

RNA Hepatitis Viruses (Hepatitis A, Hepatitis C, Hepatitis E and Hepatitis G)

Reading: Schaechter's Mechanisms of Microbial Disease, Fourth Edition, Chapter 43.

I. **Overview.** Hepatitis viruses are one of the few groups of viruses that are characterized by the disease that they cause. While they all share a similarity in their tropism for the liver, the severity of infection and the ability to persist varies greatly among these viruses.

II. **Hepatitis A virus** – 1.5 million cases worldwide

A. Properties of the virus:

1. Picornavirus, (+) ssRNA genome
2. Icosahedral capsid (non-enveloped)
3. Virions very stable in the environment
 - a) heat stable at 60°C
 - b) can survive in water for months
4. Only one serotype of virus is known

B. Clinical features (“infectious hepatitis”)- 40% of acute cases of hepatitis

1. Oral ingestion and primary replication in oropharynx and intestinal epithelial cells
2. Virus spreads from intestine to blood stream (viremia) which results in infection of the liver.
3. Incubation period is 2 – 6 weeks
4. Most infections worldwide occur in children and are subclinical- 90%
5. Severity of infection increases with age (2/3 of adult infections are icteric)
6. Large amounts of virus can be isolated in feces, virus is cytopathic in intestine with lots of virus released; smaller amounts in blood, saliva and the throat. Virus is shed 10-14 days before symptoms
7. *No chronic carrier state*
8. Case-fatality rate is low (0.5%)
9. Virus is not cytopathic in liver, where damage caused by cell mediated immune response.

C. Epidemiology and Control

1. Spread from person to person by fecal-oral route
2. Can cause wide-spread epidemics when water and/or food supply is contaminated. Largest US outbreak 2003 over 600 people had hepatitis from green onions in fast food restaurant. 9000 people who ate at the restaurant were given immune globulin.
3. Control primarily depends on high standards of personal and public hygiene.
4. Prior to vaccine, immune globulin given and effective for 6 months
5. The first hepatitis A vaccines (inactivated virus) were licensed in 1992. 4 different vaccines, give 2 doses 1 yr apart.

II. Hepatitis C virus

A. Properties of the virus:

1. Member of the *flaviviridae* family
2. (+) ssRNA genome
3. *Enveloped* icosahedral capsid

B. Initial discovery of the infectious agent- ~200 million carriers worldwide

1. A substantial number of the post-transfusion cases of non-A, non-B hepatitis remained after sensitive screening assays for HBV were introduced in the late 1970s.
2. Causative agent could not be cultured *in vitro* or visualized by EM.
3. Molecular biologic approach was used in 1989 to clone and identify the agent, developed screening test. 6 genotypes identified now.
4. The first infectious clone was reported by Dr. Charles Rice in 1997.

C. Clinical features:

1. Incubation period averages 6 – 8 weeks. 75% are asymptomatic.
2. Clinical infections are usually less severe than with HBV.
3. Chronic infections with HCV are more common than with HBV.
4. 85% of patients with HCV have chronic infections for a year or two or longer.
5. 20% of chronic infections progress to cirrhosis of the liver.
6. Chronic HCV infection correlates with the development of hepatocellular carcinomas.

D. Epidemiology and Control

1. Transmitted by contaminated blood, blood factors and intravenous drug use in US.
2. Sexually transmitted world wide, but more rare in US. Perinatal transmission rare.
3. Recurrence of HCV infection is very common in liver transplant patients.
4. In the US HCV more important cause of cirrhosis than alcoholism.
5. Interferon can be effective for treatment, but only for certain genotypes.

III. Hepatitis E virus

A. Properties of the virus:

1. (+) ssRNA genome
2. Icosahedral capsid; stable virion
3. Member of the *Hepevirus* unclassified family

B. General features

1. Fecal-oral route of transmission (mainly water-borne).
2. Mainly seen in under-developed countries.
3. The virus initially multiplies within the intestinal epithelial cells.
4. After entering the bloodstream, it infects the liver

C. Clinical features:

1. Incubation period averages 2 – 8 weeks
2. Mostly a sub-clinical infection in children.

3. Acute Hepatitis E is clinically similar to HAV *except*:
 - a) Bilirubin levels are higher.
 - b) Jaundice is deeper and more prolonged.
 4. Normal case-fatality rate is 0.5 – 3%, BUT in pregnant women it is 10 – 20%
 5. There is no chronic carrier state.
 6. Diagnosis is on the basis of the exclusion of HAV and HBV (and specific sera).
- D. Epidemiology and Control
1. Cook foods and avoid contaminated water when traveling to endemic regions.
 2. Ig from western countries not helpful.
 3. Protein vaccine in clinical trials.

