Hepatitis A
and
Hepatitis E

Luis S. Marsano, MD
Professor of Medicine
Division of Gastroenterology, Hepatology & Nutrition
University of Louisville and Louisville VAMC
2020

Viruses that cause Hepatitis in Humans

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Coxsackie
- Echovirus
- Yellow fever
- Rubella
- Junin virus (Argentina)
- Machupo virus (Bolivia)
- Lassa virus
- Rift Valley virus
- Marburg virus
- Ebola virus
- Measles virus
- Human adenovirus
- CMV
- EBV
- HSV
- Varicella-Zoster

Hepatitis A

Hepatitis A

- Hepatovirus from Picornavirus family.
- 27-32 nm, linear, (+) sense, simple stranded RNA.
- Reservoir: human only
- Acquisition: fecal-oral; concentrated in oysters. Contaminated water or food, men having sex with men, blood during short viremic phase.
- Non-cytopatic; immune mediated injury by lymphocytes

Groups at Risk for HAV

- Healthy persons who travel to endemic areas,
- Workers in occupations with high likelihood of exposure,
- Family members of infected patients,
- Persons who adopt infants or children from endemic areas,
- Men who have sex with men,
- Persons who have tested positive for human immunodeficiency virus,
- Persons with chronic liver disease,
- Persons with clotting factor disorders,
- Users of injection and noninjection illicit drugs.

Hepatitis A
Sero-Prevalence

- ***Poor sanitation countries***:
  - near 100 % by age 5.
- ***Good sanitation countries (USA)*** :
  - 10 % by age 14;
  - 37 % in adults.

