Hepatitis E from A to Z: Discovery and Characterization

Robert H. Purcell, MD

Hepatitis Viruses Section
Laboratory of Infectious Diseases
National Institute of Allergy and Infectious Diseases
NIH, Bethesda, MD
HEV Research: Milestones

Discovery
Hepatitis A: Detection by Immune Electron Microscopy of a Viruslike Antigen Associated with Acute Illness

Stephen M. Feinstone, Albert Z. Kapikian and Robert H. Purcell
Study of an Epidemic of Non-A, Non-B Hepatitis
Possibility of Another Human Hepatitis Virus Distinct from
Post-Transfusion Non-A, Non-B Type

MOHAMMED SULTAN KHURROO, M.D., D.M.
Serologist, Kashmir, India

A common source water-borne epidemic of viral hepatitis was studied in Kashmir valley over the period November 1978 to April 1979. hawked virus was shown to be non-A and non-B and

Reprinted from THE LANCET, October 25, 1980, p. 882–885

EPIDEMIC AND ENDEMIC HEPATITIS IN INDIA:
EVIDENCE FOR A NON-A, NON-B HEPATITIS VIRUS AETIOLOGY

DORIS C. WONG
MANDYAM AMMANJEE SREENIVASAN
S Baba RAMA PRASAD

ROBERT H. PURCELL
KHORSHED M. PAVRI

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland U.S.A., National Institute of Virology, Pune, India.
HEV Research: Milestones

Discovery

Visualization, transmission to monkeys
HEV Research: Milestones

Discovery

Visualization, transmission to monkeys

Cloning, sequencing, expression of proteins
HEV Research: Milestones

Discovery
Visualization, transmission to monkeys
Cloning, sequencing, expression of proteins
Serologic, diagnostic tests
HEV Research: Milestones

Discovery

Visualization, transmission to monkeys

Cloning, sequencing, expression of proteins

Serologic, diagnostic tests

Seroepidemiology
HEV
Important pathogen in tropical, subtropical regions

United States: All Ages (Sentinel Counties)
- Non A-E 2.0%
- 11,500 cases (all ages)
  S. Goldstein et al., J. Inf. Dis., 2002

Egypt (Cairo)
- E 49.0%
- 4.9%
- 10.9%
- Non A-E 12.4%

Saudi Arabia (Jedda, Mecca)
- E 38%
- 17.5%
- 13.4%
- Non A-E 13.4%

India (New Delhi)
- Non A-E 22.7%
- A 5.3%
- B 10.7%
- C 8.0%

2nd or 1st most important cause of acute hepatitis in adults in the Middle East, North Africa and Asia
Changing Epidemiology of Viral Hepatitis Cairo

Zakaria et al., 1988 (Adults & Children)

Gomatas et al., 1996 (Adults)

Zakaria et al., 2007 (Adults & Children)
Age-Specific Prevalence of Anti-HEV in Three Regions

Egypt, 1997

India, 1992

USA, 2001

Arankalle et al., 1995; Fix et al., 2000 Purcell, unpublished; Meng et al., 2002
Age-Specific Prevalence of Anti-HAV and Anti-HEV: Urban Pune, India, 1998

Prevalence of Antibody (%)

HAV
- High SE Status
- Low-middle SE Status

HEV

Age
- 6-10
- 11-15
- 16-25
- 25 & Older

Arankalle et al., 2001
HEV Research: Milestones

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Serologic, diagnostic tests
Seroepidemiology
Molecular biology, molecular epidemiology
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family</td>
<td>“Hepeviridae”</td>
</tr>
<tr>
<td>Genus</td>
<td>“Hepevirus”</td>
</tr>
<tr>
<td>Genotypes</td>
<td>Five</td>
</tr>
<tr>
<td></td>
<td>(1,2: human; 3,4: human &amp; swine; 5: avian)</td>
</tr>
<tr>
<td>Serotypes (1-4)</td>
<td>One</td>
</tr>
<tr>
<td>(5, etc)</td>
<td>(?)</td>
</tr>
</tbody>
</table>
HEV Research: Milestones

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Seroepidemiology
Molecular biology, molecular epidemiology
Host range, geographic range, animal reservoirs
Hepatitis E Epidemic, Delhi, India, 1955: Age-Specific Clinical Attack Rate

