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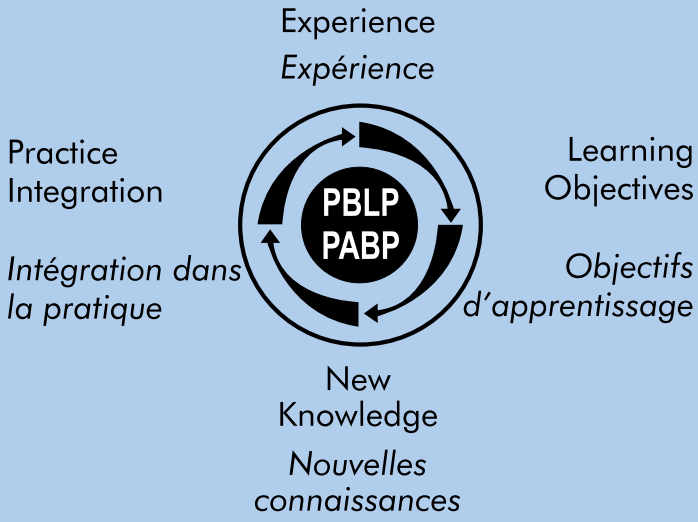

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LIVER ENZYMES: HANDLING ABNORMAL RESULTS

Although elevated liver enzymes are often encountered in the primary care setting, interpreting these results can be a challenge, particularly for asymptomatic patients or those with vague systemic complaints. A rational approach to evaluation of elevated liver enzymes can guide follow-up testing, and facilitate diagnosis and treatment.

This module will enable clinicians to:

- identify risk factors and predisposing conditions for liver disease to determine when testing is needed.
- develop a rational approach to dealing with liver enzyme abnormalities, recognizing that some elevations may arise from non-hepatic sources.

Notes:

- It is important to recognize that liver enzyme tests are not tests of liver function. The commonly tested liver enzymes (AST, ALT, GGT, and ALP) actually do not measure or correlate well with liver function and metabolic activity. 'Liver function tests' include direct bilirubin, INR and albumin.
- This module focuses on "liver enzyme tests" and will be used as the preferred term throughout.
- The reference ranges ("normal values") for various investigations are those used by the Medical Council of Canada. In practice, these values may vary between different laboratories.

CASES

Case 1: Wendy, female, age 55

Wendy sees you for follow-up of her hypertension and elevated lipids. She is feeling well. She has been on ramipril 10 mg po daily and atorvastatin 20 mg po daily for over five years. Wendy smokes cigarettes and admits to drinking about 14 alcoholic drinks/week. She has had a cholecystectomy. Her BMI is 28. Physical exam is normal. Her last blood work was approximately one year ago.

Which tests would you order and why?

Part Two

Her labs results are as follows:
- AST: 221 U/L (0–35 U/L)
- ALT: 100 U/L (3–36 U/L)
- GGT: 96 U/L (10–30 U/L)
- Creatinine: 88 µmol/L (50–90 µmol/L)
- Lytes normal
- Fasting blood sugar: 4.0 mmol/L (3.3–5.8 mmol/L)
- LDL 2.0 mmol/L: (< 3.37 mmol/L)
- HDL 1.2 mmol/L: (> 0.9 mmol/L)
- TG 1.4 mmol/L: (< 2.20 mmol/L)
- Total cholesterol 4.12 mmol/L: (< 5.2 mmol/L)

What further information would be helpful for you to know?

Part Three

She is taking no OTC meds. She mentions that her brother has hepatitis C, but she has not lived with him since they were children and she has never shared any personal items (e.g., razors) with him. She has no other risk factors for liver disease. Previous liver enzymes were within the normal range. Physical exam is negative for signs of liver disease.

What would be your next step?

Part Four—Eight weeks later

Wendy went for repeat labs and the results reveal:
- AST: 1436 U/L (0–35 U/L)
- ALT: 588 U/L (3–36 U/L)
- ALP: 348 U/L (35–100 U/L)
- GGT: 294 U/L (10–30 U/L)
- Anti-HBsAb: neg
- Anti-HCV Ab: neg
- Anti-HAV Ab IgG present but anti-HAV Ab IgM absent (i.e., immunity to Hep A but no active infection)

You call and ask her if she has started any new medications or herbals, which she denies. You reinforce the importance of abstaining from alcohol and also ask her to temporarily hold her atorvastatin while you further investigate her liver abnormalities. Results of further blood work the following week are:
- AST: 1165 U/L (0–35 U/L)
- ALT: 593 U/L (3–36 U/L)
- ALP: 493 U/L (35–100 U/L)
- Total bilirubin: 154 µmol/L (< 26 µmol/L)
- GGT: 219 U/L (10–30 U/L)
- Ferritin: 1993 µg/L (10–250 µg/L), transferrin saturation 77%
- CBC: Hb 144 g/L (123–157 g/L), WBC 4.7 X 10^9/L (4-10 X 10^9/L), platelets 78 X 10^9/L (130–400 X 10^9/L)
- ANA: positive, speckled pattern > 1:640

Physical exam now reveals jaundice and suggests mild ascites.

