Optimizing Protection Against Hepatitis A

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OUTLINE

• The virus
• The disease
• Prevention Strategies
  – Improved sanitation
  – Immunization
Hepatitis A Virus

- First described by Hippocrates in 5 B.C.
- 27 outbreaks in 17th-18th century
- Attacked Napoleon’s troops in 1799
- 1908: transmission via contaminated food and water
- 1938: hepatitis A virus isolated for the first time
Hepatitis A Virus

- Naked RNA virus
- Related to enteroviruses, formerly known as enterovirus 72, now put in its own family: heptovirus
- One stable serotype only
- 6 genotypes exist, but in practice most are group 1
- Difficult to grow in cell culture: primary marmoset cell culture and also in vivo in chimpanzees and marmosets
Capsid
VPG
ss RNA (2.5 x 10^6 daltons)

Viral Polypeptides
VP1
VP2
VP3
VP4
Hepatitis A: The Disease

- Incubation period: Average 30 days, Range 15-50 days
- Jaundice by age group:
  - <6 yrs: <10%
  - 6-14 yrs: 40%-50%
  - >14 yrs: 70%-80%
- Complications:
  - Fulminant hepatitis
  - Cholestatic hepatitis
  - Relapsing hepatitis
- Chronic sequelae: None
Hepatitis A Infection
Typical Serological Course

- Fecal HAV
- Symptoms
- ALT
- Total anti-HAV
- IgM anti-HAV

Months after exposure

0 1 2 3 4 5 6 12 24
## Hepatitis A Virus Transmission

<table>
<thead>
<tr>
<th>Close personal contact</th>
<th>household contact, sex contact, child day care centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contaminated food, water</td>
<td>infected food handlers, raw shellfish</td>
</tr>
<tr>
<td>Blood exposure (rare)</td>
<td>injecting drug use, transfusion</td>
</tr>
</tbody>
</table>
## Global Patterns of Hepatitis A Virus Transmission

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Disease Rate</th>
<th>Peak Age of Infection</th>
<th>Transmission Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low to High</td>
<td>Early childhood</td>
<td>Person to person; outbreaks uncommon</td>
</tr>
<tr>
<td>Moderate</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</td>
<td>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>
Laboratory Diagnosis

- Acute infection is diagnosed by the detection of HAV-IgM in serum by EIA.
- Past Infection i.e. immunity is determined by the detection of HAV-IgG by EIA.
- Cell culture – difficult and take up to 4 weeks, not routinely performed
- Direct Detection – EM, RT-PCR of faeces. Can detect illness earlier than serology but rarely performed.
Hepatitis A Vaccination Strategies
Epidemiologic Considerations

- Many cases occur in community-wide outbreaks
  - no risk factor identified for most cases
  - highest attack rates in 5-14 year olds
  - children serve as reservoir of infection
- Persons at increased risk of infection
  - travelers
  - homosexual men
  - injecting drug users
Why is there a need to protect against Hepatitis A?

• Worldwide distribution:
  – Estimated 1.5 Million cases per year

• Subclinical/asymptomatic in children BUT severity increases with age:
  – Relapsing
  – Fulminant
  – CFR > 50 years: 1.8 – 2.0%
  – Overall mortality rate: 0.2 – 0.3%
Aetiology of acute hepatic failure
PGH, 2000-2006
(n=26)

Bravo LC. et al. Presented in WSPID Congress, Argentina 2009
# Laboratory tests for viral hepatitis as measured by ELISA

