

Viral Hepatitis

Learning Objectives

Upon completion of this content the learner will be able to:

1. Discuss the epidemiology of HAV (hepatitis A virus), HBV (hepatitis B virus), HCV (hepatitis C virus), HDV (hepatitis Delta virus) and HEV (hepatitis E virus) hepatitis.
2. Describe and contrast routes of transmission, clinical manifestations and complications of viral hepatitis.
3. Describe the recommended lab tests/techniques for the diagnosis of viral hepatitis.
4. Discuss the management and counseling of patients with viral hepatitis.
5. Utilize available prevention strategies including exposure risk reduction, screening, active immunization and post-exposure prophylaxis as appropriate.
6. Discuss principles of primary care management and indications for referral of patients identified with chronic viral hepatitis.

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Hepatitis A (HAV)

Single-stranded RNA virus transmitted chiefly by the fecal-oral route. Generally causes a self-limited illness which confers solid immunity, but deaths do occur (case/fatality ratio 0.5%). Endemic worldwide, more prevalent in developing countries, children under age 5 serve as asymptomatic reservoir. In developed countries, immunity is acquired less often in childhood: sexual transmission (sexual practices involving oral-anal and oral-genital contact) along with sporadic and common source outbreaks among adolescent and adult susceptibles is more significant in western/industrialized nations. Outbreaks among men who have sex with men (MSM) have been reported frequently. No chronic state has been described. Persons with chronic liver disease from hepatitis C appear to be at greater risk for developing fulminant hepatitis A.

Hepatitis B (HBV)

Circular, double-stranded DNA virus transmitted by parenteral, sexual and maternal-fetal routes. Clinical illness may be more insidious and potentially more severe (case fatality rate 1.4%). Both clinical and subclinical infection may result in a chronic infectious state. The prevalence of chronic HBV infection ranges from 0.5% in the US and Western Europe, to 8 to 20% in SE Asia, Africa, and the Pacific Islands. Chronic infection perpetuates HBV transmission within a population and leads to cirrhosis and/or hepatocellular carcinoma in a small but significant proportion of cases.

Hepatitis C (HCV)

Single-stranded RNA virus, most common chronic blood-borne infection in US, with 1.8% prevalence among general population. Used to be responsible for 80 to 90% of post-transfusion hepatitis prior to 1990. Currently the risk per unit transfused is estimated to be less than 2 per million. Injection drug use (IDU) has always been the primary risk factor for acquiring HCV infection in the US. Sexual transmission appears to be much less efficient than with hepatitis B. Chronic infection develops more frequently with HCV (55-85% of those infected), resulting in a significant morbidity due to cirrhosis and hepatic carcinoma.

Hepatitis D (HDV)

A defective RNA virus which requires concurrent HBV infection for replication and transmission. Co-infection (HBV-HDV) can be fulminant and fatal. People with chronic HBV infection who are "superinfected" with HDV are more likely to become chronically infected with HDV and have poorer outcomes. Data for sexual transmission is poor and as such is not considered a significant mode of transmission.

Hepatitis E (HEV)

Transmission (fecal-oral) and clinical course similar to that of hepatitis A, with an unusually high mortality rate among pregnant women (20%) and their fetuses. Initially recognized in India, cases have been reported mostly from developing countries: Pakistan, Burma, Algeria, Somalia, Ethiopia, Mexico. Virtually all US cases have occurred among travelers returning from high HEV-endemic areas. Appears to be two geographically distinct strains: Asian and Mexican. Sexual transmission has not been documented.

Hepatitis A (HAV)

I. Epidemiology

- A. Developing countries - asymptomatic children provide reservoir; as sanitary conditions improve, the susceptible population will increase with a shift to infection in young adults. Highest rates in Africa, Middle East, and Asia.
- B. Developed countries: median age of infection increasing.
 - 1. Incidence varies cyclically in the US with most disease from community wide outbreaks. Peak in 1994-95 was primarily associated with increase in reported cases among MSM and IDU.
 - 2. Average annual incidence in US for 1985-95: 10.86/100,000 pop. Dramatic decline in annual incidence since 1995 has continued with 2003 national incidence being lowest yet recorded at 2.6/100,000. Routine vaccination of children in selected states might have impacted this decline.
 - 3. About one-third of US population has evidence of prior infection (total anti-HAV positive) based on NHANES (1988-94) with prevalence increasing in age: 6-19 yr olds (9%); 20-29 yr olds (19%); 40-49 yr olds (33%); >70 yrs (75%).
 - 4. Historically incidence is higher in persons < 40 yrs. of age though recent declines in incidence have been the highest among children ages 5-14 years; highest rates in 2003 among persons 25-39 years of age. Rates among males are higher than among females.
 - 5. Outbreaks among IDU and MSM continue to occur periodically in the US.
 - 6. The Western region of the US has typically had the highest rate, but this disparity is no longer evident – rapid decline in incidence in Western states since 1999 recommendations for routine vaccination of children in states with high incidence.

II. Pathogenesis

- A. Single-stranded RNA virus.
- B. Incubation period is relatively short: average 4 weeks (range 15 -50 days).

C. Viral shedding in stool peaks toward end of incubation and drops dramatically with onset of jaundice; usually no longer infectious 2 weeks after onset of illness but viremia may last longer. Children and infants may shed HAV for longer time periods (up to several months) though chronic shedding does not occur.

D. Modes of transmission:

1. Fecal-oral:

a) Dominant mode of transmission is person to person by household contact or sex contact with an infected person.

b) Virus heavily concentrated in stool, and to a much lesser extent in serum.

1) Pre-school and day-care facilities enrolling those under 2 years: majority of those infected do not become symptomatic but shed high titers of virus.

2) Diaper handling may result in infections in care-givers.

3) Older siblings, parents, babysitters, daycare center staff are at risk. In one study of adults without an identified source of infection, 52% of their households had a child < 6 yrs. of age and presence of a young child was associated with HAV transmission within the household.

4) Injecting and non-injecting drug users.

5) Community-based epidemics may occur related to contaminated food (fast food, shellfish, green onions).

2. Sexual transmission (sexual practices involving oral-anal and oral-genital contact):

a) Plays a larger role in developed countries with adequate sanitation and water systems.

b) Seroprevalence varies among different populations: some studies have shown MSM have rates of approximately 30%, compared with 12% of heterosexual males.

- c) Anti-HAV positive persons reported more frequent oral-anal contact, greater number of sexual partners and longer time period of MSM activity than persons without evidence of prior HAV infection in some surveys.
 - 3. Percutaneous transmission: possible during viremic phase of infection. Rare among blood donors and likely more common among injecting drug users who share needles or other drug paraphernalia: unclear whether this is related to hygiene vs. true percutaneous transmission.
 - 4. Saliva: animal studies have detected infectious virus in saliva, although transmission has not been documented.
- E. Immunity: infection with HAV confers solid immunity and there is no chronic state.

III. Clinical Manifestations

A. Symptom development:

Likelihood of developing symptoms is related to age.

1. <10% of children < 6 yrs have symptoms.
2. 70-80% of children and adults > 14 yrs have symptoms.

B. Manifestations:

1. Onset typically more abrupt than with HBV; symptoms are non-specific and may include fever, malaise, anorexia, nausea, abdominal pain (esp. RUQ), dark urine, jaundice.
2. Serum aminotransferase levels are elevated as with HBV, but resolve more quickly (most will be normal within 6 weeks; 20% may have abnormalities persisting to 3 months).

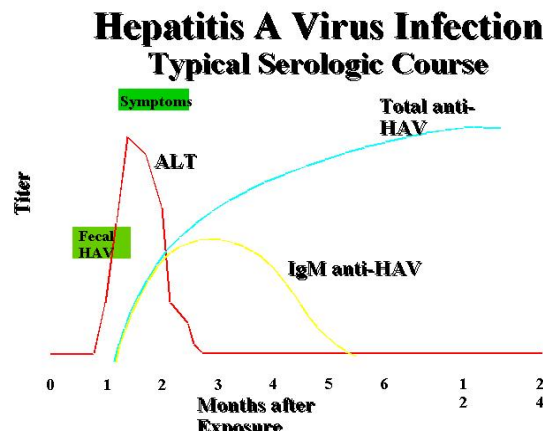
C. Course of disease:

1. Generally self-limited (usually < 2 months).
2. Relapsing or prolonged HAV (up to 6 months) occurs in 10-15% of symptomatic infections.
3. HAV accounts for less than 10% of fulminant hepatitis (mortality 0.1 to 0.6%; increased in persons > 50 years of age: 1.8% case fatality rate); persons with

chronic liver disease from HCV infection appear to be at increased risk for development of fulminant hepatitis A.

IV. Diagnosis

- A. Suspect hepatitis based on symptoms (see above: nausea, anorexia, fever, RUQ pain), with or without jaundice.
- B. Diagnosis based on serologic findings as symptoms are not specific to HAV infection:
 1. IgM anti-HAV: present in acute infection, persists up to 6 months (ELISA).
 2. Total anti-HAV: persists indefinitely and confers lifelong immunity.
 3. Elevated transaminases (AST, ALT) and GGT.



V. Treatment: None available. Supportive care.

VI. Prevention

- A. Hand washing.
- B. Avoid direct or indirect fecal-oral contact during sex – fingers, penis, condoms, toys, etc).

C. Counseling

1. Infected patients should be counseled regarding the need for careful personal hygiene (hand washing), sanitary disposal of feces, and the avoidance of oral-anal and oral-genital sex for at least one week after jaundice onset.
2. Partners should be counseled about vaccine and / or prophylaxis.

D. Passive and active immunization:

1. Passive immunization: IG provides protection via passive transfer of anti-HAV.
 - a) IG administered within 2 weeks of exposure, is 80 to 90% effective in protecting against illness produced by HAV infection.
 - b) Post-exposure prophylaxis dose is 0.02ml/kg IM (deltoid or gluteal muscle).
 - c) Post-exposure prophylaxis should be administered to:
 - 1) all previously unvaccinated household and sexual contacts of serologically confirmed cases of HAV.
 - 2) unvaccinated day care center staff and attendees, and persons in common source of outbreaks under certain circumstances (see MMWR 1999; 48 (No. RR-12).
 - d) IG can be used for temporary pre-exposure protection (i.e. for travelers) though its use is being rapidly supplanted by hepatitis A vaccine. Dose is 0.02 ml/kg (1-2 month coverage) or 0.6 ml/kg (3-5 month coverage).
2. Active immunization with hepatitis A vaccine provides protection by eliciting neutralizing antibodies (anti-HAV). May take 2-4 weeks post-vaccination for development of anti-HAV.
 - a) Two inactivated vaccines: Havrix™ (SmithKline Beecham) and Vaqta™ (Merck). Vaccine administered to deltoid according to schedule:

Recommended Immunization Schedule for Havrix™ (Smith Kline Beecham)

Vaccine Recipient's Age (yrs.)	Dose (EL. Units)	Volume (ml) per dose	No. of doses	Schedule (months)
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2-18	720	0.5	2	0 and 6-12
>18	1440	1.0	2	0 and 6-12

Recommended Immunization Schedule for Vaqta™ (Merck)

Vaccine Recipient's Age (yrs.)	Dose (Units)	Volume (ml) per dose	No. of doses	Schedule (months)
2-18	25	0.5	2	0 and 6-18
>18	50	1.0	2	0 and 6-12

- b) If series is delayed, no need to repeat doses. For long-term protection, the full 2-dose series should be completed.
- c) Safety in pregnancy has not been determined, however because hepatitis A vaccine is produced from inactivated HAV, the theoretical risk to the developing fetus is expected to be low.
- d) Both vaccines immunogenic (99-100% of adults and children develop protective antibodies after second dose) and efficacious (protective efficacy 94-100% in two studies of children).
- e) Long-term protection estimated to be >20 years based on modeling studies with follow-up studies demonstrating protection for up to 12 years.
- f) Pre-vaccination serologic testing for susceptibility likely to be cost-effective for persons from areas of high endemicity, older adolescents and adults from certain populations (American Indian, Alaska Native, Hispanic) and adults from high risk groups (e.g., IDU) and possibly for adults >40 yrs. (based on expected prevalence of 33%).
- g) CDC recommends vaccine for the following persons 2 years of age or older:
 - 1) Travelers to areas with increased rates of hepatitis A.
 - 2) Men who have sex with men.
 - 3) Injecting and non-injecting drug users.
 - 4) Persons with chronic liver disease.
 - 5) Persons with clotting factor disorders (e.g., hemophilia).
 - 6) Persons who have work with live hepatitis A virus.

- 7) Children living in states, counties, or communities where during the baseline period of 1987-1997, the hepatitis A rate was at least twice the national average (>20 cases/100,000).
- h) IG is recommended for use in outbreak settings. If hepatitis A vaccine is recommended for a person being given IG, it can be administered simultaneously with IG at a separate anatomic injection site. The use of hepatitis A vaccine alone is not recommended for postexposure prophylaxis.
- i) Combined hepatitis A and B vaccine (Twinrix[®] – Glaxo SmithKline) is FDA approved for adults age 18 and over. Probably useful for those at risk for both hepatitis A and B. Short-term studies show similar safety and immunogenicity to monovalent vaccines.
- j) Targeted or mass immunization with vaccine indicated in community-wide outbreaks.

VII. References: (See end of module)

Hepatitis B (HBV)

I. Epidemiology

A. United States:

1. The incidence of Hepatitis B has declined since the 1980s with an average annual incidence of 2.8/100,000 in 2002 compared to 11.5/100,000 in 1985 (70% decline). There are an estimated 1.25 million chronically infected people in US.
2. Sexual transmission (MSM, sexual contact with a case or multiple sex partners) accounts for most new cases of hepatitis B in the US. The number of cases attributable to MSM has been increasing from 4% of cases in 1992 to 8.9% of cases in 2002. Injection drug use is also a common risk factor associated with new cases.
3. Seroprevalence varies with age, with highest rate of disease in 2002 among 25-39 year olds. Greatest decline since 1990 in rates among children and adolescents (likely due to routine vaccination).
4. Males have consistently accounted for more cases than females. Male:female case ratio in 2002 was 1.6.
5. Incidence among health care workers (HCWs) has declined since 1985: 9% of reported cases in 1985 vs. 0.5% in 2002, likely due to widespread vaccination.
6. Rates have declined among all racial/ethnic groups except non-Hispanic blacks, in which the rate has been unchanged since 1999.

B. Worldwide:

1. Highly endemic areas (SE Asia, Africa, and Pacific Islands): chronic infection rates exceed 10% with past evidence of infection in 80-90% of the population; perinatal transmission plays a much larger role.
2. Estimated 300-350 million people with chronic HBV infection worldwide: persons with chronic HBV infection are the major reservoir.

II. Pathogenesis

- A. Circular, double-stranded hepadnavirus, more antigenically complex than HAV.
- B. Incubation 45 to 180 days (average 60-90 days) until clinical symptoms develop – longer than hepatitis A.
- C. Recent studies indicate that the DNA genome of HBV replicates via transcription of an intermediate RNA molecule (the "pre-genome"). The replication cycle of HBV thus resembles, in gross detail, that of RNA-containing retroviruses, including HIV.
- D. Virus gains access to the liver via the bloodstream; the liver is the primary site of replication.
- E. Modes of transmission:
 - 1. Sexual:
 - a) Strong evidence exists for sexual transmission among MSM, usually resulting from anal intercourse (receptive or insertive). Less risk in those reporting mostly oral-genital contact. Among 2002 cases for which risk exposures were determined, 25% of cases were attributed to sexual contact. Number of cases attributed to MSM contact has increased from 4.0% (1992) to 8.9% (2002).
 - b) Strong evidence exists for heterosexual transmission: 27% of spouses with chronic HBV infection had either HBsAg or anti-HBs vs. 11% controls. In households where there is acute infection, cohabiting and susceptible spouses often become infected.
 - c) Multiple sex partners associated with risk of infection for both MSM and heterosexual transmission.
 - 2. Percutaneous:
 - a) Injecting drug users.
 - b) Occupational injuries: hollow-bore needle-stick exposures (and possibly mucosal or non-intact skin).
 - c) Contaminated medical equipment (i.e., multiple use vials in hemodialysis units).

- d) May occur from contaminated tools used in tattooing or body piercing if the artist or piercer does not follow sterilization practices.
3. Perinatal:
- a) Most infections acquired at time of birth. Less than 5% of infections occur in utero.
 - b) Maternal HBeAg associated with higher infectivity.
4. Horizontal: in areas of high endemicity occurs from child to child from bites or skin lesions.
- F. Immunity: anti-HBs is protective against infection.

III. Clinical Manifestations

- A. About 30% of persons have no signs or symptoms. Signs and symptoms are less common in children than adults.
- B. Symptom onset may be insidious and typically includes: malaise, anorexia, nausea with or without jaundice. Among patients with acute hepatitis B reported in 2002, 67% had jaundice, 31% were hospitalized for hepatitis, and 1% died.
- C. Prodrome occurs in 15-20% adults and may include serum-sickness syndrome with rash (maculopapular or urticarial), polyarthralgias, arthritis (migratory, large joints or hands). Other immunopathologic diseases (necrotizing vasculitis, glomerulonephritis, mixed cryoglobulinemia) have been found to be associated with chronic hepatitis B.
- D. Chronic infection occurs in:
 - 1. 90% of infants infected at birth.
 - 2. 30% of children infected at age 1-5 yrs.
 - 3. 6% of persons infected after age 5 yrs.
- E. Among all patients with chronic HBV infection, 20%-25% will die prematurely of cirrhosis or liver cancer.

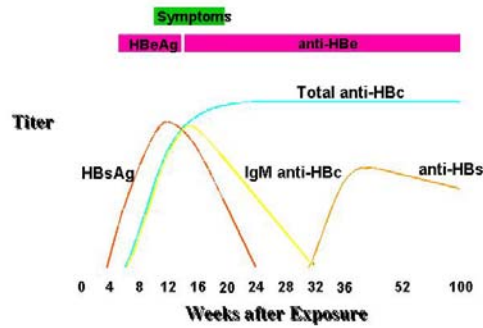
- F. Among patients who develop icteric disease (jaundice), 1% will develop acute hepatic failure, and 3/4 of these will die without liver transplant.
- G. HIV-infected persons are more likely to become chronically infected.

IV. Diagnosis

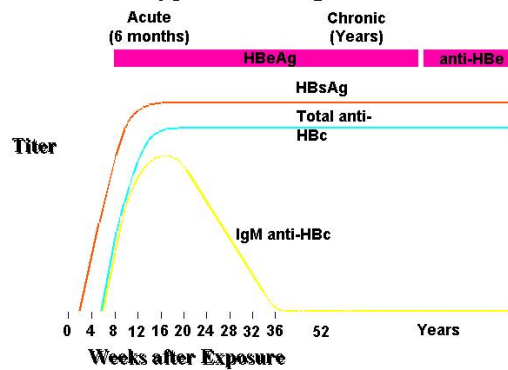
- A. Clinical presentation: see previous section.
- B. Diagnosis based on serologic findings, as symptoms are not specific to HBV infection.
- C. Laboratory findings:
 - 1. Elevated liver enzymes with or without elevated bilirubin.
 - 2. On average, HBsAg can be detected one month after exposure to the virus, but detection can range from about 1 week to 9 weeks. In persons who recover, the duration of HBsAg positivity is variable. About 50% of patients will be HBsAg-negative by 7 weeks after onset of symptoms, and all patients who do not remain chronically infected will be HBsAg-negative by 15 weeks after onset.
 - 3. IgM anti-HBc is a marker of acute infection.
 - 4. Total anti-HBc persists indefinitely, marker of prior or current infection.
 - 5. HBeAg presence indicates higher infectivity. HBeAg positivity is associated with very high titers (10^{8-9}) of circulating virions. In chronically-infected persons, the conversion from HBeAg to anti-HBe may signal resolution of hepatocellular disease.
 - 6. Anti-HBs becomes detectable during convalescence after the disappearance of HBsAg (among those who clear infection).
 - 7. Lag occurs between disappearance of HBsAg and the appearance of anti-HBs: anti-HBc (IgM and total anti-HBc) and anti-HBe are the only markers during this "window" period during transition from acute illness to convalescence.

8. Chronically infected people have persistently detectable HBsAg and total anti-HBc. Such individuals often have little or no evidence of acute liver disease when initially infected.
9. HBsAg may persist in high titers with chronic infection. Spontaneous conversion with development of protective surface antibody and clearance of antigens occurs about 1% per year for people who have chronic HBV infection.

**Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course**



**Progression to Chronic Hepatitis B Virus Infection
Typical Serologic Course**



Interpretation of Hepatitis B Serologies

<u>Condition</u>	<u>HBsAg</u>	<u>anti-HBs</u>	<u>anti-HBc</u>	<u>IgM anti-HBc</u>
Susceptible	neg	neg	neg	

Immune due to infection	neg	pos	pos	
Immune due to vaccine	neg	pos \geq 10 mIU	neg	
Acutely infected	pos	neg	pos	pos
Chronically infected	pos	neg	pos	neg
Equivocal interpretation*	neg	neg	pos	

*(1) May be recovering from acute infection. (2) May be distantly immune and test not sensitive enough to detect very low levels of anti-HBs in serum. (3) May be susceptible with false-positive anti-HBc. (4) May have undetectable level of HBsAg present in serum in person with chronic HBV infection.

V. Treatment

A. Acute hepatitis B: supportive care.

B. Chronic hepatitis B (persistence of HBsAg > 6 months):

1. Management of hepatitis B should be undertaken in conjunction with an expert.
2. Indications for evaluation for therapy: chronic active hepatitis or possibly even cirrhosis, circulating HBV DNA and HBeAg, desire to eliminate infection or prevent sequelae, acceptance of limited efficacy vs. risks.
3. Treatment efficacy has improved for hepatitis B with the introduction of newer drugs and combination therapy. There are 4 FDA-approved medications currently in use: interferon alpha, lamivudine, adefovir dipivoxil, and entecavir. Each of these medications has its limitations. Intereron alpha has many contraindications and frequent side effects. While lamivudine is better tolerated, significant drug resistance develops in many patients over time. Adefovir is a newer treatment that is particularly useful in treating patients who are HBeAg+ and/or have lamivudine-resistant strains, although it is more costly. Entecavir has shown significant improvements in reducing viral levels and the amount of liver damage.
4. There are other nucleoside analogs in development.
5. Abstinence from alcohol is important for people with chronic hepatitis B, or any liver disease, to reduce additional liver injury.

VI. Prevention

- A. Standard precautions in healthcare and laboratory settings.
- B. Persons who inject drugs should be counseled to stop using and get into treatment. If they do not stop using, they should be counseled on how to inject safely (i.e., use of sterile, single-use equipment, including needles, syringes, cookers, cottons, water, etc., each and every time they inject).
- C. Persons should be counseled on methods to reduce the transmission of STDs, including abstinence, monogamy, decreasing the number of sexual partners, and barrier method use. The efficacy of latex condoms in preventing HBV is unknown, but the correct and consistent use of latex condoms may reduce transmission.
- D. Screening to detect HBsAg-positive women in pregnancy (prevent transmission to infant):
 1. Screen all pregnant patients at the first prenatal visit (preferably during first trimester).
 2. Repeat screen in third trimester for high-risk HBsAg-negative (injecting drug users and those with concomitant STDs).
 3. For pregnant women who are HBsAg-positive: evaluate household and sexual partners for vaccination.
- E. Active immunization: hepatitis B vaccine.
 1. Recombivax-HB[®] (Merck) and Engerix B[®] (Smith-Kline) are recombinant vaccines. (Brands may be used interchangeably: see exceptions below.)

Hepatitis B Immunization Schedule for Adolescents and Adults

<u>Group*</u>	<u>Recombivax HB[®] Dose</u> <u>mcg (ml)</u>	<u>Engerix-B[®] Dose †</u> <u>Mcg (ml)</u>	<u>Schedule</u> <u>(months)</u>
Adolescents (11-19 yrs)	5 (0.5)	10 (0.5)	0,1,6 or 0,1,4 or 0,2,4
Adolescents (11-15 yrs)**	10 (1.0)		0, 4-6
Adults (>19 yrs)	10 (1.0)	20 (1.0)	0,1,6 or 0,1,4 or

			0,1,2,12
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*Persons, such as travelers, who require rapid protection – using Engerix-B® only.

**Adolescents age 11-15 only may use the two-dose option with Recombivax-HB®. The second dose must be given a minimum of 4 months after the first, and both doses must be administered by the 16th birthday. No data are available to assess long-term protection > 2 yrs. Engerix-B® has not been approved for this schedule.

Note: dialysis patients receive different dosages. Information on this available at the Immunization Action Coalition website (<http://www.immunize.org/index.htm>).

2. Missing doses should be given ASAP, no need to restart series.
3. Highly immunogenic: protective antibody present in 50% of young adults after one dose, 85% after two doses and 90-95% after three doses; duration of protection not known (>15 years). Persons with normal immune status who respond to initial series remain protected against clinical disease and chronic HBV infection even when antibody titers fall below detectable level.
4. CDC does not recommend periodic serologic testing or booster doses among vaccine recipients with normal immunity. For hemodialysis and other immunocompromised patients, the need for booster doses should be assessed by annual anti-HBs testing. A booster dose should be given when anti-HBs levels decline to <10 mIU/mL.
5. HCWs with substantial risk of future exposure should undergo post-vaccination serology 1-2 months after administration of the last dose of the vaccine series. Persons found to have anti-HBs levels of <10mIU/mL after the primary vaccine series should be revaccinated with a full 3-dose series. This is usually more practical than serologic testing after one or more doses of vaccine. Vaccination and testing results should be documented in the HCW's occupational health record. Nonresponders to vaccine should be counseled that HBsAg testing is recommended. Persons found to be HBsAg-positive should be provided with appropriate medical management, counseling, and vaccination of household or sexual contacts. Nonresponders who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled about precautions to prevent HBV infection and the need to obtain appropriate postexposure prophylaxis for any known or likely parenteral exposure to blood.
6. Must be administered IM (in the deltoid), NOT intradermal and not in the buttock.

7. Safe in pregnancy / lactation.
8. Safe to administer hepatitis B immune globulin (HBIG) at same time, but different anatomic site.
9. Contraindicated if allergic to yeast.
10. Efficacy about 50% in HIV-infected persons with low CD4 count.
11. Serologic testing to determine susceptibility prior to vaccination is not necessary and is not routinely recommended. Pre-vaccination serologic testing may be cost-effective for adults with high prevalence of HBV infection (adults attending STD clinics, MSM, injecting drug users, persons from endemic countries (Asia and Pacific Islands)). If pre-vaccination testing is done, the first dose of vaccine should be administered at the same visit after the blood is drawn. Further vaccination can then be done depending on testing results.
12. CDC has expanded target for vaccine. Current recommendations now include:
 - a) Routine vaccination of 0–18 year olds.
 - b) Vaccination of risk groups of all ages:
 - 1) Persons who have had more than one sex partner in the previous 6 months.
 - 2) Persons who have had a recently-acquired STD, or treatment for an STD.
 - 3) Adolescent and adult males who have sex with males.
 - 4) Sex contacts of infected persons.
 - 5) Injecting drug users.
 - 6) Household contacts of chronically-infected persons.
 - 7) Infants born to infected mothers.

- 8) Infants / children of immigrants from areas with high rates of HBV infection.
 - 9) Health care and public safety workers at occupational risk of exposure to blood or blood-contaminated body fluid.
 - 10) International travelers to areas with high or intermediate levels of endemic HBV infection.
 - 11) Staff and inmates of long-term correctional facilities.
 - 12) Patients who receive clotting-factor concentrates.
 - 13) Clients and employees of facilities for the developmentally disabled.
 - 14) Hemodialysis patients.
 - 15) Victims of sexual assault.
- c. Post vaccination serologic testing is recommended for:
- 1) Infants born to HBsAg positive mothers.
 - 2) Chronic hemodialysis patients and other immunocompromised persons.
 - 3) Health care workers who are exposed to blood in the workplace.
 - 4) Sex partners of people with chronic HBV infection.
- d. Revaccination of non-responders with three doses should be considered [see MMWR 1991:40(No. RR-13) 1-25 and MMWR 1997: 46(No. RR-18) 22-23].
- e. Combined hepatitis A and B vaccine Twinrix[®] (Glaxo Smith Kline) FDA-approved for adults age 18 and over. Probably useful for those who are at risk for both hepatitis A and hepatitis B. Limited short-term studies show similar safety and immunogenicity to monovalent vaccines.

F. Post-exposure prophylaxis:

1. HBIG provides passive transfer of antibodies and should be used along with first dose of hepatitis vaccine for increased efficacy.
2. HBIG plus vaccine recommended for:
 - a) Infants of infected mother: hepatitis B vaccine and HBIG 0.5 ml administered within 12 hours after birth (both IM at separate sites), followed by completion of a three-dose vaccine series by age 6 months.
 - b) Sexual exposure: previously unvaccinated sex partners should receive postexposure immunization with HBIG (0.06 ml/kg) and hepatitis B vaccine within 14 days after the most recent sexual contact. Testing sex partners for susceptibility to HBV infection (anti-HBc) can be considered if it does not delay postexposure immunization beyond 14 days.
 - c) Occupational exposure: see table below. Management based upon knowledge of the source's status or risk factors, exposed's vaccination history, and response (if known). May include do nothing, HB vaccine or HBIG (or both), depending on the situation.

Recommended Hepatitis B Post-Exposure Prophylaxis for Percutaneous Exposure

Vaccination and antibody status of <u>exposed person</u>	<u>Source is HBsAg +</u>	<u>Source is HBsAg -</u>	<u>Source not tested or status unknown</u>
Unvaccinated	HBIG* x 1 and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Vaccinated, known responder**	No treatment	No treatment	No treatment
Vaccinated, non-responder, not revaccinated***	HBIG x 1 + HB revaccination series	HB revaccination series	If known high-risk source, HBIG x 1 + HB revaccination series. If low-risk source, HB revaccination series
Vaccinated, non-responder,	HBIG x 2 [§]	No treatment	If known high-risk source, HBIG x 2 [§] . If

revaccinated			low-risk source, no treatment
Vaccinated, antibody response unknown	Test exposed person for anti-HBs: 1) if adequate, no tx 2) if inadequate, HBIG x 1 + HB vaccine booster dose ^{§§}	No treatment	Test exposed person for anti-HBs: 1) if adequate, no tx 2) if inadequate, give HB vaccine booster dose ^{§§} and check anti-HBs in 1-2months

*HBIG dose 0.06 ml/kg intramuscularly

** Known responder is a person with adequate levels of serum antibody to HBsAg (i.e., anti-HBs ≥ 10 mIU/mL)

***Revaccination = additional three-dose series of hepatitis B vaccine administered after the primary series

[§]First dose as soon as possible after exposure and the second 1 month later

^{§§} Vaccine booster = single dose of HB vaccine appropriate for person's age

4. Previously unvaccinated infants in households where a primary care giver has acute HBV infection should receive HBIG along with first dose of vaccine. Other nonsexual household contacts to persons with acute HBV infection are not at risk unless there has been blood exposure. (If blood exposure has occurred, give HBIG plus first dose of vaccine within 7 days.)

VII. References: (See end of module)

Hepatitis C (HCV)

I. Epidemiology

A. United States

1. HCV infection is the most common chronic bloodborne infection in the US. An estimated 3.9 million persons have been infected (1.8%) with 2.7 million chronically infected. National reported rate in 2002 was 0.5/100,000.
2. New infections declining since the 1980's with an estimated average of 240,000 in the 1980's compared to about 30,000 in 2003. Persons >25 years of age account for majority of cases.
3. HCV infection accounts for about 40-60% of chronic liver disease (8,000-10,000 deaths per year) and is the leading cause for liver transplantation among adults.
4. Before 1990, post transfusion non-A, non-B hepatitis (PTNANBH) occurred in 10% of transfusion recipients, with 90% of PTNABH attributed to HCV infection. Since the introduction of a sensitive screening test for hepatitis C in 1992, the risk for infection is estimated to be less than one per 2 million units transfused.
5. Despite a decline in number of reported cases among injecting drug users, injecting drug use continues to be the most frequent risk factor for HCV infection.
6. Sexual transmission appears to be inefficient. Long-term monogamous partners of patients with hepatitis C have low prevalence of infection (1.5%). However, some experts argue that sexual exposure may account for up to 17% of cases in whom higher risk sexual behavior is the only risk factor identified.
7. The rate of hepatitis C in 2002 was higher among males (0.5 per 100,000) than among females (0.3 /100,000). The male:female case ratio has remained relatively stable with a range of 1.6-1.9 during the past 5 years.
8. Health care workers (HCWs) are at risk from needlestick injuries (average incidence 1.8% post-needlestick from an HCV-positive person); however, prevalence among HCWs is lower than for the general population.
9. Epidemiology of acute HCV infection is difficult to sort out because of its asymptomatic nature, imperfect screening tests, evolving test technology, and long lag-time before seroconversion. On average, antibody to HCV becomes positive about 7 weeks after exposure and generally remains positive for life. Rarely,

antibody seroconversion might be delayed for months after exposure. HCV RNA can be found in the blood as early as 1-2 weeks after exposure and usually becomes transiently undetectable when anti-HCV starts to rise.

B. Worldwide

1. Global prevalence estimated at 3%, with 170 million chronic infections.
2. Up to 5-10 million chronically infected persons in Europe, up to 12 million in India.

C. Modes of transmission:

1. Percutaneous:

- a) Injection drug use (IDU) – well-documented in multiple studies.
- b) Blood and blood products: well-characterized, e.g., transfusions before 1992, clotting factor recipients before 1987. Risk from a blood transfusion is now less than 1 per 2 million transfused units.
- c) Contaminated medical equipment, unsafe injection practices.
- d) Occupational (needlestick injury); average incidence 1.8% post-needlestick from HCV-positive person.
- e) Household contacts of infected persons; thought to occur via blood contaminated household items (razors, toothbrushes).
- f) Intranasal cocaine use (via blood contamination of straws) has been found in limited studies to be a possible risk factor. Not been associated independently from IDU.
- g) Insufficient data in the US to determine if tattooing or body piercing is a percutaneous risk factor for general population, though limited studies show possible association between tattooing among select populations (prisoners).

2. Per mucosal:

- a) Perinatal: average rate of infection ~5%, with higher risk of transmission if woman co-infected with HIV. One recent meta-analysis found ~ 2 times

greater odds of vertical transmission for HCV viremic (HCV RNA +) /HIV+ mothers compared to HCV viremic / HIV - mothers. Other smaller studies have found risk of transmission with HIV coinfecting up to ~20%. Role of HCV viral load uncertain. There appears to be no transmission difference according to type of delivery (caesarian vs. vaginal). Breast-feeding not thought to be a risk for transmission.

b) Sexual: appears to be inefficient, but data are conflicting:

- 1) Studies that compare HBV with HCV sexual transmission rates show a cumulative incidence of HCV seroconversion of 2.5% compared with 26% for HBV, suggesting that HCV is about 10 times less efficiently transmitted to sexual partners than HBV.
- 2) Higher prevalence of HCV among commercial sex workers (6% average, range 1-19%), persons with multiple sex partners, and STD clinic attendees (4% average, range 1-10%) without reported injecting drug use. A Baltimore study of non-IDU STD clients found no condom use (for males) and having more than one partner (for males and females) were risk factors for HCV. Some partner studies suggest male-to-female transmission may be more efficient.
- 3) Average prevalence among long-term partners of patients with HCV (without other risk factors for infection) remains low (1.5%), with risk of acquisition ranging from 0% to 0.6% per year. Factors associated with greater risk for transmission unclear, may relate to viral load, stage of liver disease, as well as other factors.
- 4) Nucleotide sequencing of HCV of spouses in a few studies demonstrate probable evidence for interspousal transmission. Other studies have used nucleotide sequencing to reveal discordant strains in monogamous couples as evidence for non-sexual transmission.
- 5) HCV RNA has been detected in semen of HCV infected men and in cervicovaginal secretions of HCV infected women using highly sensitive PCR testing.

II. Pathogenesis

- A. HCV is a single-stranded RNA virus related to the flaviviruses / togavirus family (arboviruses, dengue).
- B. HCV targets hepatocytes and possibly B-lymphocytes.
- C. Six distinct genotypes with some strains. Type 1a and 1b are most common in US. Genotype appears to influence response to antiviral therapy. Genotype 1a and 1b are less responsive to antiviral therapy.
- D. Incubation is highly variable, depending on route and titer of exposure; average incubation period 6-7 weeks (range 2-26 weeks).
- E. Superinfection with a different genotype or strain of same genotype appears to be possible based on limited studies.

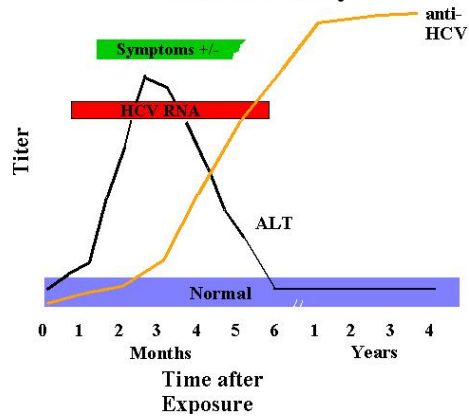
III. Clinical Manifestations

- A. Symptom development: natural history difficult to assess as most acute cases are asymptomatic (80%).
- B. Manifestations:
 1. Acute disease: jaundice, malaise occurs in 20% and is mild.
 2. Chronic disease may be asymptomatic for years, may have nonspecific symptoms: fatigue, extrahepatic manifestations (cryoglobulinemia, other autoimmune syndromes).
- C. Course of disease:
 1. Approximately 55-85% of infected individuals develop chronic HCV infection; of these, 70% will develop chronic liver disease, with mortality of 1-5% due to chronic liver disease (cirrhosis and liver cancer). Nevertheless, current data suggest that most infected people will die *with, not from*, HCV infection.
 2. Time frame for disease progression is highly variable. Factors associated with more rapid progression or poorer outcome are: alcohol use, onset age >40, HIV or HBV co-infection, and possibly male gender.
 3. Persons with chronic hepatitis C who are superinfected with HAV may have a more severe acute infection with possibly fulminant hepatitis.

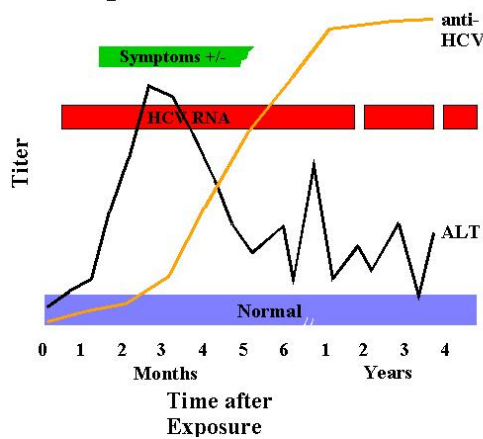
IV. Diagnosis

- A. Clinical presentation: non-specific symptoms (nausea, vomiting, malaise), with or without jaundice.
- B. Diagnosis based on serologic findings, as symptoms are not specific to HCV infection.
- C. Laboratory findings: current assays
 - 1. Enzyme immunoassay (EIA): detects antibody to HCV. Indicates past or present infection. Can detect antibodies within 7 weeks, on average. Need confirmatory tests. Low positive predictive value in low prevalence populations. Some laboratories use signal-to-cutoff ratios to predict true positives.
 - 2. Recombinant immunoblot assay (RIBA): detects antibody to HCV. Used as a confirmatory test to EIA. May have indeterminate result (uncommon with newer assays) and need to test for HCV RNA. Less commonly used with advent of HCV RNA testing.
 - 3. Qualitative detection of HCV RNA with nucleic acid tests (NATs) can detect virus as early as 1-2 weeks post exposure. The FDA- approved NATs use the reverse transcriptase polymerase chain reaction (RT-PCR) and include AMPLICOR[®] HCV Test and COBAS AMPLICOR[®] HCV test. These tests are used to confirm diagnosis. Detection of HCV RNA may be intermittent, so a single negative test is not conclusive.
 - 4. Quantitative HCV RNA testing (by RT-PCR or branched chain DNA) and genotype testing are not used for diagnosis, but useful when initiating and monitoring treatment.

Serologic Pattern of Acute HCV Infection with Recovery



Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection



V. Treatment

Management of HCV infection should be undertaken in conjunction with an expert.

- A. Acute infection: generally patients are asymptomatic. Early seroconverters (i.e. post needlestick exposure) may benefit from early treatment, though the timing of therapy, best regimen, and patient groups most likely to benefit are unclear. There are no formal recommendations on management of acute infection, though considerable research is underway that may lead to future recommendations. Little is known about the impact of treatment for acute HCV infection upon the

natural history of this infection. It appears that HCV infection needs to be present for antiviral therapy to work.

- B. Chronic HCV infection: patients should be evaluated to determine need for therapy. NIH currently recommends treatment of those with increased risk of developing cirrhosis: detectable HCV RNA > 50 IU/mL, liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis. Many of those also have elevated alanine aminotransferase (ALT) levels, though patients with normal ALT levels can be considered for treatment based on individual patient factors. Those with genotype 1 tend to have poorer response to therapy, and genotype influences treatment duration (6-12 months).
1. Combination therapy with pegylated interferon (long-acting interferon with once-weekly dosing) plus ribavirin is the current treatment of choice: improved efficacy (54-56% sustained response) compared to standard interferon plus ribavirin (43% sustained response). Many who otherwise might benefit from therapy are not candidates due to concurrent chemical dependency, mental illness, or underlying physical health problems.
 2. Weight-based ribavirin dosing is now being used for genotype 1 patients.
 3. Monotherapy with interferon has a lower sustained response (15-20%) but may be considered if contraindications exist to combination therapy.
 4. Common side effects to combination therapy include: neuropsychiatric symptoms, influenza-like symptoms and hematologic abnormalities.

VI. Prevention

- A. IG in post-exposure prophylaxis is not effective.
- B. Patient counseling and prevention issues:
1. Regardless of test results, persons who use illegal drugs or have multiple sex partners should be provided with information regarding how to reduce their risk for acquiring bloodborne and sexually transmitted infections or of potentially transmitting infectious agents to others, including the need for vaccination against hepatitis B and, if the client is using injection drugs or is a man who has sex with men, hepatitis A vaccine should be given.

2. Persons who inject drugs should be counseled to stop using and get into treatment. If they do not stop using, they should be counseled on how to inject safely (i.e., use of sterile, single-use equipment, including needles, syringes, cookers, cottons, water, etc., each and every time they inject).
3. Persons with multiple sex partners should be counseled to reduce the transmission of STDs, including abstinence, monogamy, decreasing the number of sexual partners, and use of barrier methods. The efficacy of latex condoms in preventing HCV is unknown, but the correct and consistent use of latex condoms may reduce transmission.

C. Standard precautions in healthcare and laboratory settings.

D. No recommendations on sexual practice changes in the setting of steady monogamous relationships. Education regarding low risk of sexual transmission: persons in a monogamous relationship where one partner is HCV-positive should be educated that risk is low, but not absent (may consider barrier methods to reduce risk). They should be counseled to discuss the risk with their partner.

E. HCV-positive women do not need to avoid pregnancy or breastfeeding. CDC recommends that HCV-positive women abstain from breastfeeding if nipples are cracked or bleeding.

F. Caesarian section is not routinely recommended for HCV-positive pregnant women.

G. Knowledge of serostatus by routine testing of high-risk persons is recommended by CDC and other experts. (Note: US Preventive Services Task Force found insufficient evidence to recommend routine screening even among those at high risk.) Groups at increased risk or at risk for severe outcomes include:

1. Injecting drug users (past or current).
2. Persons with select medical conditions (received clotting factors produced before 1987, ever on hemodialysis, chronic liver disease).
3. Persons who received blood transfusions before July 1992.
4. Health care workers after a known exposure.
5. Children born to HCV positive mothers.

6. Persons who were notified that they received blood from a donor who later tested positive for hepatitis C.

VII. Counseling

- A. To protect their livers from further harm, HCV-positive persons should be advised to:
 1. Avoid drinking alcohol.
 2. Avoid starting any new medications (including over-the-counter or herbals) without checking with their doctors.
 3. Get vaccinated against hepatitis A if they have liver damage.
 4. Get vaccinated against hepatitis B if in a group for whom hepatitis B vaccine is recommended.
- B. To reduce the risk for transmission to others, HCV-positive persons should be advised to:
 1. Avoid donating blood, body organs, other tissue, or semen.
 2. Cover cuts and sores.
 3. Avoid sharing any personal items that may have blood on them (e.g., toothbrushes, razors).

VII. References: (See end of module)

Hepatitis D (HDV)

I. Epidemiology

- A. HDV infection occurs in less than 10% of HBV cases.
- B. Precise epidemiological tracking is difficult, but prevalence of anti-HDV among people with chronic HBV infection has been found to be associated with injection drug use, hemophilia, or history of multiple transfusions.
- C. Worldwide, anti-HDV prevalence is more common among people with chronic HBV infection from the Middle East and Mediterranean countries than from China or Southeast Asia. Outbreaks of fulminant hepatitis D among people with chronic HBV infection in South American countries have been reported.

II. Pathogenesis

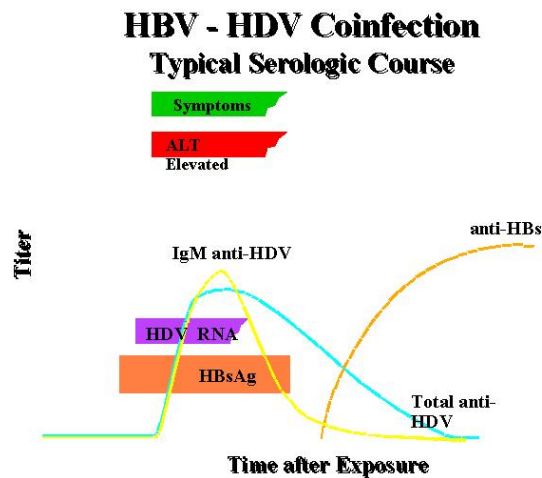
- A. Defective RNA virus that is unable to replicate without the assistance of hepatitis B virus. It packages its RNA genome in the same protein coat as HBV and can only survive and replicate in the presence of HBV.
- B. Modes of transmission:
 - 1. Sexual transmission occurs, but is not as efficient as for hepatitis B.
 - 2. Percutaneous transmission is the most efficient.
 - 3. Transmission is either concurrent (co-infection) with HBV, or as a "superinfection" to someone already chronically infected with HBV. "Superinfection" may result in fulminant fatal hepatitis presenting as a clinical exacerbation of acute hepatitis B.
 - 4. Most cases that occur domestically are among injection drug users. Abroad, traditional (or even contemporary) medical procedures with unsafe equipment are the primary cause of transmission.
 - 5. Perinatal transmission is thought to be rare.

III. Clinical Manifestations

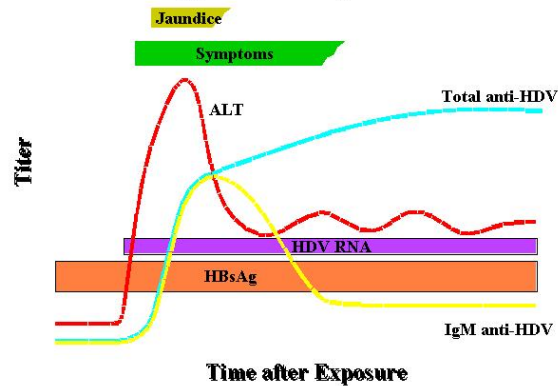
- A. Co-infected persons (HBV-HDV): more severe acute disease and a higher risk of fulminant hepatitis (2%-20%) compared with those infected with HBV alone; appear to develop chronic HBV infection less frequently.
- B. Persons with chronic HBV infection who are superinfected with HDV usually develop chronic HDV infection and tend to have poorer outcomes when compared to patients with chronic HBV infection alone (chronic liver disease development with cirrhosis: 70%-80% among superinfected HDV-HBV versus 15%-30% among chronic HBV infection alone).
- C. Risk and speed of progression of chronic HBV infection increased by presence of HDV.

IV. Diagnosis

Diagnosis is dependent on serologic detection of total anti-HD (the only widely available test). Diagnosis is difficult as antigen and antibody markers are transient. Other tests are only available in research settings.



HBV - HDV Superinfection Typical Serologic Course



V. Treatment: No specific therapy is available. Supportive care indicated.

VI. Prevention

- A. Hepatitis B vaccination: HBV-HDV co-infection can be prevented with either pre- or post-exposure prophylaxis for HBV (see Hepatitis B).
- B. Prevention of HDV superinfection by education of people with chronic HBV infection about risk of superinfection. Behavioral modification: barrier protection and no sharing of drugs, needles or drug paraphernalia.

VII. References: (See end of module)

Hepatitis E (HEV)

I. Epidemiology

- A. Initially recognized in India; outbreaks have been reported from developing countries (Pakistan, Somalia, Burma, Algeria, Ethiopia, Southeast and Central Asia, and parts of Africa and Mexico).
- B. Appear to be two geographically distinct strains: Asian and Mexican.
- C. US cases have been described primarily in travelers returning from developing countries and Mexico.
- D. Fecal-oral transmission via contaminated water supply, food or shellfish. Low secondary attack rates in household contacts.
- E. Very high mortality among pregnant women: 15%-25%.
- F. Clinical attack rates highest among young adults.

II. Pathogenesis

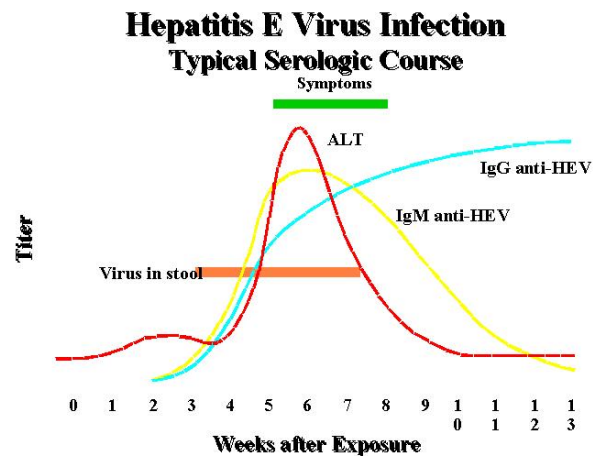
- A. Short incubation: average 40 days (range 15-60 days).
- B. No evidence of chronic sequelae or chronic HEV infection.
- C. Sexual transmission has not been described.

III. Clinical Manifestations

- A. Clinical illness similar to other hepatitis, with insidious onset of fever, malaise, abdominal pain, nausea, vomiting, dark urine, diarrhea, followed by jaundice.
- B. Pregnant women tend to have severe clinical illness with more frequent fulminant hepatitis.

IV. Diagnosis

- A. Serologic tests to detect HEV infection are not commercially available and are limited to research settings.
- B. IgM anti-HEV appears early and declines rapidly during early convalescence (4-5 months).
- C. Total anti-HEV persists and may provide at least short-term protection against disease.



V. Treatment

Supportive care.

VI. Prevention

IG (prepared from US donors) is not effective, and limited studies assessing IG from HEV-endemic regions are not conclusive. There is no vaccination available. However, vaccine research is on-going. Ensuring clean food and water supply is the best preventive mechanism.

VII. References: (See end of module)

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