IV. Hepatitis G virus

- A. Properties of the virus:
1. (+) ssRNA genome, 9.1 – 9.4 kb
 2. Icosahedral capsid
 3. Member of the *flaviviridae* family
- B. General features
1. Newly characterized NANBH (non-A, non-B hepatitis).
 2. Occasionally referred to as “GBV-C” virus.
 3. Parenteral transmission (especially i.v. drug use).
 4. Sexual transmission?
- C. Pathogenesis:
1. Estimated to cause 0.3% of acute viral hepatitis
 2. 900 – 2000 infections per year, mostly asymptomatic.
 3. Chronic disease? controversial.
 4. Analysis by RNA detection
- D. Risk groups
1. Transfusion recipients.
 2. Injection drug users.
 3. May be a frequent co-infection with HCV?
- E. Prevention/treatment
- None until virus can be grown.

(+) Stranded RNA Viruses III

RNA Hepatitis Viruses

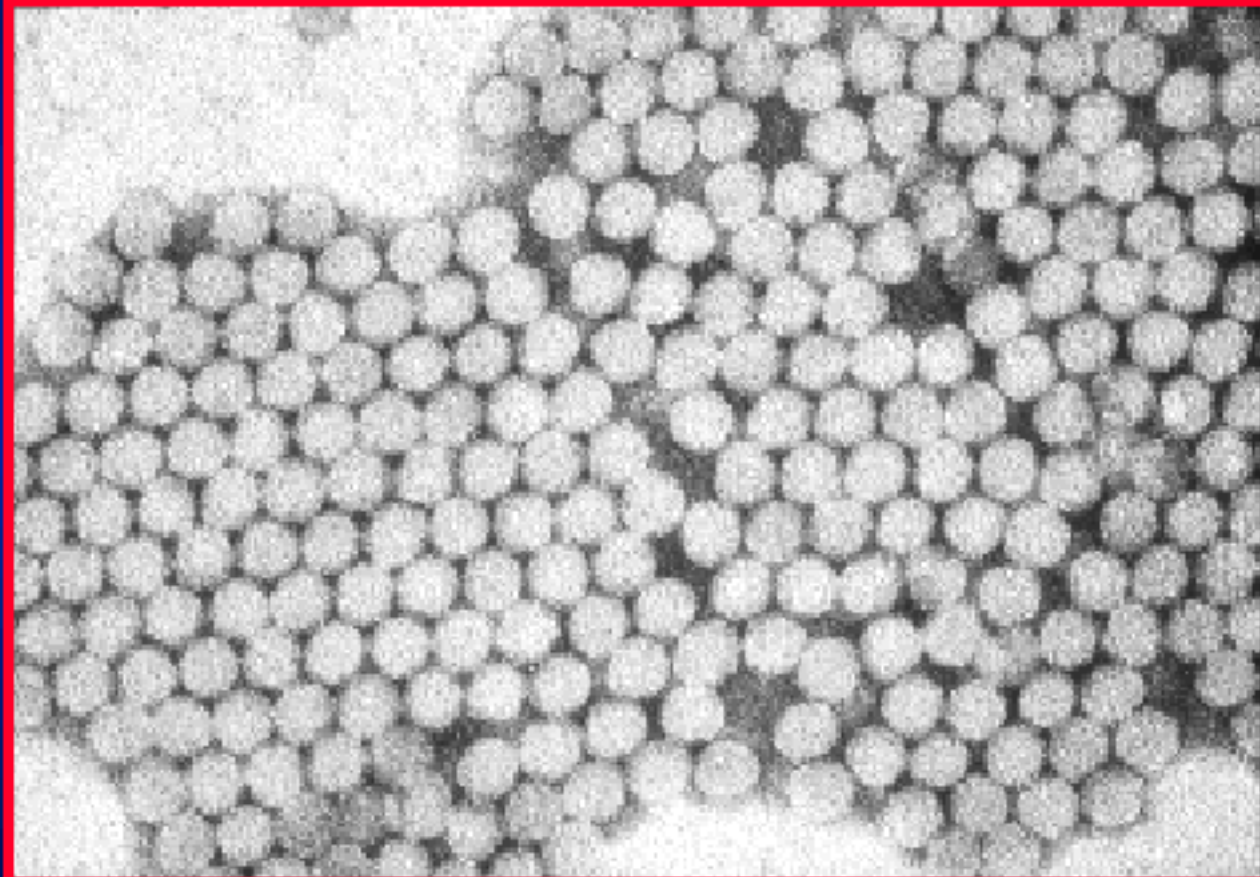
**Hepatitis A, Hepatitis C,
Hepatitis E, Hepatitis G**

