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Clinical Review

# ELEVATED LIVER ENZYMES: EMERGENCY DEPARTMENT–FOCUSED MANAGEMENT

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☐ **Abstract—Background: Liver function test (LFT) abnormalities are a common problem faced by emergency physicians. This has become more common with the introduction of laboratory panels and automated routine laboratory testing. Fortunately, not all patients with irregularities in liver enzymes possess underlying pathology. This emergency medicine focused review provides a discussion of the various biochemical tests, their underlying biological basis, and an algorithmic approach to the interpretation of abnormalities. Objective: Our aim was to provide emergency physicians with an overview of the evaluation and management of patients with elevated LFTs. Discussion: The liver is a complex organ with multiple roles. The key biochemical markers of hepatic function can be organized into the groupings of hepatocellular, cholestatic, or functioning liver, based on underlying enzymatic roles. Pathologic alterations to these markers can be algorithmically assessed by separating disease processes of these groupings, followed by assessment of the magnitude of enzymatic elevation. This review conducts an in-depth evaluation of the differential diagnosis and emergency department–centered clinical response of elevated LFTs based on subcategories of mild, moderate, and severe transaminase elevation. Conclusions: By understanding the biochemical basis of each LFT, it is possible to correlate laboratory findings to a patient's clinical presentation. An algorithmic approach can be taken to help narrow the spectrum of a differential diagnosis. This may assist providers in ensuring appropriate management and evaluation of the patient with elevated LFTs. Published by Elsevier Inc.**

☐ **Keywords—liver function test; hepatitis; aspartate aminotransferase; alanine aminotransferase; γ-glutamyl transpeptidase; alkaline phosphatase; prothrombin time; albumin**



## INTRODUCTION

In today's medical system, abnormal laboratory values can prompt expensive, unnecessary, and potentially harmful further diagnostic evaluations. A 2012 retrospective, multicenter cohort study of patients presenting to the emergency department (ED) found that laboratory testing had a direct effect on ED length of stay, with a mean increase of 10 min for every five individual tests ordered (1). With routine incorporation of hepatic tests in blood chemistry panels, an understanding of the pathophysiologic basis of liver function tests (LFTs) is important in order to establish appropriate clinical correlation and patient disposition.

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**Table 1. Key Biochemical Markers Involving Hepatic Function (2–5)**

| Function Assessed | Test | Physiological Function | Site Found |
|---|---|---|---|
| **"Hepatocellular Arrangement"** | Aspartate Aminotransferase | Important enzymes in amino-acid metabolism, allowing for entrance to Krebs Cycle | Liver, skeletal muscle, heart, kidney, brain |
| | Alanine Aminotransferase | | Greatest concentration in the Liver |
| **"Cholestatic Arrangement"** | Alkaline Phosphatase | Enzyme that transports metabolites across cell membranes. Is present in the bile duct epithelial cells, therefore: biliary stasis = release of the enzyme | Liver, Bone > intestine, placenta, kidney |
| | γ – Glutamyl transpeptidase | Catalyzes the transfer of a γ – Glutamyl group between amino acids. Important for the synthesis and breakdown of glutathione. | Hepatocytes, biliary epithelial cells and renal tubules |
| | Bilirubin | Catabolic product of hemoglobin which is released in the unconjugated form, and conjugated to a water soluble product by hepatic cells. | Serum and Liver. Comparison of 'conjugated' and 'unconjugated' bilirubin elevations will determine whether intrahepatic. |
| **Functional Liver Mass** | Albumin | Main protein of human blood plasma. | Liver or dietary |
| | Prothrombin Time | Assay of the extrinsic pathway of coagulation. Assesses factors I, II, V, VII, and X. | Liver (synthesizes vitamin k dependent clotting factors) |

## LIVER BIOLOGY: A LITTLE UNDERSTANDING GOES A LONG WAY

The liver is a complex organ with multiple roles. Hepatocytes are organized into primary functioning units called the liver acinus, each of which is bordered by the "portal triad" consisting of a branch of the hepatic artery, portal vein, and bile duct. This organization allows the liver to complete a wide array of tasks: glucose storage, glycogen breakdown, carbohydrate–fat–protein metabolism, bile synthesis, liproprotein–plasma protein synthesis, detoxification, and waste product metabolism. All of these interacting roles can be impacted during liver disease, with corresponding alteration in LFT panel.

An LFT panel typically includes aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), and albumin. Clinically, LFT results are described as being in a "hepatocellular" or "cholestatic" arrangement based on the pattern of elevation. Of the commonly available liver chemistries, the only true measurements of hepatic synthetic function are the PT and albumin (2). A hepatocellular pattern depicts a disproportionate elevation in the AST and ALT in comparison to ALP. The inverse, a disproportionate elevation of ALP in comparison to the transaminases, represents a cholestatic pattern. Total bilirubin can be elevated in either pattern and may indicate an extrahepatic disorder. Table 1 explains the physiologic function and anatomic location of these laboratory tests in relation to the referenced "patterns of elevation."

Aminotransferases are used to monitor and detect the progression of hepatocellular injury. AST and ALT are abundant hepatic enzymes crucial to citric acid cycle function. ALT and AST are released from damaged hepatocytes into the blood after hepatocellular injury or death. Both aminotransferases are highly concentrated in the liver, but ALT is considered to be more specific to liver damage. AST is amply expressed in the brain, skeletal muscle, kidney, and heart. Aminotransferase levels vary based on age and sex, so institutional reference limits should be specifically defined (3).

ALP is an enzyme that transports metabolites across cell membranes. Liver and bone disease are the most common causes of pathological elevation, though other sites of origin include the intestines, kidney, and placenta (4). Due to the high body tissue prevalence, nonpathologic processes, like pregnancy, can cause elevation in laboratory values. During pregnancy, ALP begins to rise by late in the first trimester and can reach twice normal values by term (6). In the liver, ALP is present in the bile duct epithelial cells; thus, biliary stasis can increase the release of the enzyme (5). Given the overlap in values with liver and bone disease, GGT can be used to differentiate the location of release. GGT is a glycoprotein located on the membranes of cells with high secretory or absorptive activities, which is not abundant in bone. GGT is not routinely included in liver enzyme panels, but should be considered if the clinical picture does not clearly identify the source of an ALP elevation. Table 2 demonstrates the associated conditions that are