

HEPATITIS

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to the slide * _ ^

Viral hepatitis: is a group of systemic infections affecting the liver predominantly caused by 5 kinds of viruses at least. Those five viruses come from five different families but they share almost the same clinical presentations and symptoms.

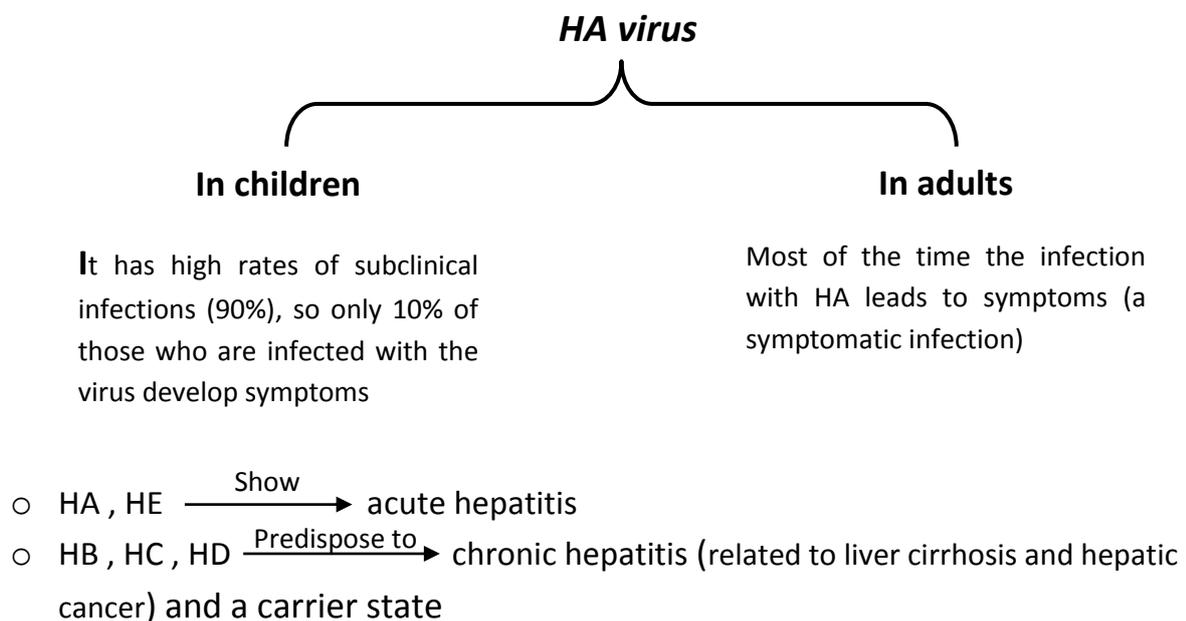
Viral hepatitis may be divided into 5 types according to etiology, that is hepatitis A, B, C, D and E... other viruses can cause hepatitis but not as the main manifestation so we'll not talk about them, they're: Epstein-Barr virus, cytomegalovirus, herpes simplex viruses.

Although the agents can be distinguished by its antigenic properties, the 5 kinds of viruses may produce clinically similar illness.

❖ Clinical manifestations are characterized by:

1. Anorexia – loss of appetite
2. Nausea
3. Lassitude
4. enlarged liver and abnormal liver function
5. a part of cases may appear jaundice

Subclinical infection is common. The occurrence of subclinical infections varies from virus to virus and between individuals according to their age. Let's take Hepatitis A virus as an example:



- Chronicity in HB is seen in 10-15% of those infected by HB
- HC : chronic rates reach up to 85%
- The course of acute hepatitis (A,E) is about 2-4 months generally. The acute infection and the symptoms as a whole may need up to 6 months to resolve completely, and even after markers return to normal patient may still complain of non-specific symptoms such as anorexia, nausea, general fatigue and they will resolve completely by about 4-6 months.
- Recently, 2 kinds of viruses named HGV, and TTV are discovered and considered to relate to viral hepatitis
- HG , HF , TTV are hypothesized virus; it means that some scientists in the 90s came up with a hypothesis says that this hepatitis (certain type found at their time) is caused by a viral agent and they named it HF, but after that no studies were done to confirm this so we don't know much about them!