TABLE 66-1. Comparative Features of Hepatitis Viruses

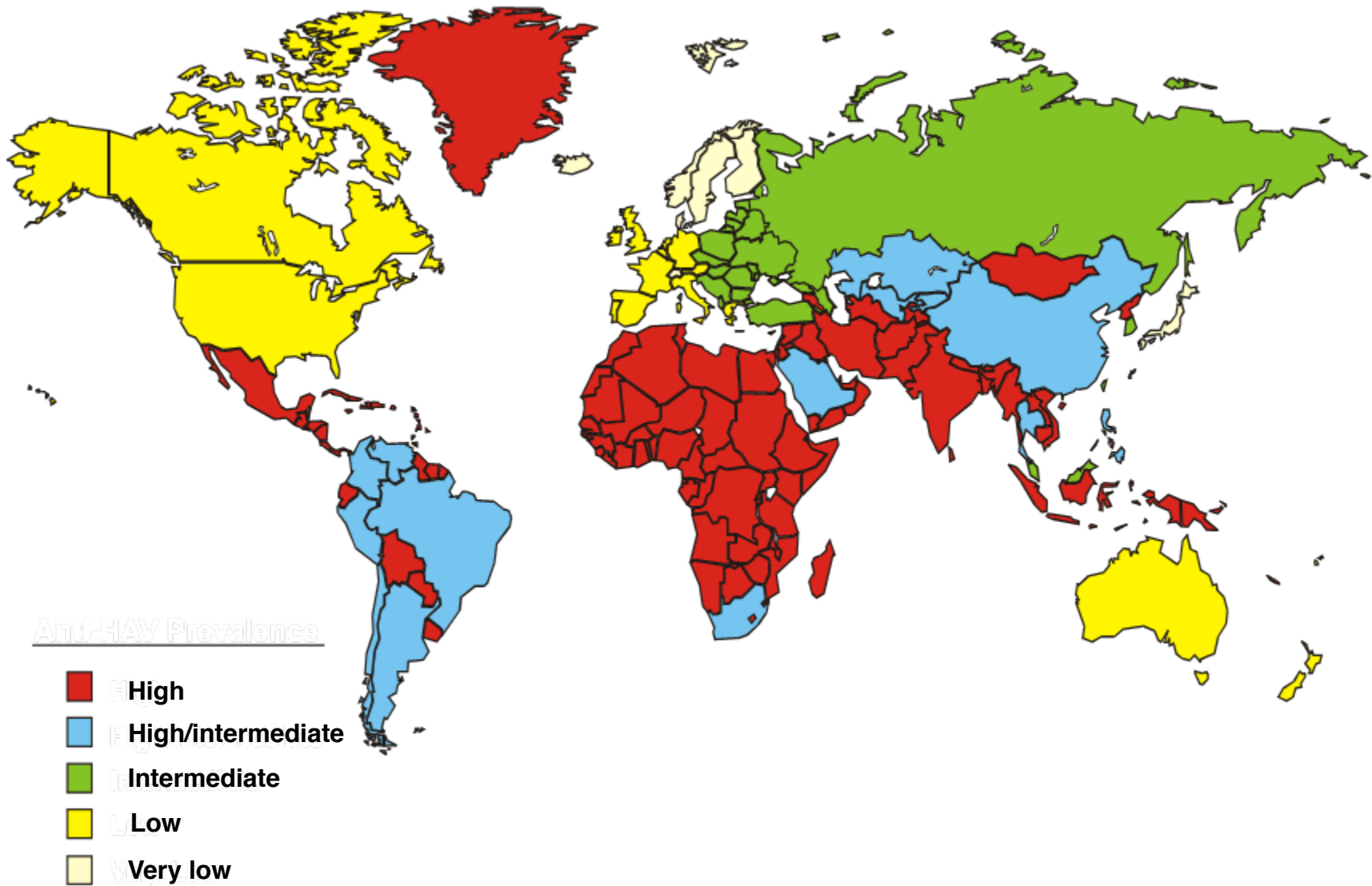
Feature	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Common name	"Infectious"	"Serum"	"Non-A, non-B-post-transfusion"	"Delta agent"	"Enteric non-A, non-B"
Virus structure	Picornavirus; capsid, RNA	Hepadnavirus; envelope, DNA	Flavivirus; envelope, RNA	Viroidlike; envelope, circular RNA	////////// hepe capsid, RNA
Transmission	Fecal-oral	Parenteral, sexual	Parenteral, sexual	Parenteral, sexual	Fecal-oral
Onset	Abrupt	Insidious	Insidious	Abrupt	Abrupt
Incubation period (days)	15-50	45-160	14-180	15-64	15-50
Severity	Mild	Occasionally severe	Usually subclinical; 70% chronicity	<i>Coinfection</i> with HBV occasionally severe; <i>superinfection</i> with HBV often severe	Normal patients, mild; pregnant women, severe
Mortality	<0.5%	1%-2%	~4%	High to very high	Normal patients, 1%-2%; pregnant women, 20%
Chronicity/ carrier state	No	Yes	Yes	Yes	No
Other disease associations	None	Primary hepatocellular carcinoma, cirrhosis	Primary hepatocellular carcinoma, cirrhosis	Cirrhosis, fulminant hepatitis	None
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	—

ELISA, Enzyme-linked immunosorbent assay; HAV, hepatitis A virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IgM, immunoglobulin M.

