Hepatitis E: Epidemiology, Diagnosis and Management

AASLD Postgraduate Course
November 2, 2013

Tim Davern, MD
CPMC Liver Transplant Program
davernt@sutterhealth.org
### World-Wide Burden of Hepatitis

<table>
<thead>
<tr>
<th>Virus</th>
<th>No. Infected</th>
<th>No. Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>5.7 billion</td>
<td>None</td>
</tr>
<tr>
<td>HBV</td>
<td>4.5 billion</td>
<td>400 million</td>
</tr>
<tr>
<td>HCV</td>
<td>0.2 billion</td>
<td>193 million</td>
</tr>
<tr>
<td>HDV</td>
<td>0.02 billion</td>
<td>17 million</td>
</tr>
<tr>
<td>HEV</td>
<td>2.3 billion</td>
<td>Few?</td>
</tr>
</tbody>
</table>
Hepatitis E: The Dogma

- Epidemic form of viral hepatitis that is common in the developing world
- Causes acute self-limited disease with few complications except in pregnant women
- Not a cause of acute hepatitis in the US, except in rare travelers returning from epidemic regions
- Does not cause chronic hepatitis
- No special need for diagnostic assays, preventive measures, vaccine or therapy
- Should be of academic interest only to healthcare providers in the West
Discovery of Hepatitis E

- Large epidemic of viral hepatitis in Delhi in the winter of 1955-56 with ~ 30,000 cases of jaundice

- Initially thought to be classic example of epidemic, acute hepatitis A: waterborne, acute & self-limited
Discovery of Hepatitis E

- Several atypical features compared with HAV infection
  - Average age ~ 27 years
  - Average incubation period ~ 40 days
  - Lack of secondary spread in households
  - High mortality rate in pregnant women

- Subsequent serologic testing of samples from the Delhi and other outbreaks in India determined that they could not be attributed to hepatitis A (Wong et al Lancet 1980; Khuroo MS Amer J Med 1980)
  - “Epidemic non-A, non-B hepatitis”
Discovery of Hepatitis E

- 1981: outbreak of acute hepatitis among Russian soldiers in Afghanistan; outbreak of hepatitis A had occurred the year before among the same troops.
Discovery of Hepatitis E

- Human volunteer given pooled stool extract → prospectively collected stool & serum
  - Day 37: nausea, fever and abdominal pain
  - Day 43: jaundice, ALT 3011 U/L
  - Symptomatic for 25 days
- Immune electron microscopy on acute phase stool samples using recovery phase antiserum: 34 nm virus like particles

Hepatitis E
1990’s

- HEV: small single stranded RNA virus: hepevirus
- Similar to hepatitis A (fecal-oral spread)
- Causes epidemic and self-limited hepatitis
- Found predominantly in developing world; considered rare in US and Europe
- Four genotypes described
  - Genotype 1 & 2, common cause of epidemic hepatitis E
  - Genotype 3 & 4, zoonoses found mostly in swine
## Comparison of Hepatitis A and E

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HAV</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>~25 d</td>
<td>~40 d</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>&lt;1%</td>
<td>1 - 4%</td>
</tr>
<tr>
<td>Chronicity</td>
<td>None</td>
<td>Rare</td>
</tr>
<tr>
<td>Size</td>
<td>28 nm</td>
<td>32 - 34 nm</td>
</tr>
<tr>
<td>Genome</td>
<td>7.5 kb (ssRNA)</td>
<td>7.2 kb (ssRNA)</td>
</tr>
<tr>
<td>ORF</td>
<td>1 (polyprotein)</td>
<td>3</td>
</tr>
<tr>
<td>Titers in feces</td>
<td>$10^6$ to $10^9$</td>
<td>$10^4$ to $10^7$</td>
</tr>
<tr>
<td>Host range</td>
<td>Humans (Primates)</td>
<td>Broad</td>
</tr>
</tbody>
</table>

*Purcell & Emerson  J Hepatol 2008*
Hepatitis E
More Recent Insights

- Although initially cases appeared to be limited to the "developing world", sporadic cases reported in Western countries (UK, Europe, Japan, Australia)
- Not associated with foreign travel ("autochthonous")
- Unusual epidemiology: middle-aged & elderly men
- Generally genotype 3
- Case controlled study from Germany using food-frequency survey and epidemiologic data
  - Eating undercooked pork, "offal" and wild boar
- HEV strains also found in deer, elk, sheep, rats

