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Learning Outcomes

Upon completion of this exercise, the participant will be able to:

- discuss the use of enzyme levels in the diagnosis of liver disease.
- interpret laboratory results in which the following enzymes are elevated: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT)
- discuss factors which can affect the reference ranges of AST, ALT, ALP, and GGT.

In the United States chronic liver disease caused by alcohol consumption, hepatitis B and C viruses, drugs, autoimmune reactions, and other conditions is the eighth leading cause of death. Often an elevation of one or more of the enzymes included in a screening panel is the first indication of asymptomatic liver disease. Even though the composition of liver function panels may differ between institutions, these panels typically include the following enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and possibly gamma glutamyl transferase (GGT).

When tissue damage occurs, cellular enzymes may be released into the serum and the elevation of certain enzymes is often associated with damage to specific tissue or organs. Although the enzymes previously mentioned are present in tissues throughout the body, their elevation (particularly in combination) is most often associated with liver injury or disease. Elevation of the aminotransferases AST (formerly named SGOT) and ALT (formerly named SGPT) often reflect hepatocellular damage. As with all abnormal laboratory tests, repeat testing for an unexpected elevated AST and/or ALT level(s) should be performed to verify the results. If the patient has engaged in strenuous exercise the retesting for an elevated AST should be done after a period of abstinence from exercise. AST is found in decreasing concentrations in liver, cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes; whereas ALT is

found primarily in liver and kidney. Thus, an elevation of ALT is more specific for liver injury than an elevation of AST. Elevated AST levels may be caused by disorders of other organs and tissues, particularly striated muscle. The most common causes of elevated levels of aminotransferases are: alcohol-related injury, chronic hepatitis B and C, autoimmune hepatitis, fatty infiltration of the liver (hepatic steatosis), nonalcoholic steatohepatitis, hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, and celiac sprue. Specialized testing is required to determine the specific diagnosis when elevated aminotransferase levels occur.

Reference ranges for the aminotransferases are method dependent, which can make comparison of elevated AST and ALT levels difficult, but the AST:ALT ratio has been used in the differential diagnosis of liver disease. The AST:ALT ratio (with elevated levels of both enzymes) is approximately 1:1 for most primary liver disease. The ratio is generally lowest in viral hepatitis (both acute and chronic) and this ratio is typically less than 1:1. The levels of both AST and ALT are very high (greater than 10 times the highest normal level) in acute hepatitis and are lower (often less than 4 times the highest normal level) in chronic hepatitis. In patients with chronic hepatitis C, there is a subset of patients with normal ALT levels. In one study, almost half of these patients developed persistently elevated ALT levels following alpha-interferon (INF) treatment and this finding was used to suggest that INF treatment may be harmful to these patients. Patients with nonalcoholic steatohepatitis usually also have a ratio of less than 1:1. On the other hand, a high AST:ALT ratio of 2:1 or 3:1 occurs in patients with chronic alcohol-induced liver damage. In patients with alcohol abuse, the AST level is rarely more than 8 times the normal range and the ALT is seldom more than 5 times the normal range and may, in fact, be normal. An elevation of another liver function enzyme, GGT, is also helpful in the diagnosis of alcohol abuse.

Almost any medication, including herbal preparations and illicit drugs, may cause a transient elevation of the aminotransferases. Common prescription medications known to affect the liver include: nonsteroidal anti-inflammatory drugs, antibiotics, antiepileptics, cholesterol-lowering statins, and antituberculosis drugs. Many herbs or homeopathic treatments, including ephedra

(mahuang), chaparral, alchemilla (lady's mantle), scutellaria (skullcap), and shark cartilage, have been reported to cause elevations in aminotransferases. Use of anabolic steroids, cocaine, ecstasy, PCP, glue, and solvents may also injure the liver causing elevated aminotransferase levels.

Several recommendations concerning laboratory testing of aminotransferases have been made in the National Academy of Clinical Biochemistry Laboratory Guidelines for Screening, Diagnosis, and Monitoring of Hepatic Injury (www.nacb.org). This document includes performance specifications and precision goals for liver function enzyme testing. Recommendations for the performance of aminotransferase assays include performance goals of a total error range of 15-20% for AST and $\leq 10\%$ at the upper reference limit for ALT. Another recommendation is that laboratories have separate upper reference limits for adult males and females because AST and ALT activities are significantly higher in males than in females. Age-specific reference ranges for children and adults over 60 years old are also recommended.

Tissues containing alkaline phosphatase (ALP) are placenta, ileal mucosa, kidney, bone, and liver. Although an elevated ALP is not diagnostic of liver disease, elevations are predominantly from liver or bone. In the third trimester of pregnancy women have elevated ALP levels due to placental ALP in their blood. Serum ALP in persons with blood type O or B who are secretors may increase after the ingestion of a fatty meal due to an influx of an intestinal ALP isoform known as high molecular mass intestinal alkaline phosphatase. The exact linkage of blood type, secretor status, and intestinal ALP is not known. Elevated ALP may be due to bone growth in children and adolescents; and ALP levels increase progressively after age 40, particularly in women. There is an approximately 50% increase in bone-specific ALP induced by menopause, whereas ALP levels in elderly men are less than 10% higher than levels in young adults. These results support a need for separate reference ranges for geriatric patients, particularly women. The source of an elevated ALP may be investigated by electrophoresis or an immunoassay specific for the bone ALP isoenzyme. Older methods, including heat fractionation (bone isoenzyme is more labile than the liver isoenzyme) and urea denaturation, are considered less

reliable. An elevated ALP determined to be of hepatic origin often indicates impaired bile flow. A markedly elevated ALP, particularly if AST and ALT are normal or minimally elevated, suggests bile duct obstruction (from gallstones, scars due to previous gallstones or surgery, or from cancer) or diseases of the bile ducts, such as primary biliary cirrhosis or primary sclerosing cholangitis. Other causes include adult bile ductopenia, cholestasis induced by drugs such as anabolic steroids, and infiltration of the liver by primary or metastatic cancer, fungi, or sarcoidosis. Recommendations for ALP assays include total analytical error of $\leq 10-15\%$ at the upper reference limit and establishment of separate reference ranges for children, based on age and gender, and for pregnant women. If mildly elevated ALP levels are found in a specimen from a non-fasting patient, repeat analysis using a fasting sample should be performed.

Gamma glutamyltransferase (GGT) is present in decreasing concentration in kidney, liver, pancreas, and intestine and elevations have been reported in several clinical conditions including pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, rheumatoid arthritis, hyperthyroidism, congestive heart failure, diabetes, and alcoholism. NACB guidelines do not recommend routine use of GGT because of its low predictive value of 32% for liver disease. GGT is very sensitive to ingestion of alcohol and many prescription and non-prescription drugs, including nonsteroidal anti-inflammatory drugs, lipid-lowering drugs, antibiotics, antiepileptics, antifungal agents, and antidepressants. Even small amounts of alcohol ingested 24 hours prior to the test may cause a temporary elevated GGT. GGT levels are approximately twice as high in African-Americans. GGT is also very sensitive in the detection of bile duct problems and increases an average of 12 times the upper reference limit in patients with cholestasis. This makes GGT more sensitive than ALP, which increases an average of 3 times the upper reference limit. Suggested uses of GGT include confirmation of the hepatic origin of elevated ALP levels and support of the diagnosis of alcohol abuse in patients with elevated AST and AST:ALT ratios greater than 2:1.