Epidemiological profiles of viral hepatitis in Italy – Effects of migration

Hepatitis A and E

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Viral Hepatitis

Enterically transmitted

A → E

Parenterally transmitted

B → C → D

A

B

C

D

E
HEPATITIS A VIRUS

- non-enveloped virus particle (Ø 28 nm)
- positive sense, single-stranded RNA virus
- ~ 7.5 Kb in length
- 6 genotypes, one serotype
- Family: Picornaviridae
  (genus Hepatovirus)
Hepatitis A: clinical features

Severity

• Variable and age-dependent
• Most childhood infections are asymptomatic (>90% <5 years)
• 70-90% infected adults develop symptomatic disease
• Cholestatic hepatitis, relapsing hepatitis, fulminant hepatitis

Mortality

• Age-dependent (0.6-2.1%)

Chronic Carrier state

• No chronic infection
Geographic distribution of HAV infection

Anti-HAV prevalence:
- high
- high/intermediate
- intermediate
- low
- very low

Data from CDC, USA
Endemicity and seroprevalence

<table>
<thead>
<tr>
<th>Age group</th>
<th>Seroprevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>100</td>
</tr>
<tr>
<td>5–10</td>
<td>0</td>
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<tr>
<td>10–15</td>
<td>20</td>
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<tr>
<td>15–20</td>
<td>40</td>
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<td>40–45</td>
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<tr>
<td>45–50</td>
<td>100</td>
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<tr>
<td>&gt;50</td>
<td>100</td>
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</tbody>
</table>

Adapted from: Luxemburger C. J Travel Med 2005; 12 S12-S21
Evolving epidemiology of hepatitis A in Italy

Annual incidence has progressively declined in recent decades due to:

✓ Social, behavioural and demographic changes
✓ Improvements in the standard of living and hygiene
✓ Presence of clean water and proper sewage disposal
✓ Vaccination
The shift in Hepatitis A prevalence in Italy
Prevalence of anti-HAV in Italian recruits (18-26 years)

D’Amelio et al, Emerg Infect Dis 2005;11:1155-6
Tassi di incidenza (x 100.000) dell'epatite A per età ed anno di notifica.
SEIEVA 1985-2010.

<table>
<thead>
<tr>
<th>Anno</th>
<th>0-14</th>
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<th>≥25</th>
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<td>2010</td>
<td>1,9</td>
<td>1,2</td>
<td>1,0</td>
<td>1,1</td>
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</tbody>
</table>

![Graph showing the incidence rates of hepatitis A](image)
Hepatitis A outbreaks in Puglia

Cases per 100,000

- ~11,000 cases
- ~3,000 cases
- ~1,400 cases

P Lopalco et al, Eurosurveillance 1997; 2:31-2
Acute Hepatitis A: Time-trend of reported risk factors

- Contact with a jaundice case
- Shellfish consumption
- Travel
- Children day care
- IVDU

SEIEVA 1991-2006
Hepatitis A vaccination

✓ Schedule: 0, 6 mos or 0-12 mos or 0-18 mos
✓ Excellent immunogenicity and safety
✓ Efficacy in outbreak control and post-exposure prophylaxis *
✓ Co-administration with Ig or other vaccines (HB) is possible

HAV vaccination recommendations

- Travellers to high endemic areas
- Military personnel travelling to high endemic areas
- Sewage workers
- Individuals with blood-clotting disorders
- Intravenous drug addicts
- Homosexual men
- Prisoners
- Patient with chronic liver disease and/or cirrhosis
Regional recommendation for HAV vaccination

• Due to the periodical occurrence of large outbreaks in Puglia, vaccination against hepatitis A has been implemented for children at:
  - 16-18 months of age
  - 12 years of age

• This strategy aims to reduce the incidence of new infections and prevent infection in adulthood, when the clinical consequences of disease are more severe
## Anti-HAV prevalence in immigrants