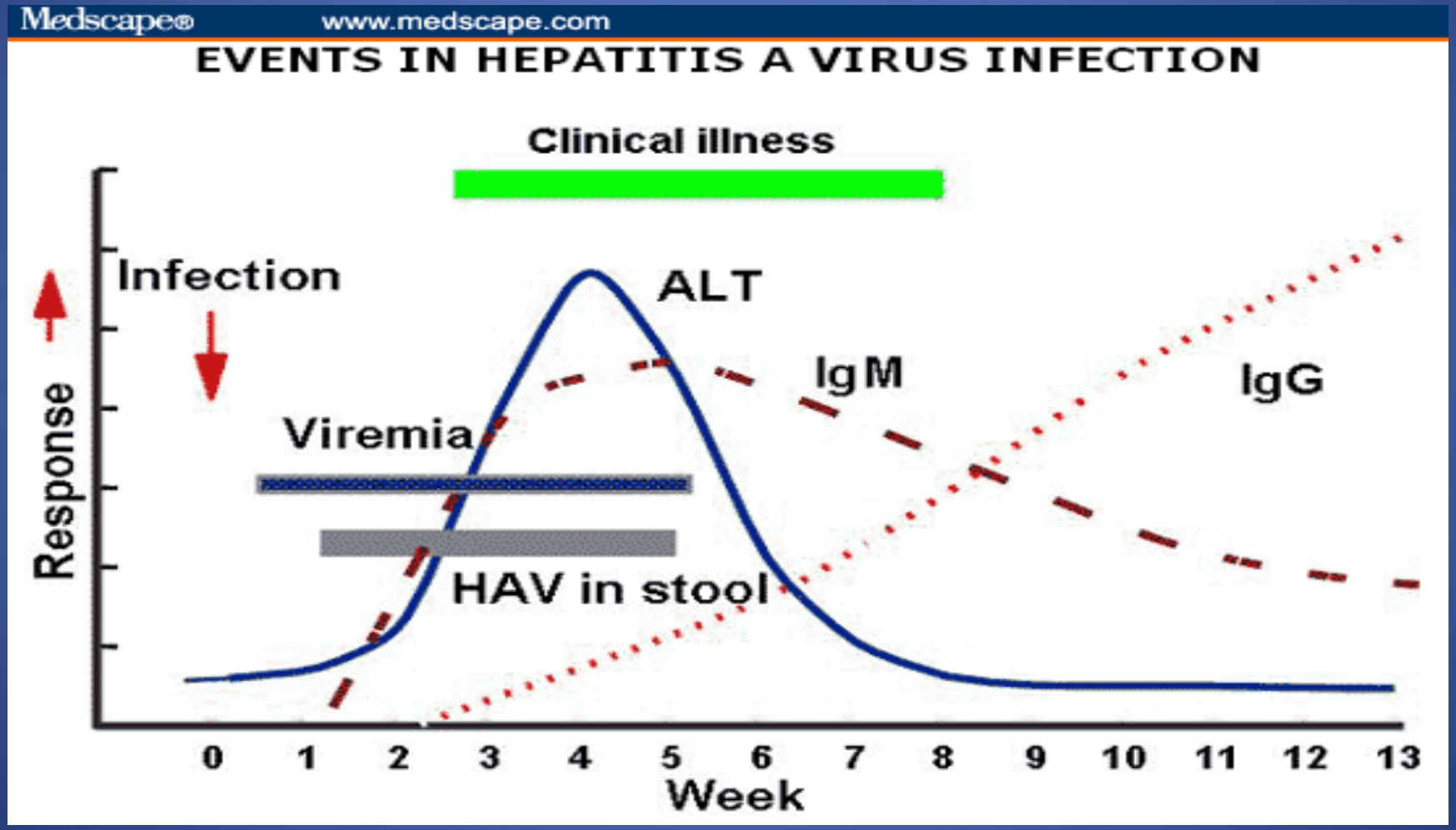
Hepatitis A
Clinical Features

- **Incubation**: 2-4 (up to 6) weeks
- Children < 2 year: 80% anicteric & asymptomatic
- Children > 2 y and adults: 80% icteric & symptomatic
- **Symptoms**: Fatigue (90%), anorexia (85%), jaundice (80%), nausea (75%), low fever (65%), headache, abdominal pain and myalgias.
- **Duration**: usually < 8 weeks

Hepatitis A
Atypical Manifestations

- **Relapsing hepatitis**: less than 10%; 2 or more bouts of elevated enzymes.
- **Cholestatic hepatitis**: Severe and prolonged jaundice > 10 weeks. Is rare.
- **Fulminant Hepatitis**: very rare but lethal in 50%. Increased risk in elderly and persons with chronic liver disease and HIV infection.
- **Auto immune hepatitis Type I:** after acute HAV in genetically predisposed.
- Mortality: Not increased by pregnancy.
  - a) younger than 49 = 0.3%;
  - b) older than 49 = 1.8%.

Sequence of Events in Acute HAV



Extra hepatic Manifestations of HAV

- Evanescent rash (14%)
- Arthralgia (11%)
- Leukocytoclastic vasculitis (legs and buttocks)
- Glomerulonephritis
- Arthritis (lower extremities)
- Cryoglobulinemia.
- Toxic epidermal necrolysis.
- Myocarditis
- Acute kidney Injury.
