HEPATITIS VIRUSES

Medically important hepatitis v. (liver) are:

1. HAV
2. HBV
3. HCV
4. HDV
5. HEV
6. HGV

Other causes (not exclusively hepatitis v.) also called sporadic hepatitis:

1. EBV
2. CMV
3. Yellow fever v.

HEPATITIS A (infectious hepatitis)

BASICS structure:

- enterovirus 72, picornoviridae family, Naked, genome SS RNA with icosahedral nucleocapsid
- Replication occurs in the cytoplasm of the cell
- Single serotype
- Worldwide distribution. Humans are the only reservoir

TRANSMISSION

- Fecal-oral
- Contaminated raw seafood- e.g oysters
- Day-care center outbreaks
- Rarely transmitted via blood because the level of viremia is low.
EPIDEMIOLOGY

• Over 100,000 infections/year in US
• Much higher prevalence in 3rd world
• Children are the most frequently infected group.

PATHOGENESIS

• Incubation 4 weeks (2-6wk range)
• Oral cavity---replicate in the GI tract, then spread to liver via blood.
• Virus in stool 2 weeks after infection, usually shed in stool prior to symptoms
• Symptoms related to immune response and not direct cytopathic effect of virus
• No chronicity, no carrier state, nor hepatocellular ca.

SIGNS & SYMPTOMS

Adults will have signs and symptoms more often than children. 70-80% of adults develop symptoms, <10% of kids (<6 years) develop symptoms

• fever
• loss of appetite
• fatigue
• nausea, vomiting
• diarrhea
• abdominal pain
• jaundice, dark urine & pale feces.
• Elevated ALT/AST
• Complete recovery in 99% within 2-4wks.

LONG-TERM EFFECTS

• There is no chronic (long-term) infection.
• Lifelong immunity after infection- i.e no repeats infection

**DIAGNOSIS**

• Hep A IgM antibody: usually present when symptoms occur
• four fold rise in IgG indicate current infection
• IgG: suggests prior infection (followed by 1-3 wks) or vaccination
• Virus culture & Isolation: not used

**TREATMENT**

• Supportive- no antiviral therapy

**PREVENTION**

• Hepatitis A vaccine (**formalin inactivated**) is the best protection.
• Two doses( Vaccine dosed at 0, followed by a booster 6-12 months later.
• Protection begins 4 weeks post vaccine
• Protection probably at least 20 years (likely lifelong)-no need for repeating
• Twinrix vaccine (for both HAV/HBV)
• Short-term protection against hepatitis A is available from **immune globulin**. It can be given before and within 2 weeks after coming in contact with HAV.
• Good hygiene- hand washing, etc

**VACCINE RECOMMENDATIONS**

Vaccine is recommended for the following persons 2 years of age and older:

• Travelers to areas with increased rates of hepatitis A
• Men who have sex with men
• Injecting and non-injecting drug users
• Persons with clotting-factor disorders (e.g. hemophilia)
• Persons with chronic liver disease
Children living in areas with increased rates of hepatitis A

HEPATITIS B (serum hepatitis)

**STRUCTURE**

HBV is a member of the Hepadnavirus family, 42-nm Enveloped virion, with Icosahedral nucleocapsid core containing a partially DS circular DNA genome.

May exist in multiple forms:
- 42 nm virions (Dane particle), few in patient serum.
- 22nm spheres and long filaments 22nm width which do not contain DNA; only HBsAg (not infectious)

Humans are the only reservoir

**Genome** contains 4 genes:

A- Surface protein (HBsAg) Austerlia Ag=envelope protein

B- core (nucleoprot) HBcAg, HBeAg

C- DNA polymerase (RNA dp RT) & (DNA dp activity)

D- X-protein, activator of viral RNA transcription
TRANSMISSION

• Blood-borne (almost never through transfusion)

• Sexual

• Perinatal (from mother to newborn)

Persons at risk for HBV infection might also be at risk for infection with hepatitis C virus (HCV) or HIV.

EPIDEMIOLOGY

• 100,000 infections/ year

• Higher seroprevalence among Asian-Americans

• World-wide- high rates in SE Asia, Alaska, Africa

• Estimated 1.25 million chronically infected Americans, of whom 20-30% acquired their infection in childhood.

