Viral Hepatitis

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Viral Hepatitis - Overview

- Primary infection of the liver caused by at least five unrelated viruses: A, B, C, D, E

- HAV and HEV
  - Fecal-oral route
  - Acute self-limited disease; no chronic infection

- HBV, HCV, HDV
  - Percutaneous or mucosal exposures to blood
  - Chronic infection – major causes of cirrhosis and hepatocellular carcinoma worldwide
Viral Hepatitis – Historical Perspective

“Infectious” A

Viral hepatitis → NANB

“Serum” B C

NANB → F, G, ?other

Enterically transmitted E

Parenterally transmitted C

“mis-reported” B
# 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><strong>Source of virus</strong></td>
<td>feces</td>
<td>blood/ blood-derived body fluids</td>
<td>blood/ blood-derived body fluids</td>
<td>blood/ blood-derived body fluids</td>
<td>feces</td>
</tr>
<tr>
<td><strong>Route of transmission</strong></td>
<td>fecal-oral</td>
<td>percutaneous/permucosal</td>
<td>percutaneous/permucosal</td>
<td>percutaneous/permucosal</td>
<td>fecal-oral</td>
</tr>
<tr>
<td><strong>Chronic infection</strong></td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>pre/post-exposure immunization</td>
<td>pre/post-exposure immunization</td>
<td>blood donor screening; risk behavior modification</td>
<td>pre/post-exposure immunization; risk behavior modification</td>
<td>ensure safe drinking water</td>
</tr>
</tbody>
</table>
Clinical Features of Hepatitis

**Common**
- malaise
- anorexia
- nausea & vomiting
- fever

**Less Common**
- diarrhea
- arthralgias

- jaundice
- abdominal pain
- hepatomegaly

- pruritis
- rash
Enterically Transmitted Viral Hepatitis
Hepatitis A—Highlights

- Estimated 1.5 million clinical cases of hepatitis A annually worldwide
- Tens of millions of hepatitis A virus infections occur each year
- Transition to lower rates of endemic HAV infection occurring on a global scale
- Universal childhood vaccination effective in countries with varying endemic rates
  - Reduces morbidity and mortality

Wasley A, Epidemiologic Reviews 2006
Hepatitis A Virus

- RNA Picornavirus
- Single serotype worldwide
- Acute disease and asymptomatic infection
- No chronic infection
- Protective antibodies develop in response to infection - confers lifelong immunity
- Vaccine preventable
Transmission of Hepatitis A Virus

- Fecal-oral transmission leads to spread between close contacts
- Greatest period of communicability: 2 weeks before onset of jaundice
- Stable in environment for months
Transmission of Hepatitis A Virus

- Close personal contact (e.g., household contact, sex contact)
- Contaminated food (water) (e.g., infected food handlers, produce)
- Blood exposure (e.g., injecting drug use, transfusion)
## Hepatitis A - Clinical Features

<table>
<thead>
<tr>
<th>Incubation period</th>
<th>Average 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range 15-50 days</td>
</tr>
<tr>
<td>Jaundice by age</td>
<td>&lt;6 yrs &lt;10%</td>
</tr>
<tr>
<td></td>
<td>6-14 yrs 40%-50%</td>
</tr>
<tr>
<td></td>
<td>&gt;14 yrs 70%-80%</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>0.3% (0.2%-2.0%)</td>
</tr>
<tr>
<td>Complications</td>
<td>Fulminant; cholestatic; relapsing</td>
</tr>
<tr>
<td>Chronic sequelae</td>
<td>None (prolonged shedding in neonates and immunocompromised)</td>
</tr>
</tbody>
</table>
Relative Frequency of Jaundice with Hepatitis A, by Age

Anicteric
Icteric

Percent

Age, years

< 6
6-14
>14
Concentration of Hepatitis A Virus in Various Body Fluids

- Feces: $10^{10}$ infectious doses per mL
- Serum: $10^{4}$ infectious doses per mL
- Saliva: $10^{2}$ infectious doses per mL
- Urine: $10^{0}$ infectious doses per mL

