**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

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**Hepatitis A – History Tidbits**

- 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

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Viral Hepatitis – Historical Epi Perspective

Before 1960s

“ Infectious” (fecal-oral) A
Viral hepatitis
“Serum” B
“NANB” C
Parenterally transmitted
Enterically transmitted

Other (non-ABCDE) D

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

![Concentration of Hepatitis A Virus in Various Body Fluids](image_url)

- Feces
- Serum
- Saliva
- Urine

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
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

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### 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

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Fecal-oral – Primary means worldwide

Close personal contact
(e.g., household contact, sexual contact, child day care centers)

Contaminated food or 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

Source: CDC (NNDSS/ VHSP)
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Risk Factors Associated with Reported Hepatitis A

United States 2007

Percentages based on total number of cases for which information about that risk factor was reported – may not total 100%
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**Availability of Risk Exposures / Behaviors Associated with Acute Hepatitis A — United States, 2013**

- 2013 – 1,781 cases
- Risk identified
- No risk identified
- Risk data missing

When risk factors were reported, about 25% of case reports had at least one risk exposure / behavior 2–6 weeks prior to onset of acute, symptomatic hepatitis A. These included: 1) having traveled to hepatitis A-endemic regions of Mexico, South/Central America, Africa, Asia/South Pacific, or the Middle East; 2) having sexual / household or other contact with suspected / confirmed hepatitis A patient; 3) being a child / employee in day care center / nursery / preschool or having contact with such persons; 4) being involved in a foodborne / waterborne outbreak; 5) being a man who has sex with men; and 6) using injection drugs.

* Includes case reports indicating the presence of at least one of the following risks 2–6 weeks prior to onset of acute, symptomatic hepatitis A: 1) having traveled to hepatitis A-endemic regions of Mexico, South/Central America, Africa, Asia/South Pacific, or the Middle East; 2) having sexual / household or other contact with suspected / confirmed hepatitis A patient; 3) being a child / employee in day care center / nursery / preschool or having contact with such persons; 4) being involved in a foodborne / waterborne outbreak; 5) being a man who has sex with men; and 6) using injection drugs.

Source: National Notifiable Diseases Surveillance System (NNDSS)

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**Geographic Distribution of HAV Infection, 2008**

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.

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**Hepatitis A - United States, 1966 - 2005**

- 2005 provisional total
- 2007 – 2,791 cases reported
- 2010 – 1,870 cases reported

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

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Average reported cases of Hepatitis A per 100,000 population
11 western states – 50% of Hepatitis A cases but only 11% of US population
http://www.cdc.gov/hepatitis/HAV/Historical-USMap.htm

Rates in the West were about the same as other US regions
http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5702a1.htm

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

Reported Number of Acute Hepatitis A Cases
United States, 2000–2013
Case counts declined by 86.7% from 2000 to 2013

Worrisome Trend?
2011 – 1,398 cases
2012 – 1,562
2013 – 1,781

Hepatitis A Incidence By Age Group, 1990 - 2004

Why is the incidence lower in this age group?
- <2 yr
- 2 - 18
- 19+ yrs
Hepatitis A Incidence by Age Group, 1990 - 2007

Incidence of Acute Hepatitis A, by Age Group
United States, 2000–2013

Hepatitis A Incidence by Gender,
United States, 1990 - 2001
Hepatitis A Incidence by Gender,
United States, 1990 - 2007

Source: National Notifiable Diseases Surveillance System (NNDSS)

Incidence of Acute Hepatitis A, by Sex
United States, 2000–2013

Hepatitis A Rates,
by Race / Ethnicity, 1994

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Hepatitis A Rates, United States, by Race / Ethnicity; 1990 - 2007

Incidence of Acute Hepatitis A, by Race / Ethnicity
United States, 2000–2013

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 vaccines
- 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

#### 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
### 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>
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</thead>
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<td>HAVRIX®</td>
<td>1-18</td>
<td>720 (EL.U.*)</td>
<td>0.5</td>
<td>0, 6-12</td>
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<td>&gt;18</td>
<td>1,440</td>
<td>1.0</td>
<td>0, 6-12</td>
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<tr>
<td>VAQTA®</td>
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<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

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### ACIP Recommendations for Routine Pre-exposure 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 (For the VFC Program, DPH recommends catch-up vaccinations through age 18 years)

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### 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

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Hepatitis A Prevention

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

- Susceptible persons traveling to or working in high- or intermediate-risk countries (e.g., Mexico or 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

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(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

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Single-antigen Hepatitis A Vaccine

Recommendations for Selected Occupational Groups

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

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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
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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

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HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A / Hepatitis B Combination Vaccine

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age (yrs)</th>
<th>Dose (mL)</th>
<th>3-Dose Schedule (mos)</th>
<th>4-Dose Schedule (days)</th>
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</thead>
<tbody>
<tr>
<td>TWINRIX®</td>
<td>18</td>
<td>720 (EL.U.*) 1.0 0 0</td>
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</tr>
<tr>
<td></td>
<td>and</td>
<td>20 mcg HBsAg 1.0 1 7</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>older</td>
<td>1.0 6 21 to 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booster, 4-dose schedule (only)</td>
<td>1.0 12 Months</td>
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</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units, HAV
* Has no preservatives

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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

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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), AND
  • Either jaundice or elevated serum aminotransferase levels

- Laboratory criteria
  • IgM antibody to hepatitis A virus (IgM anti-HAV) positive

- Case Classification - Confirmed
  • 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 that were 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