Pathology of Hepatobiliary system and Pancreas

Inflammation of the Pancreas

- 1. Acute hemorrhagic pancreatitis
  - a. Etiology
    - i. Gallstones
    - ii. Alcohol
    - iii. Hypercalcemia
    - iv. Drugs
    - v. Shock
    - vi. Infections
    - vii. Trauma
    - viii. Scorpion stings

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- b. Mechanism: Pancreatic acinar cell injury results in activation of the pancreatic enzymes and enzymatic destruction *of the pancreatic parenchyma*
- c. Clinical presentation
  - i. Stabbing epigastric abdominal pain radiating to the back
  - ii. Shock
  - iii. Hypocalcemia
- d. Lab: elevation *of serum amylase and lipase*
  - Serum amylase and lipase concentrations increase on the first day of acute pancreatitis and return to normal in 3 to 7 days.
  - Lipase is more specific for pancreatitis, but both enzymes may be increased in renal failure and various abdominal conditions (eg: perforated ulcer, mesenteric vascular occlusion, intestinal obstruction).
  - The serum of patients with hypertriglyceridemia may contain a circulating inhibitor that must be diluted before an elevation in serum amylase can be detected.
  - *Urinary amylase*
- e. Gross
  - i. Focal pancreatic hemorrhage and liquefication
  - ii. Chalky, white-yellow fat necrosis *of adjacent adipose tissue*

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- f. Micro
  - i. Liquefactive necrosis *of pancreatic parenchyma*
  - ii. Acute inflammation
  - iii. Enzymatic fat necrosis
  - iv. Necrosis *of blood vessels causes hemorrhage*
- g. Complications
  - i. May develop acute respiratory distress syndrome (ARDS) or disseminated intravascular coagulation (DIC)
  - ii. Pseudocyst
  - iii. Pancreatic calcifications
- h. Prognosis: Severe cases have a 30% mortality rate

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Ranson's prognostic signs

- **Ranson's prognostic signs** help predict the prognosis of acute pancreatitis. Five of Ranson's signs can be documented at admission:
  - Age > 55 yr
  - Plasma glucose > 200 mg/dL (> 11.1 mmol/L)
  - Serum LDH > 350 IU/L
  - AST > 250 UL
  - WBC count > 16,000/μL
- The rest of Ranson's signs are determined within 48 h of admission:
  - Hct decrease > 10%
  - BUN increase > 5 mg/dL (> 1.78 mmol/L)
  - Serum Ca < 8 mg/dL (< 2 mmol/L)
  - PaO_2 < 60 mm Hg (< 7.98 kPa)
  - Base deficit > 4 mEq/L (> 4 mmol/L)
  - Estimated fluid sequestration > 6 L
- Mortality increases with the number of positive signs: If < 3 signs are positive, the mortality rate is < 5%; if ≥ 3 are positive, mortality is 15 to 20%.
- APACHE II index calculated on the second day also correlates with prognosis.

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Chronic pancreatitis

- a. Middle-age male alcoholics
- b. Definition: chronic inflammation, atrophy, and fibrosis of the pancreas secondary to repeated bouts of pancreatitis
- c. Gross: firm, white, fibrotic pancreas
- d. Micro
  - i. Extensive fibrosis and parenchymal atrophy
  - ii. Chronic inflammation
- e. Presentation
  - i. Abdominal pain
  - ii. Pancreatic insufficiency and malabsorption
  - iii. Pancreatic calcifications
  - iv. Pseudocyst
  - v. Diabetes (late complication)

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Diabetes Mellitus

- 1. Definition: chronic systemic disease characterized by insulin deficiency or peripheral resistance,resulting in hyperglycemia and nonenzymatic glycosylation of proteins
- 2. Diagnosis: fasting glucose> 126 mg/dl on at least two separate occasions or a positive glucose tolerance test

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Insulin-dependent diabetes mellitus (IDDM)

