Gastroenterology
Lecture: 1

Diagram of the digestive system:
- Pharynx
- Oral cavity
- Uvula
- Tongue
- Esophagus
- Salivary Glands
  - Parotid
  - Submandibular
  - Sublingual
- Liver
- Gallbladder
- Common bile duct
- Stomach
- Pancreas
  - Pancreatic duct
- Colon
  - Transverse colon
  - Ascending colon
  - Descending colon
- Cecum
- Appendix
- Cecum
- Jejunum
- Ileum
- Rectum
- anus

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INTRODUCTION

Why Hepatology for a Clinical Pharmacist?

1. **Pharmacotherapist**
2. Can interfere in drug induced liver diseases (DILD) management.
3. Pharmacist consultations for DDI before initiation of any medication in liver disease patients.
4. Pharmacist consultations before initiation of anti-viral therapy can minimize DDI.
5. Sharing in prevention campaigns.
6. **Conducts research** in the area of hepatology. (Drug design & Clinical trials).

Pharmacists assisted patients with adverse effects, drug adherence, disease state & medication information and overall treatment goals, these efforts increased the probability of HCV TTT success.

LIVER

- Largest organ in body, integral to most metabolic functions of body, performing over 500 tasks
- In Right upper quadrant (RUQ) of the abdomen.
- **Only 10-20%** of functioning liver is required to sustain life.
- Removal of liver OR severe destruction of liver as in Fulminant liver will result in death within 24 hours, so liver need **urgent transplantation** within few hours.

**WHAT about Kidney?** → - can work with 25-30% of functioning kidney.
- The advantage of kidney over the liver that it has artificial machines as hemodialysis that can be used until doing kidney transplantation. (NOT urgent)
Liver Functions

### Metabolic “Metabolism”

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>1) Carbohydrate</th>
<th>2) Hormone</th>
<th>3) Lipid</th>
<th>4) Drug</th>
<th>5) Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functions</td>
<td>Gluconeogenesis</td>
<td>Synthesis of fatty acids, cholesterol, lipoproteins</td>
<td>Synthesis of plasma proteins, a Urea synthesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functions</td>
<td>Glycogenolysis and glycogenesis (Death if occur after liver failure is due to Severe hypoglycemia).</td>
<td>So familial hypercholesterolemia is fit with liver transplantation.</td>
<td>Ketogenesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Plasma protein

- Distribution of fluid to diff. body compartments.
- Carrier molecules as albumin for drugs, bilirubin, thyroid hormones & Ca. So, in case of hypoalbuminemia → use ionized Ca not total Ca
- Antibodies “Humoral immunity”
- Endocrine system “some hormones are protein in nature so synthesized in liver” & “some hormones are degraded in the liver”.
- Coagulation “as prothrombin, Prot. C &S” (In Liver damage, Bleeding tendency occur and being the early sign for the damage)
- Source of nutrients for cellular repair “Healing power”
- Enzymes

### Storage

- It stores 1) Glycogen 2) All-fat-soluble vitamins (A, D, E, K) 3) some water soluble vitamins as (B12) 4) Iron
- N.B.: 
  - In chronic liver disease → patient may become anemic (due to deficiency of Vitamin B12).
  - Beneficial (iron Storage) → as in fetus liver during pregnancy
  - Pathological {iron Storage} → 1) as hemochromatosis “xxs iron deposition in liver, pancreas & skin” which accompanied with DM due to iron deposition in pancreas.

### Protective

- Detoxification — converts noxious or insoluble compounds into less toxic or more water soluble forms
- There are 2 types of toxins: Endogenous as hormones, urea.. & Exogenous as medications…
- N.B: Liver is responsible for degradation of Traces of estrogen hormone is males, so severe liver damage → increase Estrogen level → Feminization manifestation in males.
- Kupffer cells ingest bacteria or other foreign material from blood

**How Distribution of fluid to diff. body compartments is controlled?!**

→ There are 2 opposed forces: Osmotic pressure and oncotic pressure against hydrostatic pressure.

1) **Osmotic and oncotic pressure**: driving force responsible for retaining fluids inside the vascular compartment.
2) **Hydrostatic pressure**: driving force responsible for leakage of fluids from the vascular compartment to the interstitial space.

- So decrease albumin in the blood → Hydrostatic pressure will be stronger than oncotic pressure → Leakage of fluids from the vascular compartment to the interstitial space.
Why biochemical profile are better not functions tests?