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HAV</td>
<td>Test done</td>
<td>17</td>
<td>(65.4)</td>
</tr>
<tr>
<td></td>
<td>Positive*</td>
<td>5</td>
<td>(29.4)</td>
</tr>
<tr>
<td></td>
<td>Negative*</td>
<td>12</td>
<td>(70.6)</td>
</tr>
<tr>
<td>HBS antigen</td>
<td>Test done</td>
<td>21</td>
<td>(80.8)</td>
</tr>
<tr>
<td></td>
<td>Positive*</td>
<td>1</td>
<td>(4.8)†</td>
</tr>
<tr>
<td></td>
<td>Negative*</td>
<td>20</td>
<td>(95.2)</td>
</tr>
<tr>
<td>Anti-Hep B core IgM</td>
<td>Test done</td>
<td>4</td>
<td>(15.4)</td>
</tr>
<tr>
<td></td>
<td>Positive*</td>
<td>1</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td>Negative*</td>
<td>3</td>
<td>(75)</td>
</tr>
<tr>
<td>Anti-Hep C virus</td>
<td>Test done</td>
<td>5</td>
<td>(19.2)</td>
</tr>
<tr>
<td></td>
<td>Positive*</td>
<td>1</td>
<td>(20.0)</td>
</tr>
<tr>
<td></td>
<td>Negative*</td>
<td>4</td>
<td>(80.0)</td>
</tr>
</tbody>
</table>

*Note: Percentage of positive and negative subjects was calculated based on the number of subjects for whom the laboratory test was done.
† One subject had positive result in hepatitis B surface antigen and anti hepatitis B core IgM. Both positive results belong to the same subject.

Bravo LC. et al. Presented in WSPID Congress, Argentina 2009
Why is there a need to protect against Hepatitis A?

- Direct and indirect costs of illness: economic burden especially in low-intermediate incidence areas (high symptomatic adults)
  - U.S. 1997: annual medical costs and costs of work-loss > $480 million (63,363 symptomatic cases)
  - Incidence decreasing over the years HOWEVER: in unvaccinated cases clinical characteristics remain the same, i.e. 73% had jaundice, 33% hospitalized, 0.3% died
  - Hospitalization increases with age:
    - 22% in children < 5 years old
    - 52% in > 60 years old
Optimal Protection Needed

• Depends on:
  – Disease burden
    • Level of endemicity
  – Characteristics of host
    • Age
    • High-risk lifestyle
  – Disease exposure
    • None
    • Positive exposure
Strategies for Optimal Protection

Immunization

+ 

Improved hygiene and sanitation
Worldwide distribution of hepatitis A

Endemicity based on Incidence/100,000

WHO/Centers for Disease Control. 2008; Van Damme 2007
Prevalence changes related to improvement in hygiene

Seroprevalence of anti-HAV (%)

van Damme, 1994

Improvement in hygiene

Increase in susceptibles
Epidemiologic Shift

- shift in age of acquiring infection from childhood to older age groups
World Prevalence of Anti-HAV antibodies

J. Infect Dis 1995: vol 171, Suppl 1
Age-related anti-HAV prevalence in Singapore by decade, 1975–95

- Chan (1975)
- Goh (1985)
- Fook (1995)
Age-related anti-HAV prevalence in Thailand

Age-group-specific prevalence of Anti-HAV in Filipinos living in / around Metro Manila, 1993

Results: HAV seropositivity increases with age
- > 2 yo = 6%
- 2 - 15 yo = 28 – 34%
- 16 – 30 yo = 50 – 68%
- 31 – 40 yo = 73%
- 41 – 50 yo = 82%
- 51- 60 yo = 95%
Overall Anti-HAV antibody positivity in Metro Manila, Pampanga and Cebu City was 42.3% - 43.3%; lower than 62% antibody positivity in MM in 1992 in similar socioeconomic group.
Seroepidemiology of Hepatitis A Virus Among Filipino Children and Adults of Middle Income Families 2004-2005

(N. Barzaga)

Conclusion:

– *This changing pattern of HAV infection may reflect improvements in the standard of living and sanitation, a positive impact of hepatitis A vaccination, and support universal vaccination of young children*
Role of Improving Sanitation and Personal Hygiene

- an essential pre-requisite for the success of any HAV vaccination program
- Marked reduction in virus transmission in most developed countries came several decades ago due to improvement in living standards, better sanitation and environmental states in addition to higher income
- Same trend observed in several developing countries with increasing economic prosperity during the 1990s e.g., Singapore, Malaysia, Thailand and other South East Asian countries prior to vaccine era
Impact of Socioeconomic Status on Prevalence: Philippine Experience

- Low vs. mid-upper socioeconomic status:
  - Overall seroprevalence (n=202) = 47%
    - Low income group = 67.6% vs. 26.5% in mid-upper income group