What would be your management at this point?

Case 2: Edward, male, age 61

Edward sees you at a regular follow up for his type 2 diabetes and hypertension. His medication includes metformin 500 mg po bid, enalapril 10 mg po daily, and amlodipine 10 mg po daily. His BP is 130/80; BMI 42. Physical exam is normal. Recent lab results are:
- Fasting blood sugar: 7.6 mmol/L (3.3–5.8 mmol/L)
- HbA1c: 7%
- Cholesterol: 4.51 mmol/L (< 5.2 mmol/L)
- HDL: 1.01 mmol/L (> 0.9 mmol/L)
- LDL: 2.81 mmol/L (target goal for type 2 diabetes: < 2.0)
- Triglycerides: 1.51 mmol/L (< 2.20 mmol/L)
- Creatinine: 72 µmol/L (70–120 µmol/L)
- Sodium: 143 mmol/L (135–145 mmol/L)
- Potassium: 4.0 mmol/L (5–5.0 mmol/L)
- ACR: 0.8 (< 2.0 mg/mmol for males)

What additional investigations would you order and why?

Part Two

His results are:
- AST: 115 U/L (0–35 U/L)
- ALT: 176 U/L (3–36 U/L)
- ALP: 105 U/L (35–100 U/L)
- GGT: 131 U/L (10–35 U/L)

What further information would be helpful to know?

Part Three

Edward denies any alcohol, OTC medications or infectious hepatitis risks. There is no family history of liver disease. Physical exam is normal – he has no RUQ tenderness or jaundice.

What would you do next?

Part Four—Three months later

The results from the repeat labs at three months:
- AST: 101 U/L (0–35 U/L)
- ALT: 184 U/L (3–36 U/L)
- ALP: 127 U/L (35–100 U/L)
- GGT: 136 U/L (10–35 U/L)
- Total bilirubin: 4 µmol/L (< 26 µmol/L)
- HBsAg: neg
- Anti-HBs Ab: neg
- Anti-HBc Ab: neg
- Anti-HCV Ab: neg
- Ferritin: 658 µg/L (10–250 µg/L)
- Transferrin saturation: 28%
- Albumin: 41 g/L (35–50 g/L)
- ANA: neg

Ultrasound shows hepatomegaly with severe fatty infiltration.

What would be your next steps?

Case 3: Carole, female, age 47

Carole is seen for right upper quadrant pain. She has been experiencing this pain on a daily basis. It does not seem related to meals, nor is it accompanied by a fever. The pain usually is mild-to-moderate in intensity, but is more severe today. She has a past history of depression, generalized anxiety disorder, GERD, and chronic low back pain. She has had a cholecystectomy. She is currently taking omeprazole 20 mg po daily. Physical exam indicates right upper quadrant tenderness, but no rebound, negative Murphy's, no palpable masses or ascites, and no jaundice or other stigmata of liver disease.

Carole admits to drinking alcohol on a regular basis, as much as 4–5 drinks on "bad days" to cope with her anxiety. She occasionally takes acetaminophen for pain. She denies current or past history of illicit drug use. She has never had any blood transfusions or tattoos.

Her lab results are:
- CBC, lipase, creatinine, electrolytes: normal
- ALT: 73 U/L (3–36 U/L)
- AST: 32 U/L (0–35 U/L)
- ALP: 183 U/L (35–100 U/L)
- GGT: 275 U/L (10–30 U/L)

How would you manage Carole?

INFORMATION SECTION

LIVER ENZYME TESTS: WHEN TO ORDER

1. There is scant evidence to guide the ordering of liver enzyme tests. Liver enzyme tests should be ordered in a directed manner based on a suspicion of liver disease.[1] Non-directed or routine ordering of liver enzyme screening panels is discouraged, as there is no evidence to support routine screening of asymptomatic patients with no risk factors (Table 1).[1,2]

2. Liver enzyme tests sometimes are indicated for monitoring patients taking hepatotoxic drugs (Appendix 1).[3]

   Clinical Note: In 2012, the FDA declared that "routine periodic monitoring of liver enzymes" is ***not*** necessary for patients taking statins since the reported incidence of statin-induced liver failure is only about one case per million person-years of use. It is now recommended that liver enzymes be checked one time before initiating a statin or if a patient has any symptoms of possible liver enzyme elevation/failure (e.g., unexplained nausea, loss of appetite, jaundice, severe lethargy or abdominal pain).[4] This recommendation is consistent with the recent 2012 update of the Canadian Cardiovascular Society guidelines for dyslipidemia that states that there is no indication for routine repeat measures of ALT in patients using statins unless symptoms develop.[5]

ELEVATED LIVER ENZYMES: NEXT STEPS

The key steps in evaluating elevated liver enzymes are outlined in the algorithm in Appendix 2. The information in the following section is intended to complement and expand on this algorithm.

