Hepatitis A Virus Infections

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Objectives

• Discuss the pathogenesis and epidemiology of hepatitis A virus (HAV) infections
• Discuss clinical features of HAV infections
• Discuss the risk factors for HAV infections
• Discuss methods to prevent HAV infections
• Epidemic jaundice described by Hippocrates, as early as 400 BC
• Further outbreaks of jaundice in 17th and 18th Century Europe, associated with conflicts
• Earliest recorded US outbreak, Norfolk, VA 1812
• HAV likely was one of the causes of “camp jaundice” or “field jaundice” in wartimes
• Krugman differentiated “infectious” hepatitis from “serum” hepatitis in 1967
• Serologic tests developed in 1970s
• Vaccines licensed in 1995 and 1996
Viral Hepatitis – Historical Epi Perspective

“Infectious”
(fecal-oral) → A

Viral
hepatitis

“Serum” → B & D

“NANB”

C

Parenterally
transmitted

E

Enterically
transmitted

Other (non-ABCDE)
Hepatitis A Virus (HAV)

- Picornavirus (RNA), 27-32 nm in diameter
- Spherical with icosahedral symmetry
- 1 serotype and 6 genotypes. Genotypes I, II, and III, with subtypes A & B infect humans. Genotype IIIA may cause more severe disease.
- **Humans and non-human primates are natural hosts**
- Stable at low pH (pH 1 for 2 hours)
- Inactivated by high temperature (≥185°F), formalin, chlorine, autoclaving (250°F – 30 min)
- **Complete inactivation in food, e.g., shellfish, requires heating to ≥185°F for at least one minute**
- May survive days to weeks in shellfish, soil, water, or marine sediment
Hepatitis A Virus

Electron micrograph of Hepatitis A virus
Hepatitis A Pathogenesis

- Entry into the mouth (fecal-oral transmission is the most common mode of HAV transmission)
- Acid resistant virus, passes through stomach to intestines
- Transport to liver, major site of viral replication
- Virus present in liver, bile, blood, and feces 10-12 days after infection
- Virus excretion may continue for up to 3 weeks after onset of symptoms. Virus excretion can extend up to six months in infected neonates.
- Period of infectivity, e.g., one week after jaundice appears, is shorter than duration of HAV RNA in stool
Concentration of Hepatitis A Virus in Various Body Fluids

- Feces
- Serum
- Saliva
- Urine

Infectious Doses per mL

Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890

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Acute Hepatitis A - Clinical Features

• Incubation period averages 28 - 30 days (range 15 - 50 days)
• Illness not specific for hepatitis A
• Hepatitis A virus excreted in feces for 1-2 weeks before onset and for at least one week after onset
• Likelihood of symptomatic illness and hospitalization directly related to age
  – Children generally asymptomatic, adults symptomatic
• **No chronic infection from HAV**
  – Protective antibodies develop in response to acute hepatitis A infection and confer lifelong immunity
Events In Hepatitis A Virus Infection

Week

Clinical illness

Infection

Viremia

HAV in stool

ALT

IgM

IgG

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Acute Hepatitis – Clinical Symptoms

- Asymptomatic infections > Symptomatic diseases > Fulminant Liver Failure > Death
- Symptoms (if present) are similar, regardless of cause (e.g., A, B, C, other viruses, toxins)
  - Fever
  - Nausea, vomiting
  - Loss of appetite
  - Abdominal pain
  - Dark urine
  - Jaundice (yellowing of eyes, skin)
  - Light (clay) colored stools
  - Diarrhea (more common in children with hepatitis A)
Jaundice
## Acute Hepatitis A

### Symptoms
- Jaundice: 84%
- Weight loss: 82%
- Malaise: 80%
- Fever: 76%
- Nausea: 69%
- Vomiting: 47%
- Abd pain: 37%
- Arthralgias: 6%

### Clinical Findings
- Hepatomegaly: 87%
- Splenomegaly: 9%
- Skin rashes: 3%
- Mild edema: 2%
- Petechiae: 2%
- Cardiac arrhythmias: <1%

1988 Shanghai epidemic, 8647 hospitalized patients
Acute Hepatitis A

- **Symptoms**
  - Dark urine: 68-94%
  - Anorexia: 71-85%
  - Malaise: 76-80%
  - N / V: 67-79%
  - Headache: 19-73%
  - Pale stool: 52-58%
  - Fever: 18-58%
  - Abd pain: 26-54%
  - Arthralgias: 6-19%

