Interpretation of Liver Function Tests in Infectious Disease

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Abnormalities in alkaline phosphatase, aspartate aminotransferase, and bilirubin provide valuable clues in diagnosing a broad spectrum of infections.

The infectious diseases that can affect liver structure and function cover a broad spectrum. Manifestations of liver involvement range from minimally abnormal results on biochemical determinations (alkaline phosphatase [AP], aspartate aminotransferase [AST]) and liver function tests (total bilirubin) to frank jaundice. Since no single measurement can provide an adequate clinical analysis of most problems, this article will review the use of AP, AST, and total bilirubin in combination as guides to the diagnosis of patients with infectious and noninfectious diseases.[1-3]

Neither AP nor AST is found only in the hepatobiliary system. Alkaline phosphatase is present in the liver, bile ducts, intestine, bone, kidney, placenta, and leukocytes, while AST is a component of hepatocytes, myocardium, and skeletal muscle. Despite their apparent nonspecificity, AP and AST provide helpful information. Increased AP commonly indicates increased enzyme synthesis secondary to hepatobiliary disease or osteoblastic activity, and increased AST usually reflects enzyme leakage from injured hepatocytes.

The serum total bilirubin is a direct measurement of liver function. It measures hepatic function by estimating the ability of the liver to excrete an endogenous load from the degradation of the heme moiety of hemoglobin in senescent erythrocytes, and the breakdown of nonhemoglobin hemoproteins in the liver (ie, cytochrome P-450).[4]

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When faced with abnormal liver function tests, clinicians must not limit their investigation to absolute values of their results. The pattern of liver function test elevations and their clinical association in conjunction with their absolute values can help guide the physician to the correct diagnosis.

INFECTIOUS DISEASES

Absolute values yielded by liver function tests are helpful in the diagnosis of several infectious diseases since certain diseases produce characteristic elevation patterns. Sepsis secondary to infections of the abdomen, pelvis, skin, or genitourinary tract produce extreme hyperbilirubinemia. In addition to hyperbilirubinemia, viral hepatitis, toxic shock syndrome, and yellow fever produce extremely elevated AST levels. (Viral hepatitis can produce AST levels $\geq$1,000 IU/L, which distinguishes it from toxic shock syndrome.) Liver involvement is common in Q fever, secondary and tertiary syphilis, and typhoidal tularemia. An increase in serum AP is characteristic of Q fever and secondary and tertiary syphilis, while an elevated serum transaminase, AST, or total bilirubin may be the only laboratory abnormality seen with typhoidal tularemia (*Tables 1* through *8*).[1,2,5,6]

PATTERNS OF ELEVATION

It is important for physicians to be aware of several patterns of liver function test elevation. The common patterns include increased AP out of proportion to AST and vice versa. The former is characteristic of biliary obstruction (with obstruction secondary to cancer producing higher AP levels than obstruction due to gallstones), biliary cirrhosis, Q fever, and pyogenic liver abscess. Increased AST out of proportion to AP is characteristic of viral hepatitis. Another pattern that is not often addressed is hyperbilirubinemia out of propor-

Table 1
Mildly Elevated Alkaline Phosphatase

Infectious Causes	Noninfectious Causes
Brucellosis	Alcoholic hepatitis
Gas gangrene	Cancer of lung or pancreas
Gonococcal bacteremia	Cirrhosis (Laënnec's, postnecrotic)
Legionnaires' disease	Congenital atresia of bile ducts (extrahepatic)
Leptospirosis (not *Leptospira icterohaemorrhagiae*)	Congestive heart failure
Liver abscess (amebic)	Drug fever (chlorpropamide, phenobarbital, phenytoin)
Psittacosis	Hodgkin's disease
Q fever	Giant cell arteritis (temporal arteritis)
Relapsing fever	Hepatoma (Regan isoenzyme)
Rocky Mountain spotted fever	Hyperparathyroidism
Shigellosis	Hyperthyroidism
Toxic shock syndrome	Infarction (myocardial, pulmonary, splenic, renal)
Toxoplasmosis	Normal variant
Tuberculosis (miliary)	Osteomalacia
Viral hepatitis	Posthepatic obstruction (gallstone, sarcoidosis, amyloidosis)
Weil's disease	Pregnancy
Yellow fever	Rickets
	Ulcerative colitis

Table 2
Moderately to Severely Elevated Alkaline Phosphatase

Infectious Causes	Noninfectious Causes
Clonorchiasis	Alcoholic hepatitis
Cytomegalovirus mononucleosis	Cirrhosis (postnecrotic, primary biliary)
Hepatic candidiasis	Osteitis deformans (Paget's disease)
Infectious mononucleosis (Epstein-Barr virus)	Osteoblastic tumors (osteogenic sarcoma, metastatic carcinoma)
Liver abscess (pyogenic)	Posthepatic obstruction (neoplasm)
Q fever	
Syphilis (secondary or tertiary)	
Toxic shock syndrome	
Tuberculosis (miliary)	

Table 3
Depressed Alkaline Phosphatase

Noninfectious Causes
Celiac disease
Collection of blood in EDTA, fluoride, or oxalate anticoagulant
Excessive vitamin D ingestion
Hypothyroidism
Milk-alkali (Burnett's) syndrome
Malnutrition
Pernicious anemia
Scurvy