- a. Synonyms: type I, juvenile onset diabetes, brittle diabetes
- b. Epidemiology
  - i. Represents 10% of cases of diabetes
  - ii. Affects children and adolescents usually younger than 20
- c. Risk factors
  - HLA-DR_3, DR_4, and DQ
- d. Pathogenesis
  - i. Lack of insulin due to autoimmune destruction of Beta cells
  - ii. Absolutely dependent on insulin to prevent ketoacidosis and coma
- e. Etiology: thought to be caused by an autoimmune reaction triggered by an infection (Coxsackie B virus) in a genetically susceptible individual

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- f. Micro
  - i. Lymphocytic inflammation of the islets of Langerhans (insulitis)
  - ii. Loss of Beta-cells
  - iii. Fibrosis of the islets
- g. Presentation
  - i. Polydipsia, polyuria, and polyphagia
  - ii. Dehydration and electrolyte imbalance
  - iii. Metabolic ketoacidosis
  - iv. Coma and potentially death
- h. Treatment: insulin

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Non-insulin-dependent diabetes mellitus (NIDDM)

- a. Synonyms: type II, adult onset diabetes
- b. Epidemiology
  - i. Represents 90% of cases of diabetes
  - ii. Affects obese adults usually older than 30 years
  - iii. Incidence increases with age.
- c. Risk factors: obesity, increasing age, and genetic predisposition

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- d. Pathogenesis
  - i. Relatively reduced insulin secretion
  - ii. *Peripheral insulin resistance: reduced tissue sensitivity to insulin due to* decreased numbers of insulin receptors on the cell membranes
- e. Micro
  - i. Nonspecific changes
  - ii. May have focal atrophy and amyloid deposition in islets (hyalinization)

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- f. Presentation
  - i. Frequently asymptomatic
  - ii. Polydipsia, polyuria, and polyphagia
  - iii. Hyperosmolar nonketotic diabetic coma
- g. Treatment
  - i. Diet and weight loss
  - ii. Oral antidiabetic drugs
  - iii. Insulin

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Vascular pathology

- a. Diabetes is a major risk factor for atherosclerosis
- b. Myocardial infarction (most common cause of death)
- c. Stroke (CVA)
- d. Peripheral vascular disease
  - i. Atrophy of skin and loss of hair of lower extremity
  - ii. Claudication
  - iii. Nonhealing ulcers
  - iv. Gangrene of lower extremities
- e. Microvascular disease
  - i. Diffuse thickening of basement membranes
  - ii. Hyaline arteriolosclerosis

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Diabetic nephropathy

- a. Renal artery atherosclerosis
- b. Hyaline arteriolosclerosis of afferent and efferent arterioles
- c. Diffuse glomerulosclerosis
  - i. Nephrotic syndrome
  - ii. Increased mesangial matrix and mesangial proliferation
  - iii. Thickened basement membranes

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- d. *Nodular glomerulosclerosis(Kimmelstiel- Wilson disease)*
  - i. Nephrotic syndrome
  - ii. Nodular PAS(+) deposits of mesangial matrix
  - iii. Thickened basement membranes
- e. Pyelonephritis and necrotizing papillitis
- f. Renal failure (diabetic nephropathy is the most common cause of renal transplantation in adults)

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Diabetic retinopathy

- a. Nonproliferative phase
  - i. Microaneurysms
  - ii. Retinal hemorrhages and exudates
- b. Proliferative phase: neovascularization
- c. Increased rate of cataracts and glaucoma

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Diabetic neuropathy

- a. Peripheral neuropathy
- b. Neurogenic bladder
- c. Sexual impotence

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Pancreatic Tumors

- 1. Islet cell tumors
  - a. Insulinoma (Beta-cell tumor)
    - i. Most common type of islet cell tumor
    - ii. Tumor produces insulin
    - iii. Hypoglycemia, sweating, hunger, confusion, insulin coma
    - iv. Lab: elevated insulin and C-peptides
    - v. Treatment: glucose

