### Hepatitis A Virus

Classic example of acute hepatitis, self-limiting, mild when affect children & affect large numbers of people.

First identified in 1973, classified as Picornavirus, contains single stranded RNA which could be isolated and visualized under electronic microscope → so a vaccine was developed, unlike virus C.

### Spread of infection

Fecal-oral transmission (mainly by hands), in poor countries (crowded places), incubation period 2-6 weeks.

### Additional methods of prevention:

- **Boil It or Don't Eat It**
  - Boiling or cooking food and beverage items for at least 1 minute to (85°C) inactivates the virus (makes the virus NOT infectious)
  - When in countries where hepatitis A is common
    - Do not drink beverages (with or without ice) of unknown purity
    - Do not eat uncooked shellfish (not very well done)
    - Do not eat uncooked fruits and vegetables that are not peeled or prepared by you personally

### Complications

Usually HAV infection runs a benign course, rarely cholestasis, relapse and fulminant hepatitis might occur especially in adolescents and young adults.

### Age Shift in HAV infection

HAV may affect adolescents (15-25 years) and adults with more prolonged (6-9 months) and severe form of clinically manifested disease as the individual can't return his normal life till liver enzymes become normal.

Hepatitis A in adults may develop to fulminant hepatitis which necessitate urgent liver transplantation.

### Treatment

- No specific medical treatment, rather than a symptomatic treatment is applied if vomiting → anti emetic, fever → antipyretic and so on.
- Once fully recovered, the individual:
  - Has lifelong protection against HAV
  - Is no longer infected and cannot give the infection to others, fortunately has no chronic barrier as salmonella.

### Hepatitis A Vaccine

HAV vaccine is usually given as 2 doses over a 6-18 month period (HAV vaccine is approved for persons 1 year of age) no need for it for neonates as they are passively immunized
It is not obligatory (not compulsory = not mandatory) and put an extra burden on governments as the disease is benign and self-limiting so it is **NOT COST EFFECTIVE**

Hepatitis A vaccines are safe and effective; protection will probably last for at least 20 years

<table>
<thead>
<tr>
<th>It is indicated for</th>
<th>It is not indicated for</th>
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<tbody>
<tr>
<td>All children at age 1 year (i.e., 12-23 months).</td>
<td>Persons who have occupational risk for infection.</td>
</tr>
<tr>
<td>Children and adolescents ages 2-18 who live in states or communities where routine Hepatitis A vaccination has been implemented because of high disease incidence.</td>
<td>Persons who have chronic liver disease such as HCV in such case a serological test checking IgG for virus A &amp; B have to be done.</td>
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<tr>
<td>Persons traveling to or working in countries that have high or intermediate rates of Hepatitis A.</td>
<td>Users of illegal injections and non-injection drugs.</td>
</tr>
<tr>
<td>Persons who have occupational risk for infection.</td>
<td>Wilson’s disease and glycogen storage disease.</td>
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</table>

- Immune globulin (IG) (preparation that contains hepatitis A antibodies) can be used before exposure to HAV and **within 2 weeks** of HAV exposure to prevent infection. IG can be used for all age groups.
- Wash your hands after using the toilet or changing a diaper and before preparing or eating food & Wear gloves if you have to clean surfaces contaminated with stool.
## Chronic Hepatitis

**Definition**

Silent disease, starts acute at certain point then turn chronic, has no symptoms at early stages which could be manageable.

**Inflammation of the liver cells that lasts 6 months.**

Can persist for years, even decades. In most people, it is mild and does not cause significant liver damage. In some people, continued inflammation slowly damages the liver, eventually producing cirrhosis (which is a harmful healing), liver failure, and sometimes liver cancer.

**Etiology**

<table>
<thead>
<tr>
<th>Viral</th>
<th>O HCV (75%)</th>
<th>O HBV (15%) ± HDV (super added infection): direct cytopathic effect and/or immune-mediated</th>
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</thead>
<tbody>
<tr>
<td>Drugs and alcohol</td>
<td>Through altered immune response, cytotoxic intermediate metabolites or genetically determined metabolic defects:</td>
<td></td>
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<tr>
<td></td>
<td>O Isoniazid</td>
<td>O Methyldopa “used for short period in pregnancy”</td>
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<tr>
<td></td>
<td>O Nitrofurantoin</td>
<td></td>
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<tr>
<td></td>
<td>O Acetaminophen “large doses for years”</td>
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**Treatment of chronic hepatitis:**

- antiviral + interferon
- stop the cause

**Symptoms**

- Many patients are asymptomatic, especially in chronic hepatitis C
- Nonspecific malaise, anorexia, and fatigue are common, sometimes with low-grade fever and upper abdominal discomfort
- Symptoms of cirrhosis if this occurred