Hepatitis viruses

Hepatitis A (HAV)

Picornaviridae 1973

Other names: Infectious/ Short-Incubation Hepatitis (shortest IP of all HV, average IP is around 3 weeks). HA and HE are mainly transmitted enterically (through the feco-oral route)

Hepatitis B (HBV)

Hepadnaviridae 1970

Other name: Serum Hepatitis

Hepatitis C (HCV)

Flaviviridae 1988

Hepatitis D (HDV)

Delta agent 1977 - doesn't belong to any family (incomplete virus and needs HBV to complete its replication cycle either as a co-infection or as a super infection)

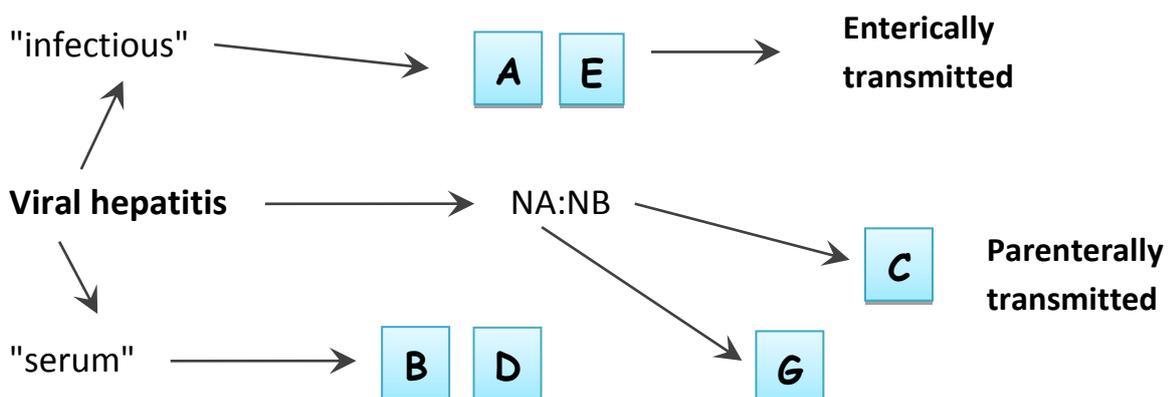
Hepatitis E (HEV)

Previouly classified as *Caliciviridae* family (shares some characteristics). Now: *Hepeviridae*

Hepatitis G (HGV)

Flaviviridae 1995

- **Viral hepatitis – historical perspectives:**



Types of hepatitis

	A	B	C	D	E
Source of virus	Feces	Blood Blood derived Body fluids	Blood Blood derived Body fluids	Blood Blood derived Body fluids	Feces
Route of transmission	Feco-oral, also by blood and sexually (esp. among homosexuals)	Parenterally or Sexually (Percutaneous Permucosal)	Parenterally or Sexually (Percutaneous Permucosal)	Parenterally or Sexually (Percutaneous Permucosal)	Feco-oral (strictly)
Chronic infection	No	Yes	Yes (highest chronicity rate)	Yes	No
Incubation period	2-3 weeks (least)	2-3 months	2 months	6 weeks	5-6 weeks
Prevention	Pre post exposure Immunization	Pre post exposure Immunization Blood donor screening	Blood donor screening	Pre post exposure Immunization	Ensure safe drinking water

- All Hepatitis Viruses are RNA viruses except Hepatitis B (partial ds DNA virus)
- Vaccines exist for Hepatitis A and B. Hepatitis D can be prevented by using HB vaccine. Hepatitis E: a vaccine was found in China but it still hasn't been approved by the US FDA. There is no vaccine for Hepatitis C.

HEPATITIS A VIRUS

- ☞ Naked +ve sense, single stranded RNA virus with icosahedral symmetry
- ☞ The capsid is composed of 4 proteins: VP1, VP2, VP3, VP4 (VP1: has role in attachment to target cell receptors)
- ☞ After attachment the virus is internalized via receptor mediated endocytosis into the cytoplasm, where it uncoats and then undergoes translation, transcription and replication by the help of RNA-dependent RNA polymerase (as +ve sense RNA viruses). The proteins synthesized are polyproteins which are then further cleaved. After that the virus assembles and is released from the cell by cell lysis (since it's a naked virus).
- ☞ (Related to enteroviruses, formerly known as Enterovirus 72, now put in its own family: picornaviridae; genus: hepatovirus.)