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- b. Gastrinoma (G-cell tumor)
  - i. Tumor produces gastrin
  - ii. Aka Zollinger-Ellison syndrome
    - . Elevated serum gastrin
    - . Gastric hyperacidity
    - . Intractable peptic ulcers
  - iii. May arise outside the pancreas
  - iv. Associated with MEN I

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- c. Glucagonoma (alpha-cell tumor)
  - i. Tumor produces glucagon
  - ii. Hyperglycemia (diabetes), anemia, and skin rash
- d. Somatostatinoma (Delta -cell tumor)
  - i. Tumor produces somatostatin
  - ii. Somatostatin inhibits
    - . Insulin secretion ~ diabetes
    - . Gastrin secretion ~ hypochlorhydria
    - . Cholecystokinin secretion ~ gallstones and steatorrhea

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- e. VIPoma
  - i. Tumor produces vasoactive intestinal peptide (VIP)
  - ii. WDHA syndrome: watery diarrhea, hypokalemia, and achlorhydria

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Pancreatic carcinoma

- a. Epidemiology
  - i. Fifth most common cause of cancer death in the United States
  - ii. Incidence is increasing
  - iii. Most common between ages 60 and 80
  - iv. Risk factor: smoking
- b. Presentation
  - i. Vague signs and symptoms until late in the course
  - ii. Abdominal pain
  - iii. Migratory thrombophlebitis
  - iv. Obstructive jaundice
- c. Site: pancreatic head (60%), body (15%), and tail (5%)
- d. Micro
  - i. Adenocarcinoma arising from the duct epithelium
  - ii. Tumor desmoplasia and perineural invasion are common
- e. Tumor markers: CEA and CA19-9
- f. Treatment: surgical excision (Whipple procedure)
- g. Prognosis: very poor; 1-year survival ~ 10%

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Gallbladder and Biliary Tract Pathology

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Gallstones (Cholelithiasis)

- 1. Cholesterol stones
  - a. Composition: mostly cholesterol monohydrate
  - b. Risk factors
    - i. Female gender
    - ii. Obesity
    - iii. Pregnancy
    - iv. Oral contraceptives and hormone replacement therapy (HRT)
    - v. Incidence increases with age
    - vi. Genetics (Native American Pima and Navajo Indians)

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- 2. Pigmented bilirubinate stones
  - a. Composition: calcium salts and unconjugated bilirubin
  - b. Risk factors
    - i. Chronic hemolytic anemias
    - ii. Cirrhosis
    - iii. Bacteria
    - iv. Parasites *(Ascarisor Clonorchis[Opisthorchis] sinensis)*
- 3. Clinical features of gallstones
  - a. Presentation
    - i. Frequently asymptomatic
    - ii. Biliary colic: right upper quadrant pain due to impacted stones
  - b. Diagnosis: ultrasound

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- c. Complications
  - i. Cholecystitis
  - ii. Choledocholithiasis: calculi within the biliary tract
  - iii. Biliary tract obstruction
  - iv. Pancreatitis
  - v. Cholangitis

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Inflammatory Conditions

- 1. Acute cholecystitis
  - a. Definition: acute inflammation of the gallbladder, usually caused by cystic duct obstruction by gallstones
  - b. Presentation
    - i. Biliary colic
    - ii. Right upper quadrant (RUQ) tenderness on palpation
    - iii. Nausea and vomiting
    - iv. Low-grade fever and leukocytosis

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- c. Complications
  - i. Gangrene of the gallbladder
  - ii. Perforation and peritonitis
  - iii. Fistula formation and *gallstone ileus (small bowel obstruction by a large gallstone)*
- 2. Chronic cholecystitis
  - a. Definition: ongoing chronic inflammation of the gallbladder usually caused by gallstones
  - b. Micro: chronic inflammation
  - c. Late complication: calcification of the gallbladder ("porcelain gallbladder")