Source: Viral Hepatitis and Liver Disease 1984;9-22; J Infect Dis 1989;160:887-890
Events in Hepatitis A Virus Infection

- Clinical illness
- Infection
- Viremia
- ALT
- IgM
- IgG
- HAV in stool

Week:
0 1 2 3 4 5 6 7 8 9 10 11 12 13

Response:
Patterns of Hepatitis A Virus Infection Worldwide

- High
- Intermediate
- Low
- Very low

Prevalence of anti-HAV (%)

Age
# Hepatitis A Virus Transmission

## Global Patterns

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Disease Rate</th>
<th>Age at Infection</th>
<th>Transmission patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Early childhood</td>
<td>Person to person; outbreaks uncommon</td>
</tr>
<tr>
<td>Intermediate</td>
<td>High</td>
<td>Late childhood/young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Low</td>
<td>Low to high</td>
<td>Late childhood/young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Adults</td>
<td>Travelers; outbreaks uncommon</td>
</tr>
</tbody>
</table>
Global Patterns of Hepatitis A Endemicity

Anti-HAV Prevalence
- High
- High/Intermediate
- Intermediate
- Low
- Very Low
Epidemiologic Features of Hepatitis A in the United States

- Wide geographic and temporal variation in incidence
  - Areas with highest rates account for most reported cases
- 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
- Groups at increased risk can be identified
  - Specific factor varies
  - Do not account for majority of cases
- No risk factor identified for 30%-40% of cases
Risk Factors Among Persons with Hepatitis A, Reported Cases, United States, 1990-2000

- Household or sexual contact: 14%
- Day care: 8%
- MSM: 10%
- Illicit drug users: 5%
- International travel: 5%
- Common source outbreak: 4%
- Other contact: 8%
- Unknown: 48%

Source: CDC Sentinel Counties
Source: Viral Hepatitis Surveillance Program
# HEPATITIS A VACCINE EFFICACY STUDIES

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Site/ Age Group</th>
<th>N</th>
<th>Vaccine Efficacy (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX ®* (GSK)</td>
<td>Thailand 1-16 yrs</td>
<td>38,157</td>
<td>94% (79%-99%)</td>
</tr>
<tr>
<td>2 doses 360 EL.U.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAQTA ®** (Merck)</td>
<td>New York 2-16 yrs</td>
<td>1,037</td>
<td>100% (85%-100%)</td>
</tr>
<tr>
<td>1 dose 25 units</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Recommended Dosages of Hepatitis A Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (yrs)</th>
<th>Dose</th>
<th>Volume (mL)</th>
<th>2-Dose Schedule (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX ® #</td>
<td>2-18</td>
<td>720 (EL.U.*)</td>
<td>0.5</td>
<td>0, 6-12</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>1,440</td>
<td>1.0</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>VAQTA ® ##</td>
<td>2-18</td>
<td>25 (U**)</td>
<td>0.5</td>
<td>0, 6-18</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>50</td>
<td>1.0</td>
<td>0, 6-12</td>
</tr>
</tbody>
</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units
** Units
# has 2-phenoxyethanol as a preservative
## has no preservative
SAFETY OF HEPATITIS A VACCINE

- Most common side effects
  - Soreness/tenderness at injection site - 50%
  - Headache - 15%
  - Malaise - 7%

- No severe adverse reactions attributed to vaccine
- Safety in pregnancy not determined – risk likely low
- Contraindications - severe adverse reaction to previous dose or allergy to a vaccine component
- No special precautions for immunocompromised persons
Immunogenicity of Inactivated Hepatitis A Vaccines

- 2-dose series 6-18 months apart (dosage varies by manufacturer)

- 95%-100% had protective levels of antibody one month after receiving one dose

- 100% had protective levels of antibody one month after receiving second dose with high geometric mean titers
Prevention of Hepatitis A

- **Worldwide**
  - Hygiene and sanitation
    - Handwashing and clean water sources
    - Prevent contamination of fresh produce

