

1. Understanding Liver Function Tests

Understanding Liver Function Tests

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2. Types of Liver Disease

Types of Liver Disease

- **Hepatocellular:** hepatitis, heart failure, toxins
- **Cholestatic (similar to bile duct obstruction)**
 - Extrahepatic: gallstones, cancer, stricture
 - Intrahepatic: Drugs, PBC
- **Infiltrative diseases:** tumor, sarcoid, Tbc
- **Cirrhosis:** hepatocellular loss and scarring
- *Hemolysis: normal liver*

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3. Liver Function Tests

Liver Function Tests

- Excretion, Detoxification
 - Bilirubin, NH₃
- Biosynthesis
 - Albumin, Clotting Factors (Prothrombin time-INR)
- Enzymes
 - Leak from damaged hepatocytes (aminotransferases)
 - Regurgitate from liver with impaired bile flow (alkaline phosphatase, 5'Nucleotidase, gamma glutamyl transferase)
- Immunologic
 - Immunoglobulins, Autoantibodies

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4. Caveats About LFT's

Caveats About LFT's

- Most informative if used as a group
- Nonspecific
 - Low serum albumin; e.g. - malnutrition, chronic inflammation
 - Elevated serum bilirubin; e.g. - hemolysis
 - Elevated AST; e.g. - myocardial infarction, muscle disorders
- Insensitive: may be normal in metastatic cancer, cirrhosis
- Rarely diagnostic: rather, suggest a type of liver disease

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Liver Function Tests

Liver Function Tests

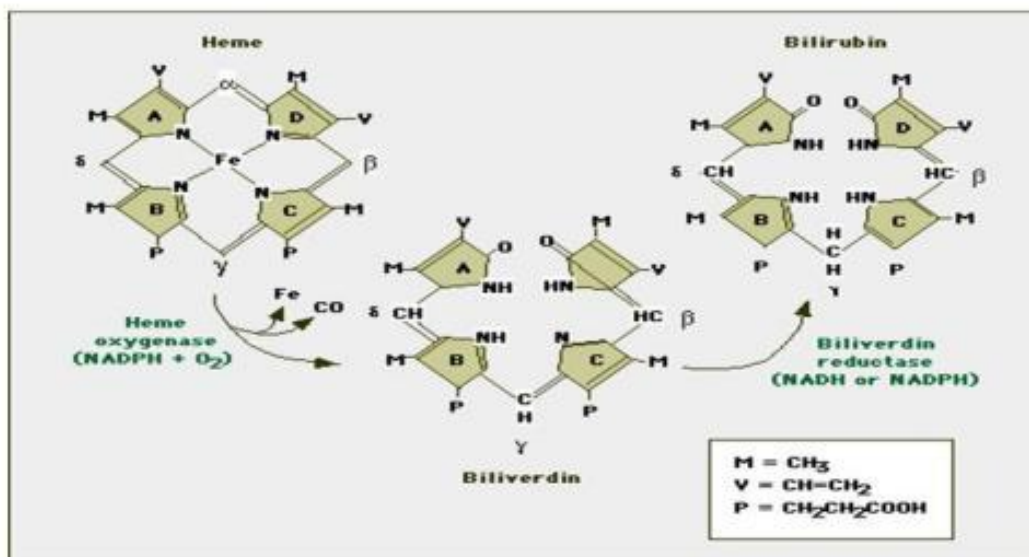
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6.

Bilirubin Synthesis



Bilirubin synthesis Conversion of heme to biliverdin and then bilirubin. Heme ring-opening at the alpha-carbon bridge of heme is catalyzed by heme oxygenase, resulting in the formation of biliverdin. This is followed by reduction of biliverdin to bilirubin in a reaction catalyzed by biliverdin reductase.

Source: M. Kaplan

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7. Liver Function Tests: Slide 7

Unconjugated (indirect) Bilirubin, Noncovalently Bound to Albumin, Enters Hepatic Sinusoids

The intercellular spaces (pores) between endothelial cells within the hepatic sinusoids are larger than intercellular spaces elsewhere in the body. The relatively large bilirubin-albumin complex can readily diffuse through these spaces, enter the Space of Disse, and come into direct contact with microvilli on the sinusoidal surface of hepatocytes.

