JAUNDICE & CHOLESTASIS:

- Jaundice or icterus is yellow discoloration of skin & sclera.
- It occurs due to bilirubin overproduction, hepatitis or obstruction to bile flow, which leads to disturbed equilibrium between bilirubin production & clearance.
- It causes accumulation of bilirubin in tissue & interstitial fluids.
- It becomes visible when bilirubin level > 2 - 3 mg/ dl.
Bilirubin is derived from,

1. 85% from breakdown of R.B.C.
2. 15% from breakdown of nonHb heme protein in liver (e.g. cytochrome p-450)
3. Small fraction from lysis of immature R.B.C. in bone marrow.
BILIRUBIN METABOLISM

- Bilirubin bound to albumin. Transformed via blood to liver sinusoids.
  Transfer into hepatocytes. Intracellular binding to glucuronic acid by UGT (Uridine Glucuronyl Transferase)
- CONJUGATED BILIRUBIN (bilirubin glucuronides): Enter bile flow – reaches intestine.
  Converted into stercobilinogen (fecal urobilinogen) excreted in stool.
  Small fraction is excreted in urine (urobilinogen).
UNCONJUGATED BILIRUBIN:

- Soluble in lipid.
- Insoluble in water at physiological pH.
- Tightly complexed to albumin.
- Cannot be excreted in urine even if the blood level is high.
- Unbound unconjugated bilirubin may diffuse into tissues, especially in the brain, producing toxic injury.
- Affinity to the brain causing KERNICTERUS in erythroblastosis fetalis.
CONJUGATED BILIRUBIN:

- Water soluble.
- Loosely bound to albumin.
- Non-toxic.
- Excreted in urine due to solubility in water.
CLASSIFICATION OF JAUNDICE:

(A) UNCONJUGATED HYPERBILIRUBINEMIA:

1. Excess production of bilirubin:
   ① hemolytic anemias
   ② resorption of blood from internal hemorrhage
      (eg. alimentary tract bleeding, hematomas)
   ③ ineffective erythropoiesis
      (eg. Pernicious anemia, thalassemia)
2. Reduced hepatic uptake:
   ① drug interference with membrane carrier systems
   ② some cases of Gilbert syndrome

3. Impaired bilirubin conjugation:
   ① physiological jaundice of the newborn
      (↓ed UGT1A1 activity, ↓ed excretion)
   ② breast milk jaundice (β-glucuronidases in milk)
   ③ Gilbert syndrome
   ④ diffuse hepatocellular disease
      (eg. viral or drug-induced hepatitis, cirrhosis)
(B) CONJUGATED HYPERBILIRUBINEMIA (Cholestasis):

Failure of bile to reach duodenum ---
Accumulation of bile in hepatocytes & bile canaliculi.

(a) Intrahepatic cholestasis:
   Hereditary -
      (1) Dubin Johnson
      (2) Rotors syndrome.
   Acquired -
      (1) Viral hepatitis.
      (2) Drugs e.g. chlorpromazine.
      (3) Alcoholic hepatitis.
(b) Extrahepatic cholestasis:
Mechanical obstruction.
   (1) Gallstone
   (2) Inflammatory stricture
   (3) Ca. head of pancreas
   (4) Extrahepatic biliary atresia

CHOLESTASIS PROGRESSES TO CIRROSIS.
Most frequent causes of jaundice

- VIRAL HEPATITIS.
- CIRRHOSIS.
- EXTRAHEPATIC BILIARY OBSTRUCTION.
- DRUG REACTION.
VIRAL HEPATITIS

- Primary hepatic infection caused by group of specifically hepatotropic viruses.
- Hepatitis A virus. (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV) Not considered pathogenic.
<table>
<thead>
<tr>
<th>Transmission Route</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Borne</td>
<td>★</td>
<td></td>
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<td>★</td>
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<tr>
<td>Fecal - Oral</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
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<tr>
<td>Water Born</td>
<td>★</td>
<td></td>
<td></td>
<td></td>
<td>★</td>
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<tr>
<td>Raw Shelfish</td>
<td>★</td>
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<tr>
<td>Intra-Institutional</td>
<td>★</td>
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<td>★</td>
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<tr>
<td>I.V. Drug Use</td>
<td></td>
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<td></td>
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<tr>
<td>Transfusion</td>
<td></td>
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<tr>
<td>Hemodialysis</td>
<td></td>
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<tr>
<td>Sexual</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Anal- Oral Contact</td>
<td></td>
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<tr>
<td>Oral-Oral Contact</td>
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<tr>
<td>Household</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mother to New Born Child</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

★ Common
△ Infrequent
■ Never
🟢 Suspected
Hepatitis A Virus

- Produces only acute hepatitis.
- Rarely acute hepatic failure.
- Also called as infectious hepatitis.
- Incubation period – 2 to 6 weeks.
- Benign self-limited disease.
- Viremia transient so transfusion acquired hepatitis does not occur. Therefore donor’s blood is not screened for it.
- Virus spread by feco-oral route.
STRUCTURE OF HAV:

- Picorna virus.
- Small nonenveloped single stranded RNA virus.
- E/M: Roughly spherical particle.
- About 27 nm. in diameter.
- Having icosahedral symmetry.
PATHOGENESIS:

- Immunologic mechanism suspected.
- HAV evokes formation of antibodies initially IgM type followed by IgG type.
- IgG antibodies persist for several years confer long term immunity.
- Elevated IgG antibodies do not indicate acute infection only exposure to HAV.
- Diagnostic test of acute hepatitis is IgM Anti-HAV.
Viral Hepatitis A: Serology

- **Incubation Period**: 15–45 days
- **Acute Disease**: 2–12 weeks
- **Convalescence and Recovery**: Months

- **Fecal HAV**
- **Jaundice Symptoms**
- **IgG-anti-HAV**
- **IgM-anti-HAV**

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Hepatitis B virus (HBV)

- Asymptomatic, healthy carrier state.
- Acute hepatitis.
- Chronic hepatitis.
- Cirrhosis.
- Acute hepatic failure with massive hepatic necrosis.
- Hepatocellular carcinoma.
  (even in absence of cirrhosis)
Spectrum of disease

ACUTE INFECTION
(185,000/yr in United States)

- Subclinical disease: 100%
- Acute hepatitis: 99%
  - Fulminant hepatitis: <1%
    - Death
  - Recovery
- "Healthy" carrier: 20%-25%
- Persistent infection: 5%-10%
  - Recovery: 67%-90%
  - Chronic hepatitis: 10%-33%
    - Cirrhosis: 20%-50%
      - Hepatocellular carcinoma: 10%
      - Death
Spread of HBV

- Parenterally such as recipients of blood & blood products.
- Intravenous drug abuse.
- Mother to baby (vertical transmission).
- Unprotected sex.
- Patients treated by renal dialysis.
- Hospital workers exposed to blood.
- HBV can withstand extremes of temperature & humidity.
Hepatitis B Virus – Modes of Transmission

- From mother to baby (perinatal transmission)

- From child to child during play or from an adult to child by contact of body fluids; (Most common cause in India)

- Unscreened blood transfusions and organ transplant

- Through unsafe needles and injections

- Through unprotected sexual contact
STRUCTURE OF HBV

- Also called as Dane particle.
- DNA virus Hepadnaviridae family.
- Genome is double stranded circular DNA.
- Virus is spherical-diameter of 42 nm.
- Viral coat made of protein, lipid, carbohydrate gives rise HBsAg (envelope).
- Envelope encloses 28 nm hexagonal core containing HBcAg & HBeAg
- HBs Ag 1st discovered by Blumberg in Australian aborigine, so known as Australia antigen.
- Envelope glycoprotein (HBsAg) consists of 3 proteins large, middle & small.
- A polymerase (Pol) that exhibits both, DNA polymerase & RNA transcriptase activity.
- HBx protein is necessary for viral replication & is responsible for hepatocellular carcinoma in HBV infection.
- HBsAg particle not infectious used to induce protective antibodies (vaccine).
SEROLOGICAL MARKERS OF HBV

- HBsAg 1st appear in blood during incubation period, peaks during overt disease & decline to undetectable level in 12 weeks.

- HBcAg-core antigen never found in serum.

- HBeAg, DNA- P, HBV-DNA appear following HBsAg signify active viral replication.

- Persistence of HBeAg is an important indicator of continued viral replication, infectivity & progression to chronic hepatitis.
- **Anti–HBc**: 1st antibody appears at the end of the incubation period, persists during acute illness & several months to years. (valuable diagnostic marker).
- **Anti-HBe**: appear as HBeAg begins to disappear. It implies that the acute infection has peaked & is on the wane.
- **Anti-HBs**: doesn’t rise until acute disease is over concomitant with disappearance of HBsAg.
- In some cases anti-HBsAg is not detected for few weeks to several months after the disappearance of HBsAg. (window period).
- During this period, only IgM anti-HBc is detectable. It persists for life providing protection against reinfection with HBV.
Interpretation of serological tests in hepatitis B

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>positive</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>positive</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>positive</td>
<td>positive</td>
<td>negative</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>Interpretation unclear; four possibilities:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1. Resolved infection (most common)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. False-positive anti-HBc, thus susceptible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. “Low level” chronic infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Resolving acute infection</td>
</tr>
</tbody>
</table>
### Diagnostic Interpretations of Hepatitis B markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Description</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBsAg</strong></td>
<td>Non infectious component of viral coat</td>
<td>Indicator of disease. If &gt; 6 months: chronic HBV</td>
</tr>
<tr>
<td><strong>Anti-HBs</strong></td>
<td>Antibody response to HBsAg</td>
<td>Indicates recovery and/or immunity</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>Antigen that correlates with replication and infectivity</td>
<td>High level of infectivity and replication</td>
</tr>
<tr>
<td><strong>Anti-HBe</strong></td>
<td>Antibody response to HBeAg</td>
<td>Decreasing level of replication Remission/resolution</td>
</tr>
<tr>
<td><strong>Anti-HBc IgM</strong></td>
<td>Non protective antibody to the HBcAg</td>
<td>Recent HBV infection</td>
</tr>
<tr>
<td><strong>Anti-HBc IgG</strong></td>
<td>As above</td>
<td>Acute or remote exposure to HBV</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></td>
<td>Replicativative genetic material of HBV; infectious agent</td>
<td>Viral replication and continues infection</td>
</tr>
</tbody>
</table>
PATHOGENESIS:

- Immunologic mechanism.
- Viruses – not directly cytotoxic.
- HBV infection pass thro’ two phases.
  1. **Proliferative phase**: Constitute viral replication. Cytotoxic T cell found at the site of liver cell damage.
  2. **Integrative phase**: Virions no longer produced. Viral DNA incorporated in genome of host.
HEPATITIS DELTA VIRUS (HDV)

- HDV: very small defective RNA virus.
- HDAg (delta antigen) is the only protein produced by the virus.
- IgM anti-HDV is the reliable indicator of infection.
- Can replicate & cause infection when encapsidated by HBsAg.
- Delta hepatitis only occur when there is concomitant HBV infection.
- Hepatitis occurs in 2 settings.
  1. Acute co-infection: higher rate of acute hepatic failure in I.V. drug abuser. Both IgM HDV & IgM anti HBeAg are present.
  2. Super infection: HDV infection in chronic carrier of HBV. Anti HDV & HBsAg are present.
HEPATITIS C VIRUS (HCV)

- Causes transfusion associated hepatitis.
- Mother to child transmission (vertical transmission) less (6%) as compare to HBV (20%).
- High rate of progression to chronic disease or cirrhosis or carcinoma.
- Small enveloped single stranded RNA virus. Flaviviridae family.
- Virus is unstable giving rise to multiple types & subtypes.
- So difficult to develop vaccine.
- Elevated titre of antibody do not confer effective immunity.
Risk factors for HCV infection are,
- I.V. drug abuse.
- multiple sex partners
- surgery within last six months
- needle stick injury
- multiple contacts with HCV infected person
- employment in medical & dental fields
- unknown.

Repeated bouts of hepatic damage due to reactivation of pre-existing infection or emergence of new mutant strain.

Persistent infection & chronic hepatitis are the hallmarks of HCV infection.
Outcome of Hepatitis C Virus

100% (100) Exposure (Acute phase)
- 25% (25) Resolved
- 75% (75) Chronic
  - 80% (60) Stable
  - 20% (15) Cirrhosis
    - 75% (11) Slowly Progressive
    - 25% (4) Liver failure, HCC Transplant Death

HIV and Alcohol
HEPATITIS E VIRUS (HEV)

- Share many features of HAV.
- Infection occurs primarily in young to middle aged adults.
- HEV: Hepevirus genus.
- Non-enveloped RNA virus.
- Transmission by feco-oral route.
- No risk of subsequent chronic liver disease (except patient with AIDS or immunosuppressed patients).
- Causes acute hepatitis.
- High mortality rate in pregnant women (20%) due to development of fulminant hepatitis.
<table>
<thead>
<tr>
<th></th>
<th>Viral Hepatitis A</th>
<th>Viral Hepatitis B</th>
<th>Viral Hepatitis C</th>
<th>Viral Hepatitis D</th>
<th>Viral Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Hepatitis A virus (HAV); ssRNA</td>
<td>Hepatitis B virus (HBV); dsDNA</td>
<td>Hepatitis C virus (HCV); ssRNA</td>
<td>Hepatitis D virus (HDV); ssRNA</td>
<td>Hepatitis E virus (HEV); ssRNA</td>
</tr>
<tr>
<td><strong>Route of Transmission</strong></td>
<td>Fecal-oral</td>
<td>Parenteral, Vertical, Sexual.</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td><strong>Age affected</strong></td>
<td>Children</td>
<td>Any age</td>
<td>Adults</td>
<td>Any age</td>
<td>Young adults</td>
</tr>
<tr>
<td><strong>Carrier state</strong></td>
<td>Nil</td>
<td>Common</td>
<td>Present</td>
<td>Nil (only with HBV)</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>10–50 days (avg. 25–30)</td>
<td>50–180 days (avg. 60–90)</td>
<td>40–120 days</td>
<td>2–12 weeks</td>
<td>2–9 weeks</td>
</tr>
<tr>
<td><strong>Chronic infection</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Specific Prophylaxis</strong></td>
<td>Ig and Vaccine</td>
<td>Ig and Vaccine</td>
<td>Nil</td>
<td>HBV vaccine</td>
<td>Nil</td>
</tr>
</tbody>
</table>
THANK YOU EVERYONE!