Hepatitis A Virus



Distribution of HAV



Hepatitis A (HAV)

General Features

- **Picornavirus**
 - Acid stable, non-cytolytic
- **Enterically transmitted (fecal/oral route)**
- **Often referred to as “infectious hepatitis”**
- **Only a single serotype exists**
- **Estimated to be the cause of 40% of acute hepatitis cases**

Hepatitis A (HAV)

Pathogenesis

Enters through the mouth (ingestion)



Multiplies in oropharynx and intestinal epithelial cells



Bloodstream



Liver

Hepatitis A (HAV)

Pathogenesis (con't)

- Virus is abundant in the feces (with some culturable from throat and saliva as well)
- Incubation time is 4 weeks
- *Abrupt* onset of symptoms (15 to 50 days p.i.) and intensify 4 to 6 days before icteric phase
- Clinical symptoms very similar to HBV (malaise, lethargy) but may be less severe

Hepatitis A (HAV)

Pathogenesis (con't)

- Most infections (90%) occur in children who are asymptomatic or *anicteric* (symptomatic without jaundice)
- Severity of the disease increases with age (50-75% of adult infections are icteric)
- By the time “dark urine” appears, most of the virus is gone
- Virus not cytopathic, liver damage due to cell mediated immune response

Hepatitis A (HAV)

Pathogenesis (con't)

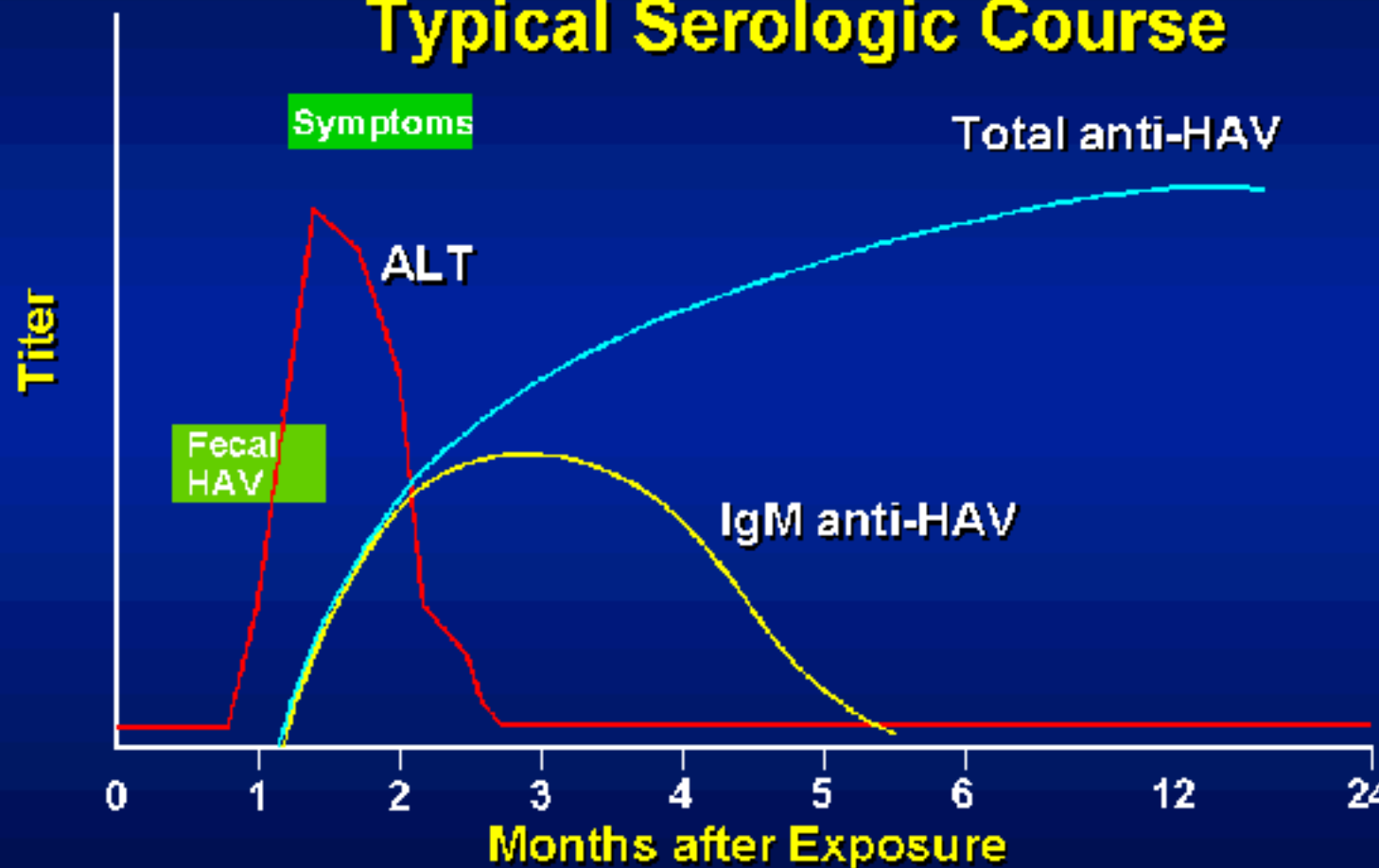
- Overall case fatality rate is $<0.5\%$ (from liver failure)
 - 1/1000 will get fulminant liver disease (80% of these cases will be fatal)
- Illness typically lasts 4 weeks (from onset of symptoms)
- Virus is shed *prior* to onset of symptoms
- There is *no chronic carrier state*

