Acute and chronic hepatitis

Morphologic classification of liver diseases

I. Parenchymal

A. Hepatitis (viral, drug-induced, toxic)
   1. Acute
   2. Chronic (persistent or active)

B. Cirrhosis
   1. Alcoholic (portal, nutritional, Laennec's cirrhosis)
   2. Postnecrotic
   3. Biliary
   4. Hemochromatosis
   5. Rare types (Wilson's disease, galactosemia, cystic fibrosis of pancreas, α1-antitripsin deficiency)

C. Infiltrations
   1. Glycogen
   2. Fat (neutral fat, cholesterol, gangliosides, cerebrosides)
   3. Amyloid
   4. Lymphoma, leukemia
   5. Granuloma (sarcoidosis, tuberculosis, idiopathic)

D. Space-occupying lesions
   1. Hepatoma, metastatic tumor
   2. Abscess (pyogenic, amoebic)
   3. Cysts (polycystic disease, Echinococcus)
   4. Gumma

E. Functional disorders associated with jaundice
   1. Gilbert's syndrome
   2. Crigler-Najjar syndrome
   3. Dubine-Johnson and Rotor syndrome
   4. Cholestasis of pregnancy and benign recurrent cholestasis

II. Hepatobiliary

A. Extrahepatic biliary obstruction (by stone, stricture, or tumor)
B. Cholangitis

II. Vascular

A. Chronic passive congestion and cardiac cirrhosis
B. Hepatic vein thrombosis (Budd-Chiari syndr.)
C. Portal vein thrombosis
D. Pylephlebitis
### Clinical and epidemiologic features of acute viral hepatitides

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
<th>GB virus C (formerly Hepatitis G)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation (days)</strong></td>
<td>15-45, mean 25</td>
<td>30-150, mean 75</td>
<td>15-120, mean 50</td>
<td>15-150, mean 30</td>
<td>15-50</td>
<td>14-20</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Acute</td>
<td>Insidious or acute</td>
<td>Insidious</td>
<td>Insidious or acute</td>
<td>Acute</td>
<td>Acute, mild</td>
</tr>
<tr>
<td><strong>Age preference</strong></td>
<td>Children, young adults</td>
<td>Young adults (sexual and percutaneous), babies, toddlers</td>
<td>Any age, but more common in adults</td>
<td>Any age (similar to HBV)</td>
<td>Any age</td>
<td>Young adults (similar to hepatitis C virus)</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td>Fecal-oral +++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Percutaneous Unusual</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Unusual</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Perinatal -</td>
<td>+++</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Sexual ±</td>
<td>++</td>
<td>±</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Clinical severity</strong></td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Moderate</td>
<td>Occasionally severe</td>
<td>Usually mild</td>
<td>Generally mild</td>
</tr>
<tr>
<td><strong>Fulminant</strong></td>
<td>0.1%</td>
<td>0.1-1%</td>
<td>0.1%</td>
<td>5 - 20%</td>
<td>no</td>
<td>Reported</td>
</tr>
<tr>
<td><strong>Chronicity</strong></td>
<td>0%</td>
<td>5%</td>
<td>85%</td>
<td>5 - 70%</td>
<td>no</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Carrier</strong></td>
<td>None</td>
<td>+ (neonatal infection)</td>
<td>0.5%-1.0%</td>
<td>Variable</td>
<td>Animal reservoirs (pig, wild boar, rabbit)</td>
<td>Variable (more common in HIV pos.)</td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td>None</td>
<td>0.1%-30%</td>
<td>+</td>
<td>±</td>
<td>Undetermined</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>0.2%</td>
<td>0.5-2%</td>
<td>0.2%</td>
<td>2%-20%</td>
<td>Particularly in pregnant women</td>
<td>Reported</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>None</td>
<td>Interferon Antiviral drugs</td>
<td>Interferon Antiviral drugs</td>
<td>Unknown</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td>pre/post-exposure immunization immunoglobulin, inactivated vaccine</td>
<td>Hepatitis B immunoglobulin Recombinant vaccine</td>
<td>pre/post-exposure immunization</td>
<td>No vaccines to date Risk behavior modification</td>
<td>HBV vaccine (none for HBV carriers) pre/post-exposure immunization</td>
<td>Vaccination exists (in China) ensure safe drinking water</td>
</tr>
</tbody>
</table>
Groups with increased risk of hepatitis B virus (HBV) infection
- Medical, dental, and laboratory workers and others with exposure to human blood
- Homosexual men
- Heterosexuals with multiple sex partners or with sexually transmitted diseases
- Highly HBV-endemic populations, eg, Alaskan natives
- Household contacts of HBsAg-positive individuals
- Parenteral drug users who share needles
- Hemophilia patients
- Hemodialysis patients
- Patients for whom multiple blood or blood product infusions are anticipated
- Prison inmates and staff
- Staff and patients of institutions for mentally disabled
- Travelers to highly HBV-endemic areas with anticipated exposure to human blood, sexual contacts with locals, or prolonged living in households with locals
- Newborn infants of serum HBsAg-positive mothers