 ➤ Not all tests reflect function of liver, it may reflect damage or destruction of liver
 ➤ **Laboratory Tests:**
   o May measure synthetic function
   o May measure excretory function
   o May indicate damage to cells: determination of specific enzymes may be used to show the location of liver damage
 ➤ **Over view of Liver Function Tests (LFT’S)**
   o Liver do variety of tasks → therefore no single test
   o Not very sensitive “may be normal as in (cirrhosis)” or specific (non-hepatic factors)
   o “function” = misnomer
   o **2 Categories of tests that assess**
     A. Synthetic function tests
     B. Liver damage tests:
        I. Hepatocellular disease (liver injury)
        II. Cholestatic disease

N.B: -The following diagram showing that *aminotransferases levels don’t correlate* with degree of damage. وهننكلم عنهم بالتفصيل بعد كده.

![Diagram showing aminotransferase levels](image)
A. SYNTHETIC FUNCTION TEST

↓ albumin
- Normal albumin: 3.5-5.5 g/dL.
- T1/2: 20d → indicate chronic liver changes
- Decrease in albumin may be also due to non-hepatic causes as {Nephrotic syndrome, diabetic nephropathy & Protien-losing enteropathy}
N.B: Protien-losing enteropathy: is loss of albumin from intestine due to absence of vil.
- Albumin is normal in ACUTE liver diseases
- CASE 1: Patient with Albumin (3.1g/dl) + Complication as ascites or edema that respond to diuretic → Not give albumin
- CASE 2: Patient with Albumin (3.1g/dl) Without Complication → Not give albumin
- CASE 3: Patient with Albumin (3.1g/dl) + Complication as ascites or edema that NOT respond to diuretic → give albumin

↑ INR
- Substantial impairment
- Not specific for liver disease
- How to know if the cause using the INR monitoring as indicator?
  - Give vitamin k IV not ORAL:
    - Responds → vit k deficiency
    - No response → liver cause as hepatocellular damage.
  - Vit k is formed by bacteria in intestine & absorbed through ileum by enterohepatic circulation using bilirubin
- Cases of Vit k deficiency: 1) Antobiotics.
  2) Obstructive liver disease {↓ bilirubin that reach ileum}.
- Rapid method to return INR to be normal is using Fresh frozen Plasma which used specially in case of ↑ INR with severe acute liver damage.
  - Why Fresh? → Due to short t1/2 of coagulation factors.
  - INR is preferred over Prothrombin time {PT}
- Q: How TO Diff. between patient has Liver injury OR Cholestasis?
  → Give Vitamin K & Measure INR

Bilirubin

Increases:
- Excessive load of bilirubin to liver (prehepatic)
  - Hemolytic diseases
  - Hemolytic Disease of Newborn-kemicterus
- Defective transport through hepatocyte (Hepatic)
- Impairment of Esterification (Hepatic)
  - Physiological Jaundice of the Newborn
- Impaired Excretion of Bilirubin
  - Hepatocellular damage {intra-hepatic cholestasis} (hepatic)
  - Obstruction of flow of bile {Extra- hepatic cholestasis} (posthepatic)

N.B: There are 2 types of cholestasis:
1) Medical Cholestasis {Intra- hepatic} → TTT with surgery.
2) Surgical Cholestasis (Extra- hepatic) → TTT with medicines.
N.B: 2 types of bilirubin are Conjugated & Unconjugated NOT Direct and Indirect.
B. LIVER DAMAGE TESTS

I. Liver injury

Interpretation of abnormal liver Injury Tests

Liver enzymes:

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Cytosol &amp; Mitochondria</th>
<th>Liver, heart, skeletal muscle, blood cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>Cytosol</td>
<td>Liver, muscle</td>
</tr>
<tr>
<td>AST</td>
<td>Cytosol &amp; mitochondria</td>
<td>Liver, heart, skeletal muscle, blood cells</td>
</tr>
<tr>
<td>Alk. Phos.</td>
<td>Microvilli of bile canaliculus=Cholangiocyte</td>
<td>Bone, intestine, kidney, placenta</td>
</tr>
<tr>
<td>GGTP</td>
<td>Membrane of cells</td>
<td>Liver, kidney, pancreas, intestine, prostate</td>
</tr>
</tbody>
</table>

Hepatocellular causes of abnormal LIT’s:

- Chronic viral hepatitis
- Hemochromatosis, Wilson’s, alpha-1 antitrypsin deficiency
  N.B: Wilson’s disease → cu storage disease cause severe hepatitis
- Autoimmune hepatitis
- Celiac Disease
- NAFLD” Non-alcoholic fatty liver disease” which is a chronic disease / steatohepatitis
- ETOH related liver diseases

II. Cholestatic disease

N.B: In Cholestatic diseases there are ↑ bilirubin, ↑ ALP, ↑GGTP & ↑INR but normal or slight ↑ in ALT & AST.

- Cholestasis = lack of bile flow
  → jaundice, pruritis, xanthomas, weight loss.
- Extrahepatic (Surgical)
  - obstruction in bile ducts
eg. strictures, stones, tumors
- Intrahepatic (Medical)
  - impairment bile formation in liver or obstruction of bile ducts within liver
eg. viral/alcoholic hepatitis, drugs, biliary cirrhosis, sclerosing cholangitis.
Case 1: Patient with Cholestasis. How to know rapidly the relief of obstruction?