History

3. A detailed history involves an assessment of risk factors for liver disease (Table 1).

4. The epidemiology of liver disease may vary by the demographics of the patient population. Inquiry about patient's recent travel history is also important. This information can "identify likely causes and reduce the number of unnecessary tests and amount of time needed to make a diagnosis."[7] A "fast and frugal" approach for diagnosing cases of viral hepatitis recommends testing:
   - all patients with a high risk of infection (e.g., evidence of IV drug use)
   - all patients who originated from countries where viral hepatitis is prevalent
   - patients who have an ALT level that is more than twice the upper limit of normal[8]

   Note: Public Health typically distributes information about local infectious outbreaks. For worldwide prevalence rates, the Center for Disease Control and Prevention (CDC) provides charts for:
   hepatitis A: http://www.cdc.gov/travel/pdf/yellowbook-2012-map-03-03-estimated-prevalence-hepatitis-a.pdf
   hepatitis B: http://www.cdc.gov/hepatitis/populations/api.htm

Physical

5. Perform a physical exam to identify any signs or symptoms of liver disease:
   - acute changes: jaundice, abdominal pain/fever (if acute right upper quadrant pain, an urgent referral for abdominal ultrasound is recommended)
   - chronic changes: spider angiomata, palmar erythema, gynecomastia, testicular atrophy, asterixis, encephalopathy, ascites, acute gastrointestinal bleeding, coagulopathy, muscle wasting, chronic generalized pruritus[1]

Table 1. Risk Factors for Liver Disease[1,6]

High-risk Behaviour	IV drug use (past & present) Multiple sexual partners High-risk sexual activity Tattoos or nonsterile body piercing Alcohol abuse Incarceration
Systemic Illness	Diabetes Obesity Hyperlipidemia Iron overload Autoimmune diseases Metastatic cancer Inflammatory bowel disease Renal failure requiring dialysis
Certain Medications	"Almost any medication can cause elevations of liver enzymes and possible liver injury. In general, any recently started medication or an increased dosage of medication should be considered the primary cause of newly elevated enzymes until proven otherwise."[1] Common medications that require monitoring of liver enzymes are listed in Appendix 1.
Herbs and Supplements	Chaparral leaf, ephreda, gentian, germander, jim bu huan, kava, ma huang, mistletoe, scutellaria (skullcap), senna, sweet wormwood shrub, shark cartilage, vitamin A
Other	Travel to or living in less developed regions or countries Needlestick injury or other exposure (e.g., razors) Receipt of unscreened blood products, especially prior to 1990 Contaminated food or water (hepatitis A)

Pattern of Elevation

6. Liver enzyme elevations can be divided into two main categories: hepatocellular and cholestatic. Identifying the pattern of enzyme elevation can provide clues as to the underlying liver disorder and narrow down the differential diagnosis (Table 2).[1,7]

Degree of Elevation

7. The degree of enzyme elevation may provide insight into the differential diagnosis.[7]
   - The highest aminotransferase levels (> 10 times the upper reference limit) are seen in acute viral hepatitis, autoimmune hepatitis, ischemic or toxic liver injury.
   - Levels 5–10 times upper reference limit can indicate acute biliary obstruction or alcoholic liver disease (AST/ALT ratio > 2).
   - Both chronic hepatitis and cirrhosis can occur with levels that are within the reference range.

8. If an asymptomatic patient has elevations of transaminases less than 1.5–3.0 times the upper reference limit, repeat tests in one to three months if patient has no risk factors for liver disease (Appendix 2).[1,2,15]

DIAGNOSIS AND MANAGEMENT OF SELECT LIVER DISEASES

It is beyond the scope of this section to cover all liver diseases. Rather, it will focus primarily on those conditions featured in the patient cases.

9. Various studies of patients with unexplained abnormal liver enzymes[16-19] have identified the more common causes (Table 3).

