Cholestasis
**Cholestasis**

**Cholestasis:** –

A pathological condition of;

• **Impaired** - *bile formation* and *flow* –

  Accumulation of *bile pigment* in *hepatic parenchyma*

**Caused by:**

• **Defects** in *hepatocyte bile secretion* or

• Intra hepatic /extra hepatic *obstruction* of *bile channels*
Cholestasis - Morphology

Morphological features:

depend on severity, duration & underlying cause of cholestasis

- **Elogated plugs of bile** - in dilated bile canaliculi.

- **Rupture** of canaliculi –
  - **extravasation** of bile – phagocytosed by kupffer cells.
Morphology:
- Enlarge hepatocytes with dilated canalicular spaces
- Apoptotic cells
- Kupffer cells with bile pig
- Apoptotic cell

In portal tracts:
- Bile stasis and back pressure – induce:
  - Prolif of bile ductules,
  - Edema &
  - Bile pigment retention

Surrounding hepatocytes - swollen & degenerating
Cholestasis

Prolonged obst cholestasis;

- Intrahepatic bile stasis –

- Bile pigment - accumulate in hepatocytes - fine foamy appearance –

Feathery degen of hepatocytes
Cholestasis

**Un relived obst:**
- portal tract fibrosis – *biliary cirrhosis*

- **Inflam** cells in *portal tract,*
- **Mild fibrosis** &
- **Intracellular cholestasis**
Morphology

Cholestasis –

• Focal dissolution of hepatocytes by detergents – bile lakes filled with cellular debris & pig.

Accumulations of bile

• both intra- & extracellular - (arrows).
Lab findings:

Elevated level of:
- Serum alkaline phosphatase and
- Gamma-glutamyl transpeptidase (GGT) –

Enzymes present on:
- Apical membrane of hepatocytes, and
- Bile duct epith cells
Cholestasis

S/S

• Jaundice,
• Pruritus,
• Skin xanthomas
  (focal accumulation of cholesterol)

• Nutritional def of fat soluble vitamins A, D or K

- due to intestinal malabsorption,
Xanthomas

Skin xanthomas:

• firm, raised waxy-appearing papules
• occur on trunk, arms, and legs.

• The lesions may be;
  • skin-colored,
  • pink or even
  • yellow.
Xanthomas

Xanthomas showing:

- lipid laden foam cells
- cholesterol clefts,
Cholestasis

Treatment;

• **Extra hepatic biliary obstruction** - by **surgical** treatment,

• **Diseases of Intra hepatic biliary tree** (intrahepatic cholestasis) –

  • Only treat - **transplantation**, 
Neonatal Cholestasis
Major Causes of Neonatal Cholestasis

‘Prolonged conjugated hyperbilirubinemia in neonate’

Bile duct obstruction
  • Extra hepatic biliary atresia

Neonatal infection
  • Cytomegalovirus
  • Bacterial sepsis
  • Urinary tract infection
  • Syphilis

Toxic
  • Drugs
  • Parenteral nutrition

Metabolic disease
  • Tyrosinemia
  • Niemann-Pick disease
  • Galactosemia
  • a1-Antitrypsin deficiency

Miscellaneous
  • Shock / hypoperfusion
  • Indian childhood cirrhosis
  • Alagille syndrome (paucity of bile ducts)

Idiopathic neonatal hepatitis

• Cystic fibrosis
Morphology:

• **Disturbed** Lobular architecture - with focal liver cell necrosis

• **Pan lobular** - giant cell transformation of hepatocytes & formation of hepatocyte "rosettes"

• Prominent hepatocellular & canalicular cholestasis

• Mild mononuclear infilt. of portal areas

• Extra medullary hematopoiesis
Inflammatory disorders
Inflammatory disorders

Viral hepatitis:

Systemic viral infections - can involve liver; e.g. in

- Infectious mononucleosis (EB virus)
- Cytomegalovirus infection
- Yellow fever virus-
- Rubella,
- Adeno virus,
- Herpes virus

Unless specified, term viral hepatitis applied for - hepatitis viruses – A, B, C, D & E - particular affinity for liver
Clinico-pathologic syndromes of viral hepatitis

Hepatitis causing viruses - Diff clinical synd – e.g.