→ Urine color which become CLEAR NOT DARK

Case 2: Patient with normal ALP & Bilirubin but Very high GGTP. What is your conclusion?

→ It is a case of Drug-induced or Alcohol liver disease.

**ACUTE HEPATITIS**

**Definition:** Inflammation of the liver cells that last for less than 6 months.

- May be caused by viruses, drugs, autoimmune diseases, metabolic diseases and alcohol.

**Causes of acute hepatitis**

- **Infectious Disease**
  - **Hepatic specific Viruses:** A, B, C, D (on B), and E
  - **Non hepatic specific viruses** “Infrequently”: include adenovirus, CMV, EBV, HSV.
  - **Bacterial:** septicemia, T.B., leptospirosis, typhoid.
- **Toxic:** Alcohol, Acetaminophen in large doses, INH, sulphonamides, antiepileptics
- **Ischemia:** after shock
- **Budd-Chiari syndrome**
- **Wilson’s disease** (Acute) & may become chronic.
- **Microvesicular steatosis (Fat) Syndromes** *(ACUTE ONLY)*
  - Acute fatty liver of pregnancy
  - Reye’s syndrome *(Immune response leads to severe vasculitis include liver & kidney)* *(occur in child <2 Yo & has Viral infection)*

**Case:** If patient with T.B. has increased liver enzymes level → so it’s mostly of **drug-induced origin** from anti-T.B. drugs & may also as **T.B. liver disease.**

- **N.B:** Any disease is Acute or Chronic According to what? → TO **DURATION** not severity.
- In liver diseases: Acute is less than 6 months & Chronic is more than 6 months duration.

**Typical patterns of viral transmission**

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
<th>HGV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal-oral transmission</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral transmission</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Sexual transmission</td>
<td>+++</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal transmission</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic (unknown) transmission</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N.B:** HDV can’t replicate alone.** Why? → because HDV is incomplete virus, can’t replicate alone → So NEED HBV.

- IF HDV occur with HBV → **It is called Co-infection**
- IF HDV occur after chronic HBV infection → **It is called Super-added infection.**
<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of virus</strong></td>
<td>RNA (picorna)</td>
<td>DNA</td>
<td>RNA (flavivirus)</td>
<td>RNA</td>
<td>RNA (calicivirus)</td>
</tr>
<tr>
<td><strong>Poor countries</strong></td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Inhibition Period (IP)</strong></td>
<td>15-45d</td>
<td>45-150d</td>
<td>15-180d</td>
<td>20-45d</td>
<td>14-60d</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cholestasis</td>
<td>Chronic hep</td>
<td>Chronic hep</td>
<td>Worsen HBV</td>
<td>Fulminant hep in pregnant</td>
</tr>
<tr>
<td></td>
<td>Relapse</td>
<td>(5% adults,</td>
<td>(85%)</td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fulmin. hep</td>
<td>95% neonates)</td>
<td></td>
<td>Co-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1%)</td>
<td></td>
<td></td>
<td>Super-</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgM: recent</td>
<td>H BsAg/Ab</td>
<td>HCV Ab</td>
<td>HDVAb (+HBV)</td>
<td>HEV Ab</td>
</tr>
<tr>
<td></td>
<td>IgG: &gt;2m</td>
<td>HBeAg/Ab</td>
<td>PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Symptomatic</td>
<td>Chronic: IFN,</td>
<td>Acute: ?</td>
<td>IFN</td>
<td>Symptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine</td>
<td>Chronic: IFN + ribavirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>Vaccine</td>
<td>Vaccine</td>
<td>Protect</td>
<td>Prevent HBV</td>
<td>Health appraisal</td>
</tr>
<tr>
<td></td>
<td>2 doses, 20 Y</td>
<td>3 doses, 15 Y</td>
<td>against infected blood product</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**N.B:** HAV & HDV have same route of transmission, prevention “food sanitation” & are only ACUTE.
- The only virus that we use medications at its acute phase is HCV, we start medications after 3 months of diagnosis if immune system not clear the virus.
- HCV Ab take months to appear in blood, So we use PCR in HCV acute cases.
- Inhibition period means the time the virus takes to appear on the patient & is longest in HBV & HCV.

**Different presentations:**
A. Anicteric hepatitis (no jaundice)
B. self-limited Icteric hepatitis
C. Icteric hepatitis with prolonged cholestasis (6 months)
D. Fulminant hepatitis

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A. Anicteric hepatitis
- Asymptomatic, or mild disease (flu-like) with no jaundice
- Passes undiagnosed
- May progress to chronicity.

