LIVER DISEASES

- Anatomy
10. Portal tract contains a portal vein radicle (1) and hepatic arteriole (2) which supply the hepatic sinusoids and a small bile duct (3) draining the biliary canaliculi which traverse the surface of each hepatocyte. (H. & E. ×160)
PHYSIOLOGY
Bilirubin metabolism:

250-300 mg/d

Unc. B

Albumin

SER

UDPG-A

Bile

B. diglucuronide

B. monoglucuronide

100-200 mg/d

Glucuronyltransferase

1

O₂

4mg In urine

Stercobilinogen

urolbilinogen

urolbilin

Stercobilin

Bacteria

O₂

O₂
Investigations:

Bilirubin

Enzymes- ALT (SGPT)
  AST(SGOT)
  ALP
  γ-gt
  5’-nucleotidase
  enzyme combinations

Plasma proteins

Immunoglobulins

Coagulation factors

α-feto protein

copper

ceruloplasmin

ferretin

Serology-

ANA

ASMA

Fe & IBC

ALKMA

SLP-PA

AMA
**Imaging:**
- U/S
- Radiography
- CT + MRI + MRCP
- Radionucleotide imaging – TC\textsuperscript{99}
- ERCP
- Cholangiography
- Arteriography
- Venography
  - Portal venography
    (Portal pressure = free hepatic vein pressure - wedged hepatic vein pressure = 3-5 mmHg)
- Endoscopy
- Ascitic fluid studies
- Liver biopsy & FNA
- Laparoscopy
Jaundice

- > 3 mg/dl
- 1. Hemolytic
- 2. Hepatocellular
- 3. Obstructive [Cholestatic]
  - Intrahepatic- canalicular (hepatocyte)
    - Biliary Obstruction
  - Extra hepatic
- Clinical features

- Cholestasis of pregnancy
- Benign recurrent intrahepatic cholestasis
Congenital Hyperbilirubinemia

Unconjugated- Gilbert’s Syndrome (Dominant)

Criggler-Najar- (I) recessive

(II) dominant

Conjugated- Dubin-Johnson (recessive)

Rotor (dominant)
Portal hypertension

**Causes:** (I) Pre-hepatic

- Portal vein obstructions  50% ?
- splenic vein thrombosis
- massive splenomegaly ( Banti’s Syndrome)

(II) Hepatic

- Pre sinosoidal
- Sinusoidal
  - Cirrhosis
  - Myoproliferative diseases
  - Drugs
  - Sarcoid
- Post-sinosoidal

(III) Post-hepatic

- Budd-Chiari
- Cardiac causes
Clinical features:
- Splenomegally
- Hypersplenism
- Collateral vessels
- Fetor hepaticus

Complications:
- Bleeding
- Hypersplenism

Contributary factor in:
- Ascites
- Encephalopathy
- Hepato renal syndrome
- Hepatopulmonary syndrome
VARICEAL BLEEDING

• Recurrent
• Risk factors

• Other sites

Management:
- Supportive
- Confirm
  1. Reduction of portal pressure
  2. Local measures
  3. Prevention of recurrent bleeding

Primary prophylaxis:
Ascites

1. Increased hydrostatic pressure
2. Decreased oncotic pressure
3. Increased portal pressure
4. Inflammation
5. Malignancy

Causes:

Investigations:
Ascites in chronic liver disease

- Poor prognostic sign
- Commonly with leg edema
- 10% right pleural effusion
- Ascites in CLD doesn’t exclude other causes (HCCA or PUTH...)
- Exudative ascites – infection, malignancy, H-V obstruction.
Cirrhosis

Incremental resistance to portal flow

Portal hypertension

Increased splanchnic capillary pressure

Ascites

Splanchnic vasodilatation

Arterial underfilling

Activation of vasoconstrictor + antinaturetic factors

Na & water retention

Expansion of plasma volume

Impaired free water excretion

Dilutional hyponatremia

Renal vasoconstriction

Hepatorenal syndrome
Management:
- Decrease Na & water by restriction
- Increase urine output
- Removal of ascetic fluid if necessary
- TIPSS
Spontaneous bacterial peritonitis