**Lab diagnosis**

- Drugs history should be taken to exclude them as a cause
- The biochemical hallmark of chronic hepatitis is an increased serum transaminase (AST and ALT). When inflammation is severe and/or prolonged, hepatic dysfunction may become apparent (decompensated liver disease) → ↑ serum bilirubin and INR/prothrombin time, and ↓ serum albumin
- Search for etiology:
  - Viral markers
  - Autoimmune markers: ANA, ASMA, Anti LKM
  - NASH: Diabetes, dyslipidemia
  - Cu in urine for Wilson’s disease, Ceruloplasmin in serum

**Liver biopsy**

- (not a surgical procedure it is called one minute technique)
- (N.B: during procedures pt is ordered not to breath to avoid hurting himself)
- Applied for pts. With normal INR under septic conditions, can’t be applied for pts with tumor in liver
- Liver biopsy is essential for definitive diagnosis: to assess severity, detect etiology and to plan for therapy
- As we can’t depend only on AST & ALT as they are not always sensitive or specific
- Histopathology examination of chronic hepatitis to:
  - assess Activity of inflammation “A”
  - Stage of Fibrosis using different scoring systems (Modified Knodell’s - Metavir) “F” (0-4) → 4 represents liver cirrhosis.
  - Steatosis: how much fat in liver “S”

- According to liver biopsy, chronic hepatitis is sub-divided into:
  - Mildest
  - Severe

- Significant inflammation in portal tract only with lots of macrophages, lymphocytes (i.e immune cells of chronic nature) with preserved liver architecture.
- Bridging necrosis i.e portal tracts “bridging” by necrotic bands. Deposition of fibrosis tissue first only near portal tracts and then eventually perportal with bridging fibrosis.
### HBV: Epidemiology
- First recognized in 1960s
- Scientifically classified as Hepadnavirus oncogenic double strand virus.
- Contains deoxyribonucleic acid (DNA)

### HBV Genetics
- Eight genotypes of HBV (labeled A through H) have been identified (Complex virus).
- The clinical significance of HBV genotypes is not as clear as that of hepatitis C virus genotypes.
  - (in virus C >> genotypes are related to TTT while that of B are related to disease pathology)
- In EGYPT genotype D is the most prevalent.
  - Although recent data have suggested that different HBV genotypes may be associated with different rates of progression of liver disease and different rates of response to interferon therapy, these data were not enough to recommend routine testing for HBV genotypes in clinical practice.

### HBV Seromarkers
- **HBsAg:** Rises first in infection. Indicates acute HBV infection
- **HBeAg:** Rises first in infection. Indicates active virus and infectious state.
- **Anti-HBe:** Rises after core antibodies. Indicates resolution of infection.
- **Anti-HBc, IgG:** Indicates exposure. Used to monitor chronic infection.
- **Anti-HBc, IgM:** First antibody to appear. Indicates acute HBV infection.
- **Anti-HBs:** Appears months after infection or vaccination. Indicates immunity.
- **HBV DNA:** Associated with viral particles, most reliable marker of circulating infectious virus.

N.B: e Ag has high mutation rate so may appear false negative on measuring it as the test kit won't be liable to measure that mutation.

### Diagnosis of HBV

#### Acute Hepatitis B Virus Infection with Recovery (Typical Serologic Course)
- Window phase between week 24 & 32
- In which only isolated anticore appears
- This may indicate one of two scenarios:
  1. Acute case seeking to be cured
  2. Chronic hepatitis with (HBsAg) mutation

- **To differentiate:** HBV DNA is done:
  - If (-) >> follow up for immune (HBs Ab) which illustrate the 1st scenario.
  - If (+) >> occult hepatitis B which illustrate the 2nd scenario.

#### Progression to Chronic Hepatitis B Virus Infection (Typical Serologic Course)
- (+) HBs Ag >> disease still present
- (+) HBe Ag
- (+) DNA
- (+) anti HBc
**Serodiagnosis of HBV**

<table>
<thead>
<tr>
<th>HBs Ag</th>
<th>Isolated antigen</th>
<th>Immune Naturally Vaccinated or past exposure</th>
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</thead>
<tbody>
<tr>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>Anti HBc</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>Anti HBs</td>
<td>-ve</td>
<td>+ve</td>
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In case of Vaccine: individuals are given surface antigen which is genetically engineered inside yeast cells so >> no core is present as it is not a complete virus just A protein

Vaccine can’t cause hepatitis

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**Why chronicity in virus b range from 5% to 95%??**

This is due to the age of occurrence of infection if occurs early in prenatal area "very early postnatal period" immune system is very weak so 95% is chronic