Hepatitis A (HAV)

Clinical diagnosis

- Based on time course of clinical symptoms
- Anti-HAV IgM

Hepatitis A Virus Infection Typical Serologic Course



Hepatitis A Vaccination Strategies

Epidemiologic Considerations

- **Many cases occur in community-wide outbreaks**
 - no risk factor identified for most cases
 - highest attack rates in 5-14 year olds
 - children serve as reservoir of infection
- **Persons at increased risk of infection**
 - travelers
 - homosexual men
 - injecting drug users

Hepatitis A (HAV)

Treatment/Prevention

- Interruption of fecal-oral spread
- Avoidance of contaminated water or food (undercooked shell fish)
- Proper handwashing in day care and healthcare facilities
- Prophylaxis with immune globulin before or early in incubation (< 2wks post exposure) is 80 - 90% effective
- Killed vaccine is available for those at risk

Hepatitis C (HCV)

General Features

- **Flavivirus, (+) ssRNA genome, enveloped icosahedral capsid**
- **Originally referred to as “non-A, non-B hepatitis”**

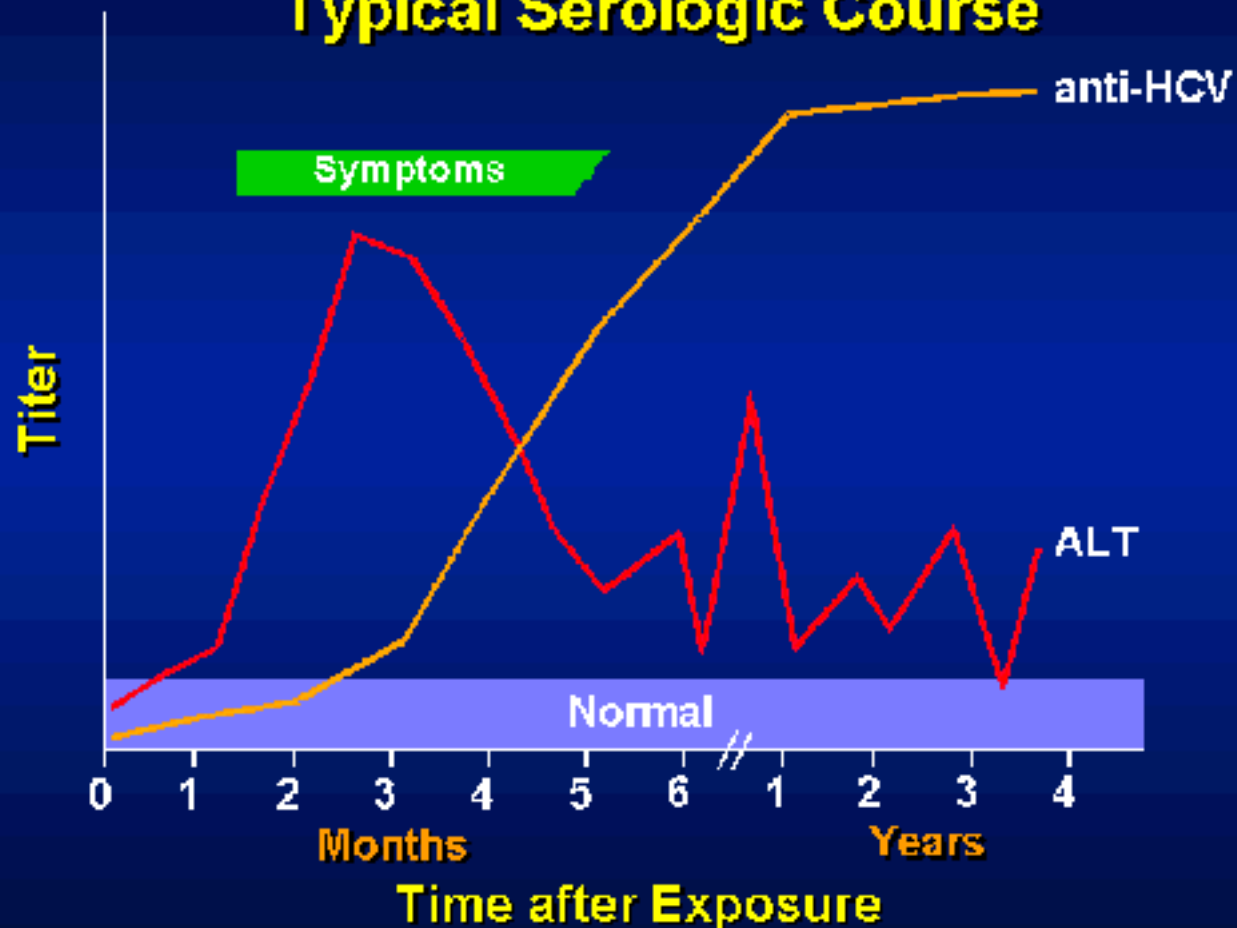
Hepatitis C (HCV)