- Optic neuritis
- Transverse myelitis.
- Polyneuritis.
- Cholecystitis.
- Thrombocytopenia,
- Aplastic anemia,
- Red-cell aplasia
- Hemolysis in G6DH deficiency
- Pancreatitis.

Hepatitis A
Vaccination Recommendation

- Children in areas with rate >20/100000
- High risk: traveler to endemic area, men having sex with men, illegal drug users, person with clotting factor disorder, researcher working with HAV.
- Chronic liver disease: HBV, HCV
- During community outbreaks.
- **Immunogenicity:** > 70% within 2-4 weeks after 1st dose, and 94-99% after second dose.

Hepatitis A
Post-Exposure Management

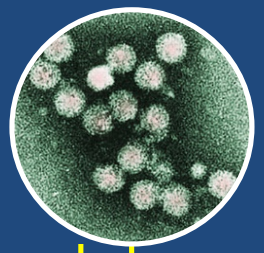
- Post-exposure prophylaxis can be done:
  - with Intramuscular “Immune Serum Globulin” (ISG) within 14 days from exposure at 0.06 mL/kg (69-89% effective and lasting 12-20 weeks) or
  - with Inactivated Vaccine given also within 14 days post-exposure.
- Response to vaccine is less robust:
  - before age 1 (due to circulating maternal antibodies), and
  - after age 40.
- Inactivated Vaccine is the preferred approach from age 1 to 40.
- Immune serum globulin is preferred in all other groups unless contraindicated due to IgA deficiency or hypersensitivity to ISG.