PATHOGENESIS

• Illness is immune mediated

• 5% chronic carriers (in adults)

• Higher rate of hepatocellular ca in chronic carriers- especially “e” antigen positive

• Surface ab likely confers lifelong immunity
• Antibody to “e” antigen indicates low transmissibility

• Incubation 60-90 d (range 45-180d)

**SIGNS & SYMPTOMS**

About 1/3 of persons have no signs or symptoms. Signs and symptoms are less common in children than adults. Chronic infection more common when infected at younger age and more likely in asymptomatic infection. I.P. = 10-12wks

• fatigue

• abdominal pain

• loss of appetite

• nausea, vomiting

• joint pain

**LONG-TERM EFFECTS WITHOUT VACCINATION**

Chronic infection occurs in:

• 90% of infants infected at birth

• 30% of children infected at age 1 - 5 years

• 6% of persons infected after age 5 years

• Death from chronic liver disease occurs in 15-25% of chronically infected persons

**RISK GROUPS**

• Persons with multiple sex partners or diagnosis of a sexually transmitted disease

• Men who have sex with men

• Sex contacts of infected persons

• Injection drug users

• Household contacts of chronically infected persons
Interpretation of the Hepatitis B Panel

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg anti-HBc anti-HBs</td>
<td>negative negative negative</td>
<td>susceptible</td>
</tr>
<tr>
<td>HBsAg anti-HBc anti-HBs</td>
<td>negative positive positive</td>
<td>immune due to natural infection</td>
</tr>
<tr>
<td>HBsAg anti-HBc anti-HBs</td>
<td>negative negative positive</td>
<td>immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>HBsAg anti-HBc IgM anti-HBc anti-HBs</td>
<td>positive positive positive negative</td>
<td>acutely infected</td>
</tr>
<tr>
<td>HBsAg anti-HBc IgM anti-HB c anti-HBs</td>
<td>positive positive negative negative</td>
<td>chronically infected</td>
</tr>
<tr>
<td>HBsAg anti-HBc anti-HBs</td>
<td>negative positive negative</td>
<td>four interpretations possible * Window phase</td>
</tr>
</tbody>
</table>

*Four interpretations are possible if
HBsAg                 negative
anti-HBc              positive
anti-HBs              negative

1. May be recovering from acute HBV infection.
2. May be distantly immune and test not sensitive enough to detect very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be undetectable level of HBsAg present in the serum and the person is actually a carrier

Hbe Ag: arise during IP, Ab against eAg= low transmission

Viral DNA detection in serum = acute infection

VACCINE RECOMMENDATIONS

• Hepatitis B vaccine available since 1982. The initial vaccine was prepared by purifying HBsAg associated with the 22-nm particles from healthy HBsAg-positive carriers and treating the particles with virus-inactivating agents. Although plasma-derived vaccines are still in use in certain countries, they have been replaced in the United States by recombinant DNA-derived vaccines. These vaccines consist of HBsAg produced by a recombinant DNA in yeast cells or in continuous mammalian cell lines.

• HBV vaccine is recommended: 1- for all children as part of their regular immunization schedule (Routine vaccination of 0-18 year olds)

2- Vaccination of risk groups of all ages (commercial name: Engerix-B , Recombivax HB)

PASSIVE IMMUNIZATION

• Hep B immune globulin (high titer of HBsAb) should be given in addition to vaccine in exposures to known HepB

* infected patients/sources

**Newborn whose mother is HBsAg+ve.

• Give immune globulin preferably within (24 hours of exposure)
TREATMENT & MEDICAL MANAGEMENT

- Adefovir dipivoxil, alpha interferon, and lamivudine are three drugs licensed for the treatment of persons with chronic active hepatitis B.
- These drugs should not be used by pregnant women.

HEPATITIS D

Structure

- Caused by delta agent- cannot infect without HepB
- Unusual virus (defective virus), it can't replicate by itself because it does not have the gene for its envelope protein.
- Enveloped ssRNA,-ve polarity. The RNA genome of HDV encodes only one internal core protein called delta antigen.
- One serotype because HBsAg has only one serotype. At least seven HDV genotypes (1 most common)
• **Transmission risks** same as Hep B, occurs only in HBsAg-positive individuals
  
either as

  • **Co-infection:** acquire infection at same time as Hep B- usually Hepatitis is more severe than those infected by HBV alone.
  
  • **Superinfection:** infection of HDV in chronic Hep B. Hepatitis in chronic carriers of HBV who become superinfected with HDV is much more severe, and the incidence of fulminant, life threatening hepatitis, chronic hepatitis and liver failure is higher.

**DIAGNOSIS**

• Detection of either delta Ag or IgM ab to HDV in patient serum.

**TREATMENT**

• No antiviral therapy, No vaccine, but a person immunized against HBV will not be infected by HDV.

• Alpha interferon
HEPATITIS C (NON-A, NON-B)- post transfusion hepatitis

CLASSIFICATION
Flavivirus
Enveloped SS RNA virus
6 serotypes (genotypes) and multiple subtypes
Humans (and chimps) only reservoir

TRANSMISSION
Recommendations for testing based on risk for HCV infection

• Occurs when blood or body fluids from an infected person enters the body of a person who is not infected.

• Persons at risk for HCV infection might also be at risk for infection with hepatitis B virus (HBV) or HIV.