B. Icteric hepatitis

<table>
<thead>
<tr>
<th>I- Pericetric stage:</th>
<th>II- Icteric stage</th>
<th>III- Convalescent stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>few days with acute onset of fever, malaise, dyspepsia, upper abdominal pain, nausea, ANOREXIA, dark urine ± pale stools.</td>
<td>few weeks with appearance of jaundice</td>
<td>Complete histopathological recovery of the liver may take 6 months</td>
</tr>
<tr>
<td></td>
<td>systemic symptoms disappear (wane), Hepatosplenomegaly.</td>
<td>o All clinical manifestations disappear.</td>
</tr>
</tbody>
</table>

N.B: Fulminant hepatitis is severe acute hepatitis leads to destroy all liver, Very high enzymes level, disturbed conscious level due to severe hypoglycemia, also there are bleeding tendency & decrease in liver size.
- **Treated by:**
  - 5%glucose to correct hypoglycemia
  - Fresh frozen plasma due to bleeding
  - Urgent liver transplantation.

N.B: Not all jaundice are infective viral hepatitis, it may be hemolytic or cholestasis.
- Not all acute viral hepatitis patients develop jaundice.

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**ACUTE HEPATITIS INVESTIGATIONS**

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Stool analysis:</th>
<th>Complete blood count (CBC) &amp; ESR</th>
<th>Viral markers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Bilirubin and bile salts: <strong>present</strong></td>
<td>o Pale (low stercobilinogen content)</td>
<td>o Moderate rise in ESR, Leucopenia with relative lymphocytosis.</td>
<td>o anti- HAV IgM , HBsAg, anti- HBC IgM, anti -HDV IgM , anti- HEV IgM, HCV</td>
</tr>
<tr>
<td>o Possible evidence of glomerular affection: Slight albuminuria, Microscopic hematuria, Granular casts.</td>
<td></td>
<td></td>
<td>o RNA by PCR, EBV, CMV IgM</td>
</tr>
</tbody>
</table>

**-More specific investigation:**

**HAV:**
- **IgG:** positive= old infection or vaccine {Exposed}
- **IgM:** recent infection (cause of hepatitis)

**HCV:**
- **Anti HCV Ab: Total (IgG):** appears few weeks after infection. -**IgM:** recent infection.
- **HCV RNA:** earliest to detect in acute infection

**HBV**
- **HBsAg:** positive 2-6 weeks after onset, lasts for 6 months (more if chronicity occurs)
- **Anti HBC Ab: Total (IgG):** previous exposure, IgM: active disease.
- **Anti HBs Ab:** 3 months after infection. Gives immunity
- **HBeAg and DNA**= replication= active disease

N.B: Not all jaundice are infective viral hepatitis, it may be hemolytic or cholestasis.
- Not all acute viral hepatitis patients develop jaundice.
SEQUELAE (PROGRESSION) OF ACUTE HEPATITIS

- **Complete recovery**: is the rule in the great majority of HAV & HEV, most HBV, and few HCV
- **Relapse**: as the original disease esp. in HCV
- **Fulminant hepatitis**: Acute liver failure complicated by hepatic encephalopathy. If the course is very rapid, jaundice may be not have time to appear!! Occur in 1% of cases of acute hepatitis A or B. **Hepatitis E** is a common cause in Asia esp. in pregnant mothers. Fatal in most case.
- **Prolonged cholestasis**
- **Chronicity**: hepatitis, cirrhosis, carrier state, hepatocellular carcinoma (HCC)

TREATMENT OF ACUTE HEPATITIS

- **Rest**: till symptoms and lab are normal
- **Normal diet**: Heavy diet is nauseating: avoid it! Stop alcohol and hepatotoxic drugs!
- **Symptomatic treatment**
  - If there is nausea: domperidone
  - If there is itching: cholestyramine
- **Prevent transmission**

**Remember**: we use also antiviral medications in acute hepatitis C infection.

In Acute Hepatitis B with recovery:
- **there are 7 markers**: 3 Antigens {Surface Ag, e Ag & Core Ag} + 3 corresponding Ab {Surface Ab, e Ab & Core Ab} + DNA.
- Note: Core Ag **not** present in blood only in liver tissue, Core Ab appear in blood **EARLY**
- In general Ag & its corresponding Ab **can't present together in blood at the same time**.
- 1st Ag to appear is the last corresponding Ab to appear.

If a patient serum has +ve HBsAg, HBe Ag, IgM anti-HBc & DNA → The case **is an ACtIVE Acute Hepatitis B**.
If a patient serum has +ve anti HBs, anti-HBc (IgG) & anti-HBe → The case is **during recovery after Acute Hepatitis B**.

Order of disappearing: HBe Ag then HBsAg then IgM anti-HBc {Because the case is ACUTE not chronic}.