Source: M. Kaplan

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8. Liver Function Tests: Slide 8

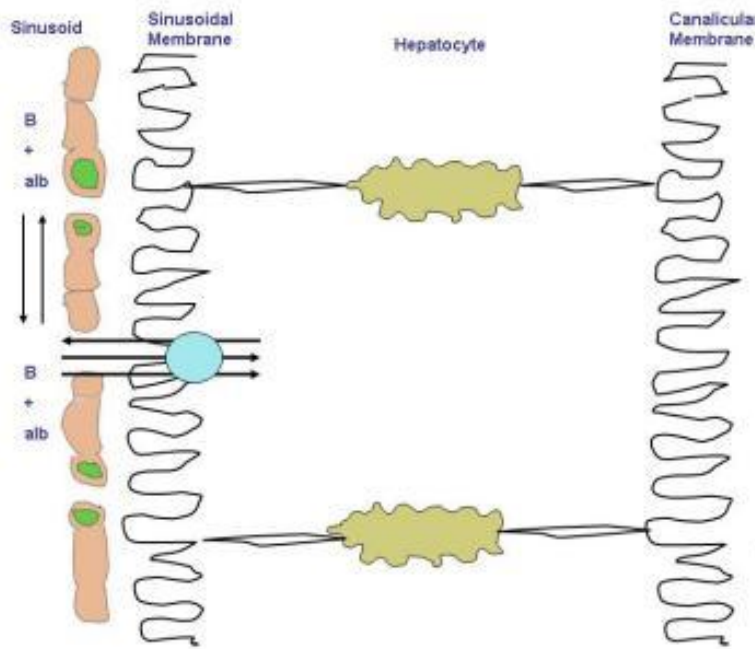
Binding of the Unconjugated Bilirubin-albumin Complex to a Transporter on Hepatocytes

Source: M. Kaplan

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9.

Liver Function Tests: Slide 9



Transport of Unconjugated Bilirubin into Hepatocytes

Bilirubin is carried into the hepatocyte by a non-energy dependent transporter. This is termed protein-mediated facilitated uptake. Albumin remains in serum. There is bidirectional movement of unconjugated bilirubin, but under normal conditions, the movement of bilirubin into the hepatocyte is favored.

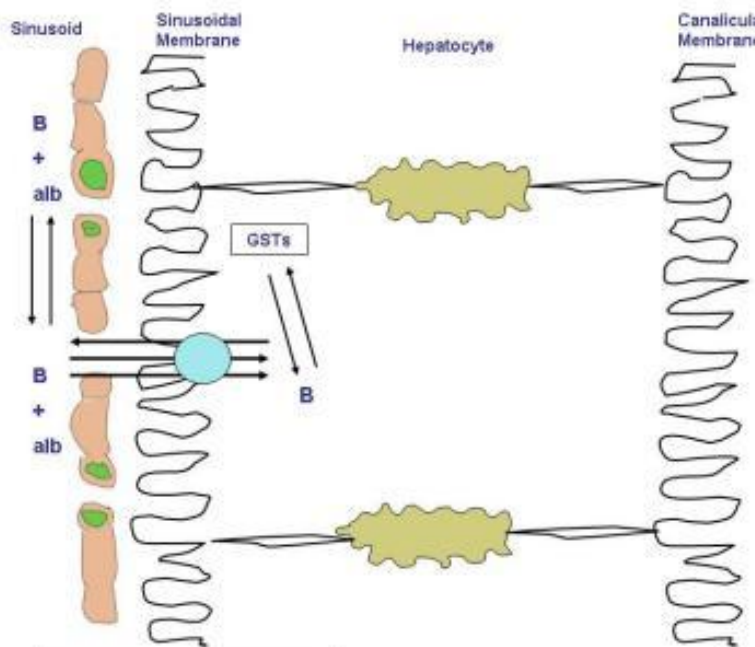
Source: M. Kaplan

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10.

Liver Function Tests: Slide 10



Solubilization of Bilirubin in the Hepatocyte

Water soluble unconjugated Bilirubin is kept in solution by binding to a number of proteins, previously called ligandins. The most abundant proteins are members of the glutathione-S-transferase superfamily.