- **Low endemic countries**
  - Preexposure vaccination
    - All children aged >1 years
    - Risk groups (travelers, MSM, illegal drug users, persons with chronic liver disease)
  - Postexposure prophylaxis (vaccine or IG)
    - Household and sex contacts
    - Common source exposure (prepared food by infected handler)
Hepatitis E Virus (HEV)
Hepatitis E—Highlights

<table>
<thead>
<tr>
<th>Like HAV</th>
<th>Unlike HAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal-oral</td>
<td>Incubation period ~10 days longer</td>
</tr>
<tr>
<td>Acute self-limiting infection</td>
<td>Clinical response dose-dependent</td>
</tr>
<tr>
<td>Exception—may persist in immunologically compromised host</td>
<td>Not age dependent</td>
</tr>
<tr>
<td>Vaccine preventable</td>
<td>Infection rare in children and household contacts</td>
</tr>
<tr>
<td></td>
<td>Higher mortality overall</td>
</tr>
<tr>
<td></td>
<td>Much higher in pregnant women</td>
</tr>
<tr>
<td></td>
<td>Sporadic disease very rare in developed countries, Ab relatively common</td>
</tr>
<tr>
<td></td>
<td>Not always associated with travel*</td>
</tr>
<tr>
<td></td>
<td>Zoonotic source</td>
</tr>
</tbody>
</table>

* Autochthonous

Purcell RH, Emerson SU, J Hepatology 2008
First Recognized Outbreak of Hepatitis E New Delhi, India (1956)

- 35,000 cases acute jaundice
- City water system contaminated by sewage
- Highest attack rate persons 15-40 years old
- Case-fatality rate 10.5% among pregnant women
- Originally thought to be hepatitis A
History

1983 human challenge experiment
- Ingested pooled stool from outbreak-related cases
- Developed acute non-A, non-B hepatitis
- Excretion of virus-like particles
- Stool infectious for non-human primates

Classified enterically-transmitted NANB hepatitis

1990 HEV genome cloned
- Classified as calicivirus
Diagnosis of Acute Hepatitis E

- Clinical illness indistinguishable from other types of acute viral hepatitis (A, B, C, D,....)
- Definitive diagnosis requires laboratory confirmation
- Serology:
  - IgM anti-HEV, IgG anti-HEV
  - Acute infection - good sensitivity and specificity
  - Prevalent infection - discordance between tests
- Research labs
  - HEV RNA by PCR (serum, stool, liver)
  - HEVAg by immunofluorescent probe (liver)
## Hepatitis E - Clinical Features

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation period</strong></td>
<td>Average 40 days; Range 15-60 days</td>
</tr>
<tr>
<td><strong>Clinical illness</strong></td>
<td>Case/infection ratio and severity increase with age</td>
</tr>
<tr>
<td><strong>Chronic sequelae</strong></td>
<td>None (&quot;chronic&quot; viremia recently reported in transplant patients)</td>
</tr>
<tr>
<td><strong>Case-fatality rate</strong></td>
<td>Overall 1-3%</td>
</tr>
<tr>
<td></td>
<td>Pregnant women 15-20%</td>
</tr>
<tr>
<td><strong>Factors related to increased severity</strong></td>
<td>Chronic liver disease, large inoculum, pregnancy</td>
</tr>
</tbody>
</table>
Hepatitis E in Pregnancy

- Reasons for poor outcomes are unclear
- Most severe in 3rd trimester
  - 1/2: asymptomatic or mild HEV infection
  - 1/2: acute HE
    - 1/3 have FHF (fulminant hepatic failure, in resource-poor settings: high mortality)
    - 2/3 preterm delivery
    - High rates of obstetric complications
- Vertical transmission is common with 3rd trimester
  - Rate 33%-100%
  - Clinical outcome in infants is highly variable
    - Asymptomatic infection to hepatic necrosis
    - Hypoglycemia and hypothermia associated with mortality
Treatment

- Supportive
- No specific antiviral therapy
- Acute HE in pregnant women
  - No published data on potential benefits of early delivery
Epidemiologic Features of HEV

