Viral Hepatitis
A large number of viruses can cause hepatitis (EBV, CMV, VZV, HSV, YF, Lassa virus … etc).

There are viruses, however, that only cause hepatitis.

At least five viruses, A through E, and two newly discovered viruses, GBV and TTV, are considered hepatitis viruses.
Viral Hepatitis

5 Major Identified Types:

A: oral-fecal transmission
B: sexual fluids & blood to blood
C: blood to blood
D: acquired with B
E: oral-fecal transmission

There are also other less common strains
Hepatitis viruses differ greatly in their taxonomy, structure, mode of replication and mode of transmission as well as in the course of the disease they cause.

Diseases caused by hepatitis viruses usually do not become clinically apparent until most or all of the liver is infected.

Furthermore, as hepatocytes are killed new cells are created to take their place.

These new cells provide a potentially endless reservoir for additional cycles of viral infection.
The specific course, nature and serology of the disease differ for each virus.

These viruses are readily spread because infected people are contagious before, or even without, showing symptoms.

Viral hepatitis has emerged as a major public health problem throughout the world affecting hundreds of millions.
Hepatitis A Virus
Hepatitis A

- “Catarrhal jaundice” known to ancient Chinese, Greeks, and Romans.

- First reference to “epidemic jaundice” in Minorca, 1745

- Infectious hepatitis, a term that was coined in 1912 to describe the epidemic form of the disease.

- The viral etiology was suggested in 1931, but the virus was first isolated in 1973 by Feinstone et al using IEM.
Pathogenesis and Pathology

- Natural infection with HAV usually follows ingestion of virus in fecally contaminated food or drink.

- The nature of the host cell receptor that determines tissue tropism has not been elucidated but replication takes place in gut epithelial cells and liver.

- The virus reaches the liver via the portal system and initiates a rapid acute infection prior to the onset of the immune response (hit and run strategy).

- During the incubation period, viremia is observed at about the same time of fecal shedding of HAV which is excreted in bile to be shed in feces.
Ingestion of infected material

Absorption from stomach or small intestine

Replication in liver

Secretion into bile

Excretion in stool or reabsorption
Fecal shedding is detected as early as 10-14 days after exposure and continues until peak elevation of serum aminotransferases, which coincide with antibody detection.

Viremia is brief and terminates shortly after hepatitis develops whereas feces remain infectious for another 1-2 weeks.

HAV replicates slowly in the liver without causing apparent CPE.
Host immune response seems to play a major role in HAV pathogenesis.

Clinical manifestations resulting from damage to the liver occur when antibody is detected and a cell-mediated immune response to the virus occurs.

There is no evidence of extrahepatic site of replication.
Events In Hepatitis A Virus Infection

Clinical illness

Infection

Viremia

HAV in stool

ALT

IgM

IgG

Response

Weeks

0 1 2 3 4 5 6 7 8 9 10 11 12 13
Pathologic Changes characteristic of HAV

- Necrosis and mononuclear cell infiltration of the periportal region with acidophilic degeneration and activation of RE cells of the sinusoids and portal tracts resulting in marked hypertrophy and hyperplasia.

- Less common conspicuous parenchymal changes than HBV, less occurrence of steatosis than HCV, and less occurrence of cholestasis than HEV

- The damaged hepatic tissue is usually restored within 8-12 weeks.

- Confluent hepatic necrosis is a rare potentially progressive lesion that may lead to fulminant hepatitis and death in up to 70% or more of cases.
Clinical Features

- The course of viral hepatitis may be extremely variable.

- Regardless of the etiology, the course of acute viral hepatitis is similar and can be divided into four clinical phases; incubation, prodrome, icterus and convalescence.

- Incubation of HAV ranges from 2-6 weeks and is followed by a short prodrome or preicteric phase (2-7 days).

- Symptoms usually appear coincident with the initiation of an immune response, as gauged by the appearance of IgM class molecules directed against viral structural proteins.
- Patients may have a prodorme of viral type illness

- Features of hepatitis gradually replace the prodromal illness after 2-7 days.