GSTs =
Glutathione-S-transferase

Source: M. Kaplan

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11. Liver Function Tests: Slide 11

Conjugation of Bilirubin to Glucuronic Acid

The unconjugated bilirubin-glutathione S-transferase complex binds to an enzyme in the microsomes, bilirubin-uridine gluconyltransferase. Bilirubin is conjugated to either one or two glucuronic acids by this enzyme. Glutathione-S-transferase is free to recycle and continue the process. This enzymatic process solubilizes bilirubin and yields two water soluble molecules, bilirubin monoglucuronic acid and bilirubin diglucuronic acid.

GSTs = Glutathione-S-transferase
B-UGT = Bilirubin-uridine phosphoglucuronosyl transferase

Source: M. Kaplan
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12. Liver Function Tests: Slide 12

Secretion of Conjugated Bilirubin into Bile

Bilirubin mono and diglucuronic acid is transported across the apical plasma membrane into the bile canaliculus by an ATP-dependent process that is catalyzed by the transporter cMOAT (the canalicular multispecific organic anion transporter). This transporter is now called MRP-2, multidrug resistance-associated protein 2.

GSTs = Glutathione-S-transferase
B-UGT = Bilirubin-uridine phosphoglucuronosyl transferase
cMOAT = Canalicular multispecific organic anion transporter

Source: M. Kaplan
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13. Enterohepatic and Systemic Circulation

Enterohepatic and Systemic Circulation of Bilirubin and its Metabolites in Adults

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14. Types of Bilirubin

Types of Bilirubin

- Indirect bilirubin = unconjugated bilirubin, insoluble in water and not excreted in urine
- Direct bilirubin = mono- or diglucuronide conjugated bilirubin; water soluble and excreted in urine
- Total bilirubin; the sum of direct and indirect

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15. Serum Bilirubin Elevations

Serum Bilirubin Elevations

Causes of Elevated Bilirubin	Disorder	Direct Bilirubin	Indirect Bilirubin	Bilirubinuria
Increased Production	Hemolysis, P.A., Thal	Normal	Elevated	None
Decreased Conjugation	Gilbert's Syndrome	Normal	Elevated	None
	Crigler-Najjar Syndrome			
Decreased Excretion	All types of Liver Disease	Elevated	Elevated	Positive

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17. Tests of Biosynthesis: Serum Albumin

Tests of Biosynthesis: Serum Albumin

- Serum albumin: made exclusively in the liver
- T 1/2: 14-20 days
- Normal in acute liver disease
- May be low in chronic disease

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18. Tests of Biosynthesis

Tests of Biosynthesis

- Liver works at ~50% capacity: may double production
 - Synthesis inhibited by IL-1, TNF
 - Synthesis stimulated somewhat by thyroid hormone, glucocorticoids

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19. Serum Clotting Factors (INR/PT)

Serum Clotting Factors (INR/PT)

- Made exclusively in the liver (except for factor VIII)
- Short T 1/2 -- factor VII is 6 hrs: fibrinogen 5 days
- Evaluate with the INR or the prothrombin time
- INR/PT -- measures factors II, V, VII, and X
- Vitamin K dependent factors are II, VII, IX, X
- Because of the rapid turnover, 6 hrs, INR/PT useful in assessing severity of acute liver disease; e.g. - fulminant hepatitis

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20. Serum Globulins and Other Proteins

Serum Globulins and Other Proteins

- Immunoglobulins synthesized by plasma cells
- Alpha and beta globulin by hepatocytes
- Ceruloplasmin -- blue copper binding protein (Serum level low in Wilson's disease)
- Alpha-1-antitrypsin: comprises 90% of alpha globulin. (Levels low in alpha-1-antitrypsin deficiency)
- Ferritin: iron binding protein -- serum levels reflect body iron stores but ferritin is also an acute phase reactant; it may be elevated with any type of hepatocyte injury and parallel ALT and AST levels

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Enzyme Tests: Aminotransferases