Hepatitis E

Hepatitis E

- 27-30 nm non-enveloped, single-stranded, positive-sense RNA Hepevirus in family Hepeviridae.
- There are 4-6 genotypes. Genotypes 1 & 2 only in humans. Is not cytopathic; injury is immune mediated.
  - 1: India, China, Pakistan;
  - 2: Mexico;
  - 3: USA, France, Japan.
  - 4: China, Japan
  - There is an avian and a rat HEV variant.
- Acquisition:
  - Waterborne, fecal-oral, by organ meat ingestion, or by contact with animals. In USA swine is a common source. Deer meat and shellfish may be the source.
  - Rare person-person (1.5% intra-familial). Rare materno-fetal and by transfusion.
  - Increased risk in homosexual men.

HEV Classification



FAMILY

Hepeviridae

GENUS

Orthohepevirae

Vertebrates

GENUS

Piscihepeviridae

Fish

GROUP A HEV

Humans, Pigs, Deer, Rabbits

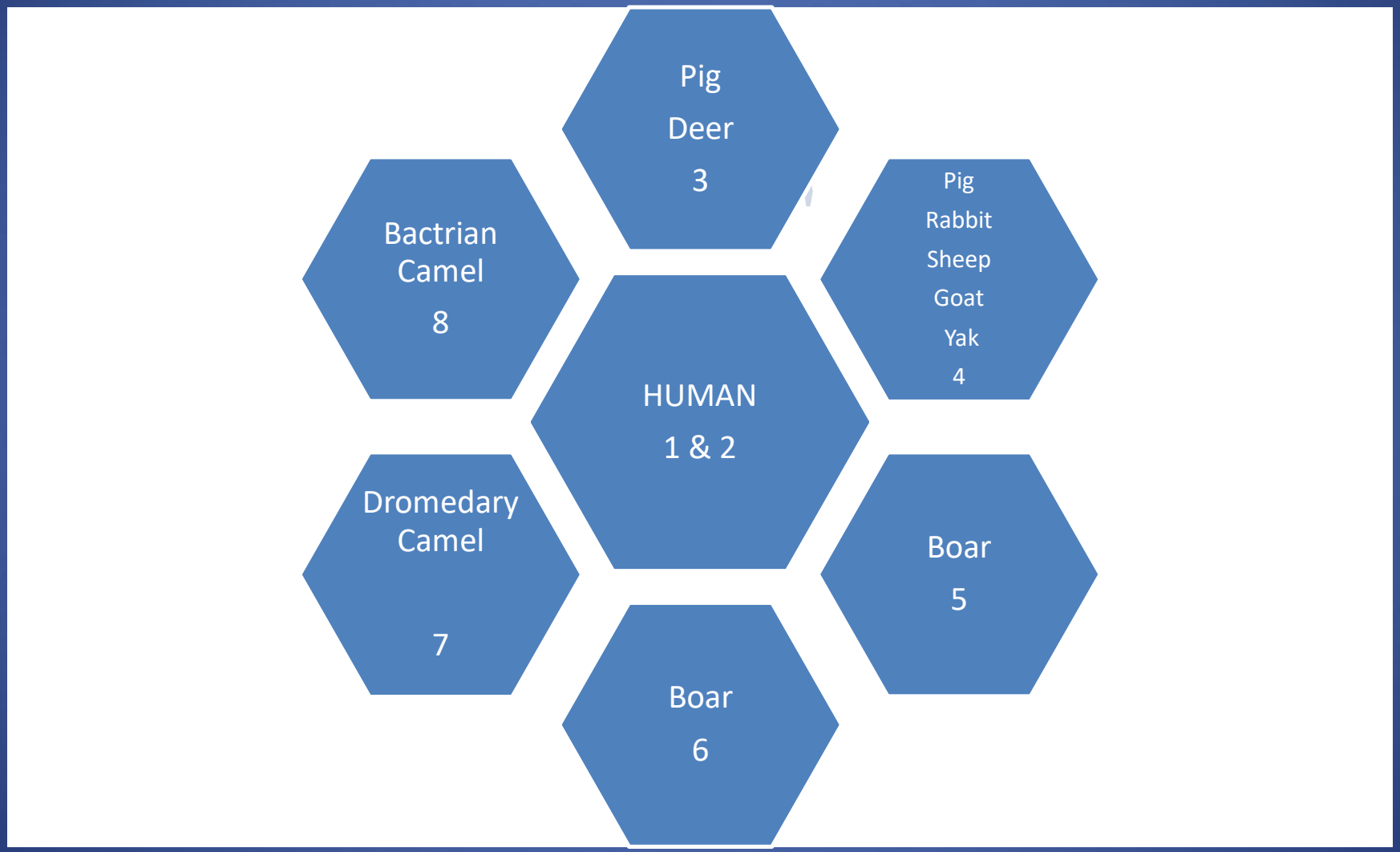
GROUP B

Avian

GROUP C HEV

Rodents

HEV Group A


Pig
Deer
3
Bactrian
Camel
8
Pig
Rabbit
Sheep
Goat
Yak
4
HUMAN
1 & 2
Dromedary
Camel
7
Boar
5
Boar
6

Hepatitis E

- **Types:** Sporadic, epidemic & endemic acute hepatitis. Rare chronic hepatitis.
  - **Sporadic:** traveler to endemic areas, pet owners, organ meat eaters, male homosexuals, military service (Midwest USA).
  - **Epidemic:** after heavy rain and flooding in areas with poor sanitation (India, China, Latin America, Africa)
  - **Endemic:** In areas were asymptomatic infection occurs at early age, like in Egypt
  - **Chronic hepatitis:** in immunosuppressed patients, with progressive liver damage an cirrhosis (worse with Tacrolimus than with CSA).
- **Reservoir: human**, pig, boar, sheep, cattle, rat,…
- **Prevention:** there is an experimental recombinant vaccine.

