Clinics, Treatment and Prevention of Viral Hepatitis E

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• HEV Virology
• HEV Transmission and Prevention
• HEV Clinical presentation
• HEV Treatment
• Wrap up
Hepatitis E virus and the global disease burden

- Nonenveloped +sense single stranded RNA virus (27-34 nM)
- 4 major genotypes:
  - 1+2 restricted to humans
  - 3+4 broad host range (zoonotic)

Hepatitis E virus is emerging

- Seroprevalence:
  - Overall ↓ until 2011 (Germany and the Netherlands)
  - ↑ young (largely unexposed) adults
  - ↑ HEV RNA positive blood donations in the Netherlands
    - Oct 2012 – Mar 2013 1:2742
    - Apr 2014 – Sep 2014 1:611

- In Belgium?
  - 2018 planned age-specific seroprevalence study (WIV/ISP, UA, UZA)
  - 2 systematic serum banks obtained in 2006 and 2014

HEV Transmission

Transmission mainly via fecal-oral route

Transfusion: possible
How big is the zoonotic risk?

Identical HEV strain in consumed meat and patients


202(6):825; PNAS, 1997, 94(18):9860

2854 Hepatitis E-virus-RNA in diverse varkensleverproducten

In recent onderzoek naar de bronnen van HEV-infectie bij mensen heeft Sanquin 43 van 55 (78%) leverworsten en 12 van 15 (80%) varkenspatémonsters, afkomstig van diverse producenten, positief getest op HEV-RNA met een PCR-test. De NVWA heeft 

How big is the zoonotic risk?

Holland: HEV IgG+
meat vs vegetarians: OR 1.78

UK: HEV IgM+
OR > 2.48-10.12 (P = 0.002)

Slot et al. PLOS ONE 2017; April 27.
Said et al Epidemiol Infect 2014; 144:1467
Zoonotic Risks in Belgium: “Pig Belt”

- 70% of fatteners HEV RNA+
- @ 1 month:
  - serum HEV RNA-
  - faeces HEV RNA+
- transmission to newborn pigs

→ True pig reservoir

Belgium (2010): slaughterhouse

→ 5/23 farms HEV RNA+
→ 8/115 (7%) pigs HEV RNA+

Number of sows by region (2013) - Source: Eurostat

BMC Res Notes, 2012. PLOS one 2011
Zoonotic Risks in Belgium: … and Wildlife

- Wild Boar: 34% HEV IgG+
- Deer: 1-3% HEV IgG+

Wild boar density shot per region (2009-2013)
Minimal infectious dose? Inactivation?

- **MID ?**: Experimental inoculation pigs, rhesus macaque and chimeric mice

- **Inactivation?**

  > 71°C for ≥ 20’: 0/4 pigs infected

<table>
<thead>
<tr>
<th>Group</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>No. of pigs excreting HEV/no. of pigs in group on the following day postinoculation:</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>5</td>
<td>0/3 0/3 0/3 0/3 0/3 2/3 2/3 2/3 1/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3</td>
<td>2/3</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>10</td>
<td>0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3 2/3</td>
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</tr>
<tr>
<td>3</td>
<td>71</td>
<td>20</td>
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</tr>
<tr>
<td>4</td>
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<td>5</td>
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<tr>
<td>5</td>
<td>68</td>
<td>10</td>
<td>0/3 0/3 0/3 0/3 0/3 1/3 1/3 1/3 0/3 2/3 1/3 1/3 1/3 1/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 2/3</td>
<td>2/3</td>
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<tr>
<td>7</td>
<td>62</td>
<td>5</td>
<td>0/3 0/3 0/3 0/3 0/3 3/3 3/3 3/3 3/3 0/3 1/3 1/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3 0/3</td>
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</tr>
<tr>
<td>8</td>
<td>62</td>
<td>20</td>
<td>0/3 0/3 0/3 0/3 0/3 3/3 3/3 3/3 3/3 0/3 1/3 1/3 1/3 1/3 1/3 1/3 1/3 1/3 1/3 1/3 1/3</td>
<td>3/3</td>
</tr>
<tr>
<td>10</td>
<td>HEV positive, no heating</td>
<td></td>
<td>0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4 0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6 0/6</td>
<td>0/6</td>
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</tbody>
</table>

Transfusion?

42% (18/43) recipients infected

Risk of HEV transmission:
RBC < platelets << plasma
~ low/absent HEV IgG
~ higher HEV RNA (p<0.0001)

Absolute risk low: HEV RNA+ donations

The Netherlands 0.037% (17/45,415)
Denmark 0.04% (11/25,637) --> 0 infections
UK 0.04% (79/225,000) --> 18 infections
Japan 0.012% (231/2,000,000)

How to translate this knowledge in Preventive Measures

“Prevention is better than cure.”

Desiderius Erasmus
HEV Prevention

- **HEV vaccine:**
  Chinese HEV genotype 1, not FDA or EMA approved
  4.5 yr efficacy of 86.8% (7 infections in vaccinees, vs 60 in controls)
  Efficacy in HEVgt 3 infections?

- **Zoonotic Risk:**
  SOT recipients: NO liver sausage/paté; shellfish; uncooked pork
  Food processing techniques?

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**Voorlopig geen leverworst of paté**

22 juni 2016

Vanuit Sanquin is voorgesteld om het dieetadvies van orgaan- en allo-stamceltransplantatiepatiënten uit te breiden met het advies om voorlopig geen leverworst of paté te eten in verband met risico's op hepatitis E infecties.

De onderbouwing hiervoor vindt u hieronder en verdere informatie kunt u vinden in de publicatie van Nijskens et al. Journal of Clinical Virology 74 (2016) 82–87
**HEV Prevention**

- **Blood donation screening? Cost-effective?**

0.2% of all HEV infections in The Netherlands (H Zaaijer)

1 year dietary risk ~ blood from 13 donors (UK)

<table>
<thead>
<tr>
<th>Country</th>
<th>HEV RNA positive donations</th>
<th>Population at risk</th>
<th>Reported TT HEV infections</th>
<th>Screening of blood donations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>allo-HSCT [51] AN (AR/p10mp)</td>
<td>SOT [52] AN (AR/pmp)</td>
<td>Implemented</td>
</tr>
<tr>
<td>Denmark</td>
<td>1:2,331 (2016) [16]</td>
<td>144 (201 – 300)</td>
<td>356 (63.6)</td>
<td>x</td>
</tr>
<tr>
<td>France</td>
<td>1:2,218 (2012–3) [18]</td>
<td>1,724 (201 – 300)</td>
<td>5,141 (79.6)</td>
<td>x</td>
</tr>
<tr>
<td>Germany</td>
<td>1:1,241 (2012) [24]</td>
<td>2,892 (&gt; 300)</td>
<td>3,710 (44.9)</td>
<td>x</td>
</tr>
<tr>
<td>Greece</td>
<td>NA</td>
<td>169 (151 – 200)</td>
<td>171 (15.4)</td>
<td>x</td>
</tr>
<tr>
<td>Ireland</td>
<td>1:2,778 (2016)</td>
<td>77 (151 – 200)</td>
<td>246 (52.3)</td>
<td>x</td>
</tr>
<tr>
<td>Italy</td>
<td>NA</td>
<td>1,625 (201 – 300)</td>
<td>3,252 (53.2)</td>
<td>x</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1:726 (2016) [7]</td>
<td>1175 (&gt; 300)</td>
<td>1,315 (78.3)</td>
<td>x</td>
</tr>
<tr>
<td>Portugal</td>
<td>NA</td>
<td>137 (101 – 150)</td>
<td>739 (69.7)</td>
<td>x</td>
</tr>
<tr>
<td>Spain</td>
<td>1:3,333 (2014) [53]</td>
<td>1,072 (201 – 300)</td>
<td>4,247 (90.2)</td>
<td>x</td>
</tr>
<tr>
<td>Switzerland</td>
<td>NA</td>
<td>191 (201 – 300)</td>
<td>504 (61.5)</td>
<td>x</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1:1,340–5,000 (2016)</td>
<td>1,602 (201 – 300)</td>
<td>4,561 (71.8)</td>
<td>x</td>
</tr>
</tbody>
</table>

Belgium? Luxemburg?

HEV RNA+ donations = 0.04%

Euro Surveill 2017;22(16):30514; TRANSFUSION 2017;57;267
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Out of 40 symptomatic Acute HEV patients:

Chronic HEV genotype 3

Chronicity rate = 65.9% in SOT recipients (n=65/85)

HIV
SOT
BMTx
Cancer chemotherapy

“Immunocompetent”: immune suppressive R/undefined CD4 defect

-> Rapid fibrosis progression

NEJM 2012, Blood 2013;122:1079
GASTROENTEROLOGY 2011;140:1481; Hepatology 2014, 60 (3).
Extrahepatic manifestations

Neurological: (~100 cases)
- Guillain-Barre
- Brachial neuritis
- Meningo-encephalitis

Kidney disease:
- Glomerulonephritis
- ± cryoglobulinemia

Replication vs HEV RNA Detection?
Animal models
Seldom HEV negative strand PCR (Placenta)

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Treatment for chronic HEV

Reduction of immune suppression --> successfull in 32.1%

<table>
<thead>
<tr>
<th>Drug</th>
<th>In vitro effect</th>
<th>In vivo effect</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin</td>
<td>Inhibition of HEV replication</td>
<td>HEV clearance in chronic hepatitis E; occasional cases of treatment failure</td>
<td>Intracellular GTP depletion through inosine 5’-monophosphate dehydrogenase inhibition</td>
</tr>
<tr>
<td>PegIFNα</td>
<td>Inhibition of HEV replication</td>
<td>HEV clearance in chronic hepatitis E</td>
<td>Immune activation</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>Inhibition of HEV replication</td>
<td>Unknown</td>
<td>Nucleotide analog; inhibition of the viral RNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>Inhibition of HEV replication</td>
<td>Unclear, possibly associated with HEV clearance in chronic hepatitis E</td>
<td>Intracellular GTP depletion through inosine 5’-monophosphate dehydrogenase inhibition; immune suppression</td>
</tr>
<tr>
<td>Mycophenolic acid prodrug</td>
<td>Inhibition of HEV replication</td>
<td>Unknown</td>
<td>Nucleotide analog; inhibition of the viral RNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>mTOR inhibitors</td>
<td>Stimulation of HEV replication</td>
<td>Higher HEV RNA levels in patients with chronic hepatitis E on mTOR inhibitors</td>
<td>Inhibition of an eIF4E binding protein 1-dependent antiviral signaling pathway downstream of mTOR</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Stimulation of HEV replication</td>
<td>Unknown; tacrolimus use associated with increased risk of viral persistence</td>
<td>Inhibition of cyclophilin A and B</td>
</tr>
</tbody>
</table>

RBV for chronic HEV

Retrospective series (n=59)

  Median 3 months
  Median dose: 600 mg per day (upto 1200mg), ~ 8.1mg/kg
  EOT= 95%
  “SVR24 wks” =78%

  ~ weight based RBV (12 mg/kg): 1000 mg vs 1200 mg (anemia!)

Prediction of response: monitor HEV RNA in stool

  + @ 1 month in 100% of relapsers
  + @ 3 months in 66% of relapsers vs 0% of responders

Conclusions: HEV

- Belgiums HEV transmission risks and preventive measures remain uncertain:
  - HEV present in pig stock and wild boars
  - Immunocompromised: no uncooked pork meat, seafood, liver sausage/liver pate
  - Transfusion: limited contribution to HEV epidemics

- Acute, mostly asymptomatic in immunocompetent
- Possible chronic in immunocompromised
- HEV PCR necessary in immunocompromised

- Treat chronic HEV with RBV
- Relapsers difficult to cure
Acknowledgements

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Het congres

Als laatste presenteerde David de uitkomsten van zijn onderzoek naar aandachtscurves van congresgangers.

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