NAFLD

10. Non-alcoholic fatty liver disease (NAFLD) is a spectrum of fatty liver diseases in patients without significant alcohol consumption. It is histologically subdivided into two groups:
    - Simple steatosis/NAFL: an excess fat accumulation (steatosis) in the liver without evidence of inflammation. Risk of progression to cirrhosis and liver failure is minimal.
    - Non-alcoholic steatohepatitis (NASH): hepatocyte inflammation and injury is present. It can progress to cirrhosis, liver failure and in rare instances, liver cancer.

Table 2. Enzyme Elevations and Causes[1,7]

Pattern	Process of Enzyme Elevation	Likely Causes	Other Causes
Hepatocellular injury (all types of hepatitis)	ALT and AST escape into bloodstream when liver cell membranes are damaged and become permeable.	ALT: Hepatitis, especially viral, autoimmune, drug induced, NAFLD, iron overload	Acute obstructive jaundice (within first 24 hours)
		AST: Hepatitis (particularly alcoholic), hepatic fibrosis/ cirrhosis	Cardiac or skeletal injury or hemolysis
Cholestasis (biliary obstruction, hepatic infiltration)	ALP and GGT are produced when intra- or extra-hepatic bile ducts are obstructed/damaged. In acute biliary obstruction, enzyme elevation can lag obstruction by approx 24 hours.	ALP: Cholestasis, especially from gallstones, liver metastases, some medications	Bone disease, pregnancy (third trimester)
		GGT: Cholestasis, alcohol	Medications, hepatic congestion (CHF)

Notes:

- An isolated mild elevation of GGT is relatively common and does not signal major liver disease. Although such an elevation may indicate alcohol abuse, it is not, on its own, sufficient to establish a diagnosis.[1,9-11] Despite this lack of specificity, the significance of elevated liver enzymes has generated substantial interest given the widespread blood test requirements for life insurance.[12] Insurance companies sometimes base decisions on epidemiological studies showing that elevated GGT levels are associated with diabetes, cardiovascular disease, cancer and increased all-cause mortality, which is independent of alcohol use.[13,14]
- Serum bilirubin may be elevated in both hepatocellular and cholestatic patterns, and therefore is not a helpful test for distinguishing between them.[1]
- Often, liver enzyme test abnormalities present as a 'mixed picture', where both hepatocellular and cholestatic enzymes are elevated. In this setting, the pattern of predominant elevation should be used to characterize the abnormality.[9] Occasionally, it will not be possible to make such a distinction, in which case either of the causes is possible.

11. NAFLD is the most common cause of mildly elevated liver enzymes.[15,20-22] However, the prevalence in primary care is uncertain. At this time, estimated worldwide prevalence ranges from 6.3–33%, depending on the population studied and the definition used. The rate of reported progression also varies considerably, with NASH being present in anywhere from 10–35% of those with NAFLD (or 3–5% of the general population). Advanced disease (significant fibrosis and cirrhosis) occurs in approximately 3–8% of patients with NAFLD.[22-24] Virtually all advanced disease occurs in those patients with NASH. Further study is required in this area.

12. The most widely supported hypothesis implicates insulin resistance as the main cause of NAFLD, with further oxidative injury required for progression to NASH and cirrhosis. Patients with NAFLD are at increased risk for liver cancer. However, this is likely limited to those with advanced fibrosis and cirrhosis. The most common cause of death in patients with NAFLD is cardiovascular disease.[25]

13. Risk factors for NAFLD include obesity, type 2 diabetes, dyslipidemia and metabolic syndrome. Other conditions that have an emerging association include obstructive sleep apnea, polycystic ovary syndrome (PCOS) and hypothyroidism.[21]

14. Most patients with NAFLD are asymptomatic, although some may present with upper right quadrant pain or fatigue.[26,27] Typically, the disease is recognized when lab testing demonstrates elevated liver enzymes, or hepatic steatosis is detected on abdominal imaging. The ratio of AST/ALT is usually < 1. As NAFLD progresses, the increasing liver fibrosis causes a loss of hepatocytes, leading to a decrease in the liver's capacity to release enzymes. Therefore, due to the loss of hepatocytes, a decrease in liver enzymes might indicate a deterioration of the condition, not an improvement.[28]

15. Before diagnosing NAFLD, other conditions also associated with fatty liver (e.g., alcohol abuse, viral hepatitis, hemochromatosis, drug-induced liver damage) should be ruled out by history and serological testing [High Evidence].[7,23,26,29,30]
    a) It is important to differentiate between patients with simple steatosis/NAFL (which is generally benign) and those with NASH (which can progress to cirrhosis and liver cancer). Liver biopsy remains the gold standard for determining this histological difference, as imaging and lab tests are not reliable in this regard. However, due to the cost and procedure-related morbidity and mortality, there has been significant interest in developing less invasive ways of identifying those with NASH.[23]
    b) Obesity, diabetes and metabolic syndrome are strong predictors for the presence of steatohepatitis and disease progression in patients with NAFLD, and may be used to "best identify patients with persistently abnormal liver biochemistries who would benefit diagnostically and prognostically from a liver biopsy" [Moderate Evidence].[23,27]
    c) The NAFLD Fibrosis Score[31] can identify those patients with higher likelihood of having bridging fibrosis and/or cirrhosis. It is based on six readily available variables (age, BMI, hyperglycemia, platelet count, albumin, AST/ALT ratio). The