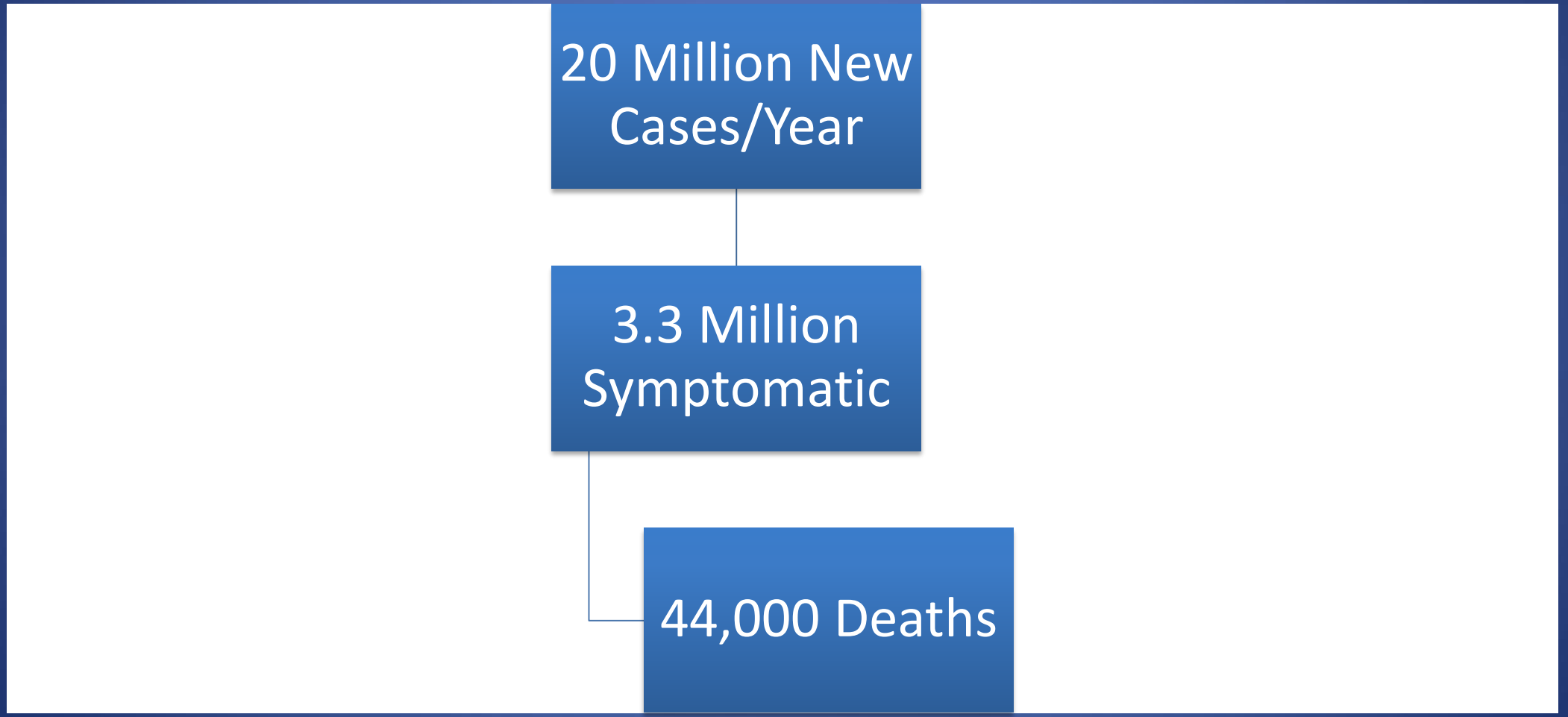
Features of HEV in Different Areas

	Highly Endemic Area	Nonendemic Area
Geographic Area	Tropical & Subtropical Asia, Africa, Central America	USA, Western Europe, Asia-Pacific.
Human Disease	Highly frequent sporadic and endemic cases	Infrequent sporadic cases
Reservoir	Primarily human; possible environmental	Zoonotic (pig, boar, deer)
Primary transmission route	Fecal-oral by contaminated water	Undercooked organ meat; contact with animals.
Affected Groups	Young and healthy.	Elderly with comorbidities.
Disease in Pregnancy	High frequency of severe disease (22% FHF)	Not reported.
Prevalent Genotypes	1,2, (4).	3, (4).
Chronic Infection	Not reported.	In immunosuppressed (g-3)

Hepatitis E

- BURDEN: Worldwide causes 20 million new infections annually,
  - 3 million cases of acute hepatitis and over 55,000 deaths.
- Seroprevalence in USA is declining:
  - 21 percent between 1988 through 1994, and 6% in 2009-2010.
- Transmission:
  - Contaminated food and water, Blood transfusions, and through Mother-to-Child transmission, ? breast-feeding;
  - Person-to-person transmission is uncommon.
- Has at least 8 Genotypes.
  - Genotypes 1 and 2 are confined to humans; transmission by fecal-contaminated water.
  - Genotypes 3 and 4 by contaminated food (uncooked pork/boar sausages, organ meats, milk) and occupational exposure.

HEV: Significance



WHO, Accessed 11/2019

Geographic Distribution of Primary Human HEV Genotypes Based on 148 bp of the ORF2 gene