EDTA = ethylenediaminetetraacetic acid

tion to increases in AP and AST. This pattern is characteristic of borreliosis and sepsis.[1,3]

Several diagnoses, including pneumococcal pneumonia, legionnaires' disease, Fitz-Hugh–Curtis syndrome, and typhoid fever, become apparent when liver function tests are elevated in conjunction with historical and physical findings. Regardless of the severity or type of pneumonia, patients with pneumonia generally do not present with jaundice. Two notable exceptions are pneumococcal pneumonia and legionnaires' disease. Twenty-five percent of patients with pneumococcal pneumonia present with increased total bilirubin; jaundice is more common in those patients with right lower-lobe pneumonia. Legionnaires' disease is accompanied

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Table 4
Mildly Elevated Aspartate Aminotransferase

Infectious Causes	Noninfectious Causes
Brucellosis	Amyloidosis
Clonorchiasis	Cirrhosis (Laënnec's, postnecrotic, biliary)
Cytomegalovirus mononucleosis	Delirium tremens
Gram-negative systemic infection	Congestive heart failure (severe)
Infectious mononucleosis	Drug fever
Liver abscess (pyogenic)	Eosinophilia-myalgia syndrome
Pneumococcal pneumonia	Hemolysis
Psittacosis	Hodgkin's disease
Q fever	Infarction (myocardial, cerebral, pulmonary)
Relapsing fever (borreliosis)	Intrahepatic cholestasis
Rocky Mountain spotted fever	Intramuscular injections
Shigellosis	Pancreatitis
Toxic shock syndrome	Postcardiac surgery and catheterization
Tuberculosis	Sarcoidosis
Viral hepatitis	Shock
Weil's disease	Sickle cell disease
	Ulcerative colitis

Table 5
Decreased Aspartate Aminotransferase

Noninfectious Causes
Beriberi
Chronic hemodialysis
Diabetic ketoacidosis
Severe liver disease
Uremia

by jaundice less often than pneumococcal pneumonia, but relative bradycardia in the presence of an infiltrate seen on chest films can help lead to this diagnosis.

Fitz-Hugh–Curtis syndrome, the best known hepatic complication of gonococcal infections, presents with increased AP and sudden onset of pain in the right upper quadrant. This can be mistaken for cholelithiasis, pleurisy, or acute abdomen. A clue to this diagnosis is the

Table 6
Moderately to Severely Elevated Aspartate Aminotransferase

Infectious Causes	Noninfectious Causes
Cytomegalovirus mononucleosis	Carcinoma (primary or secondary)
Falciparum malaria	Choledocholithiasis
Gas gangrene (clostridial myelonecrosis)	Congestive heart failure (severe)
Gonococcal disease	Dermatomyositis/polymyositis
Hepatic candidiasis	Drug fever
Infectious mononucleosis (Epstein-Barr virus)	Infiltrative liver disease
Legionnaires' disease	Muscular dystrophy
Leptospirosis (not *L icterohaemorrhagiae*)	Pancreatitis
Liver abscess (amebic)	Renal infarct
Syphilis (secondary or tertiary)	Shock
Toxic shock syndrome	
Toxoplasmosis	
Typhoidal tularemia	
Typhoid fever	
Viral hepatitis	
Weil's disease	
Yellow fever	

Table 7
Mildly Elevated Total Bilirubin

Infectious Causes	Noninfectious Causes
Brucellosis	Alcoholic hepatitis
Cytomegalovirus mononucleosis	Amyloidosis
Gonococcal bacteremia	Carcinoma (pancreatic, biliary)
Infectious mononucleosis (Epstein-Barr virus)	Choledocholithiasis
Legionnaires' disease	Cirrhosis (biliary, Laënnec's)
Liver abscess (amebic, pyogenic)	Congestive heart failure
Q fever	Drug fever
Rocky Mountain spotted fever	Gilbert's syndrome
Shigellosis	Hemolysis
Syphilis (secondary or tertiary)	Hodgkin's disease
Toxoplasmosis	Sickle cell disease
Typhoidal tularemia	Ulcerative colitis
Typhoid fever	

Table 8
Moderately to Extremely Elevated Total Bilirubin

Noninfectious Causes	Infectious Causes
Clonorchiasis	Carcinoma (pancreatic, biliary)
Falciparum malaria	Choledocholithiasis
Gas gangrene (clostridial myelonecrosis)	Cirrhosis (biliary)
Hepatic candidiasis	Drug fever
Leptospirosis (not *L icterohaemorrhagiae*)	
Pneumococcal pneumonia	
Relapsing fever	
Sepsis	
Toxic shock syndrome	
Viral hepatitis	
Weil's disease	
Yellow fever	

history of pelvic infection supported by the isolation of gonococci from a vaginal swab. Typhoid fever is a multisystem disease that results in mildly elevated total bilirubin. Recent travel to a developing country, acute or subacute febrile illness without localizing signs, and relative bradycardia (pulse-temperature deficit) also tend to support the diagnosis. Typhoid fever is the only disease common in returning travelers that is accompanied by relative bradycardia.[5,6]

CONCLUSION

By interpreting the infectious and noninfectious causes of elevated liver function tests utilizing degree, pattern, and clinical association of liver function changes, the clinician can differentiate between the many infectious and noninfectious diseases by abnormalities in liver function test patterns to arrive at an early diagnosis. □

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