Table 3. Causes of Liver Enzyme Elevations in Primary Care*[11,15]

	More Common Causes	Less Common Causes (< 1%)
Hepatocellular Diseases (ALT and AST elevations predominate)	Non-alcoholic fatty liver disease (25–30%) Alcohol-related (~10%) Chronic viral hepatitis: hepatitis B or C (< 3%) Medication toxicity Hemochromatosis (northern European ethnicity)	Autoimmune hepatitis Alpha-1-antitrypsin deficiency Wilson's disease
Cholestatic Diseases (alkaline phosphatase and GGT elevations predominate) Note: Very limited data about relative prevalence	Biliary obstruction (gallstones, etc) Drug hepatotoxicity Primary biliary cirrhosis Neoplasm (including liver metastases) Primary sclerosing cholangitis	Autoimmune cholangiopathy Sarcoidosis
* Approximately 1–9% of patients with no symptoms will have elevated liver enzymes on routine screening.		

formula is available at http://nafldscore.com [Moderate Evidence].[23]

d) The decision to do a liver biopsy should be made in consultation with a specialist.[1]

Note: Screening for NAFLD in adults attending primary care clinics, or high-risk groups attending diabetes or obesity clinics—is not currently advised because of uncertainties regarding diagnostic tests and treatment options, and the long-term benefits and cost effectiveness of screening [Moderate Evidence].[23]

16. Currently, there is no universally effective pharmacotherapy for NAFLD. The standard treatment involves diet/weight loss, exercise, and perhaps bariatric surgery [High Evidence].[23]
    a) Loss of at least 3–5% of body weight is necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve inflammation [Moderate Evidence].[23]
    b) Exercise on its own may reduce hepatic steatosis, but its effect on other aspects of liver histology is unknown [Moderate Evidence].[23]
    c) Monitoring of any associated comorbidities (e.g., diabetes, cardiovascular disease) is important.[26,27]
    d) Vitamin E 800 IU/day has been found to improve liver histology in non-diabetic adults with biopsy-proven NASH [Moderate Evidence].[23] However, since vitamin E at similar doses has also been shown to increase all-cause mortality in the general population,[32] it is not widely prescribed in this population.

17. Typically, the use of statins has not been recommended in patients with elevated liver enzymes. However, this recommendation is undergoing clarification.
    a) Recent guidelines[5,23] state that statins are ***not*** contraindicated in patients with mild to moderate elevations in ALT because of hepatic steatosis and NASH (or chronic hepatitis C or primary biliary cirrhosis) [Moderate Evidence].
    b) Indeed, some small, short-term studies have shown improvement in fatty liver when statins were given.[33] However, until quality RCTs prove their efficacy, statins should not be used specifically to treat NASH [Moderate Evidence].[23]

Hemochromatosis

18. Elevated aminotransferase levels may prompt investigations for hemochromatosis, although many patients, even those with marked iron overload, have normal enzyme liver enzymes.[30]

19. Screening for hemochromatosis begins with a fasting serum iron and total iron binding capacity (TIBC), from which a transferrin saturation can be calculated (serum iron/TIBC).[9] Often a serum ferritin, as well as transferrin saturation, is also recommended [Moderate Evidence].[34] A transferrin saturation > 45% or an elevated ferritin > 400 ug/L (men) and > 300 ug/L (women) raises the possibility of hemochromatosis.[9,34] However, elevated ferritin alone has a low specificity for hemochromatosis as it can be elevated for many reasons.

20. Management includes a referral for liver biopsy (to quantify hepatic iron and assess liver injury), genetic testing for hereditary hemochromatosis, and phlebotomy to prevent/manage the potential sequelae of iron overload.[9]

Autoimmune Hepatitis

21. Autoimmune hepatitis is a relatively rare inflammatory liver disorder, associated with elevated AST and ALT levels and the presence of autoantibodies; it has a highly variable clinical presentation.[35,36]

22. The pathogenesis is not fully understood, but unless immunosuppressive treatment is started promptly (usually steroids and azathioprine), the disease can progress rapidly to cirrhosis or liver failure.[37,38]

Cholestatic Liver Disease

23. When the liver enzyme pattern reflects cholestasis (Table 2), a reasonable first step is to assess the biliary tree with ultrasound (Appendix 2). If biliary dilatation is present, the site or cause of obstruction can be identified by CT, magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasound (EUS). Endoscopic retrograde cholangiopancreatography (ERCP) is generally reserved for situations where therapeutic interventions are very likely to be needed.[1,9]

THE BOTTOM LINE

- Liver enzyme tests should be ordered in a directed manner based on a suspicion of liver disease.
- When enzymes are elevated, assess liver disease risk factors and signs/symptoms, as well as the pattern and degree of elevation.
- NAFLD is the primary cause of liver enzyme elevations. Management focuses on weight loss.