Hepatitis A Prevention - Immune Globulin

- **Pre-exposure**
  - Travelers to intermediate and high HAV-endemic regions

- **Post-exposure (within 14 days)**
  - **Routine**
    - household and other intimate contacts
  - **Selected situations**
    - institutions (e.g., day care centers)
    - common source exposure (e.g., food prepared by infected food handler)
Epidemiology

• one of the most widespread infections transmitted via the fecal-oral route
• majority of subjects infected within 5 years of age, usually asymptomatic thus acquiring life-long immunity
• outbreaks and epidemics rare due to high herd immunity level in the population
Epidemiology

- transmitted both by direct contact with infected subjects and by ingestion of contaminated food and drinks
- large epidemics or more limited outbreaks, frequently starting in schools or day-care centers can occur
- Incidence shows a cyclic pattern, with years of peaks and years of troughs
Epidemiology

• In countries with low HAV endemicity:
  – high hygienic standards substantially limit viral spread
  – outbreaks are rare
  – hepatitis A is typically considered to be a travellers’ infection
  – subjects infected during travels abroad represent a potential source of infection for others once returned at home
Hepatitis A vaccine

• Developed in the late 1980’s
• Most are inactivated with a few live attenuated vaccines (mostly in China)
• Strongly and rapidly immunogenic
• Since mid 1990’s: shift from 3 doses to two doses 6-18 months apart
• Minimal level of anti-HAV able to confer protection after vaccination has not been definitely established:
  – Seroconversion: usually defined as the attainment of an antibody titer between 10 and 20 mIU/mL of anti-HAV
• For HAV protection:
  – Both cellular and humoral immunity
  – production of anti-HAV following active immunization:
    • directly related to availability of neutralizing antibodies
    • more importantly an indirect indication that immune memory has been established
  – Consensus Statement (Lancet 2003;362:165-71):
    • vaccine elicit immune memory that persists even after loss of detectable antibodies
    • rely more on immunologic memory rather than booster doses to protect vs. symptomatic disease
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recipient’s Age</th>
<th>Antigen content (strain)</th>
<th>Volume (ml)</th>
<th>Doses (#)</th>
<th>Schedule (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avaxim Pedia</td>
<td>12 mos. – 15 yrs. Inclusive</td>
<td>80 Ag units (GBM)</td>
<td>0.5</td>
<td>2</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Avaxim</td>
<td>&gt;15 yrs.</td>
<td>160 Ag units (GBM)</td>
<td>0.5</td>
<td>2</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Epaxal</td>
<td>≥ 12 yrs.</td>
<td>24 IU (RG-SB)</td>
<td>0.5</td>
<td>2</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Havrix 720 Junior</td>
<td>12 mos. – 18 yrs. Inclusive</td>
<td>720 ELISA units (HM175)</td>
<td>0.5</td>
<td>2</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Havrix 1440 Adult</td>
<td>&gt; 18 yrs.</td>
<td>1440 ELISA units (HM175)</td>
<td>1.0</td>
<td>2</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>Vaqta Pedia/Adol form</td>
<td>12 mos. – 18 yrs. Inclusive</td>
<td>25 units (CR 326F)</td>
<td>0.5</td>
<td>2</td>
<td>0, 6-18</td>
</tr>
<tr>
<td>Vaqta Adult</td>
<td>≥ 19 yrs.</td>
<td>50 units (CR 326F)</td>
<td>1.0</td>
<td>2</td>
<td>0, 6-18</td>
</tr>
</tbody>
</table>
Hepatitis A vaccine: Immunogenicity

- Seroconversion appears two weeks after a single dose
- 95%–100% seroconvert 4 weeks after the first vaccine administration

Studies on immunogenicity

• Following original three doses:

  ─ long-term follow-up consistently showed 100% seroconversion at month 7 (i.e., one month after the last dose), when antibody titer also peaked (GMTs of anti-HAV of 4133 and 3802 mIU/mL)
  ─ all children in the two studies still anti-HAV positive at month 60 of follow-up
Clinical Experience of AVAXIM 80u