Laboratory assessment in acute hepatitis B

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Hematologic</th>
<th>Urine/Stool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td><strong>Common</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>- Total bilirubin ↑, Direct &gt; indirect</td>
<td>- Lymphopenia</td>
<td>- Urobilinogen (bilirubinuria)</td>
</tr>
<tr>
<td>- Alkaline phosphatase ↑</td>
<td>- Neutropenia</td>
<td>- Clay-, gray-, or light-colored stool</td>
</tr>
<tr>
<td>- ALT ↑</td>
<td>- Elevated ESR</td>
<td>- Rarely proteinuria</td>
</tr>
<tr>
<td>- AST ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- LDH ↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Serum IgG and IgM increased in third of patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inconstant</th>
<th>Infrequent/rare</th>
<th>Infrequent/rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Albumin-unchanged or ↓</td>
<td>- Prolongation of prothrombin time</td>
<td>- Proteinuria</td>
</tr>
<tr>
<td>- Globulin-unchanged or</td>
<td>- Hemolytic anemia</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infrequent/rare</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cholesterol, triglycerides ↑</td>
<td></td>
</tr>
<tr>
<td>- α-Fetoprotein ↑</td>
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</tbody>
</table>

GB virus C (formerly hepatitis G): A newly discovered hepatitis virus
- 9.5-kb RNA virus, ss, positive sense
- Similar to flaviviruses and HCV
- Transmission via transfusion (and other percutaneous routes?)
- Accounts for 0.4% of all community-acquired viral hepatitis, 1.4% of community-acquired non-A, non-B hepatitis
- Causes persistent infection with slow progression, generally mild to chronic hepatitis
- Coinfection with HCV possible, and occasionally HBV
Data suggest prevalence of hepatitis G virus in blood donors exceeds HCV and is not related to ALAT status

**Hepatitis from nonhepatotropic viruses**: Herpesviruses

**Herpes simplex virus I and II**

- Varicella-zoster
- Cytomegalovirus
- Epstein-Barr virus
- Adenovirus

**Enteric viruses**

- Coxsackievirus B
- Echovirus
- Paramyxovirus
- Rubeola
- Togavirus
- Rubella

**Arboviruses**

- Yellow fever
- Crimean-Congo fever
- Rift Valley fever
- Dengue fever
- Kyasanur Forest disease
- Korean hemorrhagic fever

**Arenaviruses**

- Lassa fever
- Argentinian/Bolivian hemorrhagic fever

**Filoviruses**

- Marburg virus
- Ebola virus

**Acute alcoholic hepatitis**

**General Considerations**

- Alcohol induced parenchymal necrosis or acute or chronic inflammation.
- Most common cause of cirrhosis.
- Develops in 1/3 of heavy drinkers; the exact prevalence and incidence: not known, about 1/3. In general, the longer the duration of drinking (10-15 or more years) and the larger the alcohol consumption (usually more than 120 g of alcohol per day), the greater the probability of developing alcoholic hepatitis and cirrhosis.
• Women – are more susceptible than men.
• Diagnosis with certainty: liver biopsy.

Symptoms and Signs
• History: a recent period of heavy drinking. Nausea. Anorexia.
• Hepatomegaly, jaundice, abdominal pain and tenderness, splenomegaly, ascites, fever, encephalopathy.
• Clinical presentation: asymptomatic patient with an enlarged liver → critically ill individual who dies quickly.

Laboratory Findings
• Anemia: variable(macrocytic), Leukocytosis: shift to the left, occasionally leukopenia, thrombocytopenia.
• ASAT: usually <300 U/L. ALAT: almost invariably < ASAT. Alkaline phosphatase is ↑, rarely more than 3X the normal value. Serum bilirubin ↑ in 60-90% of patients; if >100 uM/l → severe process. Serum albumin ↓. Gamma globulin ↑.
• Liver biopsy: macrovesicular fat, PMN infiltration, Mallory bodies (alcoholic hyaline)
Micronodular cirrhosis: possible.

Special Procedures
• Ultrasound: to rule out biliary obstruction, to assess for subclinical ascites.
• CT scanning with intravenous contrast: to assess patients for collateral vessels, space-occupying lesions of the liver, concomitant disease of the pancreas.

Complications
• Unfortunate decision to perform laparotomy. The postoperative mortality rate is very high (poor nutritional status, compromised synthesizing function of the liver).

Treatment
• Discontinue all alcoholic beverages
• Sufficient amounts of carbohydrate and calories to reduce endogenous protein catabolism and to support gluconeogenesis and to prevent hypoglycemia.
• Administration of vitamins: particularly folic acid
• Methylprednisolone: beneficial in patients with alcoholic hepatitis and either encephalopathy or very elevated bilirubin and prolonged prothrombin times.
• Liver transplantation

Prognosis
• Short-Term: the presence of asterixis: increased likelihood of death. If PTI is slightly enlarged: the 1-year mortality rate is 7.1%, rising to 18% if there is progressive prolongation of that parameter during hospitalization. If PTI is moderately-severely enlarged: mortality rate at 1 year: 42%.
• Long-term: ? able to abstain from drinking

Differential diagnosis of chronic hepatitis
Viral hepatitis
• Hepatitis B
• Hepatitis D
• Hepatitis C
• Hepatitis G