CASE COMMENTARIES

Case 1: Wendy, female, age 55

Which tests would you order and why?

Appropriate tests would include:

- AST, ALT, GGT – due to her alcohol intake
- **Note**: At the time the real patient was seen, monitoring with periodic liver enzymes was recommended for patients using statins. However, this has now changed (Info point 2).
- lipid panel – due to her previously elevated lipids and current treatment with atorvastatin
- fasting blood sugar – due to her obesity and age
- creatinine and lytes – due to her hypertension and ACE inhibitor

Part Two

What further information would be helpful for you to know?

Important information would be gleaned from history exploring risk factors for liver disease (Table 1) and any OTC meds (Appendix 1), and from physical exam looking for signs/symptoms of liver disease (Info point 5). It would also be important to know the results of her previous lab tests.

Part Three

What would be your next step?

You could ask Wendy to stop drinking alcohol and repeat liver enzyme testing (AST, ALP, ALT, GGT) in one to three months (Appendix 2). It also would be worthwhile to explore her drinking in more detail; for example, with the CAGE questionnaire. Sibling to sibling transmission of hepatitis C is extremely rare, and Wendy has no other risk factors for infectious hepatitis or other liver disease (Table 1). However, her ALT level is greater than twice the upper limit of the normal range, so a viral hepatitis screen would be recommended (Info point 4; Appendix 2).

Part Four—Eight weeks later

What would be your management at this point?

Her high ferritin and transferrin saturation levels might suggest a diagnosis of hemochromatosis (Info points 19; 20). However, in the setting of either chronic alcohol consumption or active hepatitis, the ferritin and transferrin saturation can be spuriously elevated. In addition, the degree of elevation of her enzymes makes a diagnosis of hemochromatosis less likely (Info point 7). Autoimmune hepatitis should be considered due to the positive ANA. Other possible causes of an AST or ALT > 1000 are: acute viral hepatitis (which has been ruled out), toxin/drug, gallstone disease (she has had a cholecystectomy), vascular compromise from hepatic vein thrombosis and Wilson's disease crisis. An ultrasound of her liver as well as a referral to a hepatologist and/or internist would be warranted (Appendix 2).

Real Case
The patient was referred to local internist and tertiary care centre hepatologist. Further labs were done: alpha one anti-trypsin neg, copper level normal, ceruloplasmin level normal, iron level 20, IgA 9.47, IgG 50.7, IgM 4.17 (all high), monospot neg. Liver biopsy supported a diagnosis of autoimmune hepatitis with no evidence of iron overload.

Case 2: Edward, male, age 61

What additional investigations would you order?

As Edward is in the high risk category for coronary artery disease (age, HTN, T2D and BMI), a statin should be considered to lower his LDL. Liver enzyme testing would be appropriate as testing is recommended before initiating a statin (Info point 2).

Part Two

What further information would be helpful to know?

Edward's liver enzymes are elevated. It would be important to identify any risk factors for liver disease (Table 1) and determine if he is having any signs/symptoms (e.g., fatigue, abdominal discomfort). Results of any previous liver enzyme tests would be helpful for a comparison.

Part Three

What would you do next?

A hepatocellular dominant pattern is present. Edward isn't taking OTC medications, and he denies any alcohol or infectious hepatitis risks. However, because his ALT level is greater than twice the upper limit of the normal range, a hepatitis screen would be recommended (Info point 4), as well as an abdominal ultrasound and repeat of his liver enzymes in 1–3 months (Appendix 2).

Part Four—Three months later

What would be your next steps?

Hemochromatosis would be considered as a possibility, but transferrin saturation is not elevated. Although his serum ferritin is elevated, it is less specific since it can be elevated for many reasons. NAFLD is a distinct possibility due to the following:

- ALT reading is the most marked elevation (Table 2)
- AST/ALT ratio is < 1 (Appendix 1)
- Edward is obese and has diabetes – both risk factors for NAFLD (Info point 13)
- Ultrasound result indicates that Edward has severe fatty infiltration of his liver

He would be advised about the importance of weight loss achieved through a low fat diabetic diet and exercise (Info point 16). As he is in the high risk category for coronary artery disease, it would also be recommended that he consider (despite his mildly elevated liver enzyme tests) starting a statin drug to bring his cholesterol to target (Info point 17).