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- 3. Ascending cholangitis
- a. Definition: bacterial infection of the bile ducts ascending up to the liver, usually associatedwith obstruction of bile flow
- b. Presentation: biliary colic, jaundice, high fever and chills
- c. Organisms: gram-negative enteric bacteria

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Miscellaneous Conditions

- 1. Cholesterolosis
  - a. Gross: yellow speckling of the red-tan mucosa ("strawberry gallbladder")
  - b. Micro: collections of lipid-laden macrophageswithin the lamina propria
- 2. Hydrops of the gallbladder (mucocele):
  - chronic obstruction of the cystic duct leads to the resorption of the normal gallbladder contents and enlargement of the gallbladder by the production of large amounts of clear fluid (hydrops) or mucous secretions (mucocele)
  - Complication: infection

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Biliary Tract Cancer

- 1. Gallbladder cancer
  - a. Clinical presentation
    - i. Frequently asymptomatic until late in the course
    - ii. Cholecystitis
    - iii. Enlarged palpable gallbladder
    - iv. Biliary tract obstruction (uncommon)
  - b. X-ray: may have a calcified *"porcelain gallbladder"*
  - c. Micro: adenocarcinoma
  - d. Prognosis: poor; 5-year survival ~1 %

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- 2. Bile duct cancer
  - a. Bile duct carcinoma: carcinoma of the extrahepatic bile ducts
  - b. Cholangiocarcinoma: carcinoma of the intrahepatic bile ducts
  - c. Klatskin tumor: carcinoma of the bifurcation of the right and left hepatic bile ducts
  - d. Risk factors
    - i. Asia ~ *Clonorchis (Opisthorchis) sinensis (fluke)*
    - ii. Primary sclerosing cholangitis
  - e. Presentation: biliary tract obstruction
  - f. Prognosis: poor

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Liver Pathology

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Jaundice

- 1. General
  - a. Clinical jaundice occurs with bilirubin levels >2-3 mg/dl
  - b. Classic presentation: yellow skin (jaundice) and sclera (icterus)
  - c. Causes of jaundice
    - i. Overproduction of bilirubin
    - ii. Defectivehepatic bilirubin uptake
    - iii. Defective conjugation
    - iv. Defective excretion
- Unconjugated Versus Conjugated Bilirubinemia
  - CG → Unconjugated
  - DR → Conjugated

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- Increased RBC turnover
  - a. RBCs are the major source of bilirubin
  - b. Etiology
    - i. Hemolytic anemia
    - ii. Ineffective erythropoiesis (thalassemia, megaloblasticanemia, etc.)
  - c. Lab: increased unconjugated bilirubin
  - d. Chronic hemolytic anemia patients often develop pigmented bilirubinate gallstones
- 3. Physiologic jaundice of the newborn
  - a. Definition: transient unconjugated hyperbilirubinemia due to the immaturity of the liver
  - b. Risk factors
    - i. Prematurity
    - ii. Hemolytic disease of the newborn (erythroblastosis fetalis)
  - c. Complication: kernicterus
  - d. Treatment: phototherapy

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- Hereditary hyperbilirubinemias
- a. Gilbert syndrome
  - i. Common benign inherited disorder
  - ii. Unconjugated hyperbilirubinemia
  - iii. Jaundice is related to stress (fasting, infection, etc.).
  - iv. Mechanism: bilirubin glucuronosyltransferase (UGT) deficiency
  - v. No clinical consequences
- b. Crigler-Najjar syndrome
  - i. Unconjugated hyperbilirubinemia
  - ii. Type I: fatal because of kernicterus
  - iii. Type II: jaundice
  - iv. Mechanism: bilirubin glucuronosyltransferase (UGT) absence or deficiency
- c. Dubin-Johnson syndrome
  - i. Benign autosomal recessive disorder
  - ii. Decreased bilirubin excretion due to a defect in the canalicular transport protein
  - iii. Conjugated hyperbilirubinemia
  - iv. Gross: black pigmentation of the liver
  - v. No clinical consequences
- d. Rotor syndrome
  - i. Autosomal recessive
  - ii. Conjugated hyperbilirubinemia
  - iii. Similar to Dubin-Johnson but without liver pigmentation
  - iv. No clinical consequences

