HEPATITIS E INFECTION IN LATIN AMERICA
Hepatitis E

- Hepatitis related to an orofecal transmitted non-A/non-B virus
  Balayan et al. Intervirol 20:23, 1983

Discovery of HEV
- Isolation of the cDNA of an enteric transmitted non-A/non-B hepatitis virus

Cloning of HEV
- HEV molecular virology

Gender *Hepevirus*; family *Hepeviridae*
- non-enveloped, single-chain, 7.2Kb, RNA virus
  - 4 main genotypes and many subtypes for each genotype
  - only one serotype

HEV epitope identification

Production of first serological test
Hepatitis E

Hepatitis E – an update

Epidemiology

tropical and subtropical countries
  - African and Asian subcontinents
    - orofecal transmission; contaminated water (+ genotype 1)

industrialized countries
  - parts of Europe, USA, Japan
    - zoonosis (+ genotype 3)

Latin America
  - Mexico (genotype 2)

Causes significant morbimortality
  - acute hepatitis, fulminant hepatitis
  - chronic hepatitis and cirrhosis in special populations
Hepatitis E

Burden of HEV (genotypes 1 and 2 in 2005)
Mathematical model used in determined regions represent 71% of population
Estimates: 20.1 million patients infected
- 3.4 million symptomatic cases
- 70,000 deaths
- 10 times worse during pregnancy
- 3,000 stillborns
Hepatitis E

- Hepatitis E virus
  Emergence of genotype 3
    in industrialized countries
    more frequent than hepatitis A
    France, UK e Japan
  zoonosis (pigs) and transfusion
    in general, male patients > 55 yrs
    mortality ranges between 7.5-10.8%
    effects on pregnancy unknown

- HEV Infection
  Parvez MK. Intervirology 56:213, 2013
  Importance of ingestion of raw or badly done meat
    pork liver sausage
    hunted meats, wild pigs...
Hepatitis E

Spain: 7 yrs of experience with HEV
Mateos-Lindemann et al. Enf Infecc Microbiol cli 2013
Prevalence of 0.6% in populations without risk factors
  18.6% in farmers
  10.11% in HIV+ patients
49 patients with HEV
  acute hepatitis, fulminant hepatitis and chronic liver disease
Hepatitis E

- Hepatitis E virus

**Immunocompetent patients**
Clinical presentation indistinguishable from other viral hepatitis
  - majority asymptomatic
During pregnancy it is frequently symptomatic
  - risk of fulminant hepatitis (20-30%)
    - death frequently related to obstetric complications
      - eclampsy and hemorrhage
  - well-documented vertical transmission
Extra-hepatic manifestations
  - neurological (G-B), pancreatitis, thrombocytopenia, glomerulonephritis.
Hepatitis E

HEV in patients suspected of drug-induced liver disease
Darven et al. Gastroenterology 141:1665, 2011

318 patients suspected of drug-induced liver disease (DILI)

- 50 (16%) were positive for anti-HEV IgG
- 9 (3%) were positive for anti-HEV IgM (4 positive for HEV RNA, genotype 3)
  + frequent in ♂, mean age 67 yrs
  2 HIV+

Serologic tests for HEV must be done in patients suspected of DILI
Hepatitis E – an update

Immunodeficient patients
- In general genotype 3
  - Patients during chemotherapy
    - around 2% of patients with ALT alteration
    - High rate of chronification (> 50%)
  - Transplanted patients
    - Around 3-6% of kidney and liver transplant patients
    - Majority assymptomatic
    - High rate of chronification (> 2/3)
    - \( \approx \) tacrolymus; ↓ immunosupression \( \approx \) clearence
- HIV-positive patients
  - Around 4%
  - Chronification is also possible
  - \( \approx \) CD4 < 200 mm\(^3\) and/or RNA-HIV+
Hepatitis E

- Hepatitis E – an update

- HEV in patients with chronic liver disease
  - Superinfection with genotype 1 in patients with cirrhosis
    † in 12 months of 70% (India)
    - Superinfection with genotype 3 in patients with chronic liver disease
      † of 65%

- Fulminant liver failure and HEV
  More frequent in active alcoholics and cirrhotics
Hepatitis E

- Hepatitis E virus


- Serologic tests
  - Elisa: anti-HEV IgM
    - Improving
    - Wantai’s and Adaltis’ essays
      - Highly sensitive and specific (>95%)
  - Elisa: anti-HEV IgG
    - Detects previous contact
    - Needs improving (sensitivity)

- RNA HEV
  - Important for immunodeficient patients
  - Important to evaluate chronicity
**Acute Hepatitis E Diagnosis**