- Responsible for sporadic cases of acute hepatitis and outbreaks
- Mode of transmission fecal-oral
  - Recent report of solid organ transplant-related
- Pattern
  - Outbreaks - fecally contaminated drinking water
  - Sporadic cases - not known
- Highest attack rate in young adults
- Minimal person-to-person transmission
- Animal reservoir
HEV may be most common etiology of acute viral hepatitis
“Endemic” Countries

- Outbreaks
  - Waterborne
  - Flooding, disruptions in water systems

- Sporadic Hepatitis E
  - HEV accounts for a variable proportion of acute viral hepatitis
  - Source of transmission not clear
“Non-Endemic” Countries

- No outbreaks
- Sporadic HE
  - Travel-related
    - Most commonly after travel to Asia, especially India and China
  - Domestically acquired
    - Rare
    - Source unknown
Prevention of Hepatitis E

- Treatment - None
- Vaccine – potentially effective
- Immune globulin - Not effective
- Clean and reliable water supply
  - Virus probably inactivated by boiling
  - Effect of chlorination not known
- Proper sanitation (e.g., safe disposal of human and animal sewage)
Bloodborne Viral Hepatitis

Hepatitis B Virus
Hepatitis C Virus
Hepatitis D Virus
Bloodborne Viral Hepatitis
HBV and HCV—Highlights

- HBV
  - Status of universal childhood immunization
- HBV and HCV
  - Transfusion Safety
  - Injection Safety
  - Changing epidemiology
  - Chronic disease burden
Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

<table>
<thead>
<tr>
<th>Titer</th>
<th>Symptoms</th>
<th>HBeAg</th>
<th>anti-HBe</th>
<th>Total anti-HBc</th>
<th>HBsAg</th>
<th>IgM anti-HBc</th>
<th>anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>32</td>
<td>36</td>
<td>52</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weeks after Exposure
# Ten Leading Causes of Infectious Disease Deaths Worldwide (2000)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower resp tract infections</td>
<td>~3.5 million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>~3.0 million</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>~2.2 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>~2.0 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>~1-3 million</td>
</tr>
<tr>
<td>Measles</td>
<td>~888,000</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>~750,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>~355,000</td>
</tr>
<tr>
<td>Neonatal tetanus</td>
<td>~300,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>~250,000</td>
</tr>
</tbody>
</table>

Source: CDC, WHO, UNICEF, UNAIDS
## Global and US Disease Burden from Bloodborne Viral Infections

<table>
<thead>
<tr>
<th></th>
<th>Estimated No. Chronic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global</td>
</tr>
<tr>
<td>HBV</td>
<td>370 million</td>
</tr>
<tr>
<td>HCV</td>
<td>130 million</td>
</tr>
<tr>
<td>HIV</td>
<td>40 million</td>
</tr>
<tr>
<td>HIV / HBV</td>
<td>3–4 million</td>
</tr>
<tr>
<td>HIV / HCV</td>
<td>4–5 million</td>
</tr>
</tbody>
</table>

Sources: WHO and CDC, unpublished data.
<table>
<thead>
<tr>
<th></th>
<th><strong>HBV</strong></th>
<th><strong>HCV</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus Classification</strong></td>
<td>DNA</td>
<td>RNA</td>
</tr>
<tr>
<td></td>
<td>Hepadnavirus</td>
<td>Flaviviruses</td>
</tr>
<tr>
<td><strong>Incubation period</strong></td>
<td>8–12 wks</td>
<td>6–7 wks</td>
</tr>
<tr>
<td>– range</td>
<td>6–26 wks</td>
<td>2–26 wks</td>
</tr>
<tr>
<td><strong>Specific serologic markers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute infection</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>active infection</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>chronic infection</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clinical illness (jaundice)</strong></td>
<td>30%–50%</td>
<td>20%</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>90% (infants)</td>
<td>~70%</td>
</tr>
<tr>
<td></td>
<td>5–10% (adults)</td>
<td></td>
</tr>
<tr>
<td><strong>Mortality from CLD, cirrhosis, HCC</strong></td>
<td>25%</td>
<td>1-5%</td>
</tr>
</tbody>
</table>
## Relative Efficiency of Transmission by Type of Exposure

