The Emerging Challenge of Hepatitis E

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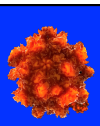
Talk outline

- HEV:
  - Acute infection
  - Chronic infection
- Places HEV hides:
  - in the history books
  - in populations
  - at patient level
  - Diagnostic algorithms
- Clinical phenotype of HEV is still emerging

HEV



- RNA virus
- Genotypes 1 & 2: human disease only
- Genotype 3 (& 4):
  - Human disease
  - Found in animals (asymptomatic)
    - **Pigs**
      - Worldwide
      - 85% UK pigs affected
    - Boar, deer, rabbits
    - Rats, ferrets, bats, cut-throat trout, mongoose

HEV in developing countries

- Major health issue
  - Large outbreaks
- Genotypes 1 & 2
- Faeco-oral route via infected water
- Affects young adults
- Mortality in pregnant women 25%

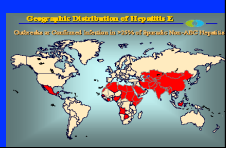
HEV in developing countries: global burden of disease

- 9/21 Global Burden Disease regions:
  - 20 million infections/year
  - 70,000 deaths & 3,000 stillbirths/year

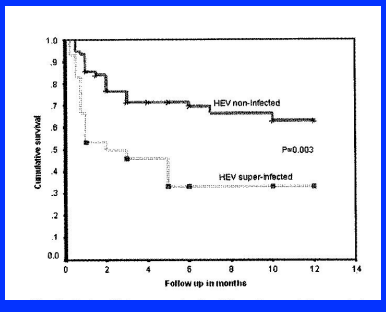
Rein et al Hepatology 2012

•1,000 maternal deaths/yr in Bangladesh

Labrique et al EID 2012



HEV: in chronic liver disease



Kumar Acharya et al J Hepatol 2007

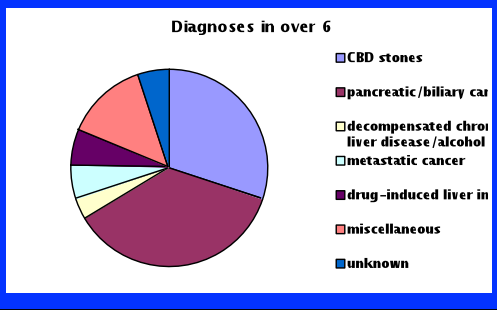
HEV in developed countries: received wisdom

- A bit like HAV
  - Acute illness
  - Self-limiting
- Mainly seen in travellers
- v. rare in non-travellers
- Of little relevance in developed countries

Cornwall

- Good location to do epidemiological studies
- <0.5% immigrants

Jaundice hotline clinic: 1998-2014 (n > 2,600)



Acute viral hepatitis in Cornwall, UK

1. **Acute HEV**
2. Seronegative hepatitis
3. EBV hepatitis
4. Acute HBV
5. HAV
6. Acute HCV

Dalton et al EuroJMicro 2008, Vine et al APT 2012, Donaghy et al EJGH 2013

Acute HEV3: Cornish experience

- 122 cases of HEV in non-travellers
  - Genotype 3
- M:F = 3:1
- Median age 63.5 years (range 32-92)

Dalton et al J Viral Hepatitis 2007, Dalton et al EurJGastro 2008, Vine et al APT 2012, Woolson et al 2014, APT

Acute HEV3: symptoms

COMMON
- Jaundice
- Anorexia
- Lethargy
- Abdominal
- pain
- Vomiting
- Fever
- Myalgia

LESS COMMON
- Pruritis
- Weight loss
- Headaches
- Arthralgia
- **Neurological (n=9)**
- No symptoms

Dalton et al EJGH 2008, Woolson et al APT 2014

Acute HEV3: Spectrum of severity

- Asymptomatic – mild hepatitis –liver failure
- Most recover 4-6 weeks

- High mortality in patients with pre-existing chronic liver disease : *Dalton et al Lancet 2007*
  Peron et al JViralHepat 2007
  - 27% in Anglo/French study (n=372)
  - No clinical or laboratory clues to diagnosis
  - Varies by geographical location
    Blasco-Perrin et al, submitted