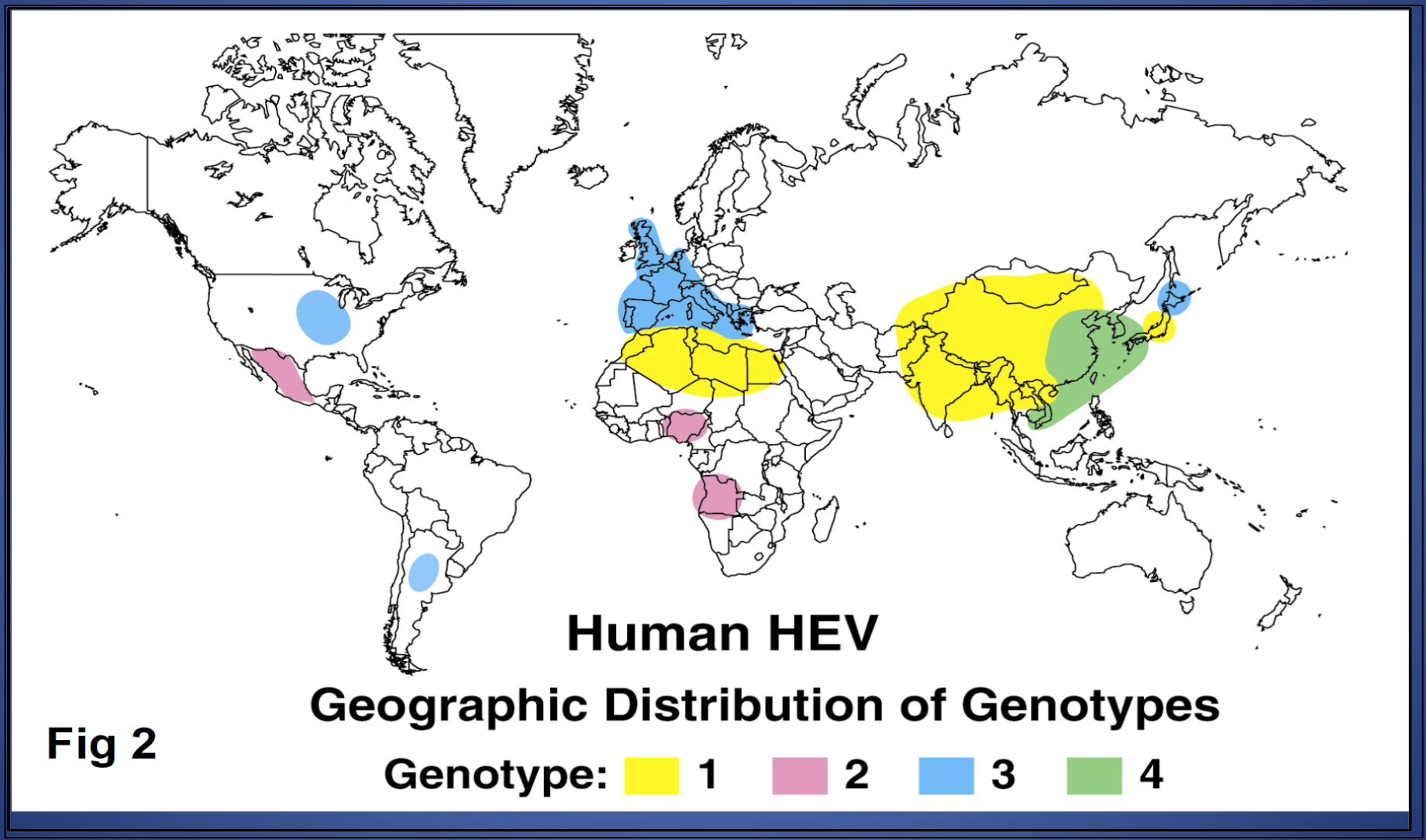