If occurs from 2 to 3 years old in child it will develop chronic by 50%

But if occurs in adult the chronicity will be from 5 to 10%

Patient who develop chronic infection can inter immune tolerance phase, immune tolerance phase may reach immune clearance and then totally cured So when we see the patient in immune tolerance phase we give body some time "six months" to let the body defeat the virus itself which may lead to immune clearance

Chronicity depend on age of infection and has bad prognosis in small age

For example infection at day 1 of life will lead to chronic hepatitis infection by the 6th month and then at 15 years old liver cirrhosis occurs, at 20 years Hepatocellular carcinoma may develop

So the problem when the mother not know that she is infected by B virus.
Chronic phase of Hepatitis B

- Inactive HBsAg carrier
- Chronic hepatitis
  - 90% of infants infected with HBV at birth
  - 30% of children infected at age 1-5 years
  - 2-6% of people infected after age 5 years: adults have more symptoms than children
- Cirrhosis (15-40%) ± its complications
- HCC: HBV is mutagenic even with no cirrhosis

Extrahepatic manifestations of Hepatitis B

- Polyarteritis nodosa
- Cryoglobulinemia
- Glomerulonephritis

They are immune based pathology.

Extrahepatic manifestations are immune based pathology.

Proteinuria is a hallmark of glomerulonephritis.

Protection against blood and blood product transmission

- Blood bank supervision
- Prevent healthcare transmission (Universal precautions)
- Do not share toothbrushes, razors, or other personal care articles that might have blood on them
- Avoid tattoo & body piercing or do the procedure in sterile fashion

Prevent sexual transmission:

- Legitimate sexual practice. Protection of spouses: use condoms till vaccine is protective

Test pregnant ladies for HBV to protect babies.

N.B:

A Couple: one of them has Hepatitis B virus are they married or engaged??
If engaged delayed marriage to 6 months and vaccination of the normal one
If married: protected sex should be taken in consideration & vaccination of the normal one

HBV Therapy:

Goals of therapy:

Primary aim: is to eliminate or reduce or suppress HBV DNA to the lowest possible level.

Secondary aim: prevent progression to cirrhosis, liver cell failure (LCF), HCC

Outcome of the disease caused by B virus is related to the viral load "DNA level of virus" that when increase >> complication increase pathology related to viral DNA so suppress it to the lowest level

Who to treat?

Evidence of active HBV infection

1. HBV DNA 5 10⁴ copies (2000 IU)/ml in patients +ve or -ve for HBeAg.

2. Abnormal liver chemistry. Treatment may be offered to patients with a normal ALT level, but it may be less efficacious.

3. Better to have liver biopsy before treatment to confirm clinical diagnosis document severity of liver disease.

Other Ways to Prevent Hepatitis B

- Protection against blood and blood product transmission
  - Blood bank supervision
  - Prevent healthcare transmission (Universal precautions)
  - Do not share toothbrushes, razors, or other personal care articles that might have blood on them
  - Avoid tattoo & body piercing or do the procedure in sterile fashion

- Prevent sexual transmission:
  - Legitimate sexual practice. Protection of spouses: use condoms till vaccine is protective

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### Egyptian MOH Regulations

**HBeAg (+) OR HBeAg (-)**

<table>
<thead>
<tr>
<th>N.B</th>
<th>HBV DNA IU/ml</th>
<th>ALT</th>
<th>ACTION</th>
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<tbody>
<tr>
<td>The 2 parameters are ↑</td>
<td>≥2000</td>
<td>&gt;UNL (upper normal level)</td>
<td>treat</td>
</tr>
<tr>
<td>1 normal the other is ↑</td>
<td>≥2000</td>
<td>NORMAL</td>
<td>Do Liver Biopsy to assess fibrosis (±40 days) Treat if ≥ A2 or F2</td>
</tr>
<tr>
<td>1 normal the other is ↑</td>
<td>&lt;2000</td>
<td>&gt;UNL</td>
<td>Do Liver Biopsy to assess fibrosis (±40 days) Treat if ≥ A2 or F2</td>
</tr>
<tr>
<td>The 2 parameters are normal</td>
<td>&lt;2000</td>
<td>Normal + normal clinical or imaging evidence of CLD “NO activity of inflammation and no evidence of fibrosis”</td>
<td>Follow up &amp; Do Liver Biopsy Treat if ≥ A2 or F2</td>
</tr>
</tbody>
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**Treatment Landscape**

Treatment has advanced dramatically due to the introduction of new agents with different safety, efficacy, and resistance profiles

**Cytokines: Patient with HBeAg (+)**
- Interferon 3 times/week,
- Peg Interferon α-2a 1 time/week

N.B:
- Although INF has S.E but it is better used when recommended as 6 months of use is better than life long TTT.
- Avoid INF in: pregnancy, with chemotherapy and immune diseases as it is immune modulator.