- Acute asymptomatic infection with recovery – (serological evidence only)
- Acute symptomatic Hep - with recovery-
- Ch hepatitis with / without progression to cirrhosis
- Fulminant hepatitis - with sub massive - massive hepatic necrosis
Clinico-pathologic syndromes of viral hepatitis

- **Acute asymptomatic infection with recovery** –
  - Incidental finding - serological evidence only;
  - Elevated - S.Transaminases / antiviral antibodies)

- **Acute symptomatic Hep with recovery** -
  - Caused by any hepatotropic virus.
  - Disease pattern is same with **four phases**, 
    - Incubation p,
    - Asymptomatic **pre icteric** phase,
    - Symptomatic **icteric** phase,
    - Convalescence

- **Peak infectivity** –
  - Last asymptomatic days of **incubation P** &
  - Early days of **acute symptoms**
<table>
<thead>
<tr>
<th>Virus</th>
<th>Type and family</th>
<th>Infection route</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A (HAV)</td>
<td>RNA Hepatovirus Picornaviridae</td>
<td>Fecal–oral</td>
<td>Acute</td>
</tr>
<tr>
<td>Hepatitis B (HBV)</td>
<td>DNA Orthohepadnavirus Hepadnaviridae</td>
<td>Parenteral</td>
<td>Acute, chronic</td>
</tr>
<tr>
<td>Hepatitis C (HCV)</td>
<td>RNA virus Flaviviridae</td>
<td>Parenteral or sporadic</td>
<td>Acute, chronic</td>
</tr>
<tr>
<td>Hepatitis D (HDV)</td>
<td>RNA virus (related to plant viroids)</td>
<td>Pathogenic when combined with HBV</td>
<td>Acute, chronic</td>
</tr>
<tr>
<td>Hepatitis E (HEV)</td>
<td>RNA virus unclassified</td>
<td>Fecal–oral Epidemic or sporadic</td>
<td>Acute</td>
</tr>
</tbody>
</table>

Other hepatitis viruses include: hepatitis G virus (HGV or GVB-C); transfusion transmitted virus (TTV); a novel DNA virus, SEN-V; a toga-like virus sometimes referred to as hepatitis F; and a paramyxovirus causing giant cell hepatitis (see text).
Acute Viral Hepatitis

- Icteric or anicteric
- Gross
  - Enlarged liver with a tense capsule
- Histology
  - Ballooning degeneration of hepatocytes and liver cell necrosis
- Signs and symptoms (last 4 - 6 weeks)
  - Malaise, anorexia, fever, nausea, upper abdominal pain and hepatomegaly -> jaundice, putty-colored stools and dark urine
  - In HBV – urticaria, arthralgias, arthritis, vasculitis and glomerulonephritis
  - Elevated transaminases and alkaline phosphatase
    - Elevated serum bilirubin if icteric
Acute Hepatitis

HAV, HBV, HCV & HEV – Same morph

A. Parenchymal changes:

- **Hepatocyte injury**: diffuse swelling (ballooning degeneration)
- **Rupture of cell memb**: cell death - macrophage agg.
- **Apoptosis**: by anti viral T cells
- **Cholestasis**: canalicular bile plugs
- **Mild focal fatty change**: of hepatocytes - HCV
- **Hepatocyte necrosis**:
  - In severe cases: confluent nec - bridging necrosis (p-p, c-c, p-c)
- **Hepatocyte swelling & regen**: loss of normal architecture around central vein.
Acute Hepatitis

B. Sinusoidal cell reactive changes:

• Kupffer cell **hyperplasia**
• Accumulation of **phagocytosed cellular debris in** Kupffer cells

C. Portal tracts:

• Inflammation: mixture of inflam. cells
• Inflammatory **spillover** into
  • Adjacent parenchyma,
  • Hepatocyte **necrosis**

• **HBV** - ground glass hepatocytes- due to HBsAg in cytoplasm – **finally granular cytoplasm**
• **HCV** – infected liver – **lymphoid agg** in portal tracts, **macrovesicular steatosis**
Serologic Markers in HAV Infection

• Sequence of serologic markers in acute hepatitis A infection.
HBV Acute and Chronic Infection

A - Acute infection with resolution,  

B – Progression to ch. Infection

**Diagram Details:**

- **Acute Infection:**
  - **Incubation Period:** 4–26 weeks (average 8)
  - **Acute Disease:** 4–12 weeks
  - **Convalescence and Recovery:** 4–20 weeks
  - Serum markers: HBeAg, HBV-DNA, HBsAg, IgM-anti-HBc, IgG-anti-HBs, Anti-HBe
  - Serum transaminases

- **Chronic Infection:**
  - **Incubation Period:** 4–26 weeks (average 8)
  - **Acute Disease:** 4–12 weeks
  - **Chronic Disease:** Months to Years
  - Serum markers: HBeAg, HBV-DNA, HBsAg, IgM-anti-HBc, IgG-anti-HBs, Anti-HBe, IgG-anti-HBc
Out Come of HBV Infection