**Immunocompetent patients**
- Anti-HEV IgM detection
  - IgM -
    - No recent infection
  - IgM +
    - Recent infection confirmation by HEV-RNA tests

**Immunodeficient patients**
- Anti-HEV IgM detection
  - IgM -
    - HEV-RNA -
      - No recent infection
    - HEV-RNA +
      - Recent or active infection
  - IgM +
    - Status determination (clearance or persistent) by HEV-RNA

Abravanel et al. Med Mal Infect 2013 (modified)
Hepatitis E

Hepatitis E – an update

Treatment

- Self-limited in general
- Case reports of severe acute hepatitis treated with ribavirin
  - Only in genotype 3
- No reports in pregnancy because of teratogenicity
- Little experience treating chronic hepatitis
  - Reduce immunosuppression
  - Ribavirin for 3 months
  - Peginterferon
  - Peginterferon and ribavirin
Acute hepatitis E

ACLF

yes → Ribavirin

no → Ribavirin if: Encephalopathy coagulopathy extra-hep. manif.

Chronic hepatitis E

Tx → Reduce immunosup.

Ribavirin

HEV-RNA+

Rib./PEG

HIV infection

Hematologic disease

Ribavirin

*Barciela-Riveiro et al. Ann Hepatol 6:861, 2013*
Hepatitis E

Prophylaxis
- Developing countries
  - Basic sanitation improvement
- Developed countries
  - Avoid raw food
    - Cook pork meat at 71º for 20 minutes
Hepatitis E

**Prophylaxis**
- **Phase 2** study of recombinant vaccine (55-kDa)
  Shrestha et al. NEJM 356:895, 2007
  PRTb controlled with placebo
  - 2000 individuals from the *Royal Nepalese Army* were randomized
  - 7.4% events in placebo arm X 0.3%
  - efficacy of 95% (*intention to treat*: 88.5%)

- **Phase 3** study of recombinant vaccine (26-kDa)
  PRTb controlled with placebo
  - 112,604 civilians randomized (baseline immunity was not exclusion criteria)
  - efficacy of 100% (*intention to treat*: 95.5%)
  Licenced for production in China in January 2012
Hepatitis E

- HEV in Latin America
- Prevalence of antibodies against HEV in Venezuela
- First report of serologic evidence in Latin America
  - 1.6% (3/184)
    - pregnant women in Caracas
  - 3.9% (8/204)
    - countryside population (San Camilo, Edo Apure)
  - 5.4% (12/223)
    - countryside Amerindians (Padamo, Edo Amazonas).
HEV in Latin America

Moderate endemicity
ranges between 1-10%, never reaching 20%

No significant regional differences

Isolated Amerindian communities have higher prevalence: 5-17%
Venezuela, Chile, Bolivia

*one study in Bolivian Amazon demonstrated a prevalence of 20-41%
Hepatitis E

Serologic diagnosis of HEV

Despite being known for more than 30 yrs

- huge inconsistency among tests with IgM and G
- diversity of recombinant antigens used
- genetic variation among HEV strains

Difficulty in establishing the actual prevalence of the infection
HEV in Latin America
Subclinical infection in general
No reports of fulminant cases

- 2 outbreaks in México of non-A/non-B hepatitis
    - Huitzolla: 94 cases of jaundice in 1157 inhabitants
    - Telixtac: 129 cases of jaundice in 2194 inhabitants
  - EM: viral particles ≈ to that of outbreaks of enteric transmission in Asia
  - Posterior molecular studies suggest genotype 2a
Hepatitis E

HEV in Latin America

- epidemic outbreaks described in Cuba
- cases of coinfection with HAV
- reports of coinfection with HAV in sparse cases in Venezuela
- reports of sparse cases in ConeSul countries
  Argentina, Brasil, Chile, Perú, Uruguai

There are reports of circulation of HEV genotypes 1 and 3 in Latin America
HEV in Latin America

Latin America is considered an endemic region for HEV except for the Caribbean, there is no evidence. More consistent studies in Brazil, Argentina, .... low endemicity

Serologic tests need better standardization then, it will be possible for us to know the burden of HEV in our region
Hepatitis E

**Take home message**

- HEV exists in endemic form in some regions of Latin America
- Increase in HEV cases in industrialized countries
  - zoonosis
- Acute hepatitis E may cause death
  - Mainly in immunodeficient patients (alcoholic cirrhosis)
- HEV may lead to chronic liver disease
  - Mainly in immunodeficient patients
- Ribavirin may be a treatment option
  - acute-on-chronic liver failure / chronic infection
- Prophylaxis with sanitary measures and avoiding raw food
- Wait for safety profile of vaccines
- **DESPITE INFREQUENT, HEPATITIS E IS A REALITY IN LATIN AMERICA, AND NOT A FICTION.**