Biliary tract obstruction

- a. Etiology
  - i. Gallstones
  - ii. Tumors (pancreatic, gallbladder, and bile duct)
  - iii. Stricture
  - iv. Parasites (liver *flukes-Clonorchis [Opisthorchis]sinensis)*
- b. Presentation
  - i. Jaundice and icterus
  - ii. Pruritus due to increased plasma levels of bile acids
  - iii. Abdominal pain, fever,and chills
  - iv. Dark urine (bilirubinuria)
  - v. Pale clay-colored stools
- c. Lab
  - i. Elevated conjugated bilirubin
  - ii. Elevated alkaline phosphatase and 5' -nucleotidase

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Primary biliary cirrhosis (PBC)

- a. Definition: chronic liver disease of unknown etiology (autoimmune) characterized by inflammation and granulomatous destruction of intrahepatic bile ducts
- b. Epidemiology: males : females=1:10;age 30-65 years
- c. Presentation
  - i. Middle-aged women
  - ii. Obstructive jaundice
  - iii. Pruritus
  - iv. Xanthomas, xanthelasmas, and elevated serum cholesterol
  - v. Fatigue
  - vi. Cirrhosis (late complication)
- d. Lab
  - i. Elevated conjugated bilirubin
  - ii. Elevated alkaline phosphatase and 5'-nucleotidase
  - iii. *Antimitochondrial autoantibodies (AMA) are present in more than 90%*
- e. Most patients have another autoimmune disease (scleroderma, RA, or SLE)
- f. Micro: lymphocytic and granulomatous destruction of interlobular bile ducts

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Primary sclerosing cholangitis (PSC)

- a. Definition: chronic liver disease of unknown etiology characterized by segmental inflammation and fibrosing destruction of intrahepatic bile ducts
- b. Epidemiology
  - i. Males : females= 2:1, age 20-40 years
  - ii. Majority are associated with ulcerative colitis
- c. Presentation: similar to PBC
- d. Micro
  - i. Periductal chronic inflammation
  - ii. Concentric fibrosis around bile ducts
  - iii. Segmental stenosis of bile ducts
- e. Cholangiogram: "beaded appearance" of bile ducts
- f. Complications: biliary cirrhosis and cholangiocarcinoma

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Cirrhosis

- 1. Definition: end-stage liver disease characterized by disruption of the liver architecture
- by bands of fibrosis that divide the liver into nodules of regenerating liver parenchyma
- 2. Etiology
  - a. Alcohol
  - b. Viral hepatitis
  - c. Biliary tract disease
  - d. Hemochromatosis
  - e. Cryptogenic/idiopathic
  - f. Wilson disease
  - g. alpha-1-antitrypsin deficiency
- 3. Gross
  - a. Micronodular: nodules <3 mm
  - b. Macronodular: nodules> 3 mm
  - c. Mixed micronodular and macronodular
  - d. At the end stage, most diseases result in a mixed pattern, and the etiology may not be distinguished based on the appearance
- 4. Mechanism: Fibrosis is produced by the Ito cell (hepatic stellate cells)

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- 5. Consequences
  - a. Portal hypertension
    - i. Ascites
    - ii. Splenomegaly/hypersplenism
    - iii. Esophageal varices
    - iv. Hemorrhoids
    - v. Caput medusae
  - b. Decreased detoxification
    - i. Hepatic encephalopathy
    - ii. Spider angiomata
    - iii. Palmar erythema
    - iv. Gynecomastia
  - c. Decreasedsynthesis
    - i. Hypoalbuminemia
    - ii. Decreasedclotting factors
  - d. Hepatorenal syndrome
  - e. Hepatopulmonary syndrome