<table>
<thead>
<tr>
<th>Type of exposure to infected source</th>
<th>Efficiency of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td>++++</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>++++</td>
</tr>
<tr>
<td>Unsafe injections</td>
<td>+++</td>
</tr>
<tr>
<td>Needlestick</td>
<td>+++</td>
</tr>
<tr>
<td>Sexual</td>
<td>+++</td>
</tr>
<tr>
<td>Perinatal</td>
<td>++++</td>
</tr>
<tr>
<td>Non-intact skin</td>
<td>++</td>
</tr>
</tbody>
</table>
### Relative Infectivity of HBV, HCV, HIV

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Copies/mL</strong></td>
<td>$10^{8-9}$</td>
<td>$10^5$</td>
<td>$10^3$</td>
</tr>
<tr>
<td><strong>Environmental stability</strong></td>
<td>++++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Infectious after drying at room temperature</td>
<td>$\geq$7d</td>
<td>$\geq$16h</td>
<td>0 ($&lt;4d$)</td>
</tr>
</tbody>
</table>

Environmental Stability of HBV and HCV Facilitates Their Transmission

- More rapid acquisition among IDUs
  - Clean needles and syringes alone insufficient to interrupt transmission because virus can live on contaminated drug preparation equipment (i.e., cookers and cotton)

- Iatrogenic transmission
  - Virus can live in contaminated multi-dose vials and on needles and syringes
# Routes of HBV Transmission

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Routes of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>Mother to infant (perinatal)</td>
</tr>
<tr>
<td>Childhood</td>
<td>Household (non-intact skin)</td>
</tr>
<tr>
<td>Adolescent/Adult</td>
<td>Sexual contact</td>
</tr>
<tr>
<td></td>
<td>Injecting drug use equipment</td>
</tr>
<tr>
<td></td>
<td>Occupational exposures</td>
</tr>
<tr>
<td>All ages</td>
<td>Unsafe injections</td>
</tr>
<tr>
<td></td>
<td>Transfusion from unscreened donors</td>
</tr>
<tr>
<td></td>
<td>Other health care related</td>
</tr>
</tbody>
</table>
## Global Differences in HBV Transmission Patterns

<table>
<thead>
<tr>
<th>Chronic infection (% immune)</th>
<th>Primary Age at Infection</th>
<th>Primary Modes of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>High &gt;8% (&gt;60%)</td>
<td>Infants</td>
<td>Perinatal, horizontal, unsafe injections, unscreened blood</td>
</tr>
<tr>
<td>Intermediate 2-7% (20-60%)</td>
<td>Young children</td>
<td>Perinatal, horizontal, unsafe injections, sexual, IDU</td>
</tr>
<tr>
<td>Low &lt;2% (5-20%)</td>
<td>Adolescents Adults</td>
<td>Sexual, IDU</td>
</tr>
</tbody>
</table>
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence
- ≥8% - High
- 2-7% - Intermediate
- <2% - Low
Outcome of HBV Infection by Age at Infection

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Chronic Infection (%)</th>
<th>Symptomatic Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1-6 months</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>7-12 months</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>1-4 years</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

Chronic Infection

Symptomatic Acute Hepatitis B
Global Strategy to Prevent HBV Transmission

- Hepatitis B Vaccination
  - Routine infant vaccination (all countries)
  - Catch-up vaccination of older children/adolescents
  - Vaccination of high-risk groups

- Prevention of iatrogenic transmission
  - Routine screening of transfused blood
    - developed countries - 100% screen
    - least developed countries - 35% screen (?)
  - Safe injection practices
  - Proper infection control practices
Risk Factors Reported by Cases of Acute Hepatitis B, United States, 2000-2003

- Heterosexual: 39%
- MSM: 26%
- Injecting drug use: 17%
- None identified: 14%
- Other: 4%*

* Other - Household contact, occupational exposure, hemodialysis, institutionalization, transfusion

Source: Adapted from Sentinel Counties and NNDSS, CDC
Recent HBV Outbreaks Associated with Blood Glucose Monitoring