ACUTE INFECTION

(185,000/yr in United States)

60%-65%

Subclinical disease

100%

Recovery

99%

Acute hepatitis

<1%

Fulminant hepatitis

Death

20%-25%

"Healthy" carrier

5%-10%

Persistent infection

67%-90%

Recovery

10%-33%

Chronic hepatitis

20%-50%

Cirrhosis

10%

Death

20%

Hepatocellular carcinoma
Chronic Hepatitis:

“Symptomatic, biochemical / serological evidence of continuing / relapsing hepatic disease for - 6 months”

Etiology:-
- HBV
- HCV – (> common)
- HDV
- Autoimmune hepatitis
- Drug induced hepatitis
Chronic Hepatitis…

Clinical symptoms –

• Variable, not predictive of outcome
• Some pts – only persistent elevation of s. transaminases
• Most common symp. – fatigue
• Less common symp; –
  • Malaise,
  • Loss of appetite &
  • Mild jaundice
Chronic Hepatitis…

- **Physical findings;**
  - Spider angiomas,
  - Palmer erythema,
  - Mild hepato - splenomegaly &
  - Hepatic tenderness

- **Lab findings** –
  - Prolonged prothrombin time,
  - Hyperglobulinemia,
  - Hyperbilirubinemia &
  - Mildly raised Alk. phosphatase levels
Chronic Hepatitis…

**Chronic HBV infection** - major risk factors;

- HBV infection occurring at younger age
- Maternal to infant transmission –

- **Complete cure** – difficult

- **Goal of treatment** of ch hep B – TO;
  
  - Slow - disease progression,
  - **Reduce** - liver damage &
  - **Prevent** - liver cirrhosis / liver cancer
**Chronic Hepatitis…**

**HCV infection**

- Most common cause - of ch viral hepatitis.

- May have - Mild / no symp

- High risk of developing - permanent liver damage
  
  (even with normal transaminases)

- A curable disease so
  
  - Any individual with detectable HCV - RNA in serum – should be treated
Chronic Hepatitis

Carrier state

- HBV and HCV
- Asymptomatic or with liver disease (elevated transaminases)
- Most common in immunodeficient, drug-addicted, Down syndrome and dialysis
- Histology
  - Asymptomatic carriers have “ground glass” hepatocytes with finely granular eosinophilic cytoplasm
Serologic Markers of **HCV**
Acute and chronic Relapsing Infection
Chronic Hepatitis

Changes shared with acute hepatitis:

• Hepatocyte injury, necrosis, & regeneration

• Sinusoidal cell reactive changes

Portal tracts: - Inflammation:

• Mild - Confined to portal tracts

  (lymph, macrophages, pl, neut / eos)

• "Interface hepatitis"

• Bridging necrosis (P – P, P - C),
Chronic Hepatitis

**Fibrosis:**
- Portal deposition, or
- Portal & periportal deposition, /
- Formation of bridging fibrous septa

**HBV:**
- "ground-glass" hepatocytes,

**HCV:**
- Lymphoid aggregate formation,
- Bile duct prolif. in portal tract
- Mild to mod steatosis

**Cirrhosis:** The end-stage outcome
Out Come of HCV Infection

ACUTE INFECTION

- 85% Chronic hepatitis
- 15% Resolution
- Rare Fulminant hepatitis

Chronic hepatitis

- 80% Stable disease
- 20% Cirrhosis

Cirrhosis

- 50% Stable cirrhosis
- 50% Hepatocellular carcinoma

Hepatocellular carcinoma

- 50% Death

(40,000/yr in United States)
HBV Positive Chronic Hepatitis

**HBV:**

**Ground glass hepatocytes**

- Diffuse granular cytoplasm –
- homogeneous eosinophilic staining
- Caused by presence of **HBsAg**.
Chronic hepatitis...

**Portal area** with:

- Dense lymphoid aggregate – *(Chronic hepatitis C.)*

- Proliferating bile ductules *(ductular reaction).*

- bile duct - *intact / slightly damaged.*
Chronic viral hepatitis.