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Viral Hepatitis

- 1. Hepatitis viruses
- a. Clinical presentation
  - i. Asymptomatic
  - ii. Malaise and weakness
  - iii. Nauseaand anorexia
  - iv. Jaundice
  - v. Urinemaybedark
- b. Lab : markedly elevated alanine amino transferase (ALT) and aspartate amino transferase(AST)
- c. Diagnosis: serology

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- 2. Acute viral hepatitis
  - a. Definition: signs and symptoms <6 months
  - b. Caused by all of the hepatitis viruses
  - c. Micro
    - i. Lobular disarray
    - ii. Hepatocyte swelling (balloon cells)
    - iii. Apoptotic hepatocytes (Councilman's bodies)
    - iv. Lymphocytes in portal tracts and in the lobule
    - v. Hepatocyte regeneration
    - vi. Cholestasis

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- 3. Chronic viral hepatitis
- a. Definition: signs and symptoms >6 months
- b. Caused by hepatitis virus B, C, and D
- c. Micro
  - i. Chronic persistent hepatitis: inflammation confined to portal tracts
  - ii. Chronic active hepatitis: Inflammation spills into the parenchyma, causing an interface hepatitis (piece meal necrosis of limiting plate)
  - iii. Hepatitis B often has "ground glass" hepatocytes (cytoplasmic HBsAg)

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Common Virus Name	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
Common disease name	"Infectious"	"Serum"	"Post-transfusion" or "non-A, non-B"	"Delta"	"Enteric"
Virus	Picornavirus naked capsid RNA	Hepadnavirus enveloped DNA	Flavivirus enveloped RNA	Defective enveloped circular-RNA	Calicivirus naked capsid RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Severity	Mild	Occasionally severe	Usually subclinical	Co-infection with HBV occasionally severe; super-infection with HBV often severe	Normal patients: mild; pregnant patients: severe
Chronicity or carrier state	No	Yes	Yes (high)	Yes	No
Clinical diseases	Acute hepatitis	• Acute hepatitis • Chronic hepatitis • Cirrhosis • Hepatocellular carcinoma (HCC)	• Acute hepatitis • Chronic hepatitis • Cirrhosis HCC • HCC	• Acute hepatitis • Chronic hepatitis • Cirrhosis	Acute hepatitis
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBcAg, and anti-HBc IgM	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	
Prevention	Vaccine, hygiene	Vaccine			Hygiene

Interpretation of Tests for Acute Hepatitis B

Anti-HBc IgM	Anti-HBc IgG	HBsAg	Anti-HBs	Interpretation
Positive	Negative	Positive	Negative	Acute HBV infection
Negative	Negative	Positive	Negative	Early acute HBV infection
Negative	Positive	Negative	Positive	Resolved acute HBV infection
Negative	Negative	Negative	Positive	Not infected Prior vaccination for HBV
Negative	Negative	Negative	Negative	Not infected
Negative	Positive	Positive	Negative	Chronic HBV infection

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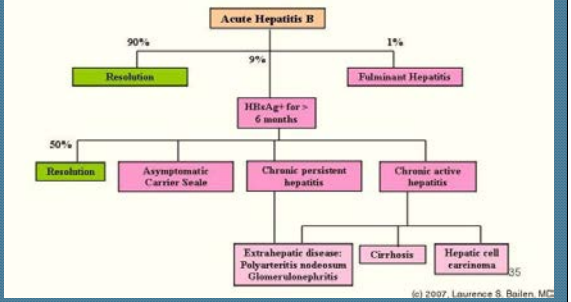
Hepatitis B: Clinical Outcomes of Acute HBV Infections