- The urine darkens ad bilirubinuria increases and the stools may be noticeably pale.

- Jaundice then develops, first seen in the sclera and later in the skin.

- The fever resolves as jaundice becomes established.
- At this stage, virus excretion ceases and the patient is no longer infectious.

- Most patients feel better once the jaundice appears.

- After a few days, the appetite returns and the jaundice begins to resolve.

- Older children and adults often complain of right upper quadrant pain or discomfort which usually precedes jaundice by 1 to 2 weeks.
Fulminant hepatitis occasionally occurs in the first 6-8 weeks of illness.

Ascites, a bleeding diathesis, and decerebrate rigidity lead to death in 70-90% of cases.

Mortality rate increases with age and survival is unlikely over the age of 45 years.

Clinical indicators of liver failure are persistent vomiting, rapid decrease in liver size, disturbed behavior, tremor of the outstretched hands and increasing drowsiness.
- Poor cerebral function is classically demonstrated by showing the patient’s inability to copy a drawing of a five-pointed star, although he or she may be able to copy a square (constructional apraxia).

- Hepatitis A commonly causes cholestasis with a rise in alkaline phosphatase to 250-400 IU.

- Occasionally, cholestasis is prolonged with deepening jaundice and severe pruritis persisting for months if untreated.
Resolution of uncomplicated viral A hepatitis is slow but patient recovery is complete.

Relapsing hepatitis occurs in 3-20% of cases within 4-15 weeks after resolution of initial symptoms. More than one relapse can occur.

The disease is milder in children and mortality is age related.

Two thirds of cases occur in children and 70% of deaths are in those above 49 years of age.
HAV: Clinical

- Usually mild, especially among children
- Loss of appetite, nausea
- Cigarette aversion
- Abdominal discomfort
- Fever to 38.5
- Jaundice
- Fulminant hepatitis rare
- No chronic infection
Hepatitis A – Clinical Features

• **Incubation period:**
  - Average 30 days
  - Range 15-50 days

• **Jaundice by age group:**
  - < 6 yrs: <10%
  - 6 – 14 yrs: 40%-50%
  - > 14 yrs: 70%-80%

• **Rare Complications:**
  - Fulminant hepatitis
  - Cholestatic hepatitis
  - Relapsing hepatitis

• **Chronic sequelae:**
  - None
# Age Specific Mortality

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Case-Fatality (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3.0</td>
</tr>
<tr>
<td>5–14</td>
<td>1.6</td>
</tr>
<tr>
<td>15–29</td>
<td>1.6</td>
</tr>
<tr>
<td>30–49</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;49</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4.1</strong></td>
</tr>
</tbody>
</table>

Source: Viral Hepatitis Surveillance Program, 1983-1989
HEPATITIS A

Age related case rate

Cases reported (thousands)

0-4
5 14
15-29
30-49
>49

Age

0
10
20
30
40
50
60
70
80
90
100
Laboratory Diagnosis

- **Virus isolation**

- **PCR**

- **Serology**

  - Acute infection is diagnosed by the detection of HAV- IgM in serum by EIA.

  - Past Infection (immunity) is determined by the detection of HAV- IgG by EIA.
Epidemiology

- Approximately 40-60% of cases of acute hepatitis are caused by HAV

- It is endemic throughout the world and hyperendemic in the developing countries.

- Epidemics are common and they are common source epidemics.
Geographic Distribution of HAV Infection
Hepatitis A Virus Transmission

- Fecal-oral
- Close personal contact (e.g., household contact, sex contact, child day care centers)
- Contaminated food, water (e.g., infected food handlers)
- Blood exposure (rare) (e.g., injecting drug use, transfusion)
Concentration of Hepatitis A Virus in Various Body Fluids

- Feces
- Serum
- Saliva
- Urine

Infectious Doses per mL

Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890
## Global Patterns of Hepatitis A Virus Transmission