Disease

- Spread via infected blood and sexual contact-
Target organ liver
- 6 - 8 week incubation period
- most infections are sub-clinical
- Clinical infections are generally less severe than HBV, damage due to cell mediated immune response
- HVC has *a higher incidence of chronic liver disease than HBV* (70% of patients remain viremic for more than 1 year)

Hepatitis C Virus Infection

Typical Serologic Course



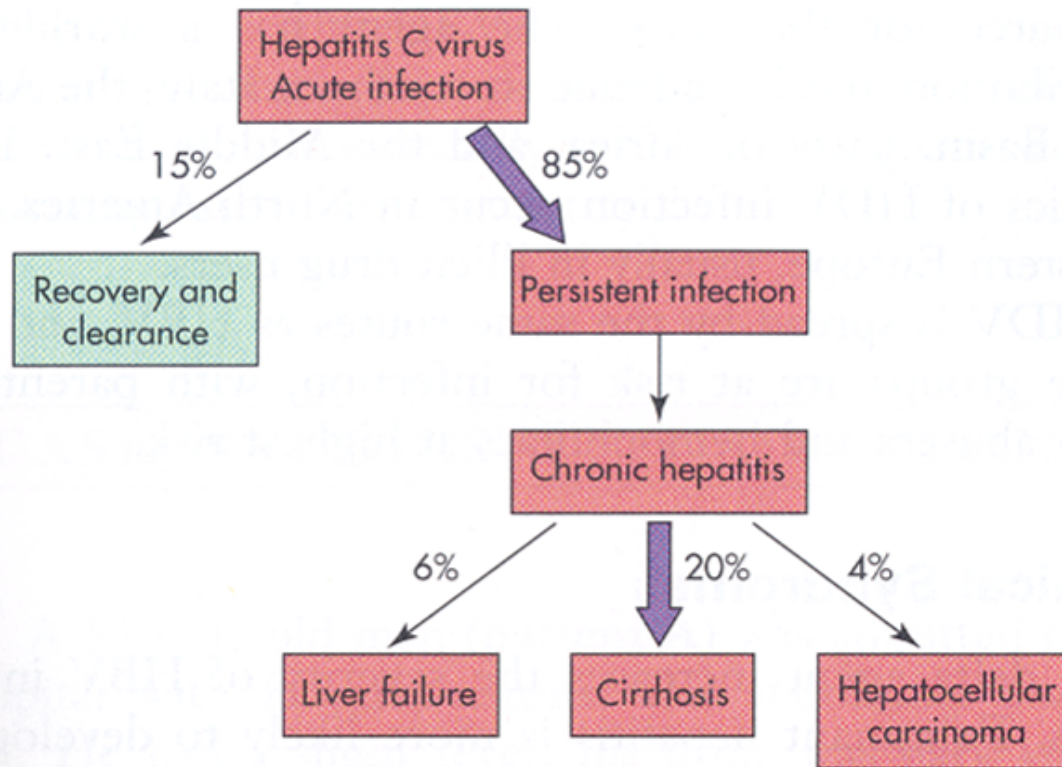


FIGURE 66-13 Outcomes of hepatitis C virus infection.

From Murray et. al., Medical Microbiology 5th edition, 2005, Chapter 66, published by Mosby Philadelphia

Hepatitis C (HCV)

Clinical diagnosis

- Based on time course of clinical symptoms
- Anti-HCV IgM, although not all viremic patients have antibody
- RNA analysis and genotyping

Public Health Service Guidelines for Counseling Anti-HCV-Positive Persons

Anti-HCV-positive persons should:

- Be considered potentially infectious
- Keep cuts and skin lesions covered
- Be informed of the potential for sexual transmission
- Be informed of the potential for perinatal transmission
 - no evidence to advise against pregnancy or breastfeeding

Anti-HCV-positive persons should not:

- Donate blood, organs, tissue, or semen
- Share household articles (e.g., toothbrushes, razors)

Hepatitis C (HCV)

Treatment/Prevention

- Only recently grown in cell culture
- Poor homologous immunity makes a vaccine unlikely
- Immune globulin not helpful
- Alpha-interferon is the only reliable treatment and only moderately successful- serotype specific