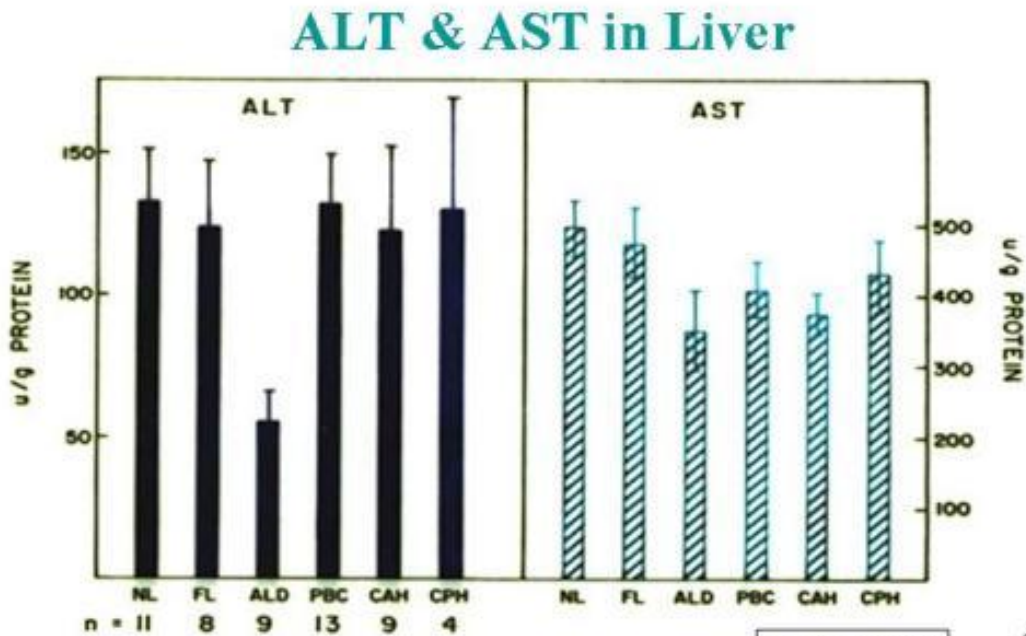
Enzyme Tests: Aminotransferases

- Leak from damaged cells
 - [Hepatocytes: Serum] Ratio = 5000
- Height of ALT, AST have no correlation with clinical outcome or severity of histologic lesion
- Values of ALT, AST above 300 IU are rare in ETOH liver disease
- ALT varies with BMI, elevated lipids, glucose
- ALT levels higher in men than women

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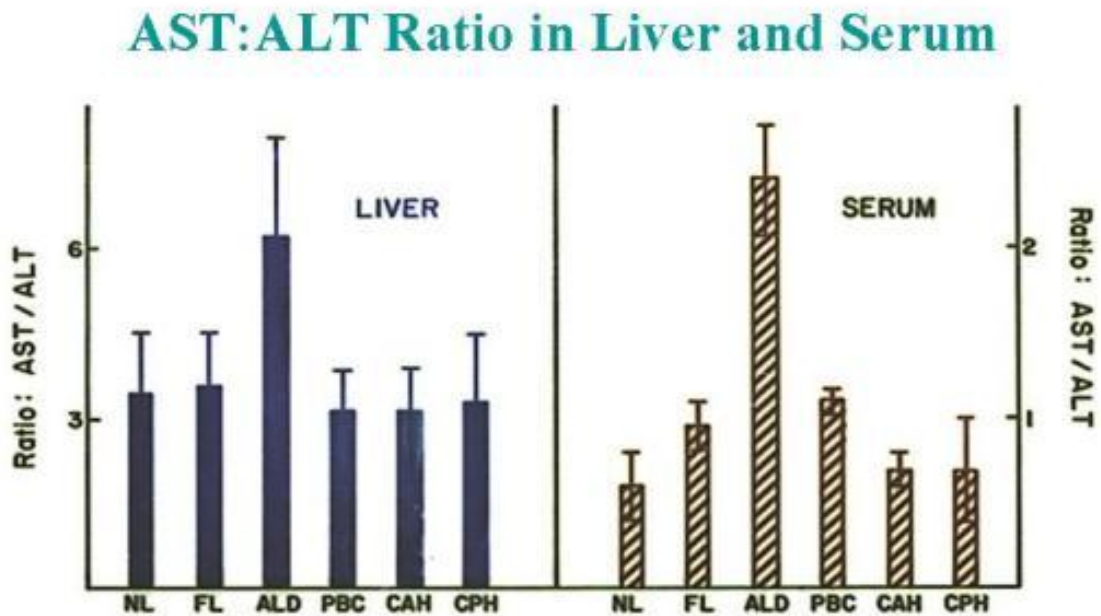
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25. ALT & AST in Liver