- **Shared fingerstick devices**
  - 1999 – VA – Assisted Living Centers – 4 cases
  - 1999 – CA – Nursing Home – 4 cases
  - 2003 – MS – Nursing Home – 15 cases
  - 2003 – CA – Assisted Living Center – 8 cases
  - 2005 – VA – Assisted Living Centers (2) – 11 cases

- **Dedicated fingerstick devices**
  - 1999 – CA – Skilled Nursing Facility – 5 cases
  - 2002 – CA – Subacute Hospital – 3 cases
  - 2003 – NC – Nursing Home – 11 cases
Hepatitis B in Health-Care Personnel
Prevalence of HBV Serologic Markers in 624 Hospital Personnel and 462 Nonhospital Controls

Occupational Category

- Emergency Ward Nurses
- Blood Bank Personnel
- Laboratory Technicians
- Pathology Staff
- Intravenous Teams
- Surgical House Officers
- Intensive Care Nurses
- Medical House Officers
- General Ward Nurses
- Dieticians
- Volunteer Blood Donors

Cumulative Percent Positive

N

- 30
- 26
- 39
- 85
- 68
- 66
- 94
- 89
- 76
- 19
- 462

Stenies, J.L. and Ryan, D.M. 1982
Immunogenicity of Heptavax-B® (Hepatitis B Vaccine MSD)

1st dose 2nd dose 3rd dose

Percent of Anti-HBs Positive Vaccines

0 25 50 75 100

0 1 2 3 4 5 6 7 8

Months

41% 90% 96%

Immunogenicity of Hepatitis B Vaccine

Szmuness, W. et al., 1980
**Hepatitis B Vaccine**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Response</th>
<th>Factor</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 20-29</td>
<td>95%</td>
<td>Diabetes</td>
<td>70-80%</td>
</tr>
<tr>
<td>Age 30-39</td>
<td>90%</td>
<td>Liver disease</td>
<td>60-70%</td>
</tr>
<tr>
<td>Age 40-49</td>
<td>86%</td>
<td>Gender</td>
<td>Female&gt;male</td>
</tr>
<tr>
<td>Age 50-59</td>
<td>71%</td>
<td>Obesity</td>
<td>Decreased</td>
</tr>
<tr>
<td>Age ≥60</td>
<td>47%</td>
<td>Smokers</td>
<td>Decreased</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>70-70%</td>
<td>Gluteal injection</td>
<td>Decreased</td>
</tr>
<tr>
<td>HIV infection</td>
<td>50-70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response is defined as</td>
<td>≥ 10 mIU/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hepatitis B Vaccine: Administration 2

- **Schedule**
  - 0, 1, 6 mo
  - 0, 1, 2, 12 mo (more rapid antibody rise) (Engerix)

- **Pre-exposure**
  - ACP: Three doses, obtain titer (1-6 mo). If antibody negative, provide up to 3 additional doses (titer 1-2 mo after each dose)
  - If no response after 6 doses, provide HBIG for exposures
Figure 1. Long-Term Persistence of Anti-HBs in Persons in Whom Anti-HBs Levels above 9.9 SRU Developed after Standard Three-Dose Vaccination.
### HBV: POST-EXPOSURE PROPHYLAXIS

<table>
<thead>
<tr>
<th>Exposed person</th>
<th>Source HBsAg+</th>
<th>Source HBsAg-</th>
<th>Source unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>HBIG x 1 HBV vaccine</td>
<td>HBV vaccine</td>
<td>HBV vaccine</td>
</tr>
<tr>
<td>Vaccinated, Responder</td>
<td>No therapy</td>
<td>No therapy</td>
<td>No therapy</td>
</tr>
<tr>
<td>Vaccinated, Nonresponder</td>
<td>HBIG x 2 or HBIG x 1 &amp; HBV vaccine</td>
<td>No therapy</td>
<td>If known high-risk source, treat as if source HBsAg+</td>
</tr>
<tr>
<td>Vaccinated, Response unknown</td>
<td>Obtain anti-HBs * If ok, no therapy * If low, HBIG x 1 &amp; vaccine</td>
<td>No therapy</td>
<td>Obtain anti-HBs * If OK, no therapy * If low, vaccine booster</td>
</tr>
</tbody>
</table>

