HEV UPDATE

Diagnostics and Management

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DISCLOSURES RELEVANT TO THIS PRESENTATION

• NONE

• Off label use of drugs will be discussed
HEPATITIS E

• Enterically transmitted zoonotic RNA virus in the genus Hepevirus
  • 7200 bases
  • 3 ORFs

• There are 4 genotypes capable of human infection (maybe 6) and at least 7 or more total genotypes
HEV IN FRANCE

- Phylogenetic Analysis of Cases in Humans
- Full length sequencing performed

RESULTS
- Recombinant HEV3 found and likely derived from wild boar
- Rabbit HEV identified

Luk KC et al, AASLD, 2017 Abs. 1634
Geographic Distribution of Primary Human HEV Genotypes
Based on 148 bp of the ORF2 gene
Innate Immune response may drive primary clearance
Debing et al, J HEPATOL, 2016
DIAGNOSTICS

Not Ready for Prime Time
CLINICAL CASE

- 46 yo woman with biopsy-proven PBC (with possible AI-overlap). AMA positive and anti-actin positive. F2 on 2013 biopsy
- Treated with urso starting 2/20/2014 (13 mg/kg).
- Increased LFTs including alk phos and ALT in recent months
- FibroScan 12/30/2016 27.4 kPa; Ultrasound 8/10/2016 “Subtle nodularity”
- 10/18/2017 Started obeticholic acid 5 mg/day. Presumed to be cirrhotic but not decompensated.
- 10/25/2017 Patient reports she is “yellow”. Increased fatigue, dark urine, light stool, epigastric discomfort. OCA held and labs obtained.
  - ALT 477; AST 1,000; ALK PHOS 184; BILI 10.8 (Direct 7)
  - HEV IgM from outside lab 5 days later POSITIVE
TESTS FOR HEV

• Serologic
  – HEV IgG EIA
  – HEV IgM EIA
  – HEV serotyping
  – HEV ELISPOT

• Virologic- Serum/Plasma or Stool
  – Nested PCR
  – Real-time PCR
  – HEV Antigen Testing
HEV
Typical Clinical/Serological Course

Symptoms
Virus in stool

Virus in sera

ALT

IgG anti-HEV

IgM anti-HEV

Weeks after Exposure

Titer

0 1 2 3 4 5 6 7 8 9 10 11 12 13

CDC
HEV in Immunosuppressed Host

CHRONIC Clinical/Serological Course

**Symptoms**

**Virus in stool**

ALT

IgG anti-HEV

IgM anti-HEV

Virus in sera

Weeks after Exposure

0 1 2 3 4 5 6 7 8 9 10 11 12 13
SEROLOGIC ASSAYS

HEV IgG or HEV IgM

- Low Confidence with some/most assays

- Not FDA Approved in U.S.
# HEV IgM Assays

<table>
<thead>
<tr>
<th>NAME/MANUFACTURER</th>
<th>TYPE</th>
<th>ANTIGEN</th>
<th>FDA APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEV IgM ELISA/WANTAI</td>
<td>U-chain Capture</td>
<td>ORF-2 GENOTYPE 4</td>
<td>NO</td>
</tr>
<tr>
<td>recomWell HEV IgM/Mikrogen</td>
<td>Indirect</td>
<td>ORF-3, GENOTYPE 1,2,3</td>
<td>NO</td>
</tr>
<tr>
<td>HEV IgM, ELISA 3.0/MP</td>
<td>Indirect</td>
<td>ORF-2 GENOTYPE 1 (Chinese)</td>
<td>NO</td>
</tr>
<tr>
<td>Assure HEV IgM Rapid/MP</td>
<td>Reverse flow immunochemistry</td>
<td>ORF-2, GENOTYPE 1</td>
<td>NO</td>
</tr>
<tr>
<td>Anti-HEV ELISA/Euroimmune</td>
<td>Indirect</td>
<td>ORF-2 GENOTYPE 3 (US)</td>
<td>NO</td>
</tr>
<tr>
<td>EIAggen HEV/Adaltis</td>
<td>Capture</td>
<td>ORF-2/3 ALL GENOTYPES</td>
<td></td>
</tr>
</tbody>
</table>
## HEV IgM Assay Comparison

<table>
<thead>
<tr>
<th>Assay</th>
<th>WHO-Ref (GT 1) IU/mL (Dilution)</th>
<th>Donor Sample (GT 3) (Dilution)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detection Limit</td>
<td>Linearity ($R^2$)</td>
</tr>
<tr>
<td><strong>Anti-HEV IgM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wantai</td>
<td>1:4</td>
<td>0.9937</td>
</tr>
<tr>
<td>Mikrogen</td>
<td>1:4</td>
<td>0.9474</td>
</tr>
<tr>
<td>MP-Bio</td>
<td>1:8</td>
<td>0.9950</td>
</tr>
<tr>
<td>Euroimmun</td>
<td>1:4</td>
<td>0.9499</td>
</tr>
<tr>
<td><strong>All-AB</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP-Bio</td>
<td>1:64</td>
<td>0.9969</td>
</tr>
<tr>
<td><strong>Anti-HEV IgG</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wantai</td>
<td>0.4 (1:256)</td>
<td>0.9324</td>
</tr>
<tr>
<td>Mikrogen</td>
<td>3.1 (1:32)</td>
<td>0.9197</td>
</tr>
<tr>
<td>MP Biomedical</td>
<td>1.5 (1:64)</td>
<td>0.9508</td>
</tr>
<tr>
<td>Euroimmun</td>
<td>1.5 (1:64)</td>
<td>0.9934</td>
</tr>
</tbody>
</table>

Vollmer T et al, VIRUSES, 2016
HEV IgM Assay Comparison

Abravanel F et al, J CLIN VIROL, 2013
HEV IN HIV-INFECTED PATIENTS AFTER LIVER AND KIDNEY TRANSPLANTATION

- Longitudinal Epidemiologic Analysis
- N= 171
  - Liver n=70
  - Kidney n= 101
- Analyzed for seroconversion and seroreversion
- RESULTS
  - Pre-Transplant HEV +
    - Liver 21.4%
    - Kidney 18.8%
  - Seroconversion
    - Liver 5.5%
    - Kidney 0%
  - Seroreversion
    - Liver 40%
    - Kidney 32%

Sherman et al, AASLD, 2017 Abs. 1635
Evaluation of HEV-specific immune responses in HEV infected subjects

HEV-specific IFN-gamma ELISPOT assay

No of ISCs/one million cells

Negative
Positive

Human subjects

P=0.001

DIAGNOSIS

Virologic

• Blood
  – Short Window of Viremia

• Stool
  – Longer period of shedding
  – Generally not available
HEV REAL TIME PCR

HEV ORF 3

- HEV type 2, 100 genome eqs
- HEV type 2, 10 genome eqs
- Patient serum
- Negative control

Fluorescence (a.u.)

Cycles

0 10 20 30 40
HEV ANTIGEN TESTING

Sandwich ELISA testing of stool from HEV-infected macaques

Wen G-P et al, J CLIN MICROBIOL, 2015
PROPOSED DIAGNOSTIC CRITERIA

• ACUTE HEV INFECTION
  – ALT>2x baseline + HEV IgM Reactive using 2 different assays or
  – ALT> 2x baseline + HEV IgM Reactive + HEV RNA detected in stool or blood (LOD 10 copies/ml) or
  – ALT> 2x baseline + HEV IgG x 2 weeks apart with > 5-fold increase in titer or
  – ALT> 2x baseline + HEV IgM Reactive + IFN-gamma ELISPOT for HEV (>50 HEV-specific spots/10⁶ cells

• CHRONIC HEV INFECTION
  – HEV RNA detected twice over 6 months in stool or blood

Anwar & Sherman, SCIENTIFIC AMERICAN GASTRO 2017
Sherman & Kottilil, Schiff Textbook of Liver Disease 2017
Sherman, UpToDate, Accessed 11/2017
CLINICAL CASE
Followup Testing

• HEV IgM (Wantai)- Negative
• HEV RNA- Negative
• HEV IgG- Acute and Convalescent Titer
HEV
Acute and Convalescent Titer

- Initial 2 Weeks
- SN/CO Positive
- SN/CO Negative

- Initial Titer: 1.0
- 2 Weeks Titer: 0.5
<table>
<thead>
<tr>
<th></th>
<th>ACUTE DISEASE</th>
<th>CHRONIC DISEASE</th>
<th>MORTALITY</th>
</tr>
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<tbody>
<tr>
<td>Immunocompetent</td>
<td>YES</td>
<td>NO</td>
<td>LOW</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>YES</td>
<td>NO</td>
<td>VARIABLE</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>YES</td>
<td>NO</td>
<td>HIGH</td>
</tr>
<tr>
<td>Immunosuppressed - HIV</td>
<td>YES</td>
<td>YES</td>
<td>VARIABLE</td>
</tr>
<tr>
<td>- Post-Transplant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cancer Chemotx</td>
<td></td>
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</tr>
</tbody>
</table>

?Immune Trigger- Guillain-Barre
Scham N et al, Infection 2014
Van den Berg B et al, Neurology, 2014
Fukae J et al, Neurol Sci 2016
HEV
Acute on Chronic Decompensation

Kumar et al., IND J GASTRO, 2004
HEV
Acute on Chronic

Submassive necrosis in cryptogenic cirrhosis patient
Associated with eating shellfish and/or pork

HEV Acute on Chronic in HALT-C

• Frequency of acute HEV determined in relation to decompensation events in HALT-C Cohort

• Comparison of seroconverters with Selected Controls
  – OR = 2.1 (n.s.)

No difference in overall IgG prevalence

Samala N et al, CLIN GASTROENTEROL HEPATOL, 2016
10% of ALF presenting to University Hospital- Essen, German Attributed to acute HEV
Initial etiologic diagnosis was wrong in all cases

Manka P et al., CLIN GASTRO HEPATOL, 2015
Hepatitis E virus infection in Adult Americans with Acute Liver Failure

Fontana et al, Hepatology
Volume 64, Issue 6, pages 1870-1880, 23 JUN 2016 DOI: 10.1002/hep.28649
HEV and PREGNANCY

• Maternal mortality as high as 25% in some places

• Low mortality in other places

• REASON???
  – Genotype
  – Epidemiology of exposure
  – Host factors- Lower NK Count during pregnancy
  – Poor Maternal and Birth Care
ACUTE TO CHRONIC

- HIV
- Organ Transplantation
- Chemotherapy
Figure 1. Laboratory Data for a Patient with Coinfection with Human Immunodeficiency Virus (HIV) and Hepatitis E Virus (HEV).

Dalton et al., NEJM, 2009
CHRONIC HEV IN HIV
Progression to “Cryptogenic” Cirrhosis

Gurmit K. et al.
Journal of Infection 2011
CHRONIC HEV INFECTION in Transplant Recipients

Pischke et al. LIVER TRANSPLANTATION 2010
RAPID DISEASE PROGRESSION AFTER OTLTx

Attributed to Acute Rejection
150 Days Post-Tx

1 Year Post-OTLTx

Schlosser et al., J HEPATOL 2012
MANAGEMENT OF CHRONIC HEV

- Pegylated Interferon
- Ribavirin
- Withdrawal of Immunosuppression
  - 18/56 Cleared HEV with reduced immunosuppression (Kamar et al, GASTRO, 2011)
HEV TREATMENT
Ribavirin

- Retrospective, Multicenter Case Series
- N = 59
- Organ Transplant Recipients
- Chronic HEV Identified
- Treatment
  - Ribavirin Median Dose 600 mg/day
  - Median Duration 3 months

Kamar et. al, NEJM, 2014
CONCLUSION

- HEV is prevalent in Western countries where it was previously unsuspected
- HEV is under-diagnosed due to
  - Low clinical suspicion
  - Poor assays
  - Low availability of assays
- There is a low risk of Chronicity but when it occurs, it could be associated with progressive liver disease
- Chronic HEV can be treated
COLLABORATORS

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