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Amebic Liver Abscesses

- Rare in the Developed Countries
  - Common in India, Mexico, South America, etc.
- Organism: *Entamoeba histolytica*
- Gross: necrotic abscess filled with brown pastelike material ("anchovy paste")
- Treatment: antibiotics /surgical drainage

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Alcoholic Liver Disease

- 1. Fatty change (steatosis)
  - a. Reversible with abstinence
  - b. Gross: enlarged, yellow, greasy liver
  - c. Micro
    - i. Centrilobular macrovesicular steatosis (reversible)
    - ii. Eventual fibrosis around the central vein (irreversible)
- 2. Alcoholic hepatitis
  - a. Acute illness usually following a heavy drinking binge
  - b. Clinically variable
    - i. No symptoms
    - ii. RUQ pain, hepatomegaly, jaundice, malaise, and anorexia
    - iii. Fulminant liver failure

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- c. Micro
  - i. Hepatocyte swelling (ballooning) and necrosis
  - ii. Mallory bodies (cytokeratin intermediate filaments)
  - iii. Neutrophils
  - iv. Fatty change
  - v. Eventual fibrosis around the central vein
- d. Prognosis
  - i. Each episode has a 20% risk of death
  - ii. Repeated episodes increase the risk of developing cirrhosis

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- 3. Alcoholic cirrhosis
  - a. Develops in 15% of alcoholics
  - b. Micronodular cirrhosis
  - c. Most common disease requiring liver transplantation in adults

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Metabolic Liver Disease

- 1. Wilson disease (hepatolenticular degeneration)
  - a. Definition: genetic disorder of copper metabolism resulting in accumulation of toxic levels of copper in various organs
  - b. Genetics
    - i. Autosomal recessive (chromosome 13)
    - ii. WD gene (ATP7B) codes for a hepatocyte canalicular copper-transporting ATPase
  - c. Mechanism: decrease biliary excretion of copper
  - d. Presents in childhood or adolescence with liver disease
  - e. Distribution of disease
    - i. Liver: fatty change, chronic hepatitis, and micro nodular cirrhosis
    - ii. Cornea: Kayser-Fleischer rings (copper deposition in Descemet's membrane)
    - iii. Brain: neurological and psychiatric manifestations, movement disorder

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- f. Diagnosis
  - i. Decreased serum ceruloplasmin levels
  - ii. Increased tissue copper levels (liver biopsy)
  - iii Increased urinary copper excretion
- g. Treatment
  - i. Copper chelators (D-penicillamine)
  - ii. Liver transplantation is curative

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- 2. Hemochromatosis
  - a. Definition: increased levels of iron, leading to tissue injury
  - b. Hereditary (primary)
    - i. Recessive disorder (HLA-H gene on chromosome 6p)
    - ii. Mechanism: increased small-intestine absorption of iron
  - c. Secondary (example: transfusions for chronic anemias)
  - d. Epidemiology
    - i. Males : females= 5:1
    - ii. Common in people of Northern European descent

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- e. Distribution of disease
  - i. Liver : micronodular cirrhosis and HCC (200 times the normal risk ration [RR])
  - ii. Pancreas: diabetes mellitus
  - iii. Skin: hyperpigmentation ("bronzing")
  - iv. Heart: congestive heart failure and cardiac arrhythmias
  - v. Gonads: hypogonadism
- f. Diagnosis
  - i. Markedly elevated serum iron and ferritin
  - ii. Prussian blue stain and increased tissue iron levels (liver biopsy)
- g. Treatment: phlebotomy

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- 3. alpha-1-Antitrypsin deficiency
  - a. Definition: autosomal recessive disorder characterized by production of defective alpha-1-antitrypsin , which accumulates in hepatocytes and causes liver damage and low serum levels of alpha-1-AT
  - b. Genetics
    - i. a1-AT is produced by the Pi gene (chromosome 14)
    - ii. More then 75 gene variants described
    - iii. Homozygous PiZZ have severe reductions (15% of normal) in enzyme levels
  - c. Distribution of disease
    - i. Liver: micronodular cirrhosis and an increased risk of HCC
    - ii. Lungs: panacinar emphysema ;
  - d. Micro: PAS positive, eosinophilic cytoplasmic globules within hepatocytes
  - e. Treatment
    - i. Prevention of emphysema: no smoking
    - ii. Liver transplantation is curative

