Clinical Practice Algorithms for Evaluation of Liver Function Chemistry Tests
Clinical Guideline from American College of Gastroenterology

Introduction
In January 2017, the American College of Gastroenterology (ACG) published a newly developed clinical practice guideline regarding the evaluation of abnormal liver chemistry tests.

As a general rule, it is recommended that before initiation of evaluation of abnormal liver chemistry tests, the provider should repeat the laboratory panel and/or perform a clarifying test to confirm that the liver chemistry actually is abnormal. In addition, the provider should recognize that most reference intervals are established at a confidence interval of 95%, meaning that 2.5% of all healthy individuals will have test values both slightly above and slightly below the reference interval.1

Included here in Figures 1-5 are a number of clinical practice algorithms recommended by ACG depending on the liver chemistry test that is abnormal, degree of elevation, and possible combination of test results.

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**Figure 1.** Algorithm for evaluation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) level. HCV, hepatitis C virus.

Figure 1 reprinted from Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol.* 2017 Jan;112(1):18-35, with permission from American College of Gastroenterology.
Hepatocellular injury is defined as disproportionate elevations of AST and ALT levels as compared with the alkaline phosphatase level. Also, when examining the liver chemistry profile, the patterns of elevations of AST to ALT help to guide the patient evaluation. Also, when considering liver function tests, severe AST and ALT elevations can be seen in a variety of liver-related and non-liver-related conditions as shown in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Elevation Type</th>
<th>AST/ALT Pattern</th>
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<tbody>
<tr>
<td>Moderate</td>
<td>Mixed</td>
</tr>
<tr>
<td>Severe</td>
<td>Hepatocellular</td>
</tr>
<tr>
<td>Massive</td>
<td>Cholestatic</td>
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The magnitude of AS and ALT elevation varies depending on the cause of hepatocellular injury. Prior guidelines and studies have used a variety of definitions for AST and ALT elevations. For the purposes of our guidelines, we will define borderline AST and/or ALT elevations as <2X ULN, mild AST and ALT elevations as 2–5X ULN, severe AST and/or ALT elevation as >15X ULN, and massive AST and ALT elevation as <2X ULN.

Severe elevations of AST and/or ALT can be seen in a variety of conditions, including acute hepatitis, acute biliary obstruction, diffuse infiltration of the liver, hepatic ischemia, and drug toxicity. Severe ALT elevations can also be seen in alcoholic liver disease. Certain findings on physical examination may accompany both hepatocellular and cholestatic disorders. Normal aminotransferase and alkaline phosphatase levels or may be seen in Wilson disease. A bronzing of the iris and peripheral cornea (K-F rings) in patients presenting with neurologic symptoms and abnormalities in liver tests may be seen in Wilson disease. A bronzing of the iris and peripheral cornea (K-F rings) in patients presenting with neurologic symptoms and abnormalities in liver tests may be seen in Wilson disease.


**Figure 2.** Evaluation of moderate elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels. HCV, hepatitis C virus.

**Figure 3.** Evaluation of severe elevation of aspartate aminotransferase (AST) and or alanine aminotransferase (ALT) levels. HCV, hepatitis C virus.
**Figure 4.** Algorithm for evaluation of elevated serum alkaline phosphatase.

- Normal total bilirubin and serum transaminases
  - History and physical exam confirm with serum GGT
  - If GGT normal --> evaluate for non-hepato-biliary etiologies
  - If GGT abnormal --> obtain right upper quadrant ultrasound, evaluate for potential hepatotoxic medications, check AMA, ANA, and SMA

- Elevated serum transaminases ± elevated bilirubin
  - History and physical exam
  - Check right upper quadrant ultrasound
  - If ductal dilatation --> ERCP, MRCP
  - If no ductal dilatation --> check AMA, ANA, SMA

**Figure 5.** Algorithm for evaluation of elevated serum total bilirubin.

- Elevated total bilirubin (predominant unconjugated)
  - History and physical exam
  - Assess liver transaminases and serum alkaline phosphatase
  - Review medications
  - Evaluate for hemolysis
  - Evaluate for Gilbert’s syndrome
  - If persistent elevation is otherwise unexplained, may consider diagnostic testing for Gilbert’s syndrome (UGT1A1 genotype) and evaluate for uncommon etiologies in Table 6

- Elevated total bilirubin (predominant conjugated)
  - History and physical exam
  - Assess liver transaminases and serum alkaline phosphatase
  - Review medications
  - Evaluate for clinically overt etiologies: sepsis, TPN, cirrhosis, and biliary obstruction
  - Perform right upper quadrant ultrasound
  - If ductal dilatation --> ERCP or MRCP
  - If no ductal dilatation --> check AMA, ANA, and SMA

For intrahepatic cholestasis, autoimmune markers including anti-mitochondrial antibodies, anti-smooth muscle antibodies, and anti-nuclear antibodies should be assessed. If positive, consider additional workup for autoimmune liver disease. Wilson's disease and alpha-1antitrypsin deficiency are also important diagnostic considerations.
Reference: