

# Hepatitis

## Learning Objectives

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

1. Discuss the epidemiology of HAV, HBV, HCV, HDV and HEV 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 carrier 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 carrier state. The prevalence of chronic carriers ranges from 8 to 20% in SE Asia, Africa, and Pacific Islands up to 0.5% in the U.S. and Western Europe. 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 1 per million. Sexual transmission appears to be much less efficient than with hepatitis B. Chronic infection develops more frequently with HCV (70-85% 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. HBsAg carriers who are "superinfected" with HDV are more likely to become chronic carriers and to 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%). 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 US with last peak (1994-95) 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. CDC provisional data reveal dramatic decline in annual incidence for 1998 (8.61/100,000 pop.) and 1999 (6.25/100,000 pop.). Currently estimated to infect 180,000 Americans per year.
  - 3. About one-third of US population has evidence of prior infection (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. Incidence higher in persons < 40 yrs. of age; no single age group predominates. Male:female case ratio for 1994-95 was 1.3:1.
  - 5. Highest rates in US are in Western regions (correlates with race/ethnicity, socioeconomic factors: higher incidence among American Indian, Hispanic).

### II. Pathogenesis

- A. Single-stranded RNA virus
- B. Incubation period is relatively short:
  - 1. Range 15 to 50 days.
  - 2. Average 4 weeks.
- 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.
  - b) Virus heavily concentrated in stool, and to a 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 (poor hygiene).
    - 5) Community-based epidemics may occur related to contaminated food (fast food, shellfish).
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: 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 serologic 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 prolonged carrier 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:

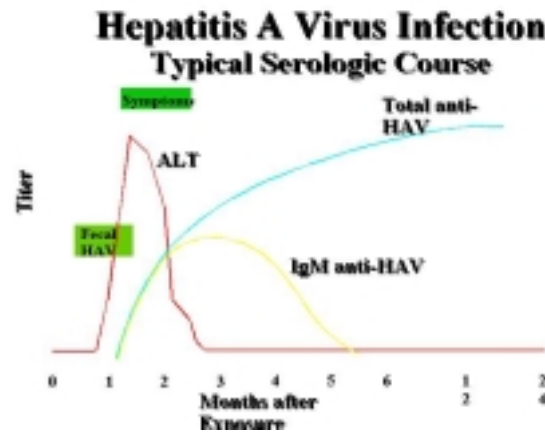
1. Generally self-limited (usually < 2 months).
2. Relapsing or prolonged HAV (up to 6 months) occurs in 10-15% of symptomatic infections.
3. HAV accounts for less than 10% of fulminant hepatitis (mortality 0.1 to 0.6%; increased in persons > 50 years of age: 1.8% case fatality rate); persons with chronic liver disease from hepatitis C 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. IgG 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: immune globulin (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)
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.
- c) Safety in pregnancy has not been determined (not FDA approved for use in pregnancy).
- 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 with follow-up studies demonstrating protection for up to 8 years.

- f) Pre-vaccination serologic testing for susceptibility likely to be cost-effective for person from areas of high endemicity, older adolescents and adults from certain populations (Native American, Alaskan 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 of increased rate of hepatitis A.
  - 2) Men who have sex with men (MSM).
  - 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 occupational risk for infection (exposure to primates).
  - 7) Children living in states, counties, or communities with average annual hepatitis rate at least twice national average (>20 cases/100,000).
- h) Vaccine is being evaluated for use in outbreak settings, though IG is recommended at this time.
- i) New combined hepatitis A and B vaccine (Twinrix<sup>®</sup> – Glaxo SmithKline) recently FDA approved (5/01) for adults age 18 and over. Probably useful for those at risk for both hepatitis A and B.
- 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. Based on seroprevalence data, the number of new infections per year has declined from an average of 450,000 in 1980 to about 80,000 in 1999. There are an estimated 1.25 million chronic carriers in U.S.
2. Sexual transmission (MSM, sexual contact with a case or multiple sex partners) accounts for most new cases of hepatitis B in the US.
3. Greatest decline among children and adolescents (due to routine vaccination).
4. Male: female case ratio for 1994-95 was 1.6:1.
5. Incidence among health care workers has declined since 1985: 9% of reported cases in 1985 vs. 0.8% in 1994-95, likely due to vaccination.
6. Seroprevalence generally increases with age and lower socioeconomic status. Highest rate of disease among 20-39 year olds.
7. African-American or Asian Americans tend to have higher seroprevalence.