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- 4. Reye syndrome
  - a. Rare, potentially fatal disease
  - b. Occurs in young children with viral illness (varicella or influenza) treated with aspirin
  - c. Mechanism: unknown; mitochondrial injury and dysfunction play an important role
  - d. Distribution of disease
    - i. Liver : fatty change (microvesicular steatosis)
    - ii. Brain: cerebral edema/encephalopathy
  - e. Prognosis
    - i. Complete recovery (75%)
    - ii. Coma, permanent neurologic deficits, and death
  - f. Treatment: supportive

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Miscellaneous

- 1. Budd-Chiari syndrome (hepatic vein thrombosis)
  - a. Definition: occlusion of the hepatic vein by a thrombus, often resulting in death
  - b. Etiology
    - i. Polycythemia vera
    - ii. Pregnancy
    - iii. Oral contraceptives
    - iv. Paroxysmal nocturnal hemoglobinuria
    - v. Hepatocellular carcinoma
    - vi. Idiopathic
  - c. Clinical: abdominal pain, hepatomegaly, ascites,and death
  - d. Micro: centrilobular congestion and necrosis

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- 2. Chronic passive congestion of the liver
  - a. Definition: "backup of blood" into the liver, usually due to right-sided heart failure
  - b. Gross: nutmeg pattern of alternating dark (congested central areas) and light (portal tract areas) liver parenchyma
  - c. Micro: centrilobular congestion
  - d. Complications
    - i. Centrilobular necrosis: ischemic necrosis of centrilobular hepatocytes
    - ii. Long-standing congestion ~ centrilobular fibrosis ~ cardiac cirrhosis

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Benign Liver Tumors

- 1. Hemangioma
  - a. Most common primary tumor of the liver
  - b. Benign vascular tumor
  - c. Gross: subcapsular, red, spongy mass
  - d. Often asymptomatic and detected incidentally
- 2. Hepatic adenoma (liver cell adenoma)
  - a. Young women
  - b. Related to oral contraceptive use
  - c. Subcapsular adenomas may rupture, causing an intraperitoneal hemorrhage
  - d. Micro: resembles normal liver except for the lack of portal tracts
  - e. May regress after oral contraceptives are discontinued

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Malignant Liver Tumors

- 1. Hepatocellular carcinoma (HCC)
  - a. Most common primary malignant tumor of the liver
  - b. Asia and Japan> United States
  - c. Etiology: cirrhosis, hepatitis B and C virus, alcohol, aflatoxin Bl
  - d. Tendency for hematogenous spread and invasion of portal and hepatic veins
  - e. Tumor marker: a-fetoprotein (AFP)
  - f. Fibrolamellar variant: younger age, fibrous bands, and better prognosis

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- 2. Cholangiocarcinoma
  - a. Uncommon(< 10%)
  - b. Risk factors
    - i. Thorotrast
    - ii. *Clonorchissinensis (liver fluke)*
  - c. Micro: adenocarcinoma arising from bile duct epithelium
  - d. Discovered late in the course
  - e. Poor prognosis (average survival is 6 months)

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- 3. Angiosarcoma
  - a. Rare, malignant vascular neoplasm
  - b. Chemical carcinogens: vinyl chloride, thorotrast, and arsenic
  - c. Aggressive tumors with a poor prognosis
- 4. Metastatic tumors to the liver
  - a. Most common tumor found within the liver
  - b. Common primary sites: colon, breast, and lung
  - c. Tend to occur as multiple well circumscribed masses

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