☞ **One stable serotype only**

☞ Difficult to grow in cell culture: (primary marmoset cell culture and also in vivo in chimpanzees and marmosets)

☞ 4 genotypes exist, but in practice most of them are group 1

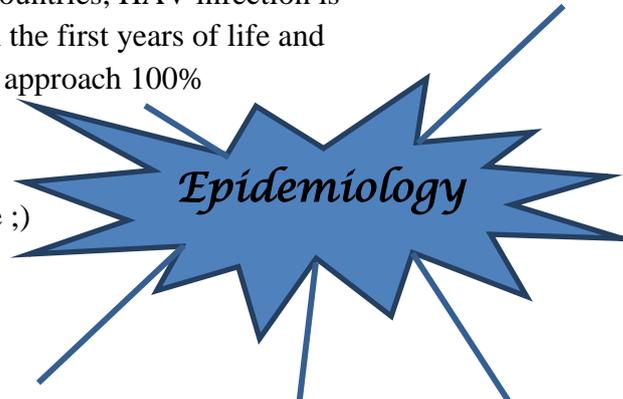
☞ Resistant to inactivation by heat at 60 C for one hour, ether & acid at pH 3.

☞ Inactivated by boiling for one minute, 1: 4,000 formaldehyde at 37 C for 72 hours & chlorine 1 ppm for 30 minutes.

• The anti-HAV seroprevalence rate is presently decreasing in many parts of the world, but in less developed regions and in several developing countries, HAV infection is still very common in the first years of life and seroprevalence rates approach 100%



Because of bad hygiene ;)



• Hepatitis A is the most common form of acute viral hepatitis worldwide.



❖ Highest risk areas:

1. Indian subcontinent
2. Africa
3. Parts of far east (except Japan)
4. South & central America
5. Middle east

• Approximately 1.5 million clinical cases of hepatitis A occur worldwide annually (actual rates are 10X more → remember : 90% are asymptomatic)

• The incidence rate is strongly related to socio-economic indicators and access to safe drinking water

• In developed countries, reduced encounters with HAV in the young have resulted in a decline in herd immunity.

• **Herd immunity**: Reservoirs for the virus are mainly in children who tend to have bad hygienic habits and therefore they can spread the virus by shedding it in the feces. Poliovirus is an example of a vaccine that is known to have herd immunity. It has 2 forms: intramuscular and oral. The oral form has an advantage which is conferring herd immunity: it's a live attenuated vaccine given in the form of oral drops → goes to the intestines, replicates there then the virus (live attenuated) is shed in the feces. In developing countries, because of poor hygiene practices among children and the general population, the vaccine will spread through feces and the community will not develop the illness but will be immunized against the virus!

- Now in case of Hepatitis A the herd immunity is because of the wild virus itself not because of the live attenuated vaccine ☺
- The most contagious period for HA is 1-2 weeks before symptoms develop, this is the period where the virus start replication and is being shed through feces
- Note: In developing countries the seroconversion rate approximately reaches 90-100% due to bad hygiene practices and since the reservoir for hepatitis A is children mainly who tend to have less hygienic measures and controls. Also, the access to the health system is less and the infrastructure is poorer than developed countries. In developed countries the percentage reaches 50% and is dropping.

❖ Risk factors and transmission :

1. Personal contact.
2. Certain occupations (e.g., residential institutions, sewage workers).
3. Travel to high-risk areas.
4. Male homosexuality with multiple partners.
5. Intravenous drug abuse.
6. People with clotting factor disorders who are receiving factor VIII and factor IX concentrates.
7. Close personal contact (e.g., household contact, sex contact, child day care centers)
8. Contaminated food, water (e.g., infected food handlers, raw shellfish)
9. Blood exposure (rare) (e.g., injecting drug use, transfusion)
10. Many cases occur in community-wide outbreaks although most occur sporadically.
 - no risk factor identified for most cases, highest attack rates in 5-14 year olds
 - **children serve as reservoir of infection**

❖ Pathogenesis :

- Causes subacute disease in children & young adults. Most of the time it is symptomatic in adults.
- Humans appear to be the only reservoir for the HAV.

- The incubation period usually lasts 2-6 weeks. The time to onset of symptoms may be dose-related.
- HAV invade into human body by **fecal-oral route**, multiplies in the intestinal epithelium & reaches the liver by hematogenous spread.
- After uptake, the viral RNA is uncoated, and host ribosomes bind to form polysomes.
- Viral proteins can then be synthesised with the viral genome being copied by a viral RNA polymerase.
- Assembled virus particles are then shed through the biliary tree into the faeces.
- Shedding of the HAV is greatest during the pre-icteric prodrome of infection (between 14 and 21 days after infection). This corresponds to the time when transmission is highest.