Recurrent

Hepatorenal syndrome

Hepatopulmonary syndrome
Hepatic encephalopathy

- Definition
- Causes- Liver cell failure
  - P-S shunting
- Features
- Precipitating factors
- Differential diagnosis
- Management
Fulminant hepatic failure

- Definition – Acute - absence of CLD
- Causes
- Pathology
- Presentation
- Investigations
- Complications
- Management
- Prognosis
Acute Hepatitis

- Pathology
- Causes: - Viral
  - Drug
  - Post-viral
- Non-viral infections
  - Immune Hepatitis
  - Metabolic- Wilson
    - $\alpha_1$-antitrypsin deficiency
    - Pregnancy
  - Ischemic- Shock
  - Tamponade- severe heart failures
  - Budd-Chiari syndrome
- Clinical features
  Frequently anicteric or asymptomatic
- Investigations
- Management
- Complications
- Prognosis
HEPATITIS A VIRUS

- Incubation 2-4 wks
- Diagnosis
- No chronic carrier
- Vaccine
- Immune serum globulin
HEPATITIS E VIRUS

- Incubation 4-8 wks
- Water borne epidemics – fecal -oral
- High mortality in pregnant woman

HEPATITIS B VIRUS

- Incubation 4-20 wks
- Not cultured
- Only man-man
- Carrier
- Vaccine

  hyperimmune serum globilin

- HBsAg
- Anti HBs Ab
- Anti- HBcAb IgM
  IgG
- HBe Ag
- Anti-HBeAb
**Chronic HBV infection**

- Activity
  - HBsAg
  - HBeAg
  - Viral load (PCR)

  → Increased enzymes
  - Anti-HBcAb
  - Anti-HBeAb

**HD virus**

- Incomplete RNA
- Incubation 6-8 wks

- Infection
  - Con-comitant
  - Super infection of chronic causes of HBV
**HC virus**

- Incubate 2-26 wks
- Chronic carrier > 50%
- Anti-HCV Ab ?
- PCR HCV-RNA in blood
CHRONIC HEPATIC + CIRRHOSIS

- 6/12
- Causes
  - Viral
  - Drugs and alcohol
  - Metabolic
    - Wilson
    - Hemochromatosis
    - α1 anti-trypsin deficiency
  - Immune
  - Nutritional (intestinal bypass)
  - Biliary obstruction:
    - Primary biliary cirrhosis
    - Sclerosing cholangitis
    - Secondary biliary cirrhosis
  - Hepatic congestion:
    - Budd-Chieri
    - Veno-occlusive disease
    - Cardiac failure
  - NAFLD
  - Cryptogenic
- Symptomatology
- Assessment & investigations
  • Is there active liver disease?
  • Liver functions
  • Staging of liver disease - clinical
## Child - Pugh

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (gm/l)</td>
<td>&gt;3.5</td>
<td>3-3.5</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Ascitis</td>
<td>None</td>
<td>Minimal</td>
<td>Large</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Excellent</td>
<td>Good</td>
<td>Poor</td>
</tr>
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</table>

## Child - Pugh Score

<table>
<thead>
<tr>
<th></th>
<th>A(5-6)</th>
<th>B(7-9)</th>
<th>C(&gt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Ascitis</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prothrombin Time (INR)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>MODIFIED HISTOLOGICAL ACTIVITY INDEX GRADING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A. periportal or periseptal interface hepatitis</strong> (Piecemeal necrosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (focal, few portal areas)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate (focal, most portal areas)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (continuous around &lt; 50% of tracts or septa)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (continuous around &gt; 50% of tracts or septa)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B. confluent necrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal confluent necrosis</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3 necrosis in some areas</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3 necrosis in most areas</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3 necrosis + occasional portal- central (P-C) bridging</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zone 3 necrosis + multiple portal- central (P-C) bridging</td>
<td>5</td>
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<tr>
<td>Panacinar or multiacinar necrosis</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C. focal (spotty) lytic necrosis, apoptosis and focal inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One focus or less per 10X objective</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One to four foci per 10X objective</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five to ten foci per 10X objective</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than ten foci per 10X objective</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D. portal inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, some or all portal areas</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate some or all portal areas</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate /marked, all portal areas</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked, all portal areas</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Description</td>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No fibrosis</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous expansion of some portal areas, with or without short fibrous septa</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas, with or without short fibrous septa</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous expansion of most portal areas, with occasional portal to portal (P-P) bridging</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrous expansion of portal areas, with marked bridging (portal - portal) (P-P) as well as portal- central (P-C)</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis, probable or definite</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- **Decompensated liver disease**
  - Bleeding
  - Ascites
  - Encephalopathy