#### B. Worldwide:

1. Highly endemic areas (SE Asia, Africa, and Pacific Islands): carrier 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 carriers 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.
    - b) Strong evidence exists for heterosexual transmission: 27% of spouses of HBsAg+ carriers 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 is 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., 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) Often follows maternal infection in the third trimester. Most infections acquired at time of birth.
    - 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**

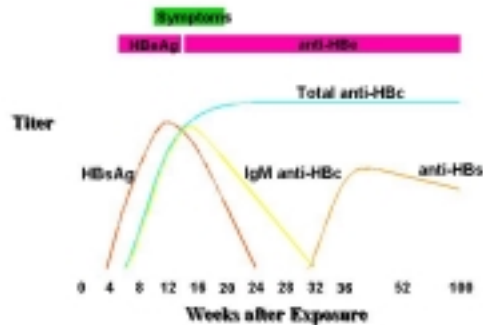
- A. Many HBV infections remain subclinical, with <10% of children and <30-50% of adults experiencing icteric disease during acute infection.
- B. Symptom onset may be insidious and typically includes: malaise, anorexia, nausea with or without jaundice.
- C. Prodrome occurs in 15-20% adults and may include 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 HBsAg carriers.
- 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 chronic carriers.

### **IV. Diagnosis**

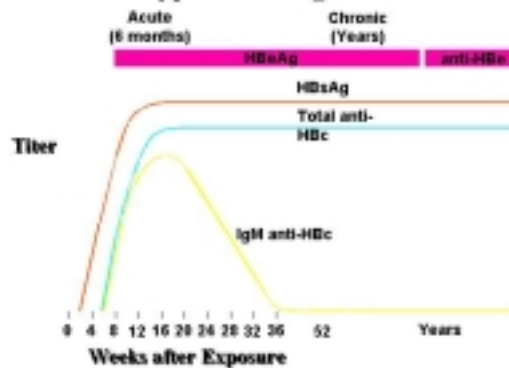
- A. Clinical presentation: see previous section.
- B. Diagnosis based on serologic findings, as symptoms are not specific to HBV infection.
- C. Laboratory findings:
  - 1. Elevated liver enzymes with or without elevated bilirubin.

2. First marker usually HBsAg+, appears in blood as early as one week or as late as 11-12 weeks, synthesis can continue up to 6 months (average 3 months) for those who clear infection. All persons who are HBsAg+ are infectious.
3. IgM anti-HBc is a marker of acute infection.
4. IgG 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 chronic carriers 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 IgG) and anti-HBe are the only markers during this "window" period during transition from acute illness to convalescence.
8. Chronic carriers have persistently detectable HBsAg and IgG 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 HBsAg+.

### 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

Condition	HBsAg	anti-HBs	anti-HBc	IgM anti-HBc
Susceptible	neg	neg	neg	
Immune	neg	pos $\geq$ 10 mIU	neg or 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 be undetectable level of HBsAg present in serum and person is actually a carrier.

## **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. Interferon alpha effective in 30-40% of patients (sustained response). Many contraindications and frequent side effects.
  4. Lamivudine (FDA approved in 1998) effective in 30-50% of patients (sustained response). Better tolerated, though major disadvantage is drug resistance.
  5. Combination therapy (interferon and lamivudine) is being evaluated, some early studies show more effective than monotherapy.
  6. Several new nucleoside analogs in development.
  7. Abstinence from alcohol is important for chronic carriers 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.
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. Heptavax (plasma derived HBsAg) is no longer available in U.S., although it was a safe and effective product.
2. Recombivax-HB<sup>®</sup> (Merck) and Engerix B<sup>®</sup> (Smith-Kline) are recombinant HBsAg vaccines. (Brands may be used interchangeably: see exceptions below.)