Source: M. Kaplan 25
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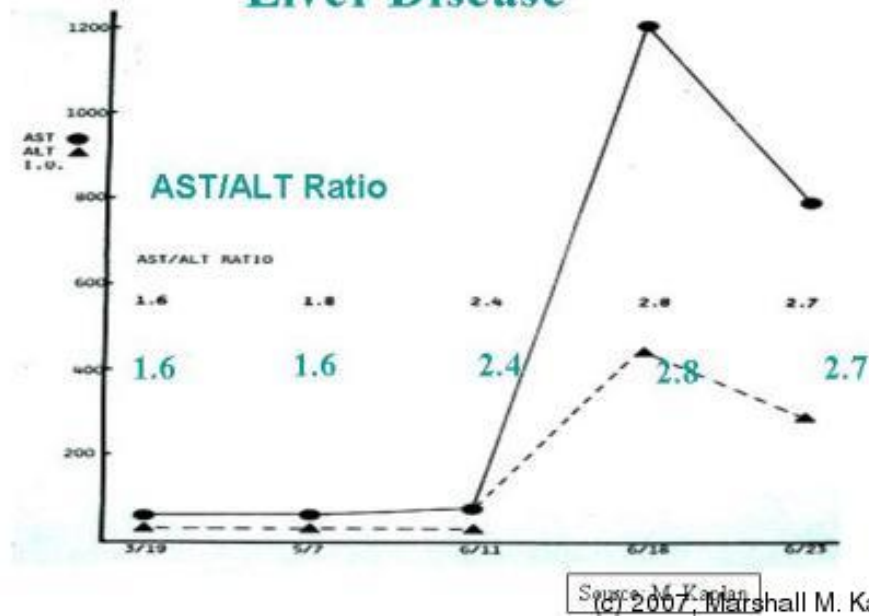
26. AST:ALT Ratio in Liver and Serum



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27. AST/ALT after Hepatitis C in ETOH Liver Disease

AST/ALT after Hepatitis C in ETOH Liver Disease



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28. Liver Function Tests

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29. Alkaline Phosphatase Isoenzymes

Alkaline Phosphatase Isoenzymes

- Identifications of glycoproteins by electrophoresis
 - Liver
 - Bone
 - Intestine
 - Placenta
 - Tumor
- May rise normally in certain situations such as 3rd trimester of pregnancy (placenta) or adolescence (bone)

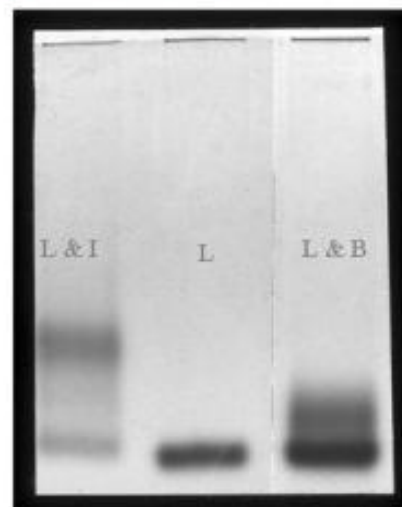
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30. Evaluation of Isolated Alkaline Phosphatase (AP) Elevation...

Evaluation of Isolated Alkaline Phosphatase (AP) Elevation

- Serum AP consists of isoenzymes from different organs: liver, bone, intestine and placenta in 3rd trimester of pregnancy
- Measure serum 5' nucleotidase or GGTP (parallel liver AP) or identify the source by electrophoresis (AP fractionation)