Real Case
The patient was advised to continue to try to lose weight – which he did! Liver enzymes subsequently improved to almost normal levels. He refused to start on a statin.

Case 3: Carole, female, age 47

How would you manage Carole?

It would be important to quantify Carole's acetaminophen use (Table 1; Appendix 1). Her GGT is elevated, potentially — though not definitively — indicating alcohol induced liver disease (Table 2). However, the ratio of her AST/ALT (1:2) is not consistent with alcohol abuse (Appendix 2).

Although it is a mixed picture of elevation (Table 2), a cholestatic dominant pattern is suggested from her blood work. Therefore, an urgent ultrasound is recommended (Appendix 2). Depending on results, referral for magnetic resonance cholangiopancreatography (MRCP) may be indicated (Info point 23). She should also be encouraged to stop all alcohol consumption until investigations are completed.

Real Case
Two weeks later, repeat lab tests were: AST 35, GGT 243, ALT 69, ALP 193, hep B, hep C serology negative. An MRCP was performed and was reported as normal. She was referred to a hepatologist for further investigation.

We always welcome your input. If you would like to provide feedback on this module, the following link will take you to an electronic survey: **https://adobeformscentral.com/?f=aujbJkiLCj2Fy7WsXgCYew**

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The Foundation's module team would like to acknowledge the assistance of Andy Delli Pizzi (Winnipeg, Manitoba), Joanne Opsteen (Toronto, Ontario), and Lori Teeple (London, Ontario) for their participation in the initial roundtable discussion. We also wish to thank the Practice Based Small Groups facilitated by John Hughes (Westmount, Quebec) and Bruce Silburt (Halifax, Nova Scotia) who pilot tested this educational module and provided suggestions for improvement.

Disclosures of competing interests:

No competing interests were declared for Christine Harrison, Adetunji Fatoye, Jennifer Mueller, Jacqueline Wakefield or Lynda Cranston.

Hemant Shah has received educational consulting fees from Boehringer-Inhelheim, Gilead Sciences, Hoffman La-Roche, Janssen, Merck and Vertex.

Web-based resources cited within the module were active as of October 2013.

You can access this module and all its appendices online. Just go to: https://members.fmpe.org/

LEVELS OF EVIDENCE

Evidence Quality	Type of Evidence Included
High	• Systematic reviews/meta-analyses that include a wide range of well-designed studies (few limitations/risk of bias, directly applicable to target population); summary estimate has a narrow confidence interval. • Large, well designed RCTs. Study conclusions are unlikely to be strongly affected by information from future studies.
Moderate	• Systematic reviews/meta-analyses of studies with more limitations/risk of bias (less well designed RCTs, cohort, case control studies), or when the summary estimate has a wide confidence interval. • Single, moderate sized, well-designed RCTs. • Well-designed, consistent, controlled but not randomized trials. • Large cohort studies. Study conclusions could change with additional information from future studies.
Low	• Small RCTs with a high risk of bias. • Controlled or cohort studies with significant limitations/risk of bias or significant variation between study results. Evidence from well-designed studies in representative populations is lacking or insufficient.
Very Low	• Expert opinion • Individual case reports or series

Sources:

1) Scottish Intercollegiate Guidelines Network-(SIGN) http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html

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APPENDIX 1. Medications and Liver Monitoring

The number of potentially hepatotoxic drugs is extensive, as almost any medication can cause elevations of liver enzymes. The majority of these reactions are idiosyncratic in nature, but some are dose-related. Although hepatotoxicity often occurs within 1–2 months of starting a medication, this is not always true. With many medications, liver enzyme elevations are mild and essential medications can be continued; however, if elevations continue to rise, the suspect medication should be discontinued.

The following list identifies categories of drugs (and some common examples in the category) which are known to be hepatotoxic, particularly when given at higher doses or with prolonged administration. In many cases initial testing or periodic monitoring is recommended. Please refer to product monographs.

- Anti-arrhythmic agents (e.g., amiodarone)
- Anticonvulsants (e.g., valproic acid, carbamazepine)
- Chemotherapy drugs
- Antituberculin agents (rifampin, isoniazid INH, pyrazinamide PZA)
- Immunomodulators/immunosuppresives (e.g., methotrexate, azathioprine [Imuran®])
- Anti-retroviral drugs
- Dantrolene
- Antifungals (ketoconazole, terbinafine [Lamisil®])
- Synthetic retinoids (e.g., isotretinoin [Accutane®])
- Anti-hyperlipidemic drugs*: niacin, fibrates, ezetimibe
- Thiazolidinediones or TZDs (e.g., rosiglitazone [Avandia®] or pioglitazone [Actos®])

Notes:

- Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs): Because these agents are used so frequently, they are considered the most important cause of the drug induced hepatotoxicity. However, rates of hepatotoxicity are low (1–8 cases per 100,000 patient years of NSAID use), so routine monitoring with liver enzymes is rarely recommended.