Portal tract with;

- Areas of interface hepatitis

- Piecemeal necrosis:
  - Destruction of limiting plate - by infiltrating lymphocytes
## Drug - and Toxin-Induced Hepatic Injury

### Hepatocellular lesions

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microvesicular fatty change</td>
<td>Tetracycline, salicylates, yellow phosphorus, ethanol</td>
</tr>
<tr>
<td>Macrovesicular fatty change</td>
<td>Ethanol, methotrexate, amiodarone</td>
</tr>
<tr>
<td>Centrilobular necrosis</td>
<td>Bromobenzene, CCl4, acetaminophen, halothane, rifampin</td>
</tr>
<tr>
<td>Diffuse or massive necrosis</td>
<td>Halothane, isoniazid, acetaminophen, methyldopa, trinitrotoluene, <em>Amanita phalloides</em> (mushroom) toxin</td>
</tr>
<tr>
<td>Hepatitis, acute &amp; chronic</td>
<td>Methyldopa, isoniazid, nitrofurantoin, phenytoin, oxyphenisatin</td>
</tr>
<tr>
<td>Fibrosis - cirrhosis</td>
<td>Ethanol, methotrexate, amiodarone, most drugs that cause chronic hepatitis</td>
</tr>
<tr>
<td>Granuloma formation</td>
<td>Sulfonamides, methyldopa, quinidine, phenylbutazone, hydralazine, allopurinol</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Chlorpromazine, anabolic steroids, erythromycin oral contraceptives, organic arsenicals</td>
</tr>
<tr>
<td>Neoplasms</td>
<td></td>
</tr>
</tbody>
</table>

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Drug- and toxin-induced hepatic injury

Drug-induced hepatitis

- With **granuloma** formation.

(Other causes should be excluded by other investigations).
Alcoholic liver disease
Alcoholic liver disease

Excessive consumption of alcohol –

• **Major cause** of liver disease - Western countries,

  (Asian countries - *viral hepatitis*).

• **Slow** - Liver damage - over a period of - **10-15 years**.
Alcoholic liver disease

Alcohol; –

- Produces toxic chemicals like acetaldehyde - damage liver cells.

- Liver cells - regenerate & function as normal - 75% damaged.

- Symptomatic, when - significant damage - irreversible.

- Eventually - cirrhosis / end-stage alcoholic liver disease
Pathogenesis of alcohol induced liver injury

Chronic ethanol intake

-> Acetaldehyde

NADH production

-> Oxidative stress

Inc lipogenesis
Dec FA oxidation

-> Fatty liver

-> Hepatocyte injury

Lipid peroxidation

-> Liver fibrosis

Hepatocyte

Sinusoidal cell

Gut derived endotoxin

Kupfer cell

Cytokines (TNF)

Inflm. cell

Inc collagen synthesis

Hepatic stellate cell activation

Chronic ethanol intake
Alcoholic liver disease

Three - overlapping forms of alcoholic liver disease
Fatty liver

A. **Hepatic steatosis** (fatty liver)
   - lipid droplets in hepatocytes

**Grossly** –
liver - large (4 - 6 kg) soft, yellow & greasy

**Micro;**
- **Moderate** alcohol intake – **micro vesicular** -
- **Chronic intake** - **macro vesicular**

Immediately - **no fibrosis** –
**Continued intake** – fibrosis around **terminal hepatic veins** – extends into adjacent sinusoids

**Fatty change** – **reversible** - if further intake is stopped
Morphology…

B- **Alcoholic Hepatitis** – ch by;

1. **Hepatocyte swelling & necrosis**

- Focal - *swelling / ballooning* - due to *accum.* of **fat, water & proteins** - (normally exported)
- **Necrosis**.
- **Cholestasis** - in **surviving hepatocytes**
- **Hemosiderin deposition** - in **hepatocytes & Kupffer cells**
Morphology...

2. **Mallory's hyaline bodies:**

- Eosinophilic cytoplasmic inclusions, - in scattered hepatocytes

- Consequence of **cellular injury**.

(accumulated **cytokeratin** filaments - complexed with other pr. as **ubiquitin**).
Alcoholic hepatitis - Mallory Bodies

Mallory Bodies;

Ch. but not specific,

May also be seen in:

- Non alcoholic fatty liver disease,
- Wilson disease,
- Primary biliary cirrhosis,
- Ch. Cholestatic synd &
- Hepatocellular tumors
Morphology…

3. **Inflammation**:
   - **Neutrophils** –
     - Permeate H lobule &
     - Accumulate around **degenerating hepatocytes** esp those with Mallory bodies.
   - **Lymphocytes & macrophages** - portal tracts & surrounding parenchyma

4. **Fibrosis**:
   - **Alcoholic Hep.** - accompanied by- **activation of**;
     - Sinusoidal **stellate cells** &
     - Portal tract **fibroblasts** – **fibrosis** -
Morphology…