PERSONS AT RISK OF INFECTION

High
Injecting drug users
Recipients of clotting factors made before 1987

Intermediate
Hemodialysis patients
Recipients of blood and/or solid organs before 1992
People with undiagnosed liver problems
Infants born to infected mothers

Low
Healthcare/public safety workers (Only after known exposure)
People having sex with multiple partners
People having sex with an infected steady partner

EPIDEMIOLOGY

• Number of new infections per year has declined from an average of 240,000 in the 1980s to about 25,000 in 2001.
• Most infections are due to illegal injection drug use.
• Transfusion-associated cases occurred prior to blood donor screening; now occurs in less than one per million transfused unit of blood.

**PATHOGENESIS**
• Damage and illness immune mediated
• Can lead to HCC
• Alcoholism is greatly enhances the rate of HCC.

**SIGNS & SYMPTOMS**

I.P. = 8wks

80% of persons have no signs or symptoms. Those who do may develop:
• jaundice
• fatigue
• dark urine
• abdominal pain
• loss of appetite
• nausea

**LONG-TERM EFFECTS**
• Chronic infection: 75-85% of infected persons (is much higher than in HBV infection)
• Chronic liver disease: 70% of chronically infected persons
• Deaths from chronic liver disease: 1-5%
• Leading indication for liver transplant
• Extrahepatic manifestations may also be present and are due to immune complex deposition/auto immune reactions (vasculitis, arthralgias, purpura..etc..)
TREATMENT & MEDICAL MANAGEMENT

• HCV positive persons should be evaluated by their doctor for liver disease.

• Interferon and ribavirin are two drugs licensed for the treatment of persons with chronic hepatitis C.

• Interferon can be taken alone or in combination with ribavirin. Combination therapy, using pegylated interferon and ribavirin, is currently the treatment of choice. *(note: pegylated interferon=alpha Interferon conjugated to polyethylene glycol)*

• Combination therapy can get rid of the virus in up to 50% of genotype 1 and in up to 80% for genotype 2 and 3

DIAGNOSIS

• Hepatitis C ELISA or EIA 99% sensitive and specific (high false +ve cases)

• Usually positive 2-5 months after infection

• RIBA and PCR used to confirm diagnosis (RIBA=recombinant immunoblot assay, should be performed)

Hepatitis E

• RNA virus- calicivirus

• Similar syndrome to Hep A

• Fecal-oral transmission

• Higher mortality in pregnant women

• No chronicity, no carrier cases. Diagnosis made by excluding HAV and other causes

• NO antiviral drug, no vaccine.

Hepatitis G

• Member of flavivirus family; as HCV.
• Transmitted by blood & sexual.

• **Unlike** HCV, not cause acute & chronic hepatitis, or HCC.

• Patient infected with HIV & HGV have lower mortality rate than those infected with HIV alone, it might interfere with the replication of HIV.

### TABLE 62–1. Comparative Features of Hepatitis Viruses

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common name</td>
<td>“Infectious”</td>
<td>“Scrub”</td>
<td>“Non-A, non-B–post-transfusion”</td>
<td>“Delta agent”</td>
<td>“Enteric non-A, non-B”</td>
</tr>
<tr>
<td>Virus structure</td>
<td>Picornavirus; capsid, RNA</td>
<td>Hepadnavirus; envelope, DNA</td>
<td>Flavivirus; envelope, RNA</td>
<td>Virion-like; envelope, circular RNA</td>
<td>Calicivirus-like; capsid, RNA</td>
</tr>
<tr>
<td>Transmission Onset</td>
<td>Fecal–oral</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Fecal–oral</td>
</tr>
<tr>
<td>Incubation period (days)</td>
<td>Abrupt 15–50</td>
<td>Insidious 45–160</td>
<td>Insidious 14–180</td>
<td>Abrupt 15–64</td>
<td>Abrupt 15–50</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Usually subclinical; 80% chronicity</td>
<td>Co-infection with HBV occasionally severe; superinfection with HBV often severe</td>
<td>Normal patients, mild, pregnant women, severe</td>
</tr>
<tr>
<td>Mortality</td>
<td>&lt;0.5%</td>
<td>1%–2%</td>
<td>~4%</td>
<td>High to very high</td>
<td>Normal patients, 1%–2%; pregnant women, 20%</td>
</tr>
<tr>
<td>Chronicity/carry-state</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other disease associations</td>
<td>None</td>
<td>Primary hepatocellular carcinoma, cirrhosis</td>
<td>Primary hepatocellular carcinoma, cirrhosis</td>
<td>Cirrhosis, fulminant hepatitis</td>
<td>None</td>
</tr>
<tr>
<td>Laboratory diagnosis</td>
<td>Symptoms and anti-HAV IgM</td>
<td>Symptoms and serum levels of HBsAg, HBeAg, and anti-HBe IgM</td>
<td>Symptoms and anti-HCV ELISA</td>
<td>Anti-HDV ELISA</td>
<td>—</td>
</tr>
</tbody>
</table>