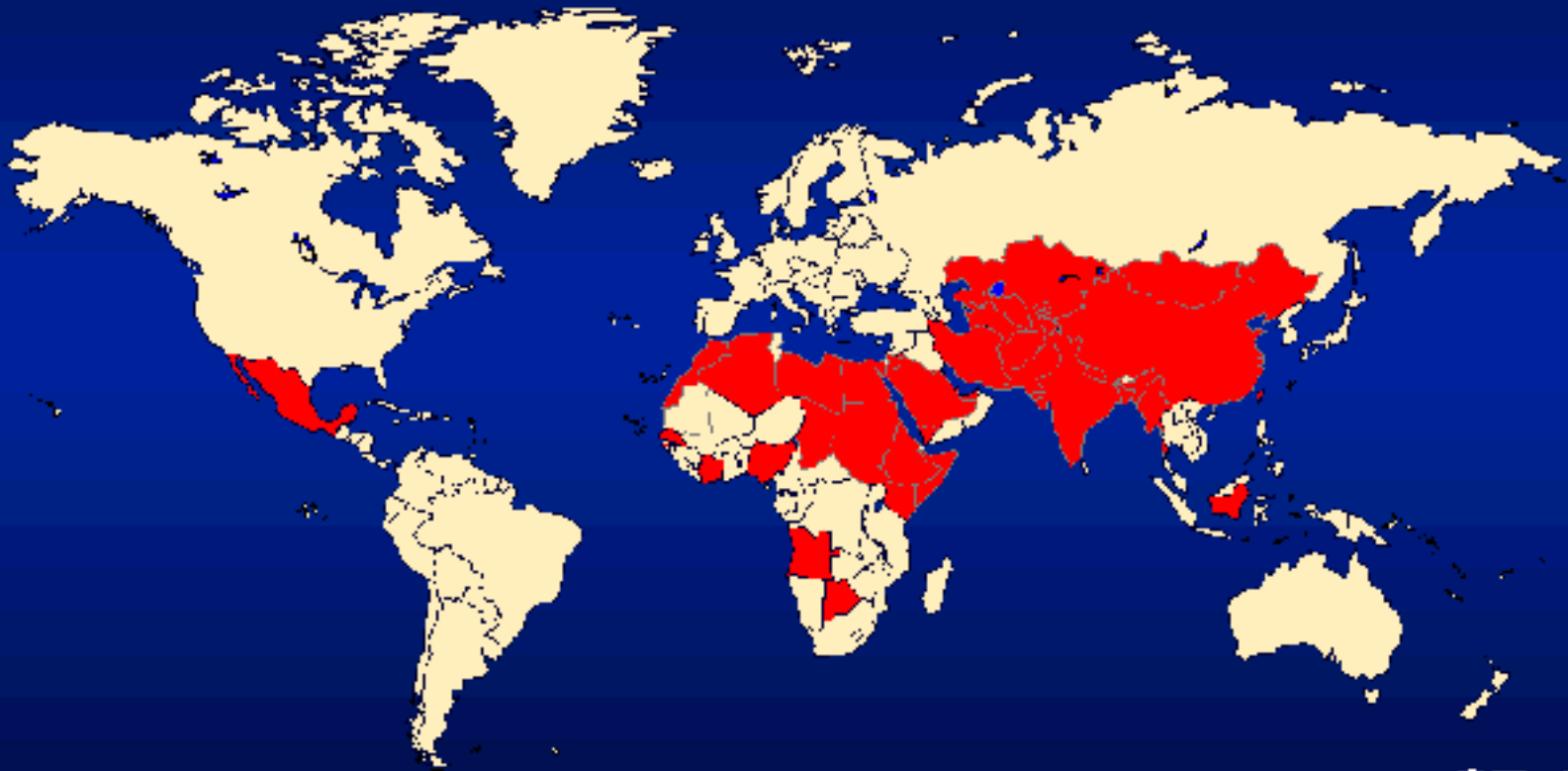
Hepatitis E (HEV)

General Features

- **Hepevirus**
 - Stable virion
- **Fecal-oral transmission (mainly water-borne)**
- **Mainly seen in under-developed countries**

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis



Hepatitis E (HEV)

Pathogenesis

Enters through the mouth (ingestion)



Multiplies in intestinal epithelial cells



Bloodstream



Liver

Hepatitis E (HEV)

Pathogenesis (con't)