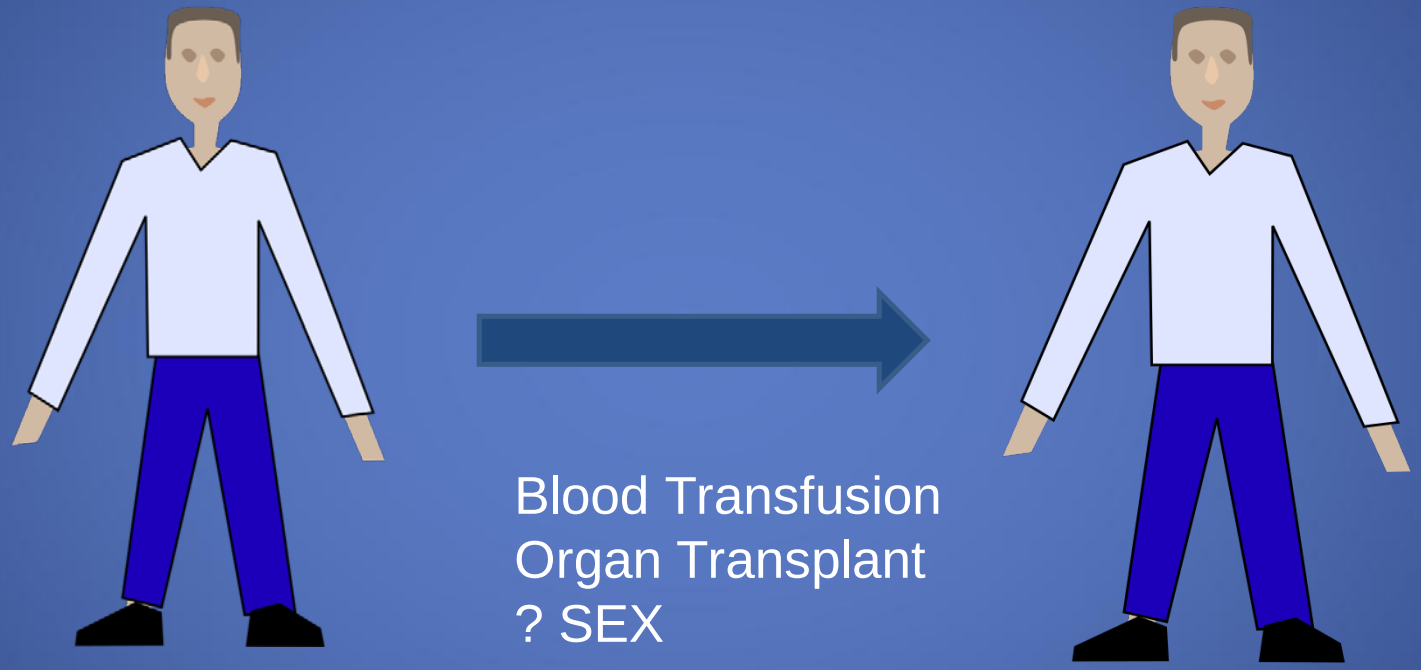