HEV: Other developed countries

- USA *Drobeniuc EID 2013*
- Japan *Mizuo ClinMicro 2002*
- France *Mansuy JMedVirol 2004*
- Netherlands *Widdowson JMedVirol 2004*
- Spain *Buti JVirolMethods 1995*
- Italy *Romano J Hepatol 2010*
- New Zealand *Dalton JGastHepatol 2007*
- Denmark, Germany, Hungary, Sweden *2009-*

HEV: demographics and outcome

	UK *Dalton et al 2008*	**France** *Peron et al 2006*	**Japan** *Okamoto et al 2003*
Cases	40	23	46
Mean age	65 yrs	54.4 yrs	59.6 yrs
% males	77.5%	73.9%	87%
Deaths	7.5%	8.7%	10.8%
Liver deaths	5%	8.7%	10.8%

HEV3: host risk factors

- Age & male sex
- Alcohol consumption >22 units/week
- ? Diabetes

- **Is subclinical hepatic steatosis/fibrosis the key factor?**

Dalton et al EJGH 2012

HEV3: incidence

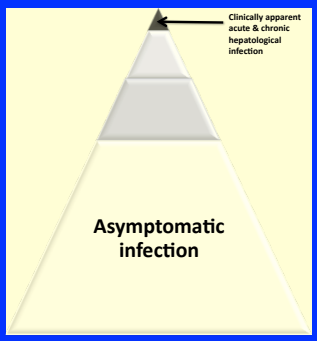
- UK: 0.2% *Ijaz et al 2009 JClinVirol*
  Ijaz et al JID 2014
  100,000 infections per year
- USA: 0.7% *Faramwi et al EpiInf2011*
- Netherlands: 1.1% *Slot et al Eurosurv 2013*
- SW France: 3.2%
  Abravenal et al JID 2014

HEV 3: Asymptomatic infection

- Asymptomatic infection probably very common

- Aurora outbreak 2008
  - 33 cases hepatitis E
  - **67% asymptomatic**

Said et al EID 2009



Re-infection with HEV

- Genotype 4, China:
  - 20% are re-infections
  - More common in females
  - Milder hepatitis than primary infection
  - IgM negative, IgG and PCR positive

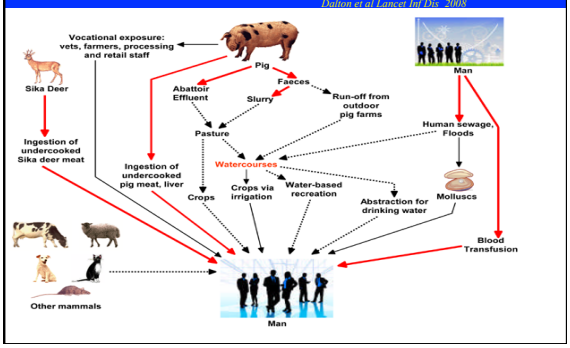
Kamar et al Lancet 2012

- Genotype 3, Toulouse, France:
  - Reinfections quite common
  - IgG <7 WHO units/ml

Abravanel et al JID 2014

HEV3: Source and route of infection

Dalton et al Lancet Inf Dis 2008



Acute HEV: Summary

- Older males, Genotype 3
- Porcine zoonosis, route of infection uncertain
- Range of severity
- High incidence of infection
  - Asymptomatic infection is common
- Prognosis poor in chronic liver disease

Chronic HEV infection: Transplant recipients

- Chronic HEV3 infection in transplant patients *Kamar et al NEJM 2008*
  - No symptoms, anicteric, ALT 200-300IU/L
- Chronicity occurs in 60% of HEV3 infections, Genotype 3 only
  - Tacrolimus
  - Low platelet count *Kamar et al Gastroenterology 2011*
- Cirrhosis rapidly progressive *Kamar et al Transplant 2010*
- Prevalence of chronic HEV
  - High in French transplant centres
  - Other European transplant centres: 1-2%

Pas et al EID 2012
Koning et al J Heart Lung Tran 2013
Moal et al JMV 2013
Halac et al Gut 2012
Pischke et al Am J Transpl 2012

Chronic HEV infection: Haematological malignancy

- 6 cases in Toulouse:
  - 3 acute, 3 chronic

Tavitian et al JCV 2010

- Allogeneic stem cell transplants, Netherlands:
  - 8 cases, 5 chronic HEV
  - 4 died with HEV viraemia

Versluis et al Blood 2013

HEV & HIV co-infection

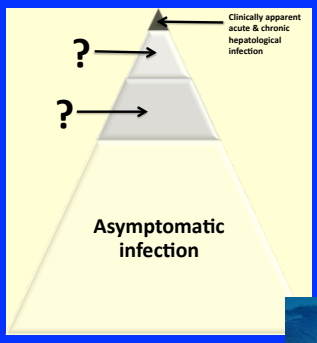
- Small number of chronic cases:
  - HEV genotype 3
  - CD4 counts <250

Dalton et al NewEngJMed 2009, Colson et al J Viral Hepatitis 2011, Foguena et al Emerg Infec Dis 2011, Kaba et al J Med Virol 2011, Jagjit Singh et al J Infection 2012, Andersson et al AIDS 2013

HEV treatment and prevention

- Acute HEV
  - No treatment required, ribavirin in severe cases
- Chronic HEV *Kamar et al, NEJM 2014*
  - Wait (3 months)
  - Reduce immunosuppression
  - Ribavirin monotherapy
    - » 3 months
    - » Longer if stool still PCR +ve
- HEV vaccine

Places HEV hides:



Places HEV hides (1) history books

- HEV as an emerging disease *Dalton et al Lancet Inf Dis 2008*
- HEV as an ancient disease:
  - Diverged into 4 genotypes 16th Century
  - 19th Century HEV1 common in Europe
  - HEV1 moved east (Asia) and south (Africa)
  - HEV3 hid in pigs, only recently recognised

Teo Epidemiol Infect 2012

Places HEV hides (2) at population level

- Insensitive IgG assays

HEV IgG seroprevalence in developed countries

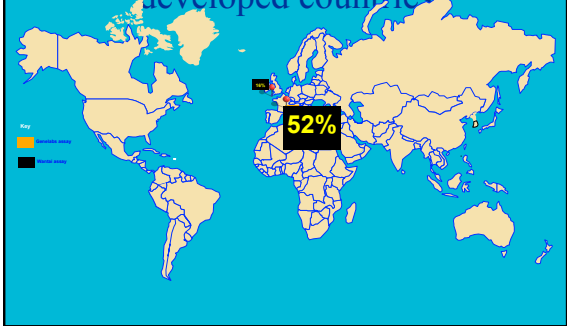
HEV IgG seroprevalence in developed countries

Wantai vs Genelabs HEV IgG assay

- PCR proven HEV3 cases (n=18)
- Serial samples n=50 (up to 7 years)
- **Genelabs underestimates true seroprevalence by a factor of 4**
  - Toulouse study showed seroprev of 16% using Genelabs