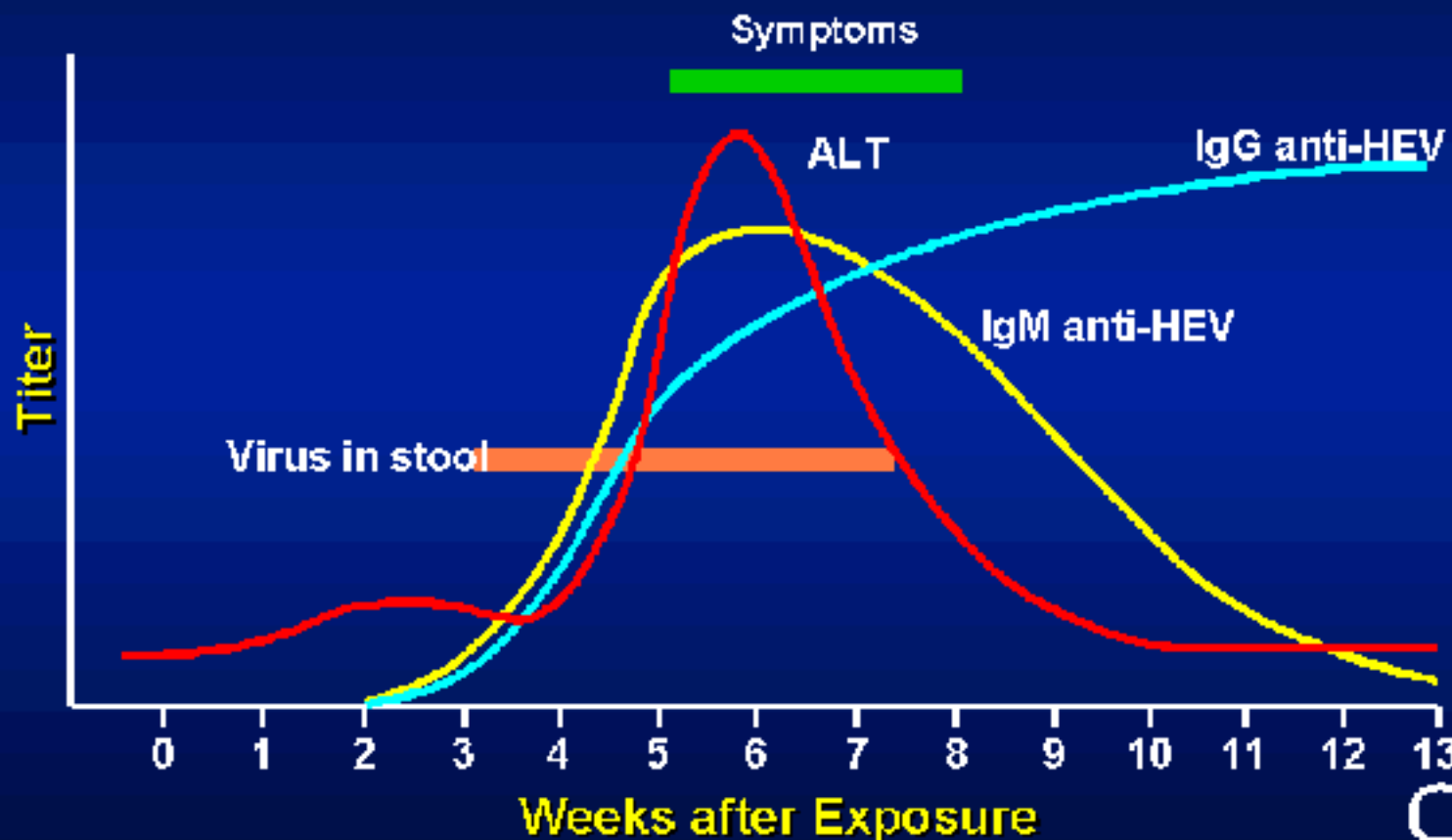
- 2 - 8 week incubation
- Mostly sub-clinical in children
- Acute hepatitis E is clinically similar to HAV

Except:

- Bilirubin levels higher
- Jaundice is deeper and more prolonged

Hepatitis E Virus Infection

Typical Serologic Course



Hepatitis E (HEV)

Pathogenesis (con't)

- Normal case-fatality rate is 1-2%

But 10- 20% in pregnant women

- No chronic carrier state

**Diagnosis by elimination of HBV, HCV & HAV
RNA based methods of detection**

Hepatitis E - Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas

Hepatitis E (HEV)

Treatment/Prevention

- Cook foods and avoid contaminated water when traveling to endemic regions
- Ig from western countries not helpful, since virus in undeveloped countries
- Vaccine?- viral protein in clinical trials

Hepatitis G (HGV)

General Features

- **Flavivirus**
- **Parenteral transmission (esp. i.v. drug use)**
 - **Sexual transmission?**
- **Newly characterized NANBH**

Hepatitis G (HGV)

Pathogenesis

- **Estimated to cause 0.3% of acute viral hepatitis**
- **900 - 2000 infections per year, mostly asymptomatic**
- **Chronic disease? Controversial**
- **Diagnosis RNA based methods**

Hepatitis G (HGV)

Risk groups

- Transfusion recipients
- Injection drug users
- Frequent co-infection with hepatitis C

RNA Hepatitis Viruses

Structure

- Various different families for HAV, HCV, HEV, HGV all positive sense ssRNA

Pathogenesis

- HAV and HEV fecal oral then viremia; others sexual and blood borne viremia
- Liver is target organ; most infections are subclinical, acute infections differ in onset and severity.
- HAV and HEV cause hepatitis with no carrier state; others cause hepatitis with chronic infection and possible carcinoma
- Liver damage due to cell mediated immune response

Diagnosis

- viral antigen detection, nucleic acid

Treatment/prevention

- HAV killed virus vaccine; HCV alpha-interferon effective for some serotypes

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HGV

Flavi