Hepatitis B Immunization Schedule for Adolescents and Adults

<u>Group</u>	Recombivax HB <sup>®</sup> Dose mcg (ml)	Engerix-B <sup>®</sup> Dose † mcg (ml)	Schedule (months)
Adolescents (11-19 yrs)*	5 (0.5)	10 (0.5)	0, 1, 6 or 1, 2, 4 or 0, 1, 4 or 0, 12, 24
Adolescents (11-15 yrs)**	10 (1.0)		0, 4-6
Adults (>19 yrs)	10 (1.0)	20 1.0	0, 1, 6 or 0, 2, 4 or 0, 1, 4

† An alternative schedule (0, 1, 2, 12) has been licensed for Engerix-B<sup>®</sup> only.

\*For adolescents aged 11-19, spacing at 0,12 and 24 months results in equivalent immunogenicity.

\*\*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 16<sup>th</sup> birthday. No data are available to assess long-term protection > 2 yrs. Engerix-B has not been approved for this schedule.

3. Missing doses should be given ASAP, no need to restart series.
4. 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 (>11 years). Persons with normal immune status who respond to initial series may remain protected against HBV infection even when antibody titers fall below detected level.
5. Recommendations for booster vary, but in the absence of an exposure, CDC does not recommend periodic serologic testing or booster doses among vaccine recipients with normal immunity. Periodic boosters are used for hemodialysis patients.
6. HCWs with substantial risk of future exposure should undergo post-vaccination serology 1 month after last dose. Non-responders should generally receive a second course of vaccine on the same schedule, with repeat serology 1 month after last dose. Then document final response status and don't vaccinate further unless exposed (see below).
7. Must be administered IM (in the deltoid), NOT intradermally.
8. Safe in pregnancy / lactation.
9. Safe to co-administer with HBIG.
10. Contraindicated if allergic to yeast.
11. Efficacy about 50% in HIV-infected persons with low CD4 count.
12. Prevacination serologic testing may be cost effective for adults with high prevalence of HBV infection (adults attending STD clinics, MSM, injecting drug users).
13. 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 with multiple sex partners or diagnosis of STDs.
    - 2) MSM.
    - 3) Sex contacts of infected persons.
    - 4) Injecting drug users.

- 5) Household contacts of chronically infected persons.
- 6) Infants born to infected mothers.
- 7) Infants / children of immigrants from areas with high rates of HBV infection.
- 8) Health care workers and those at occupational risk.
- 9) International travelers to endemic areas.
- 10) Inmates in long term correctional facilities.
- 11) Recipients of certain blood products.
- 12) Clients and employees of facilities for the developmentally disabled.
- 13) Hemodialysis patients.
- 14) Post vaccination serologic testing is recommended for: infants born to HBsAg positive mothers, immunocompromised persons, health care workers, sex partners of those with chronic HBV infection and those at continued occupational risk. 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].
- 15) New combined Hepatitis A and B vaccine Twinrix<sup>®</sup> (Glaxo Smith Kline) recently FDA approved (5/2001) for adults age 18 and over. Probably useful for those who are at risk for both hepatitis A and hepatitis B.

#### F. Post-exposure prophylaxis:

1. Hepatitis B immune globulin (HBIG) provides passive transfer of antibodies and should be used along with first dose of hepatitis vaccine for increased efficacy.
2. HBIG should be used in conjunction with vaccine to maximize effectiveness.
3. HBIG plus vaccine recommended for:
  - a) Infants of infected mother: HBIG 0.5 ml within 12 hours of birth along with the first dose of vaccine (both IM at separate sites).
  - b) Sexual: 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: 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

<u>Vaccination and antibody status of 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, known non-responder	HBIG x 2 or HBIG x 1 plus 1 dose of HB vaccine†	No treatment	If known high-risk source, may treat as if source were HBsAg +
Vaccinated, antibody response unknown	Test exposed person for anti-HBs: 1) if adequate, no tx 2) if inadequate, give HBIG x 1 plus 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

\*HBIG dose 0.06 ml/kg intramuscularly

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

† The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for non-responders who have not completed a second 3-dose vaccine series. For persons who previously completed a second vaccine series and failed to respond, two doses of HBIG are preferred.