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>50</td>
</tr>
<tr>
<td>5-9</td>
<td>100</td>
</tr>
<tr>
<td>10-14</td>
<td>120</td>
</tr>
<tr>
<td>15-19</td>
<td>250</td>
</tr>
<tr>
<td>20-24</td>
<td>600</td>
</tr>
<tr>
<td>25-29</td>
<td>700</td>
</tr>
<tr>
<td>30-34</td>
<td>500</td>
</tr>
<tr>
<td>35-39</td>
<td>200</td>
</tr>
<tr>
<td>40-44</td>
<td>100</td>
</tr>
<tr>
<td>45-49</td>
<td>50</td>
</tr>
<tr>
<td>50-54</td>
<td>20</td>
</tr>
<tr>
<td>55-59</td>
<td>10</td>
</tr>
<tr>
<td>60+</td>
<td>5</td>
</tr>
</tbody>
</table>
Sporadic Hepatitis E, by Age In:

Developing Countries (Genotypes 1 and 2)

Countries: Chad, Mexico, Nepal, Nigeria
Mean Age: 27
Sporadic Hepatitis E, by Age In:

Developing Countries (Genotypes 1 and 2)

Countries: Chad, Mexico, Nepal, Nigeria
Mean Age: 27

Industrialized Countries (Genotypes 3 and 4)

Countries: Argentina, Austria, Greece, Italy, Japan, the Netherlands, Spain, Taiwan, USA
Mean Age: 56
HIV-infected
Prevalence of Anti-HEV in Swine Handlers and Normal Blood Donors, United States

Meng et al., 2002
## Cross-Species Transmission of HEV

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Natural Host</th>
<th>Other susceptible Hosts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Human</td>
<td>Nonhuman primates (swine, rat, horse??)</td>
</tr>
<tr>
<td>2</td>
<td>Human</td>
<td>Nonhuman primates</td>
</tr>
<tr>
<td>3</td>
<td>Swine (domestic, wild)</td>
<td>Human, nonhuman primates, Sika deer, Mongoose</td>
</tr>
<tr>
<td>4</td>
<td>Swine</td>
<td>Human, nonhuman primates</td>
</tr>
<tr>
<td>5</td>
<td>Chicken</td>
<td>Other avian species?</td>
</tr>
</tbody>
</table>
Zoonotic transmission of hepatitis E virus from deer to human beings

Lancet 2003; 362:371-73
• Zoonotic transmission of hepatitis E virus from deer to human beings
  
  Lancet 2003; 362:371-73

• Consumption of wild boar linked to cases of hepatitis E
  
  J Hepatology 2004; 40:869-870
- Zoonotic transmission of hepatitis E virus from deer to human beings
  Lancet 2003; 362:371-73

- Consumption of wild boar linked to cases of hepatitis E
  J Hepatology 2004; 40:869-870

- Complete or near-complete nucleotide sequences of hepatitis E virus genome recovered from a wild boar, a deer, and four patients who ate the deer
  Virology 2004; 330:501-505
<table>
<thead>
<tr>
<th>Species</th>
<th>Antibody</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cow</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sheep</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Goat</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
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Infection of cell culture
## Enterically Transmitted Hepatitis Viruses: A Comparison

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (nm)</td>
<td>28</td>
<td>32 - 34</td>
</tr>
<tr>
<td>Stability of virus</td>
<td>Very stable</td>
<td>Less stable</td>
</tr>
<tr>
<td>Infectious titer in feces</td>
<td>$10^6 - 10^9$</td>
<td>$10^4 - 10^7$</td>
</tr>
<tr>
<td>Host range</td>
<td>Primates</td>
<td>Primates, pigs, rats, chickens, cattle, sheep, etc.</td>
</tr>
<tr>
<td>Naturally attenuated strains</td>
<td>No (?)</td>
<td>Yes (?)</td>
</tr>
<tr>
<td>Dose-response infection</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Relationship Between Challenge Dose and Severity of Hepatitis as Measured by Serum Liver Enzymes

HAV in Tamarins

HAV Challenge: Log_{10} Infectious Dose

Peak ICD (x1000)

0 2 4 6 8 10 12 14 16

HEV in Cynomolgus Monkeys

HEV Challenge: Log_{10} Infectious Dose

Peak ALT

0 50 100 150 200 250 ≤300

Purcell et al., 2002; unpublished
Hepatitis E: Emerging Disease or Emerging Awareness?
Prevalence of Anti-HAV by Year of Birth Among Danish Blood Donors

Christensen et al., 2008
Prevalence of Anti-HEV by Year of Birth Among Various Danish Populations

Christensen et al., 2008
Molecular and serologic tracing of a transfusion-transmitted hepatitis A virus

Peter Gowland, Stefano Fontana, Christoph Niederhauser, and Behrouz Mansouri Taleghani

Hepatology Research 2007; 37: 113–120

Original Article

Persistent infection of hepatitis E virus transmitted by blood transfusion in a patient with T-cell lymphoma

Akinori Tamura,¹ Yohko K. Shimizu,² Torahiko Tanaka,³ Kazumichi Kuroda,² Yasuyuki Arakawa,¹ Kazuaki Takahashi,⁴ Shunji Mishiro,⁴ Kazufumi Shimizu² and Mitsuhiro Moriyama¹
Chronic Hepatitis E with Cirrhosis in a Kidney-Transplant Recipient

To the Editor: Hepatitis E virus (HEV) is an important cause of acute viral hepatitis worldwide. Kamar et al., in this issue of the Journal, and others have recently suggested that a 52-year-old man who had undergone kidney transplantation in March 2005 presented with increased aminotransferase levels and hypogammaglobulinemia. The cause of these findings was determined as chronic HEV infection.
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Infection of cell culture
Immunoprophylaxis
# The Antigens of Hepatitis E Virus

<table>
<thead>
<tr>
<th>ORF1</th>
<th>Nonstructural, enzymatic</th>
<th>Immunogenic but no data on protection Not part of virion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORF3</td>
<td>Structural? Function?</td>
<td>Heterogeneous. Poorly immunogenic. Antibody short-lived; does not neutralize virus</td>
</tr>
<tr>
<td>ORF2</td>
<td>Capsid (structural)</td>
<td>Highly conserved. Highly immunogenic. Antibody long-lived; neutralizes virus, protects <em>in vivo</em>.</td>
</tr>
</tbody>
</table>
Protein Vaccines

1993  Purdy et al.: *E. coli*-expressed ORF2 (fusion protein)

1994  Tsarev et al.: Insect cell-expressed ORF2 (56 kDa protein)

1996  Fuerst et al.: Insect cell-expressed ORF2 (62 kDa protein)
Safety and Efficacy of a Recombinant Hepatitis E Vaccine

Mrigendra Prasad Shrestha, M.B., B.S., Robert McNair Scott, M.D., Durga Man Joshi, M.D., Mammen P. Mammen, Jr., M.D., Gyan Bahadur Thapa, M.B., B.S., Narbada Thapa, Ph.D., Khin Saw Aye Myint, M.B., B.S., Marc Fourneau, B.S., Robert A. Kuschner, M.D., Sanjaya Kumar Shrestha, M.D., Marie Pierre David, M.S., Jitvimol Seriwatana, M.S., David W. Vaughn, M.D., Assad Safary, M.D., Timothy P. Endy, M.D., and Bruce L. Innis, M.D.
Protein Vaccines

1993 Purdy et al.: *E. coli*-expressed ORF2 (fusion protein)

1994 Tsarev et al.: Insect cell-expressed ORF2 (56 kDa protein)

1996 Fuerst et al.: Insect cell-expressed ORF2 (62 kDa protein)

2001 Im et al.: *E. coli*-expressed ORF2 (23 kDa E2 protein)

2005 Li et al.: *E. coli*-expressed ORF2 (26 kDa 239 protein)
Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine

Jun Zhang\textsuperscript{1}, Chong-bo Liu\textsuperscript{2}, Rong-cheng Li\textsuperscript{3}, Yi-min Li\textsuperscript{4}, Ying-jie Zheng\textsuperscript{5}, Yan-ping Li\textsuperscript{3}, Dong Luo\textsuperscript{3}, Bai-bin Pan\textsuperscript{3}, Yi Nong\textsuperscript{3}, Sheng-Xiang Ge\textsuperscript{1}, Jun-hui Xiong\textsuperscript{1}, James Wai-kuo Shih\textsuperscript{1}, Mun-Hon Ng\textsuperscript{1}, Ning-shao Xia\textsuperscript{1,*}

\textsuperscript{1}National Institute of Diagnostics and Vaccine Development in Infectious Diseases, Xiamen University, Xiamen 361005, China
\textsuperscript{2}Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
\textsuperscript{3}Guangxi Center for Disease Control and Prevention, Nanning, China
\textsuperscript{4}Beijing Wantai Biological Pharmacy Enterprise Company, Ltd, Beijing, China
\textsuperscript{5}School of Public Health, Fudan University, Shanghai, China
Will there be an available Hepatitis E Vaccine?