- **Complications**
  - Infections
  - Portal hypertension
  - Ascites
  - Hepatic encephalopathy
  - Hepatorenal syndrome
  - Hepatopulmonary syndrome
  - Hepatoma

- **Management**
Chronic persistent hepatitis is found following acute hepatitis and in healthy carriers. This biopsy comes from a fit young man found to be HBsAg positive at a blood donor session. The portal tract is expanded with mononuclear cells but the limiting plate of hepatocytes is intact and there is no piecemeal necrosis of liver cells. The reticulin framework is normal. This picture may persist for years, but the prognosis is good. (H. & E. ×50)
90. Chronic active hepatitis, formerly called chronic aggressive hepatitis, is the pathological description of this very active liver lesion. The portal tracts are enlarged with a heavy infiltrate of chronic inflammatory cells, mainly plasma cells and lymphocytes (1). From the portal tracts, active fibrous septa extend to the central veins (2) isolating groups of ballooned hepatocytes to form rosettes (3). The limiting plate of liver cells around the portal tract is no longer distinct but eroded by piecemeal necrosis and fibrosis. Bridging hepatic necrosis (4) has developed. (H. & E. ×40)
91. Bridging necrosis accompanies chronic active hepatitis, when liver cell necrosis is followed by fibrosis. The fibrosis links portal tracts (1) to hepatic veins (2) disrupting the normal lobular architecture (reticulin×24). These active fibrous septa may be the precursors of cirrhosis.
Inactive macronodular cirrhosis may be the end result of chronic active hepatitis due to type B hepatitis. Following extensive liver cell necrosis and reticulin collapse, some liver cells regenerate to form nodules of various sizes separated by septa of inactive fibrous tissue. The normal lobular architecture of the liver is lost. (H. & E. ×10)
Immune hepatitis

- Presentation
- Associated features

- Investigations
  ANA  AMA  A-LKmA
  ASMA  SLA
Wilson disease
ATP7B gene Ch13
Presentation
Investigations
Management

Hemochromatosis
HFE gene Ch6 C282Y
Presentation
Investigation
Management
Secondary Hemochromatosis
α1-antitrypsin deficiency

PiM
PiS
PiZ

Primary biliary cirrhosis

- Pathology
- Presentation
- Associated autoimmune disease
- Investigations
- Management
  - Pruritis
  - Malabsorption
  - Lipids

Secondary biliary cirrhosis
Alcoholic liver disease

- Dose – Duration - Genetics – Sex
- Mechanism

- Pathology
  - Fatty liver
  - Alcoholic hepatitis – Mallory’s hyaline
  - Central hyaline sclerosis
  - CAH
  - Cirrhosis
  - Hepatoma

- Clinical
  - Asymptomatic
  - Gradual
  - Cholestasis and abdominal pain
  - Alcoholic hepatitis
- Investigations
  - Establish alcohol abuse
  - Exclude other causes of liver disease
  - Establish severity
  - AST/ALT > 2/1

- Management
Drugs and the liver

Liver metabolism $\rightarrow$ conversion of fat-soluble (non-polar)

Water soluble (polar) $\rightarrow$ MFO (P450) on SER

• Genetics, nutritional, hepatic blood flow, plasma protein binding, combination of drugs
• Induction and inhibition of enzymes
Hepatotoxicity of drug:

All forms of liver disease

Acute hepatic injury - Dose dependent – paracetamol, CCl4
  - Idiosyncratic
  - Cholestasis
  - Fatty liver
  - Chronic hepatitis
  - Granulomas
  - Fibrosis
  - Vascular
  - Tumors
  - Toxins
Hepatic vein obstruction

- Anywhere from the small central hepatic veins → heart
- Veno-occlusive disease
- Heart failure, tamponade
- Budd-Chiari syndrome- thrombogenic disease

PRV
PNH
AT III deficiency
Anti-phospholipid syndrome
Protein C & S deficiency
Vena Caval obstruction
Webs
Tumors

- Clinical features

SPEED

- Management