Hepatitis A and B

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Viral Hepatitis - Historical Perspective

Viral hepatitis → NANB

“Serum” → B, D, F, G, ? other

Enterically transmitted → E

Parenterally transmitted → C

Viral Hepatitis - Overview

<table>
<thead>
<tr>
<th>Type of Hepatitis</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of virus</td>
<td>feces</td>
<td>blood-borne body fluids</td>
<td>blood-borne body fluids</td>
<td>blood-borne body fluids</td>
<td>feces</td>
</tr>
<tr>
<td>Route of transmission</td>
<td>fecal/oral</td>
<td>percutaneous parenteral</td>
<td>percutaneous parenteral</td>
<td>percutaneous parenteral</td>
<td>fecal/oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Prevention</td>
<td>pre-exposure immunization</td>
<td>pre-exposure immunization</td>
<td>blood donor screening, risk behavior modification</td>
<td>blood donor screening, risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>

Acute Viral Hepatitis by Type, United States, 1982-1993

Source: CDC Sentinel Counties Study on Viral Hepatitis
Hepatitis A Virus

RNA Picornavirus
- Acute disease and asymptomatic infection
- Fecal-oral spread
- Community outbreaks
  - Water or food
  - 42% cases sporadic

No chronic infection
- Protective antibodies develop in response to infection - confers lifelong immunity

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

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HDV</th>
<th>HDV</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/yr</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</td>
<td>3.5</td>
<td>million</td>
</tr>
<tr>
<td>Chronic liver disease deaths/yr</td>
<td>5,000</td>
<td>8-10,000</td>
<td>1,000</td>
<td></td>
</tr>
</tbody>
</table>


REPORTED CASES OF SELECTED NOTIFIABLE DISEASES PREVENTABLE BY VACCINATION, UNITED STATES, 2001

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>10,609</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>7,843</td>
</tr>
<tr>
<td>Pertussis</td>
<td>7,580</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>2,333</td>
</tr>
<tr>
<td>H. influenzae, invasive</td>
<td>1,597</td>
</tr>
<tr>
<td>Mumps</td>
<td>266</td>
</tr>
<tr>
<td>Measles</td>
<td>116</td>
</tr>
</tbody>
</table>

Source: WY05, CDC
HEPATITIS A, UNITED STATES

- Most disease occurs in the context of community-wide outbreaks
- Infection transmitted from person to person in households and extended family settings
  - facilitated by asymptomatic infection among children
- Some groups at increased risk
  - specific factor varies
  - do not account for majority of cases
- No risk factor identified for 40%-50% of cases

NUMBER OF YEARS REPORTED INCIDENCE OF HEPATITIS A EXCEEDED 10 CASES PER 100,000, BY COUNTY, 1987-1997

CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS

Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890
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)
- Blood exposure (rare) (e.g., injection drug use, rarely by transfusion)

RISK FACTORS ASSOCIATED WITH REPORTED HEPATITIS A, 1990-2000, UNITED STATES

Clinical Features

- Usually Acute, self-limited illness
- Rare fulminant hepatic failure
- More common with underlying liver disease (HCV)
- Often silent in children
**Treatment and Prognosis**

- **Supportive**
  - 20% require hospitalization
  - 85% fully recovered within 3 months

**PREVENTING HEPATITIS A**

- **Hygiene (e.g., hand washing)**
- **May survive 4 hours on fingertips**
- **Sanitation (e.g., clean water sources)**
- **Hepatitis A vaccine (pre-exposure)**
- **Immune globulin (pre- and post-exposure)**

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**HEPATITIS A - CLINICAL FEATURES**

- Jaundice by:
  - <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
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

REPORTED CASES OF HEPATITIS A, UNITED STATES, 1952-2002

Hepatitis A Incidence, United States, 1980-2002*

1999 ACIP RECOMMENDATIONS FOR STATEWIDE ROUTINE HEPATITIS A VACCINATION OF CHILDREN

*2002 rate provisional
HEPATITIS A PREVENTION IMMUNE GLOBULIN

- Pre-exposure
  - travelers to intermediate and high HAV-endemic regions
- Post-exposure (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)
- Lasts for up to 6 months

ACIP RECOMMENDATIONS PERSONS AT INCREASED RISK OF INFECTION, 1996

- Men who have sex with men
- Illegal drug users
- International travelers
- Persons who have clotting factor disorders
- Persons with chronic liver disease

Hepatitis B
Characteristics of Hepatitis B Virus

- Double-stranded DNA virus
- Hepadnavirus family
- High viremia
- High infectivity
- Integrates into host genome
- Important role of host immune response in hepatocellular injury

Current Magnitude of the Problem

**Hepatitis B**
- >2 billion worldwide
- 350 million have chronic disease
- Estimated 1.25 million chronically infected in US

**Hepatitis C**
- 200 million anti-HCV positive worldwide
- 170 million have chronic disease
- 5.0 million Americans anti-HCV positive
- 3.4 million Americans have chronic disease

Cause for Concern

**Hepatitis B**
- #6 cause of liver transplantation in the US
- #1 cause of HCC worldwide
- 5,000 US deaths per year

**Hepatitis C**
- #1 cause of liver transplantation in the US
- #1 cause of HCC in US
- 13,000 US deaths per year

Prevalence of Chronic Hepatitis B

Immigration numbers summed by continent from 1996-2002

- ~2 million Asians
- ~400,000 South Americans
- ~350,000 Africans
- ~200,000 Europeans

HBSAg Prevalence
- >8% - High
- 2-8% - Intermediate
- <2% - Low

Immigration numbers summed by continent from 1996-2002

From: http://www.who.int/vaccines/en/hepatitis_b.shtml
Accessed 04/08/05

From: http://www.who.int/vaccine_research/diseases/hepatitis_c/en/
Accessed 02/08/06

Edlin BR. Hepatology 2005;42(suppl 1):213A.


**Hepatitis B**

- Hepatitis B virus (HBV)
  - bloodborne and sexually transmitted
  - chronic infection more likely in infants or young children
  - Before routine vaccination accounted for 30%–40% US chronic infections
- Chronic disease:
  - increased risk for cirrhosis and HCC
  - main reservoir for HBV transmission

**Transmission of HBV Infection**

- Transfusion (blood, blood products)
- Fluids (blood, semen)
- Organs and tissue transplantation
- Close contact to contact (Horizontal)
- Mother to baby (Vertical)
- Contaminated needles and syringes

**RISK FACTORS FOR ACUTE HBV, U.S.**

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

*Includes sexual contact with acute cases, carriers, and multiple partners.
Source: CDC Sentinel Counties Study of Viral Hepatitis

**The Clinical Outcomes of HBV Infection**

- Recovery
- Chronic infection
- Decompensation
- Transplant or death
- Inactive carrier state
- Chronic liver disease
- HCC

Outcomes of Acute HBV Infection

- Recover: < 1%
- Fulminant Hepatitis: 0.1-2.7%
- Subclinical Hepatitis: 5-20%
- Acute Hepatitis: 5-20%
- Chronic Infection: > 95%

Risk is Related to Age at Infection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Neonates, %</th>
<th>Children, %</th>
<th>Adults, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Carrier</td>
<td>90</td>
<td>20</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Recover</td>
<td>10</td>
<td>80</td>
<td>&gt; 95</td>
</tr>
</tbody>
</table>


Possible Outcomes of HBeAg+ Chronic HBV Infection

- Immune Tolerant
- HBeAg+ CHB
- Inactive HBeAg Carrier
- HBeAg+ CHB (Precore Mutant)

Patient Populations in Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Marker</th>
<th>Immune Tolerant</th>
<th>HBeAg+ CHB</th>
<th>Inactive HBeAg Carrier</th>
<th>HBeAg+ CHB (Precore Mutant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>HBeAg</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ALT</td>
<td>Normal</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>HBV DNA (copies/mL)</td>
<td>&gt; 10⁵</td>
<td>&gt; 10⁵</td>
<td>&lt; 10⁴</td>
<td>&gt; 10⁴</td>
</tr>
</tbody>
</table>

Histology: Normal/Mild, Active, Normal, Active
CHB Prevalence

- CHB Prevalence: 2 million
- 4.9% ever infected
- 21,000 acute cases/yr
- 73,000 new cases/yr
- 1.25 million with Chronic Disease
- 5000 deaths/yr


A Significant Number of CHB Patients Go Undiagnosed or Untreated

- HBV Patients in Healthcare System:
  - CHB Prevalence: 2 million
  - CHB Patients:
    - Diagnosed CHB Patients: 1.26 M
    - CHB Patients: 212k
    - Treated With Prescription Therapy: 41k
    - Not Treated With Prescription Therapy: 231k
    - None of these estimates based on analysis of Synovate Patient Record Data collected Q1, 2008.

Annual Risk of HBV Progression

- HBeAg+ chronic hepatitis B: 5.0%
- HBeAg-Neg chronic hepatitis B: 1.0-2.0%
- All HBeAg + individuals: 2.0%
- All HBeAg - individuals: 0.4%
- Decompensation
- Cirrhosis

Factors linked with progression:
- Duration of active hepatitis
- Heavy alcohol use
- Immune suppression (HIV)


Natural Clearance of HBsAg

- Occurs in ~ 0.5% of HBsAg carriers/year
- Duration of infection is primary determinant of HBsAg loss
- ~ 50% of carriers who clear HBsAg have HBV DNA present in sera in low titer (1–2 logs)

Categorization of Disease

- HBeAg positive or negative
- Replication high or low (HBV DNA)
- ALT elevated or normal
- Liver histology

Indications for Treatment of Chronic HBV

- Patients with active liver disease:
  - Abnormal liver function tests (AST, ALT)
  - HBeAg positive and $> 10^5$ HBV DNA
  - HBeAg negative and $> 10^4$ HBV DNA
    - Biopsy if HBV DNA $< 10^4$ with ↑ ALT
    - Treat if active hepatitis (biochemical or histologic)

Chronic Hepatitis B: Goals of Treatment

- Prevent disease progression
- Prevent complications
  - Cirrhosis
  - HCC
Goals of Therapy
Eradication of Virus
- Disease eradication desired
- Eradication nearly impossible
  - extrahepatic reservoirs
  - integration of HBV DNA into the host genome
  - protected intracellular covalently closed circular (ccc) DNA
    - viral rebound after therapy is discontinued

Goals of treatment
Viral Control
- Next best goal: CONTROL
  - viral suppression
  - immune modulation
- 5 US FDA approved agents
  - Interferon
  - Lamivudine
  - Adefovir
  - Entecavir
  - Pegasys
- at least 2 additional compounds seeking approval

Therapeutic questions
1. Who do I treat?
2. What do I use?
3. How long do I use it?

Goals of Treatment
Treatment Paradigm
- Treatment paradigm for HBV changing
  - Finite treatment interferon
  - Short-term nucleos(t)ide therapy
  - Long-term viral suppression in many patient populations
- Why the Shift?
  - well-tolerated oral compounds
  - emerging data viral suppression decreases downstream risk of complications
Goals of Therapy Guidelines

  Revision 2004, 2007
- EASL: de Franchis et al, 2003
- Keeffe: 2004
  Revision 2006

Goals of treatment Limitations

- All treatments have limitations
  - Cost
  - Duration
  - Side effects
  - Resistance

CLD mortality curves by viral load category at study entry

Chen G Am J Gastro;2006;101:1797-1803
**HCC mortality curve by viral load at study entry**

- High viral load: $> 10^5$
- Low viral load: $< 10^5$

**Cumulative Incidence of HCC**

<table>
<thead>
<tr>
<th>Serum HBV DNA Level at Study Entry</th>
<th>Cumulative Incidence of HCC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;300 (Undetectable)</td>
<td>1.0</td>
</tr>
<tr>
<td>300 – 9,999</td>
<td>12.1</td>
</tr>
<tr>
<td>10,000 – 99,999</td>
<td>14.4</td>
</tr>
<tr>
<td>≥1 Million</td>
<td>17.8</td>
</tr>
</tbody>
</table>

**HBV prevention**

- HBV vaccination
- HBIG

**Hepatitis B Vaccine**

- Vaccine licensed in 1982
- 3-dose series, high efficacy, no boosters, safe
- Comprehensive strategy to eliminate HBV transmission implemented in 1991
  - 1991: universal infant vaccination recommended
  - 1995: expansion to all adolescents 11-12 yrs
  - 1998: vaccination of all persons age 0-18 yrs not previously vaccinated
HBIG

- BayHep B® [DSC]; HepaGam B™; HyperHEP B™
- Passive prophylactic immunity
- given at the same time as vaccination
  - at different site
  - up to 1 month preceding vaccination
- Dose: 0.5 mL ASAP after birth
  - efficacy decreases significantly if delayed >48 hours
  - if vaccination delayed for up to 3 months, dose may be repeated

How do we do?
Screening?

- >95% of pregnant women tested for HBsAg
- 50% of expected births to HBsAg+ women
  - racial/ethnic-specific HBsAg prevalence estimates to U.S. natality data
- women without pre-natal care
  - HBsAg testing at admission for delivery
  - higher prevalence of HBsAg+ vs those screened prenatally

How do we do?
Immunoprophylaxis?

- high levels of initiation and completion of postexposure immunoprophylaxis among identified infants born to HBsAg-positive women
  - Birth dose coverage in 2004 was only 46%
  - No pre-natal care
    - administration first dose vaccine to infants <12 hours of birth
  - Even with HBsAg testing infants of HBsAg+ mothers do not receive postexposure immunoprophylaxis
  - Delay in reporting

How do we do?
Vaccination?

- 2004 U.S. children 19–35 months,
  - >92% fully vaccinated
- Hepatitis B vaccine successfully integrated into childhood vaccine schedule
  - infant vaccine coverage levels are equivalent to those of other vaccines in the childhood schedule

Anti-viral Therapy
- Vaccination and HBIG failure associated with high HBV DNA levels
- Reducing HBV DNA levels prior to delivery reduces risk
- Mothers with HBV DNA levels > 10^9 copies/mL received lamivudine in third trimester
- All babies received HBIG and HBV vaccine

Summary
- Hepatitis A
  - Fecal-oral
  - Not chronic
  - Vaccine preventable
- Hepatitis B
  - Blood born
  - Frequently chronic
  - Vaccine preventable