Infectious Disease Epidemiology BMTRY 713 (A. Selassie, DrPH)

April 13, 2017
Lecture 23
Viral Hepatitis

Learning Objectives
1. Describe the epidemiology of viral hepatitis
2. Identify the biologic characteristics of the various viruses implicated as the causes of hepatitis
3. Explain the current control strategies

Viral Hepatitis

Inflammation of the liver
- Three Stages: Acute, Chronic, Advanced Pathology

- Chronic infection with hepatitis B and C virus is the most common risk factor for hepatocellular carcinoma (HCC); obesity and excessive alcohol consumption are also among the leading causes of HCC. © Prof Dr. Robert Thimme, Freiburg University Medical Center
Viral Hepatitis

- Five hepatic viruses, specifically hepatotropic

<table>
<thead>
<tr>
<th>Virus</th>
<th>Acronym</th>
<th>Transmission Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A*</td>
<td>HAV</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Hepatitis B**</td>
<td>HBV</td>
<td>Parenteral, (sex, perinatal)</td>
</tr>
<tr>
<td>Hepatitis C**</td>
<td>HCV</td>
<td>Parenteral, (sex, perinatal)</td>
</tr>
<tr>
<td>Hepatitis D**</td>
<td>HDV</td>
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<tr>
<td>Hepatitis E*</td>
<td>HEV</td>
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</table>

Risk of chronic illness: * mainly acute; ** High chronicity

Other Viruses Affecting the Liver

- Non-hepatotropic viruses that may affect the liver include the following

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<tr>
<td>Cytomegalovirus</td>
<td>HCMV</td>
<td>Contact w. body fluids</td>
</tr>
<tr>
<td>Epstein-Barr Virus</td>
<td>EBV</td>
<td>Contact w. saliva</td>
</tr>
<tr>
<td>Yellow Fever Virus</td>
<td>As is</td>
<td>Mosquito(s)</td>
</tr>
<tr>
<td>Ebola Virus</td>
<td>As is</td>
<td>Blood, body secretions</td>
</tr>
<tr>
<td>Lassa Fever Virus</td>
<td>As is</td>
<td>Mastomy's rodent excreta</td>
</tr>
</tbody>
</table>
Incubation vs. Latency vs. Prodrome

- **Incubation period** is the time elapsing from exposure to the infectious agent until the onset of infection in the host manifested by detectable evidence of the microbial agent. This period covers the time before the symptoms of infection appear.

- **Latency** is the lag time between exposure to a disease-causing agent and the potential for infectiousness begins due to replication of the agent and when early symptoms and signs of the disease begins (Koplik’s spot in measles).

- **Prodrome** refers to the time in which a set of symptoms and signs specific to the agent that indicate the start of fully blown disease begins.

**Hepatitis A Virus (HAV)**

- RNA virus
- Transmitted by fecal-oral contact
- Incubation period = 2-4 weeks
- Stable in the environment
  - Remains infectious for 2-4 weeks at room temperature
  - Relatively resistant to free chlorine
- Single serotype, infection confers life-long immunity
- Only humans and non-human primates infected
HAV Clinical Features

- Prodromal constitutional symptoms; anorexia, nausea, abdominal discomfort, diarrhea, fever, jaundice
- No chronicity; yet 2-27% develop fulminant hepatitis in developed countries; 10-15% develop relapse within a few weeks of recovery
- Severity of illness directly correlated with age
  - Many children asymptomatic or mild disease
  - Older adults and seniors severe illness
- Dx confirmed by presence of IgM antibodies

HAV Transmission Routes

- Fecal-oral
  - Contaminated food and water
  - Person-to-person
- Household or sexual contact is most commonly reported transmission route (22%)
- Rare via blood transmission
- Common source outbreaks (8%)
  - Food infected by food handlers; raw vegetables
  - Seafood (shellfish, clams, oysters, mussels harvested from sewage-contaminated body of water)
- Day-care centers (15%)
- International travel

HAV Epidemiology

- Based on seroprevalence, three levels of endemicity: High, Intermediate, Low
- High endemicity
  - 90% seroprevalence among adults, most children infected by age 10
  - Individuals of higher SES may not be infected until adolescence or adulthood
  - Africa, Asia, Central and South America, Middle East
HAV Epidemiology (2)
- Intermediate endemicity
  - 80% seroprevalence in adults
  - 20%-30% in children under 10
  - Major increase between ages 10 & 20
  - Italy, Greece, Thailand, Taiwan, Korea
  - Cohort effect, delayed infection increases morbidity

