**Epidemiology and Prevention of Viral Hepatitis A, B, and C: An Overview**

Andrea L. Cox, M.D., Ph.D.
The Viral Hepatitis Center
The Johns Hopkins University

---

**Hepatitis**

- Inflammation of the liver
- Can be caused by:
  - Viruses
  - Medications
  - Alcohol
  - Cocaine
  - Chemicals

---

**Viral Hepatitis - Overview**

<table>
<thead>
<tr>
<th>Source of virus</th>
<th>Route of transmission</th>
<th>Chronic infection</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>feces</td>
<td>fecal-oral</td>
<td>no</td>
<td>pre/post-exposure immunization</td>
</tr>
<tr>
<td>blood/blood-derived body fluids</td>
<td>percutaneous permucosal</td>
<td>yes</td>
<td>blood donor screening; risk behavior modification</td>
</tr>
<tr>
<td>blood/blood-derived body fluids</td>
<td>percutaneous permucosal</td>
<td>yes</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
</tr>
<tr>
<td>blood/blood-derived body fluids</td>
<td>percutaneous permucosal</td>
<td>yes</td>
<td>ensure safe drinking water</td>
</tr>
<tr>
<td>faces</td>
<td>fecal-oral</td>
<td>yes</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>

---

**Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States**

<table>
<thead>
<tr>
<th>Type of Hepatitis</th>
<th>HAV (x 1000/year)*</th>
<th>HBV (140-320)</th>
<th>HCV (35-180)</th>
<th>HDV (6-13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infections</td>
<td>125-200</td>
<td>140-320</td>
<td>35-180</td>
<td>6-13</td>
</tr>
<tr>
<td>Fulminant deaths/year</td>
<td>100</td>
<td>150</td>
<td>?</td>
<td>35</td>
</tr>
<tr>
<td>Chronic infections</td>
<td>0</td>
<td>1-1.25 million</td>
<td>3.5 million</td>
<td>70,000</td>
</tr>
<tr>
<td>Chronic liver disease deaths/year</td>
<td>0</td>
<td>5,000</td>
<td>8-10,000</td>
<td>1,000</td>
</tr>
</tbody>
</table>

“Vaccination against hepatitis is the most effective means of preventing sexual transmission of hepatitis A and B.”

Integration of services for high-risk adults

• Reports of converging epidemics (STD, HIV, hepatitis) impacting MSM, IDU, and others at risk

• Integration of services that target MSM, IDU, and others at risk saves $$$ and improves services

Lack of integrated prevention activities leads to…

• Individuals infected with HIV, hepatitis and other STDs remain undiagnosed, untreated and uninformed

• Infected and uninformed have higher levels of risky behavior and continue to transmit

• Counseling is mistakenly based on limited diagnosis and individuals at risk for HAV and HBV don’t get immunized

Viral Hepatitis

• World wide distribution

• US burden of disease

• Transmission

• Symptoms and clinical features

• Diagnosis

• Treatment

• Prevention
  – Behavior
  – Vaccines
  – PEP
Hepatitis A Virus

Geographic Distribution of HAV Infection

Anti-HAV Prevalence
- High
- Intermediate
- Low
- Very Low

DISEASE BURDEN FROM HEPATITIS A UNITED STATES, 2001

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of acute clinical cases reported</td>
<td>10,609</td>
</tr>
<tr>
<td>Estimated number of acute clinical cases</td>
<td>45,000</td>
</tr>
<tr>
<td>Estimated number of new infections</td>
<td>93,000</td>
</tr>
<tr>
<td>Percent ever infected</td>
<td>31.3%</td>
</tr>
</tbody>
</table>

Hepatitis A Virus Transmission

- Close personal contact (e.g., household contact, sex contact, child day care centers)
- Contaminated food, water (e.g., infected food handlers, raw shellfish)
- Blood exposure (rare) (e.g., injecting drug use, transfusion)
**Hepatitis A Symptoms**

- Mild “flu-like” illness with fever
- Nausea, vomiting
- Jaundice (yellow skin or eyes)
- Dark urine, light stools
- Severe stomach pain and diarrhea
- Usually lasts less than 3 weeks
- Some people have to be hospitalized: rarely, death occurs
- Can be worse in someone with chronic hepatitis B or C or other liver disease