Adequate anti-HBs is >10 mIU/mL; HBIG = 0.06 mg/kg IM
Hepatitis C Virus

- RNA Flavivirus (Hepacivirus)
  - Discovery using recombinant DNA technology reported in 1989
  - Clinical entity (non-A, non-B hepatitis) in transfused patients reported late 1960s
  - Target organ liver
- Bloodborne (primarily) and sexually-transmitted
- No vaccine
  - Mutations occur during viral replication
  - Substantial heterogeneity (quasispecies) prevents effective neutralization
- Treatable and curable (most people free of virus in months)
<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>Average 6-7 weeks</td>
</tr>
<tr>
<td></td>
<td>Range 2-26 weeks</td>
</tr>
<tr>
<td>Acute illness (jaundice)</td>
<td>Mild (20%-30%)</td>
</tr>
<tr>
<td>Case fatality rate</td>
<td>Low</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>75%-85%</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>70%</td>
</tr>
<tr>
<td>Mortality from CLD</td>
<td>1%-5%</td>
</tr>
</tbody>
</table>
Hepatitis C Virus Infection
Typical Serologic Course

Time after Exposure

Titer

Symptoms

anti-HCV

ALT

Normal

0 1 2 3 4 5 6
0 1 2 3 4

Years

Months

0 1 2 3 4

Hepatitis C Virus Infection
Typical Serologic Course

Time after Exposure

Titer

Symptoms

anti-HCV

ALT

Normal

0 1 2 3 4

Years

Months

0 1 2 3 4
<table>
<thead>
<tr>
<th>Description</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>New infections per year 1985-89</td>
<td>242,000</td>
</tr>
<tr>
<td>2006</td>
<td>20,000</td>
</tr>
<tr>
<td>Deaths from acute liver failure</td>
<td>Rare</td>
</tr>
<tr>
<td>Persons ever infected (1.6%)</td>
<td>4.1 million (3.4-4.9)*</td>
</tr>
<tr>
<td>Persons with chronic infection</td>
<td>3.1 million (2.5-3.7)*</td>
</tr>
<tr>
<td>HCV-related chronic liver disease</td>
<td>40% - 60%</td>
</tr>
<tr>
<td>Deaths from chronic disease/year</td>
<td>8,000-10,000</td>
</tr>
</tbody>
</table>

* 95% confidence interval (data from 1999-2002)

Nainan OV. Gastroenterol 2006;131:478-484

*CDC, preliminary unpublished data
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)

- **Permucosal**
  - Perinatal
  - Sexual
Risk Factors For Persons with Acute or Chronic Hepatitis C 1999-2002, U.S.

Chronic (Prevalent)
- Injection Drug Use: 50%
- Transfusion: 10%
- Sexual: 20%
- Other*: 10%
- Unk: 10%

Acute (Incident)
- Injection Drug Use: 60%
- Transfusion: 10%
- Sexual: 20%
- Other*: 10%
- Unk: 10%

* Other includes occupational, nosocomial, iatrogenic, perinatal

Armstrong GL, Ann Intern Med 2006;144:705-14; CDC Sentinel Counties, unpublished data
Iatrogenic-Related Outbreaks of HCV Infections in Developed Countries

- In- and outpatient care
  - Chronic hemodialysis, surgery, endoscopy, pain management clinic, oncology clinic, in-patient ward
- Most due to unsafe injection practices, i.e., failure to use aseptic techniques
  - Contamination of multi-dose medication vials and IV solutions
  - Reuse of syringes/needles
  - Contamination of finger stick devices
- Infected HCW rarely source
  - Usually due to self-injection of patients’ narcotics

Williams IT, Clin Infect Dis 2004;38:1592-1598
Health-Care Related HCV Transmission

- Blood transfusion from unscreened donors
  - including plasma-derived products not inactivated
- Unsafe injection practices
  - inadequate sterilization of reuseable needles and syringes
  - sharing of disposable needles and syringes
- Contaminated equipment
  - inadequate cleaning and disinfection
    - health care settings
    - alternative medicine practices, rituals
Global Burden of Disease Associated with Unsafe Injections