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. HCV infection is the most common chronic bloodborne infection in the U.S. An estimated 3.9 million persons have been infected (1.8%) with 2.7 million chronically infected.
- B. New infections declining with an estimated average of 240,000 in the 1980's compared to about 40,000 in 1998. Persons age 20-49 account for >75% of cases (1994-1995 data).
- C. 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.
- D. Before 1990, nearly 10% of all blood transfusion recipients developed post-transfusion hepatitis, with about 15,000 new cases of non-alcohol-related cirrhosis per year from transmission in previous years. It appears that 90% of this post transfusion non-A, non-B hepatitis (PTNANBH) and its sequelae were due to hepatitis C (HCV). 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 million units transfused.
- E. Injecting drug use continues to be the leading risk factor for HCV infection and accounts for 60% of cases in the U.S.
- F. 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.
- G. Health care workers are at risk from needle stick injuries; however prevalence among health care workers is less than for the general population (1% vs. 1.8% in general population).
- H. 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: mean of 6-7 weeks (range 2-26 weeks).

I. Modes of transmission:

1. Percutaneous:

- a) Injection drug use (well-documented in multiple studies).
- b) Blood and blood products: well-characterized, e.g., transfusions before 1992, clotting factor recipients before 1987.
- 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) Insufficient data in the U.S. 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 6%; higher (17%) if woman co-infected with HIV. Role of viral titer uncertain, though higher titer may be linked to greater risk of transmission in limited studies. Role of type of delivery (caesarian vs. vaginal) unclear. 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-injection drug use 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%). 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 hepatitis C virus of spouses in at least one study provides probable evidence for interspousal transmission.

- 5) At least one recent study using highly sensitive PCR testing has detected hepatitis C virus in semen of infected men.

## 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 possibly being more virulent than others. Type 1a and 1b are most common in US. Genotype appears to influence response 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).

## III. Clinical Manifestations

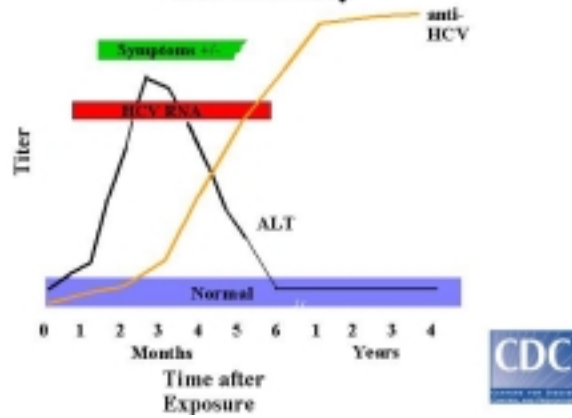
- A. Symptom development: natural history difficult to assess as most acute cases are asymptomatic (60-70%).
- B. Manifestations:
  - 1. Acute disease: jaundice, malaise occurs in 20-30% and is mild.
  - 2. Chronic disease may be asymptomatic for years, may have nonspecific symptoms: fatigue, extrahepatic manifestations (cryoglobulinemia, other autoimmune syndromes).
- C. Course of disease:
  - 1. Approximately 75-85% will progress to some degree of chronic disease; approximately 15-20% of these will show signs of cirrhosis within 20 years, and mortality from chronic liver disease occurs in approximately 1-5% of those with cirrhosis. The risk of hepatocellular cancer is estimated to be 1-4% per year among those with cirrhosis. Nevertheless, current data suggest that at least 70-80% will die *with, not from*, HCV.

2. Time frame for disease progression is highly variable. Factors associated with more rapid progression or poorer outcome are: alcohol use, age>40, HIV or HBV co-infection, and possibly male gender.
3. Persons with chronic HCV who are superinfected with HAV infection may have a more severe acute infection with possibly fulminant hepatitis.