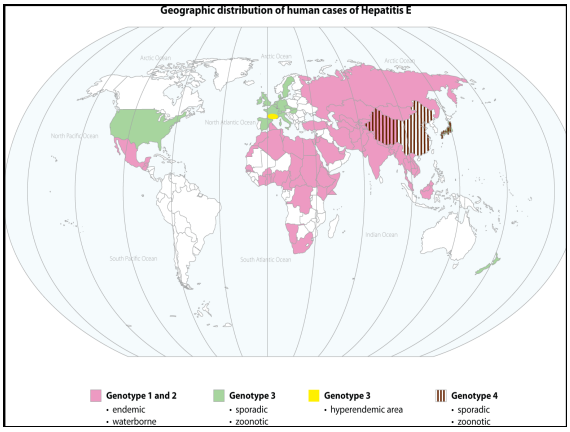
Bendall et al J Med Virol 2010

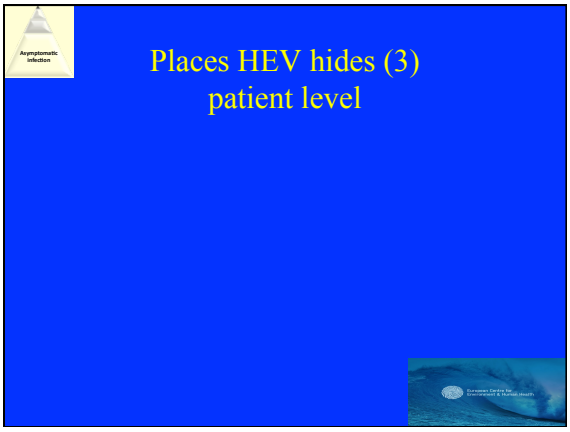
HEV IgG seroprevalence in developed countries



52%!!!!!!

- Seroprevalence in children aged 2-4 years = 2%
  Mansuy et al Emerg Inf Dis 2011
- Observed incidence of HEV infection in Toulouse = 3.2%
  Mansuy et al Emerg Inf Dis 2011





HEV and blood donors

Country	Blood donors HEV RNA positive	HEV IgG seroprevalence	Assay	Reference
France Midi-Pyrénées	1:1595	52% 16%	Wantai Genelabs	*Gallian et al, 2014* *Mansuy et al, 2011* *Mansuy et al, 2008*
Japan	1:1781			Fukuda et al, 2004
Germany	1:1200 1:4525	29.5% 18.0% 4.5%	Wantai Mikrogen MP diagnostics	*Vollmer et al, 2012* *Baylis et al, 2012* *Wenzel et al, 2013*
Netherlands	1:2671	27.0% 1.1%	Wantai Abbott	*Slot et al, 2013* *Zaaijer et al, 1993*
Sweden	1:7986	9.2%	Abbott	*Baylis et al, 2012* *Olsen et al, 2006*
England	1:2848 1:7000	12.0% 5.3	Wantai Abbott	*Hewitt et al, 2014* *Ijaz et al, 2012* *Beale et al, 2011* *Bernal et al, 1996*
Scotland	1:14520	4.7%	Wantai	*Cleland et al, 2013*

HEV and blood donors: SE England (2012-13)

- 225,000 donors
- 79 HEV RNA +ve
  - 1 in 2,848
- 60 recipients given HEV-contaminated products
- Follow-up: n=43

	Recipients of blood components	Infected recipients	Uninfected recipients
Red blood cells	16	4 (25%)	12 (75%)
Pooled platelets	10	4 (40%)	6 (60%)
Apheresis platelets	14	7 (50%)	7 (50%)
Fresh frozen plasma	2	2 (100%)	0
Pooled granulocytes	1	1 (100%)	0
Total	**43**	**18 (42%)**	**25 (58%)**

Hewitt et al, Lancet 2014

HEV and blood donors: SE England (2012-13)

- Transmission
  - » More likely with high viral load in donor (p<0.0001)
  - » Less likely if donor has anti-HEV antibodies
- Immunocompetent recipients (n=8)
  - » Spontaneous viral clearance in all
  - » Symptomatic hepatitis (n=1)
- Immunocompromised recipients
  - » Asymptomatic, later infection/seroconversion
  - » PCR +ve > 3 months n=7
  - » 4 deaths (x2 sepsis, x1 cardiac, x1 no info)

Hewitt et al, Lancet 2014

HEV and blood donors: SE England (2012-13)

'On a clinical basis alone, the resulting minimal burden of disease does not signal a pressing need for donation screening at this time'

Hewitt et al, Lancet 2014

Something is happening!!!

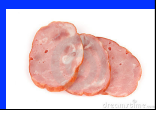
- Dutch blood donors 2014
  - **1 : 600 are HEV RNA +ve**

Zaaijer et al Hepatology 2014

- Increased incidence in England
  - HEV RNA similar to European pigs

Ijaz et al JID 2014

- Changes in EU food chain?
  - Processed ham and pig serum
  - Role of Food Standards Agency (UK)



Places HEV hides: with the transplant physician

- Chronic infection
  - Asymptomatic
  - ALT 100-300

Places HEV hides
Drug-induced liver injury (DILI)

- 13% of patients with DILI have HEV3

Dalton et al APTherap 2007

- USA: 3% of DILI is HEV3 infection

Davern et al Gastroenterol 2011

- Diagnosis of DILI not secure without testing for HEV

Places HEV hides:
?? with the Haematologist

- Monoclonal gammopathy of uncertain significance (MGUS)
  - Occurs in 1% of the elderly
  - Some develop malignancy (myeloma, lymphoma, leukaemia)
- MGUS and HEV
  - 25% of patients with acute HEV3 have MGUS at presentation
  - 0% of patients with HAV, HBV, EBV have MGUS
  - 2 patients with HEV3 » haematological malignancy
- Is HEV oncogenic?

Woolson et al APT 2014

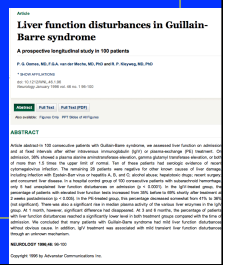
Places HEV hides:
with the Neurologist

- HEV associated neurological syndromes:
  - Guillain–Barré syndrome
  - bilateral brachial neuritis
  - Encephalitis, Bell's Palsy, ataxia/proximal myopathy, etc
- **LFTs only mildly abnormal and most cases anicteric**
- Occurs in:
  - acute and chronic HEV
  - Developed and developing countries
- Outcome:
  - Most recover, some do not

Kamar et al Emerg Inf Dis 2011

Guillain-Barré Syndrome (GBS)

- Post infectious immune-mediated polyradiculopathy
- Infectious triggers:
  - Campylobacter: 35%
  - Unknown: 50%
- **30% abnormal LFTs ? Cause**



Article

Liver function disturbances in Guillain-Barre syndrome

A prospective longitudinal study in 100 patients

P. G. Genius, MD, F.S.A. van der Meche, MD, PhD and R. P. Kleyweg, MD, PhD

ABSTRACT

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Oomes et al Neurology 1996

Places HEV hides:
Guillain-Barré syndrome

- Case control study of Dutch patients with GBS (n=201)
  - 5% of GBS have HEV infection (10/201, p=0.01 vs controls)
  - Mildly abnormal LFT's:
    - normal bilirubin
    - ALT: 70 (range 26-921); abnormal n=7
  - Outcome:
    - 1 required ventilation
    - 7 have significant disability at 6 months
  - Some patients are viraemic (HEV3) at presentation
    - ?role for early therapy with ribavirin

van den Berg et al Neurology 2014

HEV & Guillain-Barré syndrome:
outstanding questions

- 30% of GBS have abnormal LFT's
  - Are the other 25% caused by re-infection with HEV?
- Does it occur in other locations?
  - Developed/developing countries
- What are the pathogenic mechanisms?
- Role of HEV in other neurological syndromes?

van den Berg et al Neurology 2014

Places HEV hides: Brachial neuritis

- LFTs abnormal in some patients, ? Cause
- Anglo/Dutch cohort study: 47 patients tested for HEV
  - 5 (10%) had HEV at the start of the illness
  - Age 30-40 years
  - Mildly abnormal LFT's: ALT 100-300, normal bilirubin
  - 4 PCR positive: HEV genotype 3

Van Eijk et al, Neurology 2014

Places HEV hides (4): Diagnostic algorithms

Raised ALT: differential diagnosis

1. Drug-induced hepatitis
2. Autoimmune hepatitis
3. **HEV**
4. EBV
5. Acute HBV
6. HAV

Dalton et al EuroJMicro 2008, Vine et al APT 2012, Donaghy et al EJGH 2013, Panayi et al EJGH 2014

Current diagnostic algorithm: Raised ALT

- Check HAV, HBV and HCV
- If above are negative maybe think about HEV

Suggested diagnostic algorithm: Raised ALT

- Check HEV
- If above are negative maybe think about HAV, HBV and HCV

Conclusions: HEV in developed countries

- Common
  - HEV likes to hide
- Porcine zoonosis
- Significant morbidity & mortality
  - Acute and chronic
  - Prognosis poor in chronic liver disease
  - Neurological injury
- Current diagnostic algorithms are nonsense
  - **Clinic phenotype of HEV is still emerging**

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