HAV Epidemiology (3)
- Low endemicity
  - Less than 10% in children under 10
  - 30%-50% seroprevalence in adults
  - Low SES is associated with higher rates of infection
  - Europe, US, Japan
HAV Epidemiology (4)

- Generic profile of endemicity
  - High endemicity countries
    • Most cases occur in children
    • HAV is rarely the cause of hepatitis in adults
  - Low endemicity countries
    • Rare in children
    • HAV accounts for 50%-80% of adult hepatitis

HAV Epidemiology (5)

- HAV in US
  - Geographic variation
    • High—Among American-Indian population
    • Intermediate—US/Mexico border
    • Low—General US population
  - Cyclical incidence with 7-10 year peaks
  - Incidence rate highest under age 40

HAV Prevention

- Improved sanitation
- Passive-active immunization
  - Human immunoglobulin (IG) post exposure
  - Effectiveness: 100% if given before; 75-80% if given within 2 wks of exposure
- Active immunization
  - Two types of inactivated HAV Vaccines
  - Both are highly effective
  - Recommended for high risk population
Prevalence of HAV infection in the US, 1999

Hepatitis B Virus (HBV)
- Double-stranded DNA virus
- Similar clinical features to HAV
- Individuals more likely to develop serum sickness
- Like HAV, severity of symptoms is directly correlated with age—the older, the worse is the symptom
- Chronicity is inversely related with age
  - Infants 80%, adults 1%-5% to develop chronic hepatitis

HBV and Primary Liver Cancer
- Studies on HBV oncogenic potential
  - Ecologic studies
    - Increased rates of primary hepatic cancer (PHC) with high HBV rates
    - 80% of the global occurrence of PHC is among persons with chronic HBV (WHO)
    - Reduction in liver cancer following immunization
  - Cohort study, 1976-85, Taiwan
    - HBV infection and subsequent liver cancer
      - HBsAg carriers at baseline, RR=104 to noncarriers
      - Synergistic carcinogenic potential w. Aflatoxin, a common contaminant of cereal and oils seeds
  - Analogy
    - Carcinogenesis of other hepadnaviruses
      - Ducks infected with hepadnavirus develop liver ca.
Diffuse Inflammation of the liver due to HBV

Normal liver biopsy

HBV Diagnosis

- HBsAg (surface antigen) – a glycoprotein coat of HBV circulating independent of the virus
  - Indicates active HBV infection
- Anti-HBcAg (core antibody) – Determines recency
  - Indicates past infection; HBcAg doesn’t circulate
- HBeAg – Conformational portion of core antigen
  - Assesses the potential infectivity of carriers
- Anti-HBsAg (surface antibody)
  - Recovery from acute or post immunization and detect the level of protective antibodies post vaccination

Hepatic Tumor Marker Tests

- Alpha-fetoprotein (AFP) in blood
  - AFP is found mainly in liver cancer and some germ cell tumors, which are rare
  - Specificity is increased with positive result on liver cancer linked infections HBV/HCV
  - False positive results may occur in pregnancy
- Human Chorioinic Gonadotropin (hCG)
  - Hormone produced in human placenta that maintains the corpus luteum in pregnancy
  - Increased in cancer of the testicles
HBV Transmission

- Percutaneous blood exposure
  - Decreased in blood transfusion
  - Sharing IV needles
  - Acupuncture, tattoos, body piercing
- Sexual intercourse
  - Commercial sex workers, multiple partners
- Maternal-child transmission
  - Perinatal period (90% likely infant infected)
  - Prevented by administration of HBV vaccine
- Household contact
  - Sharing razors, toothbrushes
HBV Epidemiology

- Areas of high endemicity
  - 8% or more chronic carriers
  - High rates of liver cancer
  - Account for 45% of the global population
    - China, Southeast Asia, sub-Saharan Africa, several areas in Arctic, including Alaska, Canada, Greenland

HBV Epidemiology (2)

- Areas of intermediate endemicity
  - Prevalence of carriers ranges from 2%-8%
  - 20%-60% past infection
  - Eastern Europe, Russia, parts of South America, India, North Africa
  - Account for 43% of world’s population

HBV Epidemiology (3)

- Areas of low endemicity
  - <2% chronic carriers
  - Prevalence 5%-20%
  - Account for 12% of population
  - Developed countries of North America, Western Europe, Australia, some parts of South America
HBV Risk Factors