✓ **What's the effect of HA on liver cells?**

- Replication → HA goes to the intestine → blood (primary viremia) → liver cells causing inflammation (acute lytic infection) → eventually cell death and liver damage. We have inflammation, cell death, necrosis, and the degree of fibrosis seen with these acute viruses is minimal compared to that seen with chronic viruses such as B and C. And as a result of the lytic cycle and necrosis liver stasis may occur which may lead to jaundice (dark colored urine, light colored stools, yellowing of skin and sclera, increase in bilirubin levels which will lead to pruritis (itching).
- Lymphoid cell infiltration, necrosis of liver parenchymal cells and proliferation of kypffer cells all occur in the liver.
 - Complement level reduce the pathogenesis by the following:
- Activated T cell secrete γ -INF that promote the representation of HLA on the liver cells, CTL may kill the target cell that is infected with HAV: in all viral infections the cell has MHC class 1, the antigens are present on it and are expressed on the surface of the cell, they are recognized by the CD8 cells which produce granzymes and perforins which will lead to the death of the infected cell.

Clinical features:

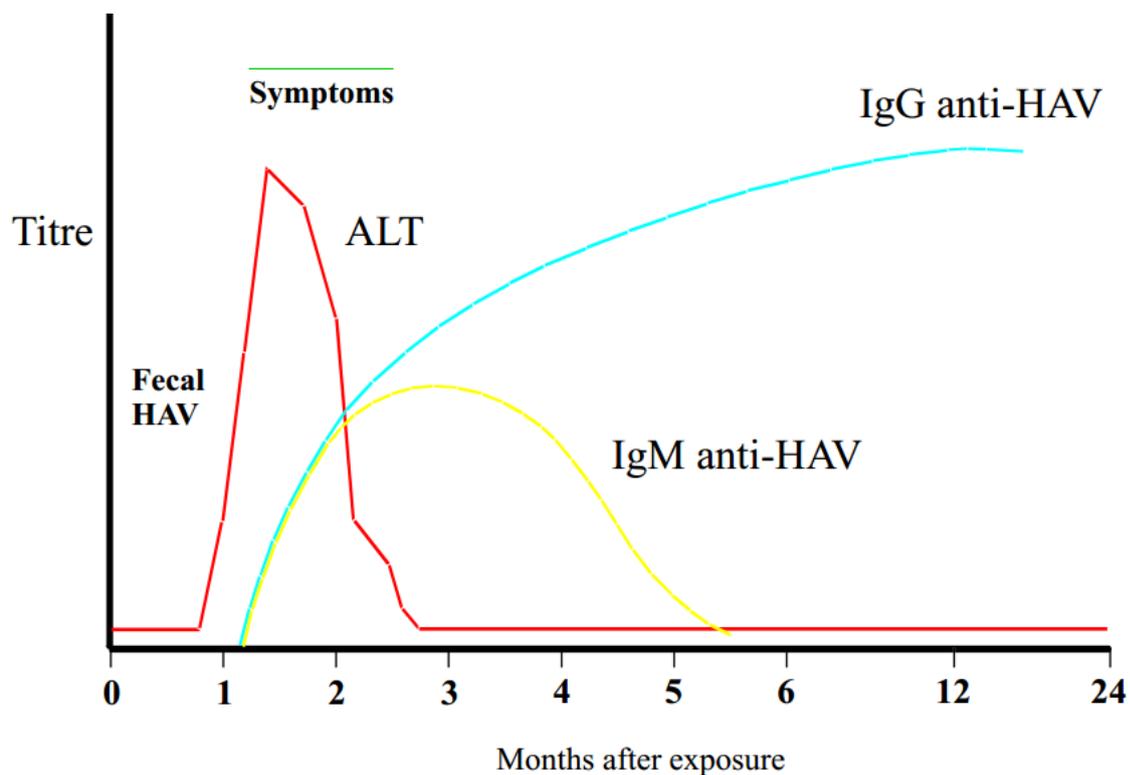
Pre-icteric phase:

Can progress to

Icteric phase

- There is a prodrome of mild flu-like symptoms (anorexia, nausea, fatigue, malaise and joint pain) preceding the jaundice. Diarrhoea can occur, particularly in children.
 - Symptoms are more pronounced in adults
 - Fever is not usually common.
- Dark urine (appears first).
 - Pale stools (not always).
 - Jaundice occurring in 70-85% of adults with acute HAV infection.
 - Abdominal pain occurring in 40% of patients.
 - Itch or pruritus (usually with jaundice but can occur without).
 - Arthralgias and skin rash. These occur less often
 - Tender hepatomegaly, splenomegaly, and lymphadenopathy may occur.
 - Joint Pain

- 🌈 Complete clinical recovery may take up to six months after the onset of the illness even after the biochemical markers have returned to normal we still have non-specific symptoms such as weight loss, anorexia, general fatigue, weakness and nausea (persist for some weeks after biochemical recovery).