- **Signs**
  - Jaundice: 40-80%
  - Hepatomegaly: 14-78%
  - Hep. tenderness: 39-46%
  - Bradycardia: 17%
  - Skin rash: 14%
  - Splenomegaly: 3-13%
  - Lymphadenopathy: 4%

Epidemic and sporadic cases of acute hepatitis A

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Acute Hepatitis A - Serology

- Detection of specific IgM anti-HAV in single acute phase serum specimen
- IgM anti-HAV remains positive for most patients for 6 to 12 months
- IgM anti-HAV remains positive for up to 12 months in up to 25% of patients and can last 2 years or longer
- IgM anti-HAV has been detected 2--3 weeks after administration of one dose of HepA vaccine in 8%--20% of adults
- Total anti-HAV antibody (IgM plus IgG) results are not clinically helpful unless reflex testing for IgM anti-HAV occurs
Hepatitis A Virus Transmission

- **Fecal-oral**
- **Close personal contact**
  (e.g., household contact, sexual contact, child day care centers)
- **Contaminated food, water**
  (e.g., infected food handlers, raw or undercooked mollusks harvested from contaminated water, contaminated produce [e.g. lettuce, strawberries, green onions or pomegranate seeds])
- **Blood exposure (rare)**
  (e.g., injecting drug use, rarely by transfusion and clotting factor concentrates)
Risk Factors Associated with Reported Hepatitis A, United States 1990 - 2000

- Unknown: 46%
- Sexual or Household Contact: 14%
- International travel: 5%
- Men who have sex with men: 10%
- Injection drug use: 6%
- Child/employee in day-care: 2%
- Food- or waterborne outbreak: 4%
- Contact of day-care child/employee: 6%
- Other Contact: 8%

Source: CDC (NNDSS/ VHSP)
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Risk Factors Associated with Reported Hepatitis A, United States 2007

- Unknown: 68%
- International travel: 18%
- Men who have sex with men: 6%
- Injection drug use: 1%
- Other contact: 9%
- Contact of day-care child/employee: 5%
- Food- or waterborne outbreak: 6%
- Child/employee in day-care: 4%

Percentages based on total number of cases for which information about that risk factor was reported – may not total 100%

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Countries outside the US other than Canada, Australia, New Zealand, Japan, and Western Europe should be considered to have high or intermediate endemicity for hepatitis A virus.
Map of Acute HAV Cases – United States

1987 - 1997

Average reported cases of Hepatitis A per 100,000 population
http://www.cdc.gov/hepatitis/HAV/Historical-USMap.htm

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2006

Reported cases of Hepatitis A per 100,000 population
Rates in the West about the same as other US regions
http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5702a1.htm
Hepatitis A - United States, 1966 - 2005*

*2005 provisional total
2007 – 2,791 cases reported
2010 – 1,670 cases reported

ACIP – Routine childhood schedule
* 1999 Vaccine – 11 High risk states
+ 2006 Vaccine – ACIP schedule

Cabinet for Health and Family Services
Hepatitis A Incidence by Gender,
United States, 1990 - 2001

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Hepatitis A Rates, by Race / Ethnicity; 1994

- **Native American/Alaska Native**: 121.2
- **Hispanic**: 20.7
- **non-Hispanic White**: 6.4
- **non-Hispanic Black**: 5.5
- **Asian**: 4.6
- **Total**: 10.3

Race/ethnicity categories and corresponding rates per 100,000.
Hepatitis A Rates, United States, by Race / Ethnicity; 1990 - 2007

Per 100,000 population
Prevention of Hepatitis A Infections

- Improved personal hygiene, particularly handwashing
- Provision of safe drinking water
- Proper sanitary waste disposal
- Preexposure immunization
- Postexposure immunization and/or administration of immune globulin

Hepatitis A chapter in Feigin and Cherry’s Textbook of Pediatric Infectious Diseases, 7th Ed, 2014
Hepatitis A Vaccines