**HEPATITIS A - CLINICAL FEATURES**

- Jaundice by age group:
  - <6 yrs: <10%
  - 6-14 yrs: 40%-50%
  - >14 yrs: 70%-80%
- Rare complications:
  - Fulminant hepatitis
  - Cholestatic hepatitis
  - Relapsing hepatitis
- Incubation period:
  - Average 30 days
  - Range 15-50 days
- Chronic sequelae: None

**Age-specific Mortality Due to Hepatitis A**

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Case-Fatality (per 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>3.0</td>
</tr>
<tr>
<td>5-14</td>
<td>1.6</td>
</tr>
<tr>
<td>15-29</td>
<td>1.6</td>
</tr>
<tr>
<td>30-49</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;49</td>
<td>17.5</td>
</tr>
<tr>
<td>Total</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Source: Viral Hepatitis Surveillance Program, 1983-1989
**Typical Serologic Course**

- **Hepatitis A Virus Infection**
  - **Symptoms**
  - **ALT**
  - **Total anti-HAV**
  - **IgM anti-HAV**

**Months after Exposure**

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Treatment of Hepatitis A**

- Bed rest
- Fluids
- Consider liver transplant if severe
- Lifelong protection: can’t get infected again.

**PREVENTING HEPATITIS A**

- Hygiene (e.g., hand washing)
- Sanitation (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)

**HEPATITIS A VACCINES**

- Highly immunogenic
  - 97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose

- Highly efficacious
  - In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose
Hepatitis A Incidence, United States, 1980-2002

Year

Cases/100,000

1980 '85 1990 '95 2000

1995 vaccine licensure
1996 ACIP recommendations
1999 ACIP recommendations

2002 rate = 2.9
2009 rate = 1.0

Hepatitis A Vaccination Strategies
Epidemiologic Considerations

- All American children at 1 year of age since 2006
- Persons at increased risk of serious illness:
  - chronic liver disease (hep B, C, D, alcoholic cirrhosis)
- Persons at increased risk of infection
  - travelers (one month before travelling)
    - U.S. America, Caribbean, Mexico, Asia, Africa, S.or E. Europe
  - men who have sex with men
  - drug users
  - persons who receive clotting factor concentrates
  - living in areas of high rates of hepatitis A (American Indian, Alaska native, Pacific Islander communities)

Recommended Hepatitis A Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose Schedule (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>VAQTA</td>
<td>0, 6-18</td>
</tr>
<tr>
<td>TWINRIX</td>
<td>0, 1, 6</td>
</tr>
</tbody>
</table>

* Combined vaccine against HAV and HBV

Should not get Hepatitis A Vaccine

- If had a serious allergic reaction to a previous dose of hepatitis A vaccine
- Moderate or severe illness at the time of the scheduled vaccine (mild illness)
- Unknown if pregnant. Thought to be safe.
**Side effects of Hepatitis A Vaccine**

- **Mild problems**
  - soreness in muscle at site of shot (1/2)
  - headache (1 of 6 adults)
  - tiredness (1 of 14)

- **Severe problems (anaphylaxis)**
  - high fever or behavior changes
  - difficulty breathing, hoarseness, wheezing, hives, paleness, fast heart beat, dizziness, weakness

**ACIP Recommendations - Hepatitis A Vaccine**

- Not recommended because of the high response rate among vaccinees
- No commercially available test to measure vaccine response

**Postvaccination Testing**

**Hepatitis A Prevention - Immune Globulin**

- **Preexposure**
  - travelers to intermediate and high HAV-endemic regions

- **Postexposure (within 14 days)**
  - Routine
    - household and other intimate contacts
  - **Selected situations**
    - institutions (e.g., day care centers)
    - common source exposure (e.g., food prepared by infected food handler)

**Hepatitis B Virus**
Geographic Distribution of Chronic HBV Infection

**HBsAg Prevalence**
- ≥8% - High
- 2-7% - Intermediate
- <2% - Low

Chronic Hepatitis B Epidemiology
- 9th leading cause of death worldwide.\(^1\)
- Approximately 1.2 million chronic HBV carriers in the US, an estimated 11,000 to 17,000 hospitalizations/year, and 4,000 to 5,500 deaths/year.\(^2\)
- In the US, ~30% of chronic HBV infections are acquired perinatally or during early childhood.\(^2\)


Transmission of HBV Infection
- Transfusion (blood, blood products)
- Fluids (blood, semen)
- Organs and tissue transplantation
- Mother to baby
- Contaminated needles and syringes
- Child to child

Risk Factors for Acute Hepatitis B
United States, 1992-1993

- Heterosexual* (41%)
- Injecting Drug Use (15%)
- Unknown (31%)
- Homosexual Activity (9%)
- Household Contact (2%)
- Health Care Employment (1%)
- Other (1%)

* Includes sexual contact with acute cases, carriers, and multiple partners.
Source: CDC Sentinel Counties Study of Viral Hepatitis
Rate of Reported Hepatitis B by Age Group
United States, 1990

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>Rate (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-14</td>
<td>2</td>
</tr>
<tr>
<td>15-19</td>
<td>5</td>
</tr>
<tr>
<td>20-29</td>
<td>10</td>
</tr>
<tr>
<td>30-39</td>
<td>15</td>
</tr>
<tr>
<td>40+</td>
<td>20</td>
</tr>
</tbody>
</table>

Source: CDC Viral Hepatitis Surveillance Program

Signs & Symptoms: Acute Hepatitis B

- May Be Asymptomatic
- "Flu-like" Symptoms
  - muscle aches, nausea, vomiting, fever
- Skin Rash
- Jaundice (yellow skin, eyes), itching
- Light-colored Stools
- Dark Urine

Figure 3.2. Incidence of acute hepatitis B, by age group — United States, 2000–2011

Source: National Notifiable Diseases Surveillance System (NNDSS)

Signs & Symptoms: Chronic Hepatitis B

- Usually Asymptomatic
- Malaise/Fatigue
- Extrahepatic Symptoms
- Signs & Symptoms of Liver Failure
- Hepatocellular Carcinoma and/or Death
Hepatitis B - Clinical Features

- **Incubation period:** Average 60-90 days
  Range 45-180 days
- **Clinical illness (jaundice):**
  - <5 yrs, <10%
  - ≥5 yrs, 30%-50%
- **Acute case-fatality rate:** 0.5%-1%
- **Chronic infection:**
  - <5 yrs, 30%-90%
  - ≥5 yrs, 2%-10%
- **Premature mortality from chronic liver disease:** 15%-25%

Outcome of Hepatitis B Virus Infection by Age at Infection

<table>
<thead>
<tr>
<th>Symptomatic Infection (%)</th>
<th>Chronic Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>100</td>
</tr>
<tr>
<td>1-6 months</td>
<td>80</td>
</tr>
<tr>
<td>7-12 months</td>
<td>60</td>
</tr>
<tr>
<td>1-4 years</td>
<td>40</td>
</tr>
<tr>
<td>Older Children and Adults</td>
<td>20</td>
</tr>
</tbody>
</table>

Natural History of Chronic Hepatitis B

- Ranges from mild infection (asymptomatic) to more severe chronic liver disease
- Fibrosis and subsequent cirrhosis
- Liver failure
- Hepatocellular carcinoma
- Mortality

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

- **HBsAg**
- **anti-HBe**
- **Total anti-HBc**
- **IgM anti-HBc**
- **anti-HBs**

Weeks after Exposure

Titer
Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course

Weeks after Exposure

<table>
<thead>
<tr>
<th>Titer</th>
<th>IgM anti-HBc</th>
<th>Total anti-HBc</th>
<th>anti-HBe</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (6 months)</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>Chronic (Years)</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
</tbody>
</table>

Test Result Interpretation

- **HBsAg negative**
  - Susceptible
- **anti-HBc negative**
  - anti-HBs negative
- **HBsAg negative**
  - Immune due to natural infection
  - anti-HBc positive
  - anti-HBs positive
- **HBsAg negative**
  - Immune due to hepatitis B vaccination
  - anti-HBc negative
  - anti-HBs positive
- **HBsAg positive**
  - Acute infection
  - anti-HBc positive
  - IgM anti-HBc positive
  - anti-HBs negative
- **HBsAg positive**
  - Chronic infection
  - anti-HBc positive
  - IgM anti-HBc negative
  - anti-HBs negative
- **HBsAg negative**
  - Interpretation unclear; four possibilities:
    1. Resolved infection (most common)
    2. False-positive anti-HBc, thus susceptible
    3. "Low level" chronic infection
    4. Resolving acute infection

Treatments for Chronic Hepatitis B

- Interferon alfa
- Lamivudine (Epivir, 3TC)
- Adefovir
- Entecavir
- Tenofovir
- those who have low levels of virus, abnormal liver tests, and moderate damage on biopsy respond best

Elimination of Hepatitis B Virus Transmission United States

**Strategy**

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
  - all unvaccinated children at 11-12 years of age
  - "high-risk" adolescents at all ages
- Vaccination of adults in high-risk groups
Hepatitis B Vaccine

- Recommended for:
  - Everyone 18 years of age and younger
  - Adults over 18 who are at risk:
    - multiple sex partners
    - men who have sex with men
    - sex contacts of infected people
    - injection drug users
    - health care and public safety workers
    - household contacts of persons with Hep B
    - hemodialysis patients

Hepatitis B Vaccine

- Adults:
  - 3 doses
  - Dose 1 at Time 0
  - Dose 2 at 1 month later
  - Dose 3 at 6 months later

Hepatitis B Vaccine Side Effects

- Do not give if patient sick.
- Do not give if person has a yeast allergy or had a serious reaction to a prior dose
  - Baker’s yeast (bread)
- Soreness at site of shot (1 of 4)
- Mild to moderate fever (1 of 100)
- Severe allergic reaction (very rare)
  - high fever, difficulty breathing, hoarseness, wheezing, hives, paleness, weakness, fast heart beat, dizziness

PEP for HBV

- Perinatal exposure to an HBsAg-, HBeAg-positive mother:
  - HBIG and initiation of the hepatitis B vaccine series at birth is 85%–95% effective in preventing HBV infection
- Occupational exposure:
  - multiple doses of HBIG initiated within 1 week following percutaneous exposure to HBsAg-positive blood provides an estimated 75% protection from HBV infection
  - Give the hepatitis B vaccine series.
Hepatitis C Virus

Hepatitis C Virus Infection, United States

- New infections (cases)/year 1985-89: 242,000 (42,000)
- 1998: 40,000 (6,500)
- Deaths from acute liver failure: Rare
- Persons ever infected (1.8%): 3.9 million (3.1-4.8)*
- Persons with chronic infection: 2.7 million (2.4-3.0)*
- Of chronic liver disease - HCV-related: 40% - 60%
- Deaths from chronic disease/year: 10,000

HCV Prevalence by Selected Groups United States

Estimated Incidence of Acute HCV Infection United States, 1960-1999

Transmission of HCV

- Percutaneous
  - Injecting drug use
  - Clotting factors before viral inactivation
  - Transfusion, transplant from infected donor
  - Therapeutic (contaminated equipment, unsafe injection practices)
  - Occupational (needlestick)
- Permuosal
  - Perinatal
  - Sexual

**Sources of Infection for Persons with Hepatitis C**

- Injecting drug use 60%
- Sexual 15%
- Transfusion 10% (before screening)
- Other* 5%
- Unknown 10%

*Nosocomial; Health-care work; Perinatal

**Injecting Drug Use and HCV Transmission**

- Highly efficient among injection drug users
- Rapidly acquired after initiation
- Four times more common than HIV
- Prevalence 60-90% after 5 years
Posttransfusion Hepatitis C

Nosocomial Transmission of HCV
- Recognized primarily in context of outbreaks
- Contaminated equipment
  - hemodialysis*
  - endoscopy
- Unsafe injection practices
  - plasmapheresis,* phlebotomy
  - multiple dose medication vials
  - therapeutic injections

Occupational Transmission of HCV
- Inefficiently transmitted by occupational exposures
- Average incidence 1.8% following needle stick from HCV-positive source
  - Associated with hollow-bore needles
- Case reports of transmission from blood splash to eye
  - No reports of transmission from skin exposures to blood
- Prevalence 1% among health care workers
  - Lower than adults in the general population
  - 10 times lower than for HBV infection

Perinatal Transmission of HCV
- Transmission only from women HCV-RNA positive at delivery
  - Average rate of infection 6%
  - Higher (17%) if woman co-infected with HIV
  - Role of viral titer unclear
- No association with
  - Delivery method
  - Breastfeeding
- Infected infants do well
  - Severe hepatitis is rare
Sexual Transmission of HCV
- Occurs, but efficiency is low
  - Rare between long-term steady partners
  - Factors that facilitate transmission between partners unknown (e.g., viral titer)
- Accounts for 15-20% of acute and chronic infections in the United States
  - Sex is a common behavior
  - Large chronic reservoir provides multiple opportunities for exposure to potentially infectious partners

Household Transmission of HCV
- Rare but not absent
- Could occur through percutaneous/mucosal exposures to blood
  - Theoretically through sharing of contaminated personal articles (razors, toothbrushes)
  - Contaminated equipment used for home therapies
    - Injections*
    - Folk remedies

Other Potential Exposures to Blood
- No or insufficient data showing increased risk
  - Intranasal cocaine use, tattooing, body piercing, acupuncture, military service
- Limited number of studies showing associations that cannot be generalized
  - Convenience or highly selected groups (mostly blood donors)
- No associations in acute case-control or population-based studies

Features of Hepatitis C Virus Infection
- Incubation period
  - Average 6-7 weeks
  - Range 2-26 weeks
- Acute illness (jaundice)
  - Mild (<20%)
- Case fatality rate
  - Low
- Chronic infection
  - 75%-85%
- Chronic hepatitis
  - 70% (most asx)
- Cirrhosis
  - 10%-20%
- Mortality from CLD
  - 1%-5%
Natural History of HCV Infection

- Exposure (Acute phase)
  - 15% (15) Resolved
  - 85% (85) Chronic
- Chronic
  - 20% (17) Cirrhosis
  - 80% (68) Stable
- Cirrhosis
  - 25% (4) Slowly Progressive
  - 75% (13) HCC, Transplant, Death

Chronic Hepatitis C Factors Promoting Progression or Severity
- Increased alcohol intake
- Age > 40 years at time of infection
- HIV co-infection
- Other
  - Male gender
  - Other co-infections (e.g., HBV)

Serologic Pattern of Acute HCV Infection with Recovery

- Symptoms +/-
- Time after Exposure
- anti-HCV
- HCV RNA
- ALT
- Normal

Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

- Symptoms +/-
- Time after Exposure
- anti-HCV
- HCV RNA
- ALT
- Normal
**HCV Testing Routinely Recommended**

*Based on increased risk for infection*
- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992
- Ever on chronic hemodialysis
- Evidence of liver disease
- As of July 2012, anyone born between 1945-1965

*Based on need for exposure management*
- Healthcare, emergency, public safety workers after needle stick/mucosal exposures to HCV-positive blood
- Children born to HCV-positive women

**Routine HCV Testing of Uncertain Need**

*Not confirmed as risk factor/prevalence unknown*
- Recipients of transplanted tissue
- Intranasal cocaine or other non-injecting illegal drug users
- History of tattooing, body piercing

*Confirmed risk factor but prevalence of infection low*
- History of STDs or multiple sex partners
- Long-term steady sex partners of HCV-positive persons

**Routine HCV Testing Not Recommended (Unless Risk Factor Identified)**

- Health-care, emergency medical, and public safety workers
- Pregnant women
- Household (non-sexual) contacts of HCV-positive persons
- General population

**HCV Infection Testing Algorithm for Diagnosis**

1. **EIA for Anti-HCV**
   - Negative (non-reactive) → **STOP**
   - Positive (repeat reactive)

2. **HCV exposed but not infected or false positive EIA**
   - Negative → **RT-PCR for HCV RNA**
   - Positive → **Medical Evaluation**
Medical Evaluation and Management for Chronic HCV Infection

- Assess for biochemical evidence of CLD
- Assess for severity of disease and possible treatment, according to current practice guidelines
- Counsel to reduce further harm to liver
  - Limit or abstain from alcohol
  - Vaccinate against hepatitis A

Old Treatment of Chronic HCV Infection

- Pegylated interferon (PEG) and ribavirin (RBV) for 6 months (gt 2, 3) to 1 year (other gt)
  - Response rates ~50% in gt 1, 80% in gt 2 or 3
  - Many of side effects

Newer Treatment of Chronic HCV Infection

- May 2011- two Protease inhibitors (Telaprevir, Boceprevir) approved
  - for gt 1 infection only
  - response rates ~70%
  - Even more side effects

Treatment of Chronic HCV Infection

- Late 2013- Simeprevir and Sofosbuvir approved
  - With PEG/RBV gt 1 infection
  - Interferon sparing for gt 2, 3
  - Response rates with new agents ~80-98%
- More new medications coming in late 2014- early 2015 with high rates of cure, low rates of side effects, and 12 weeks courses of oral Rx
Postexposure Management for HCV

- IG, antivirals not recommended for prophylaxis
- Follow-up after needlesticks, sharps, or mucosal exposures to HCV-positive blood
  - Test source for anti-HCV
  - Test worker if source anti-HCV positive
  - Anti-HCV and ALT at baseline and 4-6 months later
  - For earlier diagnosis, HCV RNA by PCR at 4-6 weeks
  - Confirm all anti-HCV results with RIBA
- Refer infected worker to specialist for medical evaluation and management

Questions?

- Email me: acox@jhmi.edu
- Call me for urgent questions: (410)502-2715