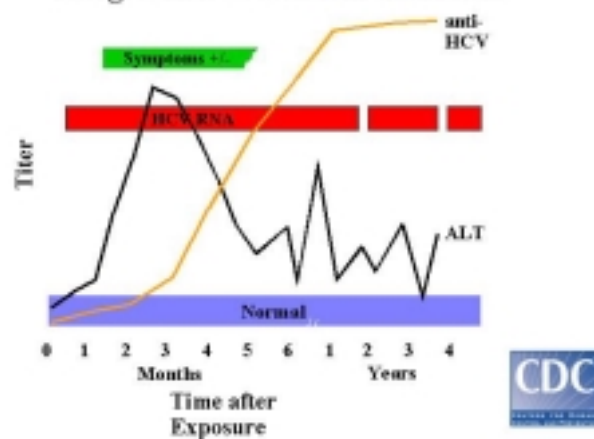
#### **IV. Diagnosis**

- 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. Second and third generation tests have greater sensitivity (EIA-2 92-95% sensitive, EIA-3 ~97% sensitive). Indicates past or present infection. Can detect antibodies within 4 to 10 weeks. Need confirmatory tests. Low positive predictive value in low prevalence populations.
  2. Recombinant immunoblot assay (RIBA): detects antibody to HCV. Used as a confirmatory test to EIA. May have indeterminate result and need to test for HCV RNA. With improved HCV RNA testing, use of RIBA may be less necessary.
  3. Qualitative detection of HCV RNA with nucleic acid amplification tests (e.g., PCR, bDNA): can detect virus as early as 1-2 weeks post exposure. Used to confirm diagnosis. Detection of HCV RNA may be intermittent, so a single negative test is not conclusive.
  4. Quantitative HCV RNA testing and genotype testing 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 hepatitis C infection should be undertaken in conjunction with an expert.

- A. Acute Infection: generally patients are asymptomatic. Early seroconverters (needlestick exposure) may benefit from early treatment (interferon and ribavarin), but no formal recommendations have supported this approach. Little is known about the impact of treatment for acute HCV upon the natural history of this infection.

B. Chronic Infection: patients should be evaluated to determine need for therapy. NIH currently recommends treatment of those with evidence of progressive disease. Those with genotype 1 tend to have poorer response to therapy. Treatment options include:

1. For those with contraindications for ribavirin, Interferon alpha: 15-20% sustained response in certain patients. However, many side effects and contraindications to therapy, and not all patients require treatment.
2. Combination therapy with interferon and ribavirin is the current standard of care: improved efficacy (30-40% sustained response) compared to monotherapy. Many who otherwise might benefit from therapy are not candidates due to concurrent chemical dependency, mental illness, or underlying physical health problems.
3. Ribavirin plus pegylated interferons (longer acting interferons with once-weekly dosing): appear to have better efficacy (pegylated interferon FDA-approved in 2001). Combination therapy with Peginterferon and ribavirin have been FDA approved.
4. Many other therapies under investigation (e.g., amantadine plus interferon, other combinations).
5. Corticosteroids and acyclovir are not effective.

## VI. Prevention

Immune serum globulin (ISG) in post-exposure prophylaxis is not effective.

A. 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 appropriate, hepatitis A.
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.
- B. Standard precautions in healthcare and laboratory settings.
- C. 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.
- D. HCV-positive women do not need to avoid pregnancy or breastfeeding.
- E. Knowledge of serostatus, with routine testing being recommended for those at high risk:
1. Injecting drug users (past or current).
  2. Persons with select medical conditions (received clotting factors before 1987, ever on hemodialysis, chronic liver disease).
  3. Persons who received blood transfusions before July 1992.
  4. Health care workers and public safety workers only after a known exposure.
  5. Children born to HCV positive mothers.