"Phylogenetic and case-control study on hepatitis E virus infection in Germany"


- Goal: determine risk factors for autochthonous HEV infections in Germany
- May 2006 - August 2007: 96 cases HEV reported, 76 interviewed, 66 met criteria (HEV defined as +PCR or HEV IgM)
- 45 (68%) had autochthonous infection, and 21 (32%) had travel-associated disease; all of the former cases genotype 3 or 4
- Logistic regression (45 cases and 135 controls): eating offal (OR 2.7; 95% CI 1.2 - 6.2) and wild-boar meat (OR, 4.3; 95% CI, 1.2 - 15.9) independently associated with autochthonous HEV infection.
Epidemiology of HEV in Developed Countries

J Infect Dis 2008, 198:1732 - 41
“Epidemiology of HEV in the US: Results from NHANES III, 1988 – 1994”

- HEV IgG ELISA on 18,695 serum samples
- Seroprevalence of HEV in the US population is 21%
- Highest seroprevalence in males, non-Hispanic whites, and those residing in the Midwest and/or metropolitan areas
- Not linked to foreign travel
- Increase odds: pet owners (odds ratio [OR], 1.19 [95% CI, 1.01 – 1.40]) and consuming organ meats (OR, 1.38 [95% CI, 1.01 – 1.88])
- Frequent subclinical or unrecognized infection?
Hepatitis E: Diagnosis

• Requires testing for IgM anti-HEV
• Confirmation:
  • HEV RNA (serum or stool)
  • Decrease in IgM anti-HEV titers
  • Rise in IgG anti-HEV titers
• Major problem: no licensed, reliable assays for anti-HEV or HEV RNA available in the U.S.
• Assays used: Genelabs, Abbott, Wantai & EIAGen
Typical Acute Hepatitis E

- HEV RNA
- ALT
- IgM anti-HEV
- IgG anti-HEV

Graph showing:
- Alanine Aminotransferase (U/L) vs. Weeks After Exposure
- Symptoms

- Normal range indicated
Acute Hepatitis E Clinical Manifestations

- Self-limited acute hepatitis
- Anicteric (~50% in adults)
- Acute liver failure (esp. pregnant women, elderly)
- Chronic hepatitis (usually immune-deficient)
- Acute-on-chronic hepatitis (pre-existing liver disease)
- Neurologic manifestations
  - Guillain-Barré Syndrome
  - Acute neuropathy
  - Ataxia and cognitive decline
  - Encephalitis
Acute Hepatitis E
Often Misdiagnosed in the West

- Drug or herbal-induced liver disease
- Atypical viral hepatitis (CMV, EBV or adenovirus)
- Acute decompensation of chronic liver disease
- Acute cholecystitis
- Nonalcoholic steatohepatitis
- Acute liver injury of indeterminate cause
LIVERTOX – a “Virtual Hy”

LiverTox
Clinical and Research Information on Drug-Induced Liver Injury
www.livertox.nih.gov
"The role of hepatitis E virus testing in drug-induced liver injury"


- Retrospective study of a cohort of suspected DILI (n=69) and HEV (n=45) in Great Britain
- Formal causality analysis: 47 of 69 deemed DILI
- HEV testing: 22/47 neg, 19/47 no sera, 6/47 were HEV + “and thus did not have DILI”
- HEV cases more likely to be male, less likely to present in Nov - Dec, had higher ALT, and lower Tbili
- No travel history
- “The diagnosis of DILI is not secure without testing for HEV”
HEV Infection in Drug-Induced Liver Injury Network (U.S.)

- First 300 cases enrolled in the DILIN Network were tested for anti-HEV
- 50 had IgG anti-HEV (16%)
- 9 were reactive for IgM anti-HEV (3%)
- 4 of which had HEV RNA, all were genotype 3
- 8 men, 1 woman; mean age 65 years
- None of the 9 had recent travel to endemic areas
- On reassessment, most cases were more likely due to HEV than the implicated drug

Davern et al., Gastro 2011
## Clinical Features of Nine Cases

<table>
<thead>
<tr>
<th>No</th>
<th>Drug</th>
<th>Age</th>
<th>Sex</th>
<th>Peak ALT</th>
<th>Peak Bilirubin</th>
<th>HEV RNA</th>
<th>Clinical Phenotype</th>
<th>HEV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Azithromycin</td>
<td>74</td>
<td>M</td>
<td>2428</td>
<td>8.9</td>
<td>Negative</td>
<td>Acute Hepatitis</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Nevirapine</td>
<td>43</td>
<td>M</td>
<td>560</td>
<td>0.9</td>
<td>Positive</td>
<td>Chronic Hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Isoniazid</td>
<td>62</td>
<td>M</td>
<td>429</td>
<td>13.2</td>
<td>Positive</td>
<td>Acute on Chronic</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Ezetimibe</td>
<td>64</td>
<td>M</td>
<td>557</td>
<td>5.1</td>
<td>Negative</td>
<td>Acute on Chronic</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Allopurinol</td>
<td>80</td>
<td>M</td>
<td>235</td>
<td>10.6</td>
<td>Negative</td>
<td>Acute Hepatitis</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Telithromycin</td>
<td>83</td>
<td>M</td>
<td>196</td>
<td>28.2</td>
<td>Negative</td>
<td>Acute Hepatitis</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Nevirapine</td>
<td>61</td>
<td>M</td>
<td>708</td>
<td>16.7</td>
<td>Positive</td>
<td>Acute Liver Failure</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>Herbals</td>
<td>59</td>
<td>F</td>
<td>3838</td>
<td>4.5</td>
<td>Negative</td>
<td>Acute Hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>Pravastatin</td>
<td>79</td>
<td>M</td>
<td>1564</td>
<td>8.6</td>
<td>Positive</td>
<td>Acute Hepatitis</td>
<td>1</td>
</tr>
</tbody>
</table>
Chronic Hepatitis E

- Case reports & small series document that HEV can become chronic
  - Persistence of ALT elevations and HEV RNA in serum
  - Chronic hepatitis on liver biopsy
- Liver & kidney transplant (Kamar, Schildgen & Gerolami 2008)
- Cancer chemotherapy (Ollier, Tamura, & le Coutre 2009)
- HIV infection (Dalton & Colson 2009)
  - Persistence of HEV RNA in serum ($10^5$ to $10^7$ copies/mL)
  - Low or moderate titers of IgM & IgG anti-HEV
  - Fluctuating levels of ALT and AST
  - Chronic hepatitis on liver biopsy, fibrosis and cirrhosis
- Non-immunosuppressed patients as well?
Chronic Hepatitis E: Therapy

- Case reports and small case series
- Peginterferon α2b alone (Alric 2010, Kamar 2010)
- Ribavirin 600 - 800 mg alone (Mallet 2010, Kamar 2010)
- For three months only
- Follow up of 3 - 6 months
- Sustained virological response rates 66% - 75%
Chronic Hepatitis E: Therapy

- 57 year old with hairy cell leukemia and chronic hepatitis E
- Treated with peginterferon α2b [1 μg/kg] weekly for 3 months

Alric et al. Ann Intern Med 2010
Hepatitis E: The Dogma Revised

- Epidemic form of viral hepatitis that is common in the developing world but also may occur in the West as autochthonous infection.
- Causes acute self-limited disease, acute liver failure, acute-on-chronic liver injury and chronic hepatitis with complications.
- Definite cause of acute hepatitis in the US that may be misdiagnosed as DILI.
- We definitely need accurate diagnostic assays, preventive measures, vaccines and therapy.
Hepatitis E: Remaining Questions

- Why are there so many subclinical cases of HEV infection in developed countries?
- What is the source of infection?
- When will have widely-available, reliable, and standardized tests for HEV?
- When will vaccines for HEV be developed and employed on a large scale? Who should be offered such vaccines?
HEV
Closing Remarks

- Think about HEV
  - Possible DILI (hepatocellular pattern)
  - Acute-on-chronic liver failure
  - Seronegative acute and chronic hepatitis
- Consider CDC testing for difficult cases
- Council patients with CLD to cook pork well
- Reference LiverTox early and often
- "Always keep an open mind - but not so open your brains fall out!"
  - Arthur Hays Sulzberger
Hepatitis E: Epidemiology, Diagnosis and Management

AASLD Postgraduate Course
November 2, 2013

Tim Davern, MD
CPMC Liver Transplant Program
davernt@sutterhealth.org