- **Pericellular** &
- **Perivenular fibrosis**

- **Collagenous tissue** *(blue)*

Surrounds individual hepatocytes, *chicken-wire appearance.*

(Masson's trichrome stain).
C - Cirrhosis:

- Final & irreversible form of alcoholic liver disease,
- Evolves slowly & insidiously

Liver:
- Initially; – yellow - tan, fatty & enlarged > 2kg
- Over the years – brown, shrunken, non fatty organ < 1 kg

- Initially fibrous septa - from - C - P & P - P
- Entrapped hepatocytes – regenerate, form uniform micro nodules –
- With time - nodules - more prominent - scattered - large nodules
Morphology…

Cirrhosis…

As fibrosis increased;

- **Liver** - more fibrotic, loses fat & shrink in size.
  - **Mixed** - micro & macro nodular pattern.

- **Bile stasis** - may develops.

- **Malory bodies** - rare.

Alcoholic cirrhosis –

- **Macro and microscopically**;
  
as - cirrhosis from **viral hepatitis** and other causes
Clinical features

A- Fatty liver may become evident as;
  • Hepatomegaly,
  • Elevation of;
    • Serum bilirubin &
    • Alkaline phosphatase level

B- Alcoholic hepatitis –
  Acute- - minimal to fulminant hepatic failure

  • Non specific symptoms of hepatitis;
    • Malaise,
    • Anorexia,
    • Wt loss,
    • Upper abd discomfort,
    • Tender hepatomegaly,
    • Hyper bilirubinemia,
    • Increased alkaline phosphatase &
    • Neutrophilic leukocytosis

C- Alcoholic cirrhosis –
  Manifestation similar - to other form of cirrhosis
Liver abscess
Liver abscess

Liver abscess: Common in developing countries

- Acc to etiology - 3 major forms of liver abscess are:

  - **Pyogenic abscess,**
    - **Polymicrobial,**
      - 80% of hepatic abscess - in united states.

  - **Amebic abscess**
    - Due to *Entamoeba histolytica*
      - 10% of cases.

  - **Fungal abscess,**
    - Mostly due to *Candida species,*
      - < 10% of cases.
Pathophysiology

Blood from **systemic** & **portal** circulations. - increased exposure to bacteria.

- Kupffer cells - **clear bacteria** - so, **infection** - rare.

- **Biliary tract disease** - **most common source** of pyogenic liver abscess (PLA).

- **Obstruction of bile flow** - bacterial prolif.

**Obst**

- **Biliary stone** disease,
- **Obstructive malig** - affecting biliary tree,
- **Stricture**,
- **Congenital** diseases
Pyogenic liver abscess:
Develop from diff sources, including:
• blood infection,
• abdominal infection, or
• abdominal injury - infected.

Common infecting bacteria;
• E. coli,
• Enterococcus,
• Staphylococcus and
• Streptococcus.

Treatment - drainage & prolonged antibiotic therapy.
Morphology

- **Right hepatic lobe** > left.
- **Bilateral** - in 5% of cases.
- **Size**: - variable
- **Solitary / multiple**
  - **Bacteremic spread** - (through arterial / portal system) - **multiple** small abscesses
  - **Direct extension / trauma** – **solitary** abscess

- Untreated, - **fatal**.
- **Antibiotics** and **drainage** procedures, reduce mortality.
Pyogenic liver abscess:

- **Sub diaphragmatic abscess** e.g. *amebic* – may **burrow into thoracic cavity** – *empyema / lung abscess*

- **Rupture of sub capsular liver abscess** – *peritonitis / peritoneal abscess*

- **Common causes of death** include:
  - Sepsis,
  - Multi - organ failure, and
  - Hepatic failure
Amoebic liver abscess,

- **Gross Pathology** of amoebic liver abscess

- **Perforation** of abscess through abdominal skin.
Liver abscess,

liver abscess - filled with neutrophils.
Clinical features

Most frequent symptoms of hepatic abscess include:

• Fever (either continuous or spiking)
• Chills
• Right upper quadrant pain
• Anorexia
• Malaise

• Cough or hiccoughs due to diaphragmatic irritation may occur

• Referred pain to the right shoulder may be present.
Echinococcus Cyst
Echinococcal Cyst

**Diagnostic features** include:

- **Cystic** lesion, **Laminated** wall
- **Cellular septae** (calcaneous bodies / corpuscles,
- Hooked protoscoleces within the cysts.
- **Rupture of cyst** - Systemic spread of organism – shock, massive immune response
thank you