Inherited metabolic disease
• Wilson's disease
• α1-Antitrypsin deficiency

Autoimmune

Cryptogenic

Drug-induced
• Isoniazid
• Methyldopa
• Diclofenac
• Oxyphenisatin
• Glafenine
• Nitrofurantoin
• Pemoline
• Dantrolene

Diagnosis and treatment of chronic viral hepatitides

Diagnosis:
• Elevated ASAT/ALAT by at least 3 times of the normal for more than 6 months
• Liver biopsy

Therapy:

<table>
<thead>
<tr>
<th>Chronic hepatitis B</th>
<th>Chronic hepatitis C</th>
</tr>
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<tbody>
<tr>
<td>Interferons</td>
<td>Interferons</td>
</tr>
<tr>
<td>• IFN-α</td>
<td>• IFN-α</td>
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<tr>
<td>• pegilated IFN-α</td>
<td>• pegilated IFN-α</td>
</tr>
<tr>
<td>Antiviral drugs</td>
<td>Antiviral drugs</td>
</tr>
<tr>
<td>• ribavirine</td>
<td>• ribavirine</td>
</tr>
<tr>
<td>• telbivudine</td>
<td>• boceprevir</td>
</tr>
<tr>
<td>• entecavir</td>
<td>• telaprevir</td>
</tr>
<tr>
<td>• tenofovir</td>
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Autoimmune chronic hepatitides

Chronic autoimmune hepatitis
• Antinuclear antibody (ANA)
• Anti-smooth muscle antibody (SMA)
- Anti-liver-kidney microsoma (LKM-1) antibody positivity

**Primary biliary chirrhosis (PBC)**
- Antinuclear antibody (ANA)
- Anti-mitochondrial antibody (AMA) positivity

**Primary scleroticizing cholangitis**
- Perinuclear antineutrophil cytoplasmatic antibody (p-ANCA) positivity

**Hepatitis associated with systemic autoimmune diseases**
- SLE, vasculitides

**Drug- and toxin-induced liver disease**

**Direct Hepatotoxic Group**
- dose-related severity
- reproducibility in animals
- a latent period following exposure
- susceptibility in all individuals.
- Acetaminophen, alcohol, carbon tetrachloride, chloroform, heavy metals, mercaptopurine, phosphorus, tetracyclines, valproic acid, vitamin A.

**Viral Hepatitis-like Reactions**
- Sporadic reaction - host idiosyncrasy
- Amiodarone, aspirin, chloramphenicol, chlorotetracycline, cinchophen, dantrolene, halothane, ketoconazole, methoxyflurane, methyl dopa, oxacillin, phenylbutazone, pyrizinamide, quinidine, streptomycin, sulfamethoxypyridazine, zoxazolamine.

**Cholestatic reactions**

**A. Noninflammatory**
- Direct effect on biliary tract
- Azathioprine, mercaptopurine, metranol, methytestosteron, norethanoldrolone

**B. Inflammatory**
- Inflammation of portal system with allergic features, e.g., eosinophilia
- Chlorthiazide, chlorpromazine, chlorpropamide, erythromycin estolate, penicillamine, prochlorperazine, promazine, sulfadiazine, thiouracils.

**Chronic Active Hepatitis**
- Clinically and histologically indistinguishable from postviral chronic active hepatitis.
- Aspirin, chlorpromazine, dantrolene, halothane, isoniazic, methyl dopa, nitrofurantoin, oxyphenisatin, sulfonamides.

**Miscellaneous Reactions**

**A. Fatty Liver**
- Large fatty inclusions: alcohol, amiodarone, corticosteroids, methotrexate
- Small cytoplasmic droplets: tetracyclines, valproic acid

**B. Granulas:** allopurinol, quinidine, phenylbutazone, phenytoin

**C. Cirrhosis:** methotrexate

**D. Peliosis hepatitis:** anabolic steroids, azathioprine, oral contraceptive steroids

**E. Neoplasm:** oral contraceptive steroids

**Fulminant hepatic failure**
Typical pathologic picture: extensive necrosis of large areas of the liver.

**Symptoms**

**Laboratory tests**
Extreme hepatocellular damage.

**Course**
- Rapidly progressive course terminating in death in <10 days
- More insidious course: progressive clinical deterioration over a 6- to 8-week period, encephalopathy and then death.

**Treatment**
- Monitoring of the patient, vigorous correction of deficits: coagulation defects; disordered fluid, electrolyte, acid-base balance; hypoglycemia; nitrogenous intoxication.
- Provide the hope that some patients will survive who might otherwise succumb before liver regeneration can occur.
- Adrenocorticosteroids, exchange transfusion, hemodialysis, perfusion through pig and baboon livers: not proved effective.
- Emergency liver transplantation: 80% survival rate at 1 year

**Mortality rate**
- Over age of 40: 80% or more.
- Under age of 40: 60-80%.

**Indications for liver transplantation**
- Cirrhosis
- Tumor
- Metabolic
- Other viral hepatitides
- Autoimmune
- HCV
- Fulminant liver failure
• Cholestatic