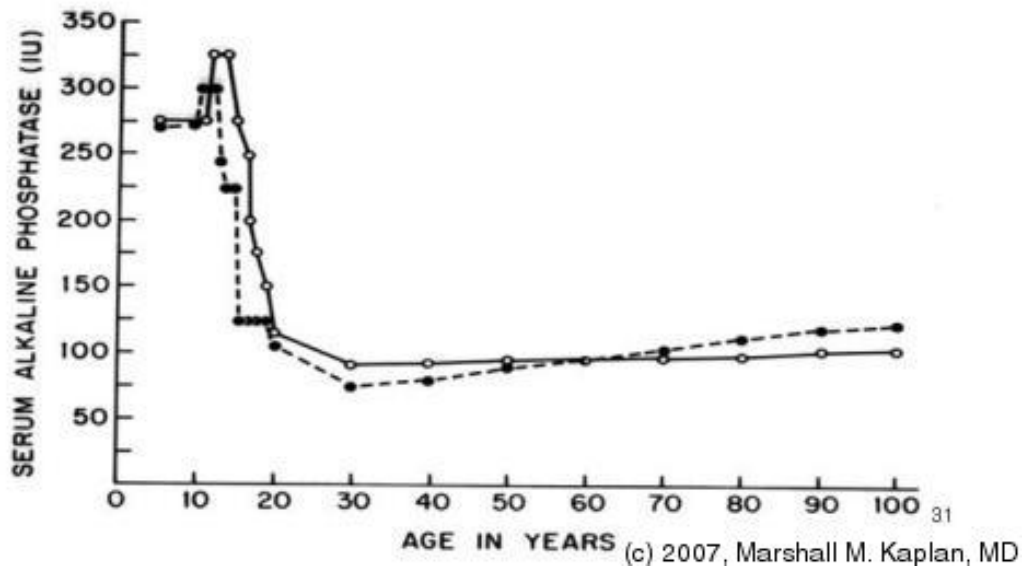


Source: M Kaplan 30

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31. Serum vs. Age in Men and Women

Serum vs. Age in Men and Women



32. Evaluation of Elevated AP

Evaluation of Elevated AP

- Identify the source by electrophoresis (AP fractionation); measure serum 5' nucleotidase or GGTP
- Differential diagnosis of chronic cholestasis
 - Partial obstruction of bile ducts
 - Infiltrative disorders: sarcoidosis, metastatic CA
 - Drug induced cholestasis
 - Primary biliary cirrhosis (PBC)
 - Primary sclerosing cholangitis (PSC)
 - Adult bile ductopenia

33. Evaluation of Chronically Elevated AP

Evaluation of Chronically Elevated AP

- Right upper quadrant ultrasound
- Antimitochondrial antibodies test (AMA)
- ERCP if bile ducts are dilated or negative AMA test
- Liver biopsy if ultrasound is normal or ERCP is suggestive PSC

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34. Source of Alkaline Phosphatase (AP) Elevation

Source of Alkaline Phosphatase (AP) Elevation

(Brensilver and Kaplan, Gastro 1975)

- 317 patients with elevated AP
- Liver source • 253
- Bone source • 58
- Liver and bone source • 4
- Intestinal source • 2

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35. Isolated or Inappropriate AP Elevation

Isolated or Inappropriate AP Elevation

- 87 of 251 patients with elevated AP
 - CHF
 - Tumor not involving the liver
 - Hodgkin's disease (stage 1 and 2)
 - Thyroid disorders
 - Infection not involving the liver
 - Diabetes, gastric ulcer

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36. Gamma Glutamyl Transferase

Gamma Glutamyl Transferase

- Sensitivity -- Cholestasis, ETOH
- Specificity -- Very Low
- Non-liver causes: pancreatic disease, MI, renal failure, COPD, DM
- High GGTP levels in pts taking phenytoin
- Sensitivity in alcoholism is 52 to 94%
- May be used in evaluating other serum enzyme levels or support ETOH disease

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37.

Disease Tests

Disease	Tests of Biosynthesis		AST	ALT	Alk Phos	Bilirubin	
	Long Half-Life Albumin	Short Half-Life Prothrombin Time				Total	Direct
Hepatocellular diseases (Acute Hepatitis, CHF, Toxin)	Normal	Normal to Prolonged	>500	>AST	Moderate Elevation	Increased	Increased
Chronic, Cirrhosis	Decreased	Prolonged	<,300	<300	Moderate Elevation	Normal or Increased	Normal or Increased
Bile Duct Obstruction	Normal	Normal	<500	<500*	Elevated, ≥4x normal	Normal or increased	Normal or increased
Partial Bile duct Obstruction & Infiltrative diseases	Normal	Normal	<100	<100	Moderate Elevation	Normal	Normal
Hemolysis	Normal	Normal	Normal	Normal	Normal	Indirect Increased	Normal

* ALT and AST levels may be >500 in acute bile duct obstruction and return to lower values within 24 hrs

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