* Statins do not require routine periodic monitoring of liver enzymes. They should be checked one time before initiating a statin or if a patient has any symptoms of possible liver enzyme elevation/failure (Info point 2).

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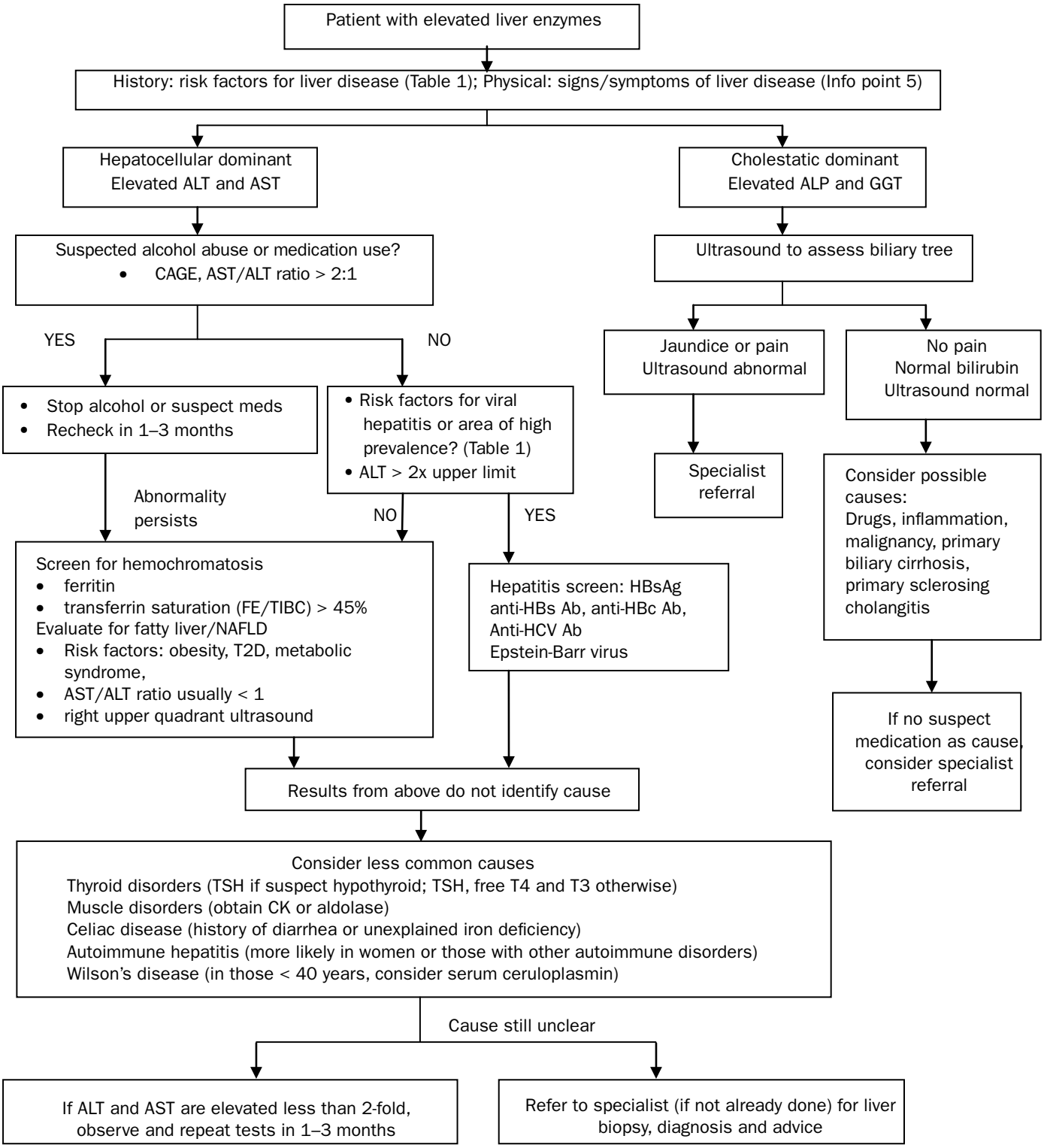
APPENDIX 2. Evaluation of Elevated Liver Enzymes



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November 2013