**Nucleoside Analogue (NA): Naive patients who have HBeAg (- ve)**
- Lamivudine: good and cheap but may develop mutation and resistant → flare
- Entecavir (0.5 mg/dl O.D)
- Telbuvidine
- Nucleotide Analogue Adefovir dipivoxii, Tenofovir (300 mg/day)

**MOH regulations**

<table>
<thead>
<tr>
<th>patient</th>
<th>Peg IFN-a therapy</th>
<th>NA therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg (+)</td>
<td>48 week</td>
<td>Stop ttt 6-12 months after seroconversion (eAg disappearance)</td>
</tr>
<tr>
<td>HBeAg (-)</td>
<td>IFN not recommended</td>
<td>Indefinitely or until HBsAg seroconversion (eAg disappearance)</td>
</tr>
</tbody>
</table>

**Medications**

Patients who have HBeAg (+) or patients who have delta virus infection will be treated by:

- Peg INF for 6 months

**HBeAg seroconversion:**
- stop therapy after another 24 weeks

**no HBeAg seroconversion:**
- treatment can then be switched to antiviral then for 6 to 12 months after HBeAg seroconversion
Nucleoside analogues for the treatment of HBV

- All have high response rate, but need to be continued for >1 year.
- All resistant mutants. Common with prolonged lamivudine, rare with others
- All can affect kidneys: rare with lamivudine, common with others
- All taken orally once/day
- Lamivudine (Epivir, Zeffix) 100mg/d
- Adefovir dipivoxil (HepSera) 10 mg/d

Special groups

- **Co-infected patients with HCV**: treat virus B according to the previous guidelines + treat Virus C according to guidelines
- **Chronic hepatitis and pregnancy**
  - **Mother don't know she has virus B**: diagnosed pregnant woman in the last trimester showing hepatitis B virus DNA level more than $10^5$ IU/ml are candidate for lamivudine 100 mg or Tenofovir 300 mg to decrease the chance of newborn infection (if diagnosed in 1st trimester no need for medication till 3rd and DNA level $>10^5$ IU/ml)
  - **HB-IG and first dose of hepatitis B virus vaccine**: for the baby in the first 6 to 12 hours after delivery reevaluate the mother’s condition after delivery and Consider treatment according to the previous guidelines
  - females who become pregnant while on treatment: **mother knows she has virus B**
    - on lamivudine monotherapy continue on treatment
    - on other lines of treatment shift or class B drugs tenofovir 300 milligrams daily

- **Healthcare workers screening for all HCW, vaccination is mandatory (main goal is preventing disease transmission)**
- chronic hepatitis B virus patient (particularly surgeons, gynecologist and dentists) should be treated with a potent antiviral agent with a high barrier to resistance (0.5 milligram Entecavir or tenofovir 300 milligram)
- **Compensated Cirrhosis**: Entecavir 0.5 mg or Tenofovir 300mg daily (doses here are IMP.)
- ** Decompensated Cirrhosis**: Entecavir 1 mg daily. (Doses here are IMP.)
- Renal Insufficiency: Entecavir preferred with dose adjustments according to creatinine clearance. (Tenofovir nephrotoxic)

Follow up

1. Monthly visits for receiving medications (drug adherence) & follow up for side effects and relapsing symptoms.
2. Checking liver enzymes every 3 months.
3. Serum creatinine is done every 3 months in those receiving Adefovir.
4. IV) Liver function tests, complete blood count, A.F.P., Abdominal U/S & HBV/DNA by PCR quantitative is done every 6 months

Patients with positive viremia after one year of therapy are considered non responders.

Antiviral Resistance

The genetic barrier to resistance refers to the number of mutations that the virus must accumulate in order to replicate efficiently in the presence of the antiviral agent.

The genetic barrier to resistance is partly dependent upon the structure of the antiviral compound and the constraints imposed by the ability of the viral polymerase to tolerate compensatory mutations without significantly impairing its enzymatic activity.

Thus, an agent with a high genetic barrier to accumulation of mutations will naturally have a lower likelihood of developing resistance.

Nomenclature of Antiviral Resistance

- Primary Non-response (not ↓ by 1 log)
- Virological Breakthrough.
- Biochemical Breakthrough.
- Genotypic Resistance.

Resistance = ↓ in DNA level by less than one log,
↑ DNA level or increase in liver enzymes

Resistance of Lamivudine after 5 years = 75%