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Country of origin</th>
<th>Anti-HAV Ig-G</th>
<th>Anti-HAV IgM</th>
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</thead>
<tbody>
<tr>
<td>Santantonio et al</td>
<td>393</td>
<td>Albania</td>
<td>96%</td>
<td>nt</td>
</tr>
<tr>
<td><em>Eur J Epidemiol</em> 1993</td>
<td></td>
<td></td>
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<tr>
<td>Chironna et al</td>
<td>526</td>
<td>Kosovo</td>
<td>81%</td>
<td>nt</td>
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<tr>
<td><em>Int J Infect Dis</em> 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chironna et al</td>
<td>1005</td>
<td>Iraq and Turkey</td>
<td>94.4%</td>
<td>nt</td>
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<tr>
<td><em>Infection</em> 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maiori et al</td>
<td>182</td>
<td>Sub-Saharan Africa</td>
<td>99.5%</td>
<td>0</td>
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<tr>
<td><em>J Travel Med</em> 2008</td>
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<td></td>
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</tbody>
</table>
Hepatitis A and migration

- High prevalence of HAV antibodies in immigrants from areas with high/intermediate endemicity

- Unlikely impact of migration on epidemiological status of hepatitis A in Italy
HEPATITIS E VIRUS

• 1980: recognized as a new virus
• 1983: identified by IEM
• 1990: cloned, sequenced, and named “hepatitis E virus”

• non-enveloped virus particle (Ø 27-34 nm)
• + sense, single-stranded RNA virus
• ~ 7.2 Kb in length
• Family: Hepeviridae
  (genus Hepevirus)
HEV: a single serotype, 4 major genotypes

Aggarwal and Naik, J Gastroenterol Hepatol 2009; 24:1484-93
World map showing regions where hepatitis E is highly endemic
Geographic distribution of HEV genotypes

Human HEV

Swine HEV

Purcell and Emerson. J Hepatol 2008; 48:494-503
Differences in epidemiological and clinical features associated with hepatitis E in disease-endemic and non-endemic regions

<table>
<thead>
<tr>
<th>Feature</th>
<th>Endemic regions</th>
<th>Non-endemic regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographical locations</td>
<td>Asia and Africa</td>
<td>Developed countries</td>
</tr>
<tr>
<td>Epidemiological patterns</td>
<td>Epidemics, sporadic cases</td>
<td>Only sporadic cases</td>
</tr>
<tr>
<td>Water-borne transmission</td>
<td>Most common route</td>
<td>Unknown</td>
</tr>
<tr>
<td>Zoonotic transmission</td>
<td>Not reported</td>
<td>Shown, a common mode of transmission</td>
</tr>
<tr>
<td>Animal reservoir</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Virus genotype</td>
<td>G1 and G2, G4 in China</td>
<td>G3</td>
</tr>
<tr>
<td>Age group</td>
<td>Young adults</td>
<td>Usually elderly</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>Not known</td>
<td>Transplant recipients receiving immunosuppressive drugs</td>
</tr>
<tr>
<td>Severity</td>
<td>Variable, including FH</td>
<td>Severity related to coexistent diseases</td>
</tr>
<tr>
<td>Relationship with pregnancy</td>
<td>High rate of symptomatic disease and FH</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Aggarwal and Naik, J Gastroenterol Hepatol 2009; 24:1484-93*
Prevalence of anti-HEV IgG

Average: 6.5%

USA: 21%
Kuniholm et al
J Infect Dis 2009;200:48-56

Viral Hepatitis Prevention Board, 2009
Anti-HEV prevalence in Italian population and in immigrants in Foggia province

- 1217 subjects
  - Italian population = 805
    - 151 blood donors
    - 450 healthy individuals
    - 100 HIV-positive patients
    - 104 hemodialysis patients
  - Immigrants = 412
    - Africa: 286
    - Asia: 86
    - East Europe: 40

- IgG anti-HEV (EIA, Western Blot), IgM anti-HEV

Scotto et al, EASL 2011
Anti-HEV prevalence in Foggia

- Anti-HEV IgG positive = 107/1217 (8.8%)
- Anti-HEV IgM positive = 20/107 (18.7%), 17 immigrants, 3 Italians
- ALT ↑ = 8/20

Scotto et al, EASL 2011
Anti-HEV prevalence in immigrants

Scotto et al, EASL 2011
Anti-HEV prevalence in Lecce province

<table>
<thead>
<tr>
<th>Group</th>
<th>Anti-HEV IgG (EIA, Western Blot)</th>
<th>n.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>2.9</td>
<td>820</td>
</tr>
<tr>
<td>IDUs</td>
<td>0.7</td>
<td>142</td>
</tr>
<tr>
<td>Hemodialized patients</td>
<td>4.3</td>
<td>211</td>
</tr>
<tr>
<td>Immigrants</td>
<td>15.3</td>
<td>98</td>
</tr>
</tbody>
</table>

De Donno et al., Ann Ig 2003; 15(3). 199-205
Anti-HAV and anti-HEV prevalence rates in Kurd refugees from Iraq and Turkey

Chironna M et al, Infection 2003; 31(2):69
Hepatitis E in Italy: a long-term prospective study

• Study population: 651 patients with acute nAnC hepatitis

• Period: 1994-2009

• Case definition:
  – IgM anti-HEV \textit{and/or}
  – HEV RNA positive in sera/stools by nested RT-PCR (ORF1 and ORF2)

Romanò et al, J Hepatol 2011; 54:34-40
Laboratory diagnosis of hepatitis E

651 patients with acute non A non C hepatitis

134 (20.6%) anti-HEV IgM and IgG positive

39 (6%) anti-HEV IgG positive

478 (73.4%) HEV negative

96 (71.6%) HEV RNA positive in sera

Romanò et al, J Hepatol 2011; 54:34-40
Risk factors associated to hepatitis E

Travel abroad 81.3% (109/134)

Autochthonous 16.4% (22/134)

Secondary cases 2.3% (3/134)

98 immigrants
11 Italians

43 Bangladesh
38 India
22 Pakistan
2 Morocco
1 Somalia
1 Angola
1 Sri Lanka
1 CapeVerde

Romanò et al, J Hepatol 2011; 54:34-40
Hepatitis E in Italy: clinical features

☑ Self-limited disease with normalization of ALT within 3-6 weeks

☑ Mean duration of HEV RNA was 10 days in sera and 15 days in stools

☑ IgM anti-HEV tended to disappear in 3-4 weeks, while IgG anti-HEV continued to be detected throughout follow-up (up to 2.5 yrs)

Romanò et al, J Hepatol 2011; 54:34-40
Sequencing and phylogenetic analysis

- 39 HEV sequences from patients travelling to endemic areas
  - Genotype 1

- 5 HEV sequences from patients with no history of travelling abroad
  - Genotype 3

Romanò et al, J Hepatol 2011; 54:34-40
Hepatitis E virus in Italy: molecular analysis of travel-related and autochthonous cases

- 17 patients with acute hepatitis E (anti-HEV IgG and/or IgM, HEV RNA positive (ORF1, ORF2)

<table>
<thead>
<tr>
<th>Infection</th>
<th>No.</th>
<th>HEV genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel-related</td>
<td>12</td>
<td>G1</td>
</tr>
<tr>
<td>Autochthonous</td>
<td>5</td>
<td>G3</td>
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</tbody>
</table>

La Rosa et al, J Gen Virol 2011; 92:1617-1626
Molecular detection of HEV in sewage samples

Molecular screening of raw sewage samples from 11 wastewater treatment plants in different regions of Italy

19/118 samples (16%) positive for HEV RNA in 9 of 11 regions analyzed

18 isolates

G1 strains

1 isolate

G3 strain

La Rosa et al, Applied and Environmental Microbiology 2010; 76: 5870-73
Hepatitis E and migration

- The increasing number of people travelling to exotic countries plus the migratory flux of people from HEV endemic areas might alter the epidemiological picture of hepatitis E in Italy.

- Epidemiological and molecular-epidemiological surveillance projects are necessary to:
  - establish prevalence
  - trace patterns of spread
  - guide prevention strategies