- ✚ After the short incubation period which generally averages around 3 weeks, the virus is detected in the blood causing primary viremia, after that the virus reaches the small intestine and replicates there and then reaches the feces.
- ✚ The first detection method could be done by isolating the virus from the feces as early as 2 weeks after infection. 2-4 weeks after infection, IgM start to rise as well as IgG around week 4-5. IgG persist for long time giving long term immunity.

❖ *Lab diagnosis:*

1. Demonstration of Virus in feces: Immunoelectron microscopy
2. Virus Isolation
3. Detection of Antibody : ELISA
 - i) **IgM antibody:** The test is sensitive and specific. It is positive with onset of symptoms (3 to 6 weeks after exposure). It remains positive for between 3 and 6 months (up to 12 months). It remains positive in relapsing hepatitis.
 - ii) **IgG antibody:** Appears soon after IgM and persists for many years. In the absence of IgM it indicates past infection or vaccination rather than acute infection. IgG remains detectable for life

4. Biochemical tests:
 - i) ALT and AST: raised due to compromise in kidney function
 - ii) Alkaline phosphatase: raised
 - iii) Bilirubin: raised
 - iv) Mild lymphocytosis
5. Molecular Diagnosis : RT PCR of feces

❖ *Treatment and prevention*

- There's no specific antiviral drug against hepatitis A
 - Acute infection therefore no medication is needed, you only need to replace fluids and electrolytes, give antiemetic medication in the case of severe vomiting, ask the patient to have some rest.
1. Mainly supportive with treatment of symptoms (fluids, antiemetics, rest).
 2. Avoid alcohol until liver enzymes are normal.
 3. Admit patients with severe systemic upset or intractable vomiting for rehydration and observation.
 4. Good hygiene and sanitation are of fundamental importance. Tap water should be avoided in high-risk areas.
 5. Public education about transmission and prevention are needed, particularly in communities where HAV is endemic.
 6. Immunization is effective and should be appropriately used:
 - a) Passive immunization (ISG): *immunoglobulins***
 - Protective if given before or during incubation period
 - For endemic areas (in cases of outbreaks or a household that has HA)
 - b) Active immunization: *virus itself***
 - Formalin killed HAV
 - 100% protective
 - 2 doses 6-12 months apart
 - Active immunization is given as prophylaxis or can be included in the vaccination program.
 - Nowadays; studies say that active immunization is as equally effective for protection in cases of outbreaks as immunoglobulins; if more studies confirm this then we don't need to use passive immunization anymore!

❖ ***Complications and prognosis:*** (very rare complications)

