Hepatitis A
The Basics
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HEPATITIS A VIRUS

HEPATITIS A - CLINICAL FEATURES

- Jaundice by age group:
  - <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

CONCENTRATION OF HEPATITIS A VIRUS IN VARIOUS BODY FLUIDS

<table>
<thead>
<tr>
<th>Body Fluids</th>
<th>Infectious Doses per mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feces</td>
<td>10^10</td>
</tr>
<tr>
<td>Serum</td>
<td>10^8</td>
</tr>
<tr>
<td>Saliva</td>
<td>10^4</td>
</tr>
<tr>
<td>Urine</td>
<td>10^2</td>
</tr>
</tbody>
</table>

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

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)

PREVENTING HEPATITIS A
- Hygiene  (e.g., hand washing)
- Sanitation  (e.g., clean water sources)
- Hepatitis A vaccine (pre-exposure)
- Immune globulin (pre- and post-exposure)
PREPARATION OF INACTIVATED HEPATITIS A VACCINES

- Cell culture adapted virus grown in human fibroblasts
- Purified product inactivated with formalin
- Adsorbed to aluminum hydroxide adjuvant

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

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</td>
<td>360 E.L.U.</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>


HEPATITIS A VACCINES

Recommended Dosages of Hepatitis A Vaccines

<table>
<thead>
<tr>
<th>Schedule Vaccine</th>
<th>Age  (yrs)</th>
<th>Dose (E.L.U.*)</th>
<th>Volume (mL)</th>
<th>2-Dose (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, 6-18</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

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

USE OF HEPATITIS A VACCINE FOR INFANTS

- Safe and immunogenic for infants without maternal antibody
- Presence of passively-acquired maternal antibody blunts immune response
  - all respond, but with lower final antibody concentrations
- Age by which maternal antibody disappears is unclear
  - still present in some infants at one year
  - probably gone in vast majority by 15 months

COMBINED HEPATITIS A HEPATITIS B VACCINE

- Approved by the FDA in United States for persons ≥18 years old
- Contains 720 EL.U. hepatitis A antigen and 20 µg. HBsAg
- Vaccination schedule: 0,1,6 months
- Immunogenicity similar to single-antigen vaccines given separately
- Can be used in persons ≥ 18 years old who need vaccination against both hepatitis A and B
- Formulation for children available in many other countries
Considerations:
- cost of vaccine
- cost of serologic testing (including visit)
- prevalence of 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)

Not recommended:
- High response rate among vaccinees
- Commercially available assay not sensitive enough to detect lower (protective) levels of vaccine-induced antibody

Pre-exposure testing to intermediate and high HAV-endemic regions
- Routine vaccination of children likely to be most effective

Post-exposure testing (within 14 days)
- Household and other intimate contacts
- Institutions (e.g., day-care centers)
- Common source exposure (e.g., food prepared by infected food handler)

Need comprehensive strategy to reduce overall rates
- Routine vaccination of children likely to be most effective

Need creative approaches
- Formulation not available that would allow integration into infant schedule
INCREMENTAL IMPLEMENTATION OF ROUTINE HEPATITIS A VACCINATION OF CHILDREN

- 1996 - Children living in communities with the highest rates
- 1999- Children living in states/communities with consistently elevated rates during “baseline period”
- All children nationwide

Lack of integrated prevention activities leads to...

- Individuals infected with HIV, hepatitis and other STDs remain undiagnosed, untreated and uninformed
- Infected and uninformed have higher levels of risky behavior and continue to transmit
- Counseling is mistakenly based on limited diagnosis and individuals at risk for HAV and HBV don’t get immunized

HEPATITIS A VACCINATION IN THE UNITED STATES CHALLENGES FOR THE FUTURE

- Continue implementation of the current recommendations for vaccination of children
  - Sustain vaccination in face of falling rates
- Further reduce incidence
  - Vaccination of high-risk adults
  - Vaccination of children nationwide

Hepatitis A Incidence

1987-97 average incidence

2002 incidence

Rate per 100,000

- >= 20
- 10 - 19
- 5 - 9
- 0 - 4
Conclusions

- Prevent by vaccinating
- Exposure- Vaccinate and Immunoglobulin
- No specific therapy once develop disease- supportive treatment.