Single-antigen Vaccines

- Inactivated whole virus
- HAVRIX (GlaxoSmithKline)
- VAQTA (Merck)
- Pediatric and adult formulations
- Licensed for persons aged 12 months and older
Hepatitis A Vaccine Immunogenicity

Single-antigen Vaccines

**Adults**
- >95% seropositive after one dose
- 100% seropositive after two doses

**Children (≥12 months) and Adolescents**
- >97% seropositive after one dose
- 100% seropositive after 2 doses
Hepatitis A Vaccines

Schedule for Single-antigen Vaccines

**Adults**
- 1 dose
- Booster dose 6-18 months after first dose

**Children and Adolescents**
- 1 dose
- Booster dose 6-18 months after first dose
### Recommended Dosages of Single-antigen Hepatitis A Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (yrs)</th>
<th>Dose (mL)</th>
<th>Volume (mL)</th>
<th>2-Dose Schedule (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX ® #</td>
<td>1-18</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>1-18</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, 6-18</td>
</tr>
</tbody>
</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, ** Units
# has 2-phenoxyethanol as a preservative, ## has no preservative
Hepatitis A Vaccination of Children

• All children should receive hepatitis A vaccine at age one year (i.e., 12 through 23 months of age)
• Vaccination should be integrated into the routine childhood vaccination schedule
• Children who are not vaccinated by 2 years of age can be vaccinated at subsequent visits
Hepatitis A Vaccine Recommendations for Pre-exposure Protection for High Risk Groups

- International travelers
- Close contact with international adoptee from a country with high or intermediate endemicity
- Men who have sex with men
- Persons who use illegal drugs
- Persons who have a clotting-factor disorder
- Persons with occupational risk
  - Persons who work with HAV-infected primates or with HAV in laboratory research
- Persons with chronic liver disease
Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP)

• Susceptive persons traveling to or working in in high- or intermediate-risk countries (e.g. Mexico & South America)

• Give single-antigen hepatitis A vaccine or IG before departure. Single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG.
  – Healthy persons (aged 40 and younger) – one dose of single-antigen hepatitis A vaccine given at any time before departure should be protective
  – Older adults, immunocompromised persons, persons with chronic liver disease or other chronic medical conditions planning to depart to an at-risk area in less than two weeks: give first dose of single antigen hepatitis A vaccine AND give IG (0.02 mL/kg) at a separate site
Hepatitis A Prevention

Recommendations for Pre-exposure Protection for International Travelers (2007 ACIP) (continued)

– Travelers who refuse vaccine, are aged less than 12 months, or who have vaccine contraindications – give a single dose of IG (0.02 mL/kg) for up to 3 months of protection against hepatitis A infection

– For such travelers whose travel period is expected to be longer than two months, give IG (0.06 mL/kg); repeat the IG administration if the travel period is longer than five months.

• Completion of the hepatitis A vaccine series is necessary for long-term protection
Recommendations for Selected Occupational Groups

- Healthcare workers: not routinely recommended
- Child care centers: not routinely recommended
- Sewer workers or plumbers: not routinely recommended
- Food handlers: may be considered based on local circumstances
Duration of Protection

After Hepatitis A Vaccination

• Persistence of antibody
  – At least 5-8 years among adults and children

• Efficacy
  – No cases in vaccinated children at 5-6 years of follow-up

• Mathematical models of antibody decline suggest protective antibody levels persist for at least 20 years

• Other mechanisms, such as cellular memory, may contribute
Pre-Vaccination Testing

- Considerations for cost vs. benefit:
  - cost of vaccine
  - cost of serologic testing (including visit)
  - prevalence of hepatitis A infection
  - impact on compliance with vaccination

- Likely to be cost-effective for:
  - persons born in high endemic areas
  - Older U.S. born adults
  - Older adolescents and young adults in certain groups (e.g., Native Americans, Alaska Natives, Hispanics, IDUs)
POST-VACCINATION TESTING

Not Recommended for Single-antigen Hepatitis A Vaccines

- High response rate among vaccinees
- Commercially available assay not sensitive enough to detect lower (protective) levels of vaccine-induced antibody
Hepatitis A Vaccines