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Disease Rate</th>
<th>Peak Age of Infection</th>
<th>Transmission Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low to High</td>
<td>Early childhood</td>
<td>Person to person; outbreaks uncommon</td>
</tr>
<tr>
<td>Moderate</td>
<td>High</td>
<td>Late childhood/young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Adults</td>
<td>Travelers; outbreaks uncommon</td>
</tr>
</tbody>
</table>
PREVENTING HEPATITIS A

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)
Hepatitis A Vaccination Strategy: Epidemiologic Considerations

- Many cases occur in community-wide outbreaks
  - no risk factor identified for 40-50% of cases
  - highest attack rates in 5-14 year olds
  - children serve as reservoir of infection

- Groups at increased risk of infection
  - travelers to developing countries
  - men who have sex with men
  - illegal drug users
  - persons with chronic liver disease
HEPATITIS A VACCINES

• Highly immunogenic
  • 97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose

• Highly efficacious
  • In published studies, 94%-100% of children protected against clinical hepatitis A after one dose
Duration of Protection after Hepatitis A Vaccination

- **Persistence of antibody:** At least 5-8 years among adults and children

- **Efficacy:** No cases in vaccinated children at 5-6 years of follow-up

- **Mathematical models of antibody decline** suggest protective antibody levels persist for at least 20 years

- **Other mechanisms,** such as cellular memory, may contribute
Use of Hepatitis A Vaccine for Infants

- Hepatitis A vaccine is licensed only for persons aged 1 year and older.

- Safe and immunogenic for infants without maternal antibody.

- Presence of passively-acquired maternal antibody blunts immune response, all respond, but with lower final antibody concentrations.

- Age by which maternal antibody disappears is unclear:
  - still present in some infants at one year
  - probably gone in vast majority by 15 months
RECOMMENDATIONS FOR PERSONS AT INCREASED RISK OF INFECTION

- Men who have sex with men
- Illegal drug users
- International travelers
- Persons who have clotting factor disorders
- Persons with chronic liver disease
HEPATITIS A VACCINE-(HAVRIX)

Dose:

>18 years old - 1 ml (1440 units), and 6-12 months later

2-18 years old - 0.5 ml (360 units), and 6-12 months later

Side effects: Pain at injection site, fever, headache
## HEPATITIS A VACCINE EFFICACY STUDIES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Site/Age Group</th>
<th>N</th>
<th>Vaccine Efficacy (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX®* (GSK)</td>
<td>Thailand 1-16 yrs</td>
<td>38,157</td>
<td>94% (79%-99%)</td>
</tr>
<tr>
<td>2 doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>360 EL.U.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAQTA ® ** (Merck)</td>
<td>New York 2-16 yrs</td>
<td>1,037</td>
<td>100% (85%-100%)</td>
</tr>
<tr>
<td>1 dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 units</td>
<td></td>
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<td></td>
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</tbody>
</table>

SAFETY OF HEPATITIS A VACCINE

- Most common side effects
  - Soreness/tenderness at injection site - 50%
  - Headache - 15%
  - Malaise - 7%
- No severe adverse reactions attributed to vaccine
- Safety in pregnancy not determined – risk likely low
- Contraindications - severe adverse reaction to previous dose or allergy to a vaccine component
- No special precautions for immunocompromised persons
FACTORS ASSOCIATED WITH DECREASED IMMUNOGENICITY TO HEPATITIS A VACCINE

- Decreased antibody concentration:
  - Concurrent administration of IG
  - Presence of passively-transferred maternal antibody
  - Age
  - Chronic liver disease

- Decreased seroconversion rate:
  - HIV infection (May be related to degree of immunosuppression)
  - Liver transplantation
Hepatitis A Prevention - Immune Globulin

- **Pre-exposure**
  - travelers to intermediate and high HAV-endemic regions

- **Post-exposure (within 14 days)**
  - **Routine**
    - household and other intimate contacts
  - **Selected situations**
    - institutions (e.g., day care centers)
    - common source exposure (e.g., food prepared by infected food handler)