Seroconversion rates and GMTs (mIU/ml) anti HAV antibodies in seronegative subjects 12 – 47 months given 2 doses of inactivated hepatitis A vaccine

<table>
<thead>
<tr>
<th>Time</th>
<th>Seroconversion %</th>
<th>GMT (mIU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>99.1%</td>
<td>98.5</td>
</tr>
<tr>
<td>Week 4</td>
<td>100%</td>
<td>190</td>
</tr>
<tr>
<td>After the booster</td>
<td>100%</td>
<td>6743</td>
</tr>
</tbody>
</table>

Safety and Immunogenicity of a Pediatric Formulation of Inactivated Hepatitis A Vaccine in Argentinean Children

Lopez et al, PIDJ 2001
Studies on immunogenicity

• Antibody persistence:
  – up to 9-12 years after immunization

• Mathematical models of antibody kinetics:
  – predict a persistence of anti-HAV at detectable level for 14–30 years
  – immune memory is expected to last much longer, making the need for booster doses later in life unlikely
Studies on immunogenicity

• Proof that immune memory already possible after first dose:
  – study based on the two-dose administration schedule on children in Alaska


• Delayed administration of second dose, with a mean interval of 27 months, still resulted in seroconversion to anti-HAV, although 17% of subjects were seronegative before the booster dose
Hepatitis A vaccine: Efficacy/Effectiveness

- Two studies performed using inactivated vaccines (Vaqta™ and Havrix™) demonstrated the excellent protection
  1. Vaqta™ study:
     - RCT (vaccine vs. placebo), New York City community with high Hep A incidence, n=1000 (2-16 yrs)
     - Results: 34 hep A cases in placebo vs. 1 in vaccine grp (already incubating on vaccination)
     - Protective efficacy = 100% (lower limit of 95% CI = 87%)

Hepatitis A vaccine: Efficacy/Effectiveness

2. Havrix™ study: evaluated effectiveness of two-dose vaccine
   - 40,000 Thai children in highly endemic community
   - Effectiveness was 94% (95% CI: 79%–99%)

1. First 2 years of life: presence of maternal antibodies

   - lower seroconversion rates and GMTs of anti-HAV were detected in infants born to seropositive vs. those born to seronegative mothers just after the completion of the vaccination course

   - BUT: priming of immune memory occurs, as demonstrated by the similar anamnestic response to a booster dose detected in subjects from both groups, independent of serological status of the mother

Piazza et al 1999 Vaccine, 17:585–8;
Issues on active immunization

2. Flexibility of vaccine schedule
   – Delayed second dose still showed anamnestic response to the second dose even as long as 2 – 5.5 yrs (Landry et al 2001); 4-6 yrs (Iwarson et al 2004); 20-31 months (Williams et al 2003)
   – Implication: persistence of immune memory for several years even after single dose
   – HOWEVER: long-term protection after second dose observed when 2 doses administered so adhere with 2 doses
Issues on active immunization

3. Flexibility of vaccine use
   – interchangeability acceptable
## WHO Recommendations for Hepatitis A Vaccination According to Endemicity

<table>
<thead>
<tr>
<th>ENDEMICITY</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Since exposure almost universal before 10 yrs, large-scale immunization efforts <strong>not recommended</strong> since clinical HAV usually a minor public-health problem in these areas.</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Transmission occurs primarily from person to person in general community with periodic outbreaks, <strong>widespread immunization programs suggested</strong> in conjunction with patient education and improved sanitation.</td>
</tr>
<tr>
<td>Low</td>
<td>Those with low endemicity and high rates of disease in specific high-risk groups (injection drug-users, homosexual men, travellers to high-risk areas, certain ethnic/religious groups), <strong>vaccination of high-risk groups recommended</strong> but might have little impact on overall national incidence.</td>
</tr>
</tbody>
</table>

Consider epidemiologic data and cost-benefit analyses before embarking on national Hep A immunization policies.
ACIP Recommendations

• All children should receive hepatitis A vaccine at age 1 year (i.e., 12–23 months), completed according to the licensed schedules and integrated into the routine childhood vaccination schedule.

• Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits.