Combination Vaccines

- TWINRIX® (GlaxoSmithKline)
- Combination of inactivated whole HAV (pediatric HAVRIX®, 720 EL.U.) and hepatitis B surface antigen (adult ENGERIX-B®, 20 mcg HBsAg)
- Licensed for persons 18 years of age and older
- Licensed by FDA in 2001 for 3-dose schedule
- FDA approved 4-dose accelerated dosing schedule in 2007
- Indicated for persons at risk for exposure to both HAV and hepatitis B viruses (see PHPR Immunization chapter)
- **Should not be used in PEP for close contacts to acute hepatitis A infection**
### Recommended Dosages of Hepatitis A / Hepatitis B Combination Vaccine

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (yrs)</th>
<th>Dose</th>
<th>Volume (mL)</th>
<th>3-Dose Schedule (mos)</th>
<th>4-Dose Schedule (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWINRIX® #</td>
<td>18</td>
<td>720 (EL.U.*) and 20 mcg HBsAg</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>and 20 mcg HBsAg</td>
<td></td>
<td>1.0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Booster, 4-dose schedule (only)</td>
<td>1.0</td>
<td>12 Months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, HAV

# has no preservatives
Hepatitis A - Postexposure Prophylaxis (PEP)

- Persons exposed to HAV who have no prior history of hepatitis A vaccination: Give single dose of single-antigen hepatitis A vaccine or immune globulin (IG, 0.02-mL/kg IM) as soon as possible (2007 ACIP recommendation)
  - Healthy persons aged 12 months through 40 years, single-antigen hepatitis A vaccine, at the age appropriate dose, is preferred over IG
  - Children younger than 12 months – give IG
  - Adults older than 40 years, preferable give IG. Use single-antigen hepatitis A vaccine if IG is unavailable.
  - Immunocompromised persons, persons with chronic liver disease diagnosed, or persons for whom vaccine is contraindicated – give IG
- Persons given IG for whom vaccine is also recommended can be given a dose of vaccine simultaneously with IG
- Persons given vaccine should complete the series
Acute Hepatitis A – Surveillance Case Definition

– 2012, Clinical criteria of an acute illness with:
  • Discrete onset of any sign and symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, fatigue, anorexia, nausea, vomiting, diarrhea, and abdominal pain), \textbf{AND}
  • Either jaundice or elevated serum aminotransferase levels

– \textbf{Laboratory criteria}
  • IgM antibody to hepatitis A virus (IgM anti-HAV) positive

– \textbf{Case Classification} - Confirmed
  • \textit{A case that meets the clinical case definition and is laboratory confirmed, OR}
  • A case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A (i.e., household or sexual contact with an infected person during the 15-50 days before the onset of symptoms).
Investigation of a case

- **Public health – urgent event**, team response
  - CONFIRM DIAGNOSIS IN INDEX CASE
  - Identify close contacts (e.g. household, sexual)
    - Limited timeline (i.e. 14 days of last exposure) to provide postexposure prophylaxis (PEP)
    - Secondary attack rates in households – 15% to 30%
    - No evidence on efficacy of PEP when given two weeks for more after last HAV exposure
    - Maintain surveillance for 50 days after last exposure
  - Infection control
    - Handwashing
    - Contact precautions for first two weeks of illness, but no more than one week after onset of jaundice
Investigation – Special circumstances

- Food handler with acute hepatitis A infection
  - Environmental inspection of establishment
  - Environmental cleaning – 1:100 dilution chlorine bleach for surfaces
  - PEP (i.e. single-antigen hepatitis A vaccine or IG) should be given to other food handlers in same establishment
- Higher risk of HAV exposure to patrons in infectious period if:
  - Food handler had diarrhea
  - Food handler had deficiencies in personal hygiene
  - Food handler prepared foods not heated
  - Food handler directly handled cooked foods
- Any response with single-antigen hepatitis A vaccine or IG has to be completed within 2 weeks of last exposure
- Maintain surveillance for 50 days after last exposure
Investigation – Special circumstances

• Day care centers; child care centers – Acute hepatitis A infections
  – PEP (i.e. Hepatitis A vaccine or IG) is indicated for ALL PREVIOUSLY UNVACCINATED adult staff and attendees when:
    • One or more cases of hepatitis A are recognized in children or adult staff
    • Two or more households of attendees have cases
    • Only treat classroom contacts of index case in centers that have no children in diapers
  – Outbreak (three or more families have hepatitis A cases), treat members of households with attendees in diapers
Questions