was the dearth of evidence indicating that PCPs had vigorously pursued the possibility of alcohol abuse in patients with ALT elevations. References to alcohol use in the provider notes were vague (using such terms as "heavy," "often," "binge drinking," or "weekend use"), and no patient charts contained precise quantifications of the amount of alcohol used daily or weekly. Consuming as little as 20 g of alcohol per day (roughly the equivalent of two drinks) increases the risk of developing significant liver disease.[15] It is important, therefore, for clinicians to counsel patients who regularly consume alcohol at this level about the need to reduce or discontinue alcohol intake. Moreover, since alcohol consumption generally accelerates the rate of liver damage associated with chronic viral hepatitis, it is prudent to encourage patients with these diseases to avoid alcohol altogether.

Recognizing NAFLD and its implications

Substantial evidence has shown insulin resistance—the defining feature of metabolic syndrome—to be the most common cause of NAFLD.[19–21] Obesity, in turn, has been recognized as a major contributing factor in the development of insulin resistance.[10,13] About half of the patients in our study were obese and many had other features of metabolic syndrome, suggesting the likelihood that NAFLD contributed to ALT elevation in a substantial proportion of the population (especially in Group B).

This finding mirrors a recent study, in which the majority of elevated ALT levels could not be explained by alcohol consumption, viral hepatitis, or hemochromatosis.[22] These unexplained elevations were significantly associated with features of metabolic syndrome (higher BMI, waist circumference, triglyceride levels, and fasting insulin levels and lower high-density lipoprotein levels), indicating possible NAFLD.[22]

The failure of PCPs in our study to recognize the possible role of NAFLD in elevated ALT levels is of concern. While the relationship between metabolic syndrome and NAFLD was not well known in 2001, the index year for elevated ALT levels in our study, it was described frequently in medical literature during the subsequent two years of follow-up included in the review period.[19–21]

The presence of NAFLD has broad implications for patient care. In some patients, this condition is progressive and leads eventually to cirrhosis of the liver or hepatocellular carcinoma. In addition, since NAFLD is very often secondary to the metabolic syndrome, the condition puts patients at higher risk for developing cardiovascular disease.[20,21] For this reason, patients in whom NAFLD is suspected

or confirmed should have fasting blood samples tested for evidence of glucose intolerance or abnormalities of circulating lipids that would require treatment. Hypertension, which is also part of the metabolic syndrome, should be treated aggressively in these patients as well.

While there are treatments available to manage most of the health problems caused by the metabolic syndrome, no medications have been shown to be effective in the specific treatment of NAFLD. It is generally recommended that patients be advised to limit alcohol intake to less than 20 g/day, to avoid medications known to cause fatty liver, and to follow a plan of dietary restriction and exercise.[23] (Dietary restriction without increased exercise appears to have little benefit in NAFLD.[20,21]) It is also important to treat comorbid conditions (such as diabetes, hypertension, and hyperlipidemia) properly in these patients. When all of these measures prove insufficient in morbidly obese patients, bariatric surgery frequently can reverse all problems related to insulin resistance, including NAFLD.[24,25] Given the risks inherent to such an invasive procedure, however, more effective pharmacologic options for managing NAFLD are highly desirable.

STUDY LIMITATIONS

Our data reflect a special population: veterans, who are predominantly male, older, and have a higher prevalance of drug and alcohol abuse and of certain medical conditions compared with the general population. For this reason, the ability to generalize our findings is limited. One could speculate that the results might be similar in a busy, private primary care practice and that subtle ALT elevations are often ignored regardless of the health care setting, but these speculations should be confirmed through further study. In addition, our retrospective review was limited somewhat by incomplete documentation of data by PCPs (such as the lack of waist circumference measurements), as well as by the subjective nature of some documentation (for example, the informal assessment of alcohol use).

NEED FOR GUIDANCE

PCPs play an important role in identifying risk factors for liver disease. When routine blood testing reveals a mildly elevated serum ALT level that can't be explained by the patient's current diagnoses, there is a temptation to ignore the isolated abnormality or to repeat the test, suspecting a laboratory error, and then disregard the elevation if the second measurement is found to be within normal limits. Giving in to such temptation, however, can allow subtle but progressively damaging liver disease to go undiagnosed and untreated, potentially leading to dire consequences for the patient. Responding promptly to ALT elevation with a thorough investigation into the possible causes, on the other hand, may allow for early recognition of treatable diseases and, thus, prevention of serious complications.

The results of this study identify a clear need to educate PCPs about the appropriate response to subtle or intermittent ALT elevations in their patients. Algorithms to guide the workup of elevated ALT levels, however, are scarce in medical literature.[26,27] We have developed an algorithm that summarizes the ideal workup with a particular focus on the veteran population (Figure 3). We plan to use this algorithm, along with the results of this study, to raise awareness of the problem among PCPs in our institution. In addition, we expect to follow-up within a year of these efforts with another chart review. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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