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

### II. Pathogenesis

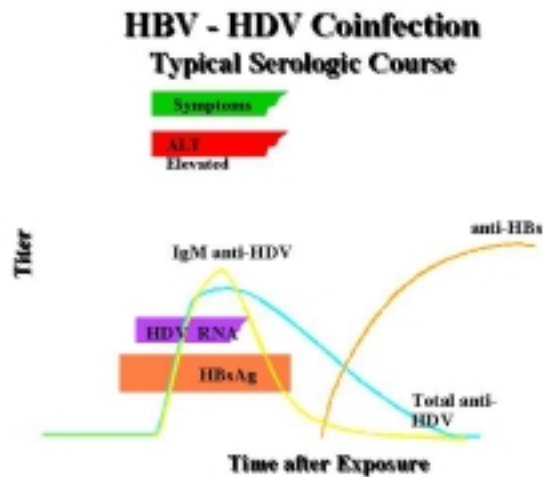
- A. Defective RNA virus that is unable to replicate without the assistance of hepatitis B virus. It packages its RNA genome in the same protein coat as HBV and can only survive and replicate in the presence of HBV.
- B. Modes of transmission:
  - 1. Sexual transmission occurs, but is not as efficient as for hepatitis B.
  - 2. Percutaneous transmission is the most efficient.
  - 3. Transmission is either concurrent (coinfection) with HBV or as a "superinfection" to someone already infected with HBV (carrier). "Superinfection" may result in fulminant fatal hepatitis: presents 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.

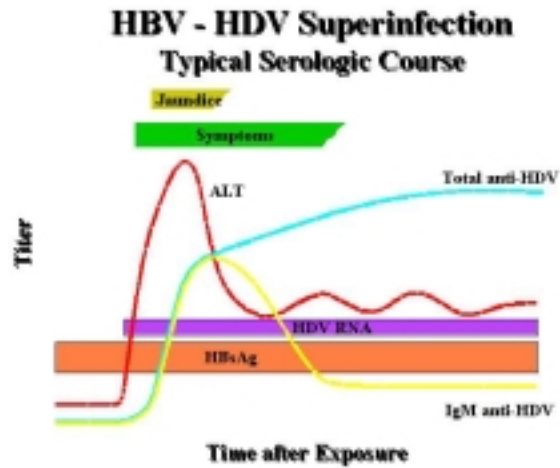
### III. Clinical Manifestations

- A. Coinfected 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 who are superinfected with HDV usually develop chronic HDV infection and tend to have poorer outcomes when compared to patients with chronic HBV 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 increased by presence of HDV.

### IV. Diagnosis

Diagnosis is dependent on serologic detection of IgG 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.





**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 HBsAg carriers about risk of superinfection. Behavioral modification: barrier protection and no sharing of 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. U.S. 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

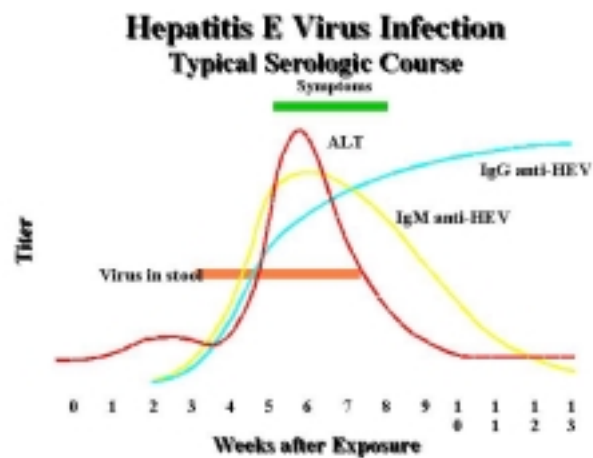
- A. Short incubation: average 40 days (range 15-60 days).
- B. No evidence of chronic sequelae or carrier state.
- C. Sexual transmission has not been described.

### 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 Hepatitis E infection are not widely available and may be limited to research settings.
- B. IgM anti-HEV appears early and declines rapidly during early convalescence (4-5 months).
- C. IgG anti-HEV persists and may provide at least short-term protection against disease.



#### V. Treatment

Supportive care.

#### VI. Prevention

Serum-immune globulin in the U.S. (prepared from US donors) is not effective, and limited studies assessing immune globulin from HEV-endemic regions are not conclusive. There is no vaccination available. However, vaccine development is underway. Ensuring clean food and water supply is the best preventive mechanism.

#### VII. References: (See end of module)

## VIII. References

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