- 41% Heterosexual contact
- 15% Injection drug use
- 9% Homosexual contact
- 2% Household contact
- 1% Health care employment
- 1% Other
- 31% Unknown
- Changing epidemiology to more IVDU
**HBV Prevention**
- Vaccination (HBV Vaccine)
  - Initial targeted strategy, largely ineffective
  - Universal immunization of children
- Post exposure vaccination
  - Used in conjunction with primary immunization for children born to infected moms
  - *Hepatitis B immunoglobulin* used as a post exposure prophylaxis and also as immunization
- Screening of HBV positives for AFP (alpha feto protein)—a tumor marker for liver cancer

**HBV Treatment**
- Goal is to prevent/delay progression
- Interferon alpha-2b and alpha-2a
  - Administered for 4 or more months
  - Effective in 25%-40% of carriers
  - 50% of those rebound
- Other drugs—adefovir, entecavir, lamivudine
- Currently developing other drugs

**HBV-HIV Coinfection**
- Due to similar modes of transmission, coinfection is very common
- Common in sub-Saharan Africa & Asia
- In the US, chronic HBV infection occur 10-fold more frequently among HIV+
- Indolent HBV infection reactivates after HIV infection
- HBV infection aggravates hepatoxicity of antiretroviral therapy and ↑ drug resistance
Hepatitis C Virus (HCV)

- Formerly known as Non-A Non-B
- Single-stranded RNA virus
- ~1x10⁴ die each yr. in the US
- Mostly asymptomatic acute phase
  - Less than 20% show jaundice or sufficient symptoms to seek medical care
  - 85% persistent viremia persisting 10-50 yrs
- Often chronic infections
- 2-25% develop liver cirrhosis and/or PHC
- Diagnosis
  - HCV antibody using an ELISA test

HCV Clinical Features

- Acute is generally asymptomatic
- <1/5 are jaundiced
- 85% have persistent viremia
- 2%-25% develop life-threatening cirrhosis or liver cancer
- Age-adjusted PHC rate in VA discharges show 3-fold increase associated with HCV infection

Pathological Changes in Liver

Affliction of Liver with HCV Localized Necrosis

Normal liver biopsy
HCV Transmission
- Transfusion
  - Prior to screening, cause of 17% of HCV infections
- Sharing IVDU needles (38%)
- Needle stick injuries 3%-8% exposed to HCV patients
- Tattooing, bites, scarification rituals
- Sexual transmission
- Perinatal transmission 2%-8%
  - Doesn’t appear increased with breastfeeding

HCV Epidemiology
- 170 million individuals infected
- Several highly endemic areas
  - Prevalent among >40, uncommon <20
  - Egypt, 10-30%, possibly due to a parenteral schistosomiasis campaign
  - Several areas in Italy and Japan
  - Baltimore MD: 18% ER, 15% STD clinic
HCV Prevention
- Prevent exposure
- No vaccines or effective post-exposure prophylaxis available
  - Post exposure administration of immunoglobulin to prevent HCV infection is of doubtful effectiveness
- Screening of blood for HCV is effective
- Use of needle exchange programs has been found to be effective

HCV Treatment
- Recent development
- Treatment effectiveness depends on:
  - How damaged the liver is.
  - Other health conditions the patients have.
  - How much hepatitis C virus in the body.
  - The genotype of hepatitis C
- Treatment more effective closer to the infection but most people don't know they have hepatitis C infection

Hepatitis D Virus (HDV)
- Also known as Delta Hepatitis
- Defective single stranded RNA virus lacking a surface antigen;
- Often occurs as a co-infection with HBV
- Similar clinical features
  - More severe infection with HBV co-infection
  - High case-fatality rate among pregnant women
Epidemiology of HDV
- Transmission via blood exposure, sex, IVDU
- Highest prevalence in Columbia, Venezuela, Amazon basin, Africa, Romania, S. Italy
- Higher among drug using populations than non-users
- HBV immunization will prevent HDV
- Fulminant type rare, but 10x common with HBV

HDV Clinical Features
- Similar clinical features as other forms of hepatitis
- Requires a helper function HBV to replicate
- Can cause infection only in the presence of HBV infection
- Co-infection increases risk of severe chronic liver disease, carcinoma, and transmissibility
- Transmission is high with IVDU; Low with perinatal and sexual activities

Hepatitis E Virus (HEV)
- RNA virus
- Self-limiting disease
- No chronic or carrier state
- Can result in fulminant hepatitis, esp. in pregnant women with 20% case fatality rate
HEV Transmission
- Fecal-oral
  - Especially related to contaminated water
- Epidemics in Asian countries during monsoon season
- Less infectious than HAV

HEV epidemiology
- Rare in developed countries
- Endemic in developing countries accounting to 50% of acute Hepatitis
- Increased transmission at age 30
- Prevention
  - Improved sanitation
  - No current vaccines