Fig 2

Human to Human - Not Genotype 1,2



Blood Transfusion
Organ Transplant
? SEX

Hepatitis E

- **Incubation**: 2-10 weeks.
- **Prodrome**: 2 weeks of malaise, mild chills & fever, transitory macular rash.
- **Symptoms & Signs**: jaundice, nausea, vomiting, anorexia, aversion to food & smoking, abdominal pain, clay-color stool. Hepatomegaly in 65-80%; symptoms usually for 4 weeks.
- **Mortality**:
  - 0.1-0.6%; 15-25% during pregnancy in the epidemic form in India.
  - Mortality in pregnancy is low in Egypt and other endemic areas.
- **Diagnosis:**
  - Anti HEV-IgM last only 3-6 months, and is not always present in acute infection;
  - Anti-HEV IgG lasts for years;
  - HEV can be found by PCR in stool, serum, and bile.
- **Treatment:** Reduction in Immunosuppression is initial therapy**;** may need Peg-IFN and Ribavirin x 3-6 months in chronic HEV.

Acute Hepatitis E

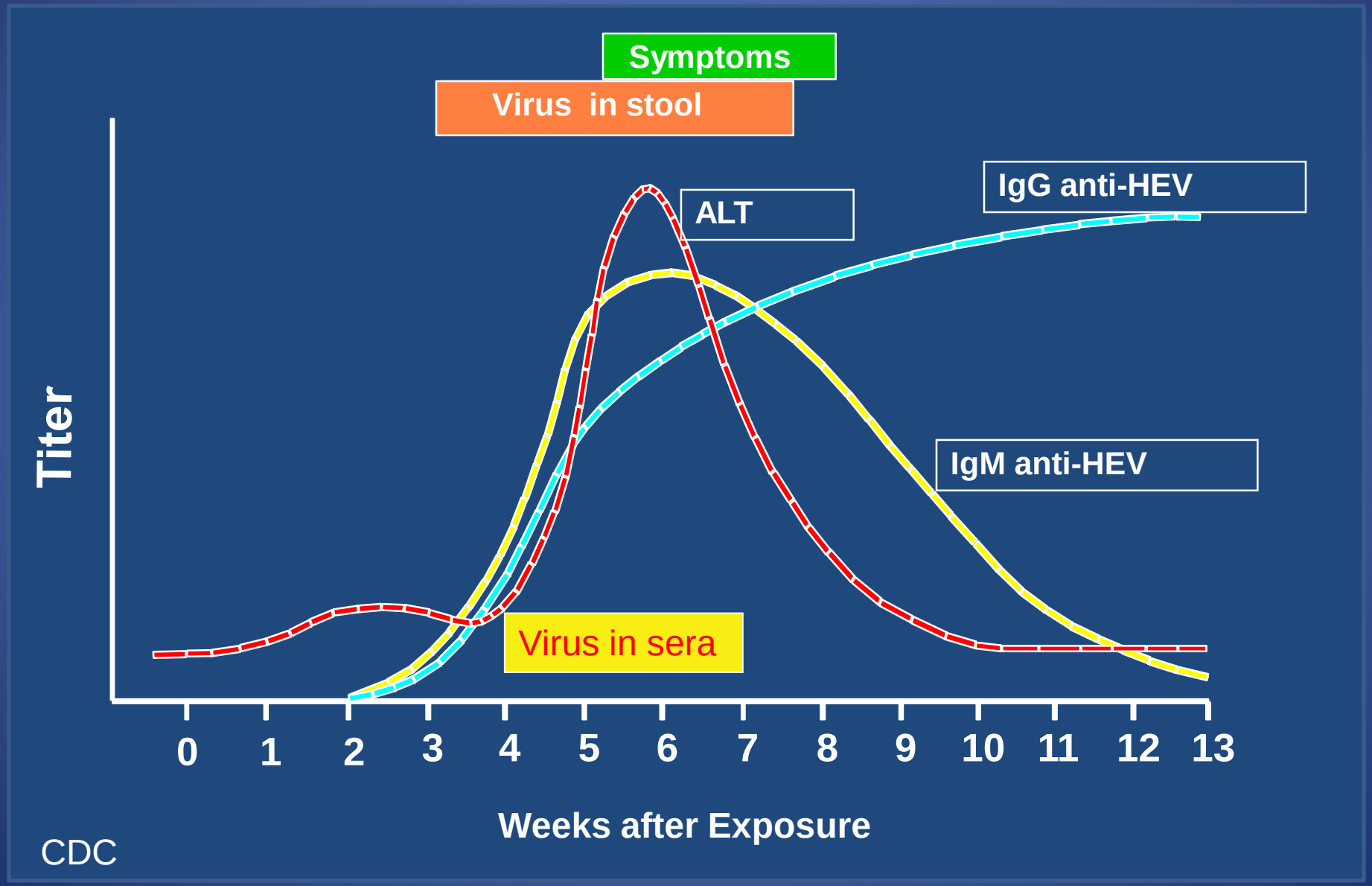
Clinical Presentation

- Incubation 15-60 days.
- Most asymptomatic or minimally symptomatic
- If symptomatic:
  - Jaundice, malaise, anorexia, nausea, vomiting, abdominal pain, fever, and hepatomegaly.
  - Less common features: diarrhea, arthralgia, pruritus, and urticarial rash
- Laboratory: Elevation of bilirubin, ALT and AST; lasts 1 to 6 weeks.
- Acute Liver Failure in 0.5-4%
- Mortality in pregnancy 1st infection: 15-25%
- May have cholestatic hepatitis for >/= 3 months
- Chronic Hepatitis in Immunocompromised; only genotypes 3 and 4.