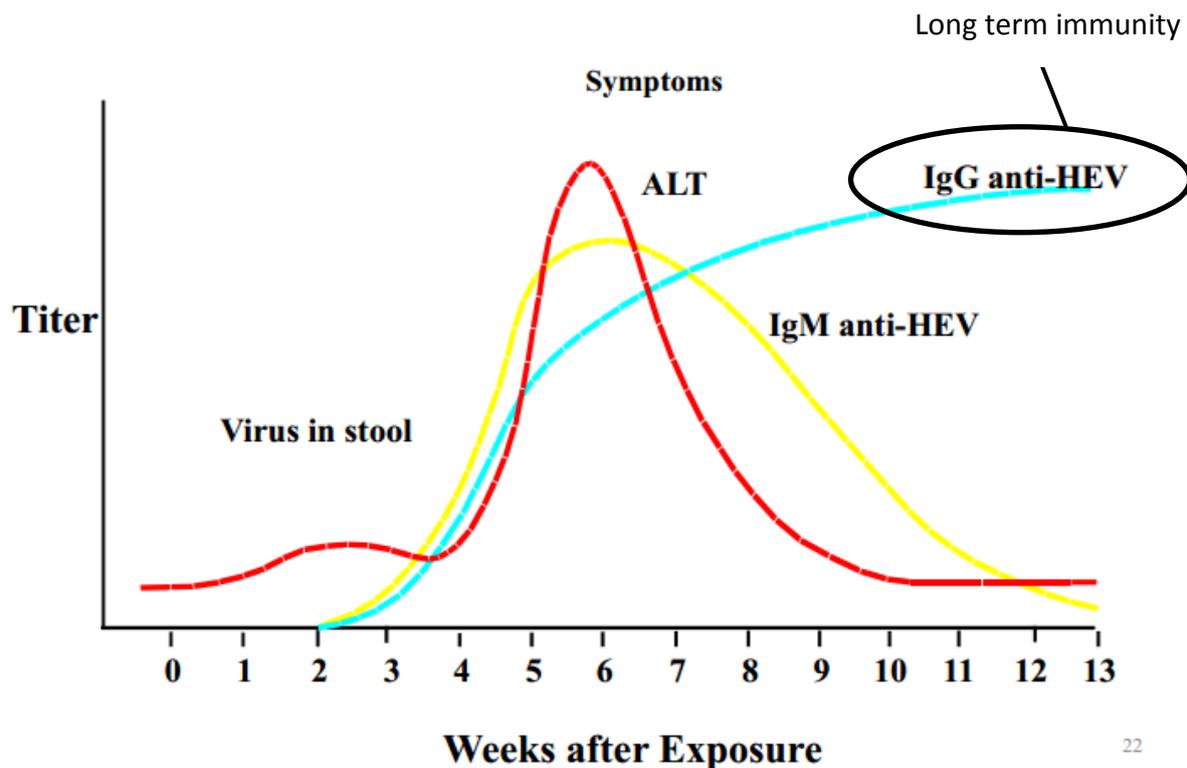
- a) Cholestatic hepatitis (8%). Features may include severe pruritus, diarrhoea, weight loss, and malabsorption. However, they usually fully recover.
 - b) Death (mortality 0.2%)
 - c) Fulminant liver failure (0.4%). Manifests during the first four weeks of illness. It is more common in those with concurrent chronic hepatitis B or C.
 - d) Relapsing HAV infection (up to 15%). In the first 6-12 months after HA infection. (In the slides: It can occur at an interval of 4-15 weeks after the original illness).
- ✓ Excellent prognosis. It is usually self-limiting with no long-term sequelae.
- ✓ There is no carrier state and chronic liver disease does not occur.

HEPATITIS E VIRUS

- a) Calici-like virus
- b) Unenveloped RNA virus, 32-34nm in diameter
- c) +ve single stranded RNA genome, 7.6 kb in size.
- d) The main reservoir are pigs**
- e) HEV genotype 3 and 4 can cause liver disease in humans.**
- f) In humans, the infection may vary in severity from inapparent to fulminant. The mortality is between 1% and 4%
- g) In resource-limited countries, HEV infection is endemic and spreads mainly through contamination of water supplies.
- h) Transmission of virus from domestic pigs to humans is common and higher rates of HEV seroprevalence are detected in slaughterhouse workers and vets.
- i) It is evaluated that one third of the worldwide population has been in contact with the virus
- j) Was cultured only recently
- k) Poses a threat to pregnant women and may be transmitted vertically to the fetus.**

❖ *Clinical features*

1. These are also similar to HAV with no apparent risk of chronic liver disease.
 2. Incubation is 2-9 weeks (average 40 days)
 3. It is usually a **self-limiting illness**.
 4. There are no reports of chronic infection with HEV.
 5. HEV usually causes an acute self-limiting illness like HAV. Fulminant disease occurs in about 10% of cases.
 6. In pregnancy, the mortality rate may be as high as 15-20%.
 7. Illness severity increases with age
 8. In immunocompromised patients, particularly in solid organ transplanted patients, hepatitis E may cause a chronic infection. Occasionally this may cause liver fibrosis and cirrhosis.
- Serology pattern: incubation period → symptoms, increase in liver enzymes → IgM → IgG: long term protection



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❖ *Epidemiologic features*

- ☒ Most outbreaks associated with faecally contaminated drinking water.
- ☒ Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.
- ☒ In the United States and other nonendemic areas, where outbreaks of hepatitis E have not been documented to occur, a low prevalence of anti-HEV (<2%) has been found in healthy populations. The source of infection for these persons is unknown.
- ☒ Minimal person-to-person transmission.

❖ *Prevention and Control Measures for Travelers to HEV-Endemic Regions*

- ☒ Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler.
- ☒ IG prepared from donors in Western countries does not prevent infection.
- ☒ Unknown efficacy of IG prepared from donors in endemic areas.
- ☒ The first vaccine batches came out in late October 2012 in China but still not approved by US FAD