- Estimated annual incidence, 2000
  - > 20 million HBV infections
    - 30% of new infections
  - > 2 million HCV infections
    - 40% of new infections
  - > 250,000 HIV infections
    - 5% of new infections

## Unsafe Injection Practices

<table>
<thead>
<tr>
<th>Developing Countries</th>
<th>Developed Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate supplies of sterile syringes</td>
<td>Failure to use aseptic techniques</td>
</tr>
<tr>
<td>Inadequate sterilization of reusable syringes and needles</td>
<td>■ Reuse of same syringe and needle to administer meds to multiple patients</td>
</tr>
<tr>
<td>Administration at home by non-professionals</td>
<td>■ Medication preparation and blood sample handling in same area</td>
</tr>
<tr>
<td>Syringes shared with others (family, neighbors)</td>
<td>■ Contamination of multiple dose medication vials</td>
</tr>
<tr>
<td>Overuse of therapeutic injections</td>
<td>■ Infected HCW rarely source</td>
</tr>
<tr>
<td></td>
<td>■ Usually due to self-injection of patients’ narcotics</td>
</tr>
</tbody>
</table>
Children Handling Medical Waste, Bangladesh
Hepatitis Delta Virus

- Referred to as “defective” virus
  - HDV RNA
  - surrounded by coat of HBsAg
- HDV dependent on presence of HBV to establish infection
  - requires a protein coat of HBsAg to be released from infected hepatocytes
  - HBsAg mfg by HBV
Infection with HDV

**HBV-HDV Coinfection**
- Simultaneous infection with HBV and HDV in a person susceptible to HBV
- Low risk of death from chronic liver disease

**HBV-HDV Superinfection**
- Infection with HDV in a person with chronic HBV
- High risk of severe chronic liver disease and death

Persons immune from HBV infection – either through vaccination or resolved infection – cannot become infected with HDV
Epidemiologic Features of HDV

- Transmission similar to HBV
  - Percutaneous – highly efficient
  - Sexual
  - Perinatal

- Uncommon in U.S. - seen mainly in IDU’s

- Worldwide, endemic in Amazon, Mediterranean, Central Asia, Africa
Prevention of HDV

**HBV-HDV coinfection**
- Hepatitis B vaccination

**HBV-HDV superinfection**
- Prevent exposure to HBV
  - screen blood for HBV (need HBV for HDV)
- Reduce high-risk behaviors
  - safer sex practices
  - safer injection practices
Current and Future Issues

- Identification of infected persons
  - Screening and testing not routinely performed
  - Lack effective methods for reaching those whose risk was in the remote past
    - Risk factor ascertainment in routine healthcare visits is rare
- Therapy regimens less than ideal, especially those with genotype 1
  - In US, treatment offered to low % of HCV-positives
- Implications of multiple co-factors on liver disease progression and response to therapies not well understood
  - Impact likely to grow creating an even greater challenge
- Need to be alert to changes in epidemiology
Viral Hepatitis - Overview

- Primary infection of the liver caused by at least five unrelated viruses: A, B, C, D, E
- HAV and HEV
  - Fecal-oral route
  - Acute self-limited disease; no chronic infection
- HBV, HCV, HDV
  - Percutaneous or mucosal exposures to blood
  - Chronic infection – major causes of cirrhosis and hepatocellular carcinoma worldwide
Acknowledgment

- Most slides provided by Miriam J. Alter, Ph.D. University of Texas, Galveston
Geographic Differences in HCV Transmission Patterns

<table>
<thead>
<tr>
<th>Exposures among prevalent infections</th>
<th>Contribution of exposures to disease burden by HCV prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>++++</td>
</tr>
<tr>
<td>Transfusions (before testing)</td>
<td>+++</td>
</tr>
<tr>
<td>Unsafe therapeutic injections</td>
<td>+</td>
</tr>
<tr>
<td>Occupational</td>
<td>+</td>
</tr>
<tr>
<td>Perinatal</td>
<td>+</td>
</tr>
<tr>
<td>High-risk sex</td>
<td>++</td>
</tr>
</tbody>
</table>