• In areas without existing hepatitis A vaccination programs, catch-up vaccination of unvaccinated children aged 2–18 years can be considered.
# Recommendations for Pre-exposure Immunoprophylaxis of Hepatitis A for Travelers

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended Prophylaxis</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 12 months</td>
<td>IG</td>
<td>0.02 ml/kg protects for up to 3 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For trips of 3 mo or longer, 0.06 ml/kg should be given at departure and every 5 mo if exposure to HAV continues.</td>
</tr>
<tr>
<td>12 mo through 40 y</td>
<td>Hepatitis A vaccine</td>
<td></td>
</tr>
<tr>
<td>41 y older</td>
<td>Hepatitis A vaccine with or without IG</td>
<td>If departure is in less than 2 wk, older adults, immunocompromised people, and people with chronic liver disease or other chronic medical conditions can receive IG with the initial dose of hepatitis A vaccine to ensure optimal protection.</td>
</tr>
</tbody>
</table>
## Recommendations for Post-exposure Immunoprophylaxis of Hepatitis A

<table>
<thead>
<tr>
<th>Time Since Exposure</th>
<th>Age of Patient</th>
<th>Recommended Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wk or less</td>
<td>Younger than 12 mo</td>
<td>IG, 0.02 ml/kg</td>
</tr>
<tr>
<td></td>
<td>12 mo through 40 y</td>
<td>Hepatitis A vaccine</td>
</tr>
<tr>
<td></td>
<td>41 y or older</td>
<td>IG, 0.02 ml/kg, but hepatitis A vaccine can be used if IG is unavailable</td>
</tr>
<tr>
<td></td>
<td>People of any age who are immunocompromised or have chronic liver disease</td>
<td>IG, 0.02 ml/kg</td>
</tr>
<tr>
<td>More than 2 wk</td>
<td>Younger than 12 mo</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td></td>
<td>12 mo or older</td>
<td>No prophylaxis, but hepatitis A vaccine may be indicated for ongoing exposure</td>
</tr>
</tbody>
</table>
Hepatitis A vaccine: Safety

• After >188 million doses administered worldwide post registration (1992) and following a revision of data from different sources collected over 5 years:
  – no serious adverse event was deemed to be causally related to hepatitis A vaccine
• Data of the US system of collection of adverse reactions following immunization (Vaccine Adverse Events Reporting System [VAERS]):
  – for those adverse reactions whose background incidence is known, rates reported in vaccinees are not higher than those found in unvaccinated subjects (CDC 1999).
Cost-Benefit Analysis of Routine Hepatitis A Immunization Among Pre-School Children in a Developing Country

Rogacion JM

College of Medicine, University of the Philippines Manila
### Summary: costs and benefits of three strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (PhP)</th>
<th>Benefit* (PhP)</th>
<th>Benefit-Cost (PhP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccination</td>
<td>3,834,420.27</td>
<td>18,667,128.69</td>
<td>14,832,708.62</td>
</tr>
<tr>
<td>Universal vaccination</td>
<td>26,917,800.00</td>
<td>6,152,640.00</td>
<td>-20,765,160.00</td>
</tr>
<tr>
<td>Screen and vaccinate</td>
<td>31,147,840.00</td>
<td>11,895,104.00</td>
<td>-19,252,736.00</td>
</tr>
</tbody>
</table>

*Foregone earnings from lost time of work and / or premature mortality due to fulminant hepatitis*
FIGURE 1. Rate* of reported hepatitis A, by age group and year — United States, 1990–2004

* Per 100,000 population.
† Advisory Committee on Immunization Practices.
Mass vaccination

Israel

- National coverage since July 1999
- Given at 18 and 24 months of age
- Decline in cases from 50.4/100,000 (ave. 1993-1998) to 2.2 – 2.5 / 100,000 (2002-2004) : over 90% reduction

SUMMARY

• Hepatitis A common but preventable disease.
• Incidence is affected by degree of sanitation.
• There is a changing pattern in seroprevalence.
• Optimal protection can be achieved by immunization AND improved hygiene and sanitation.
SUMMARY

• Available vaccines are highly immunogenic, effective and safe.
• Universal vaccination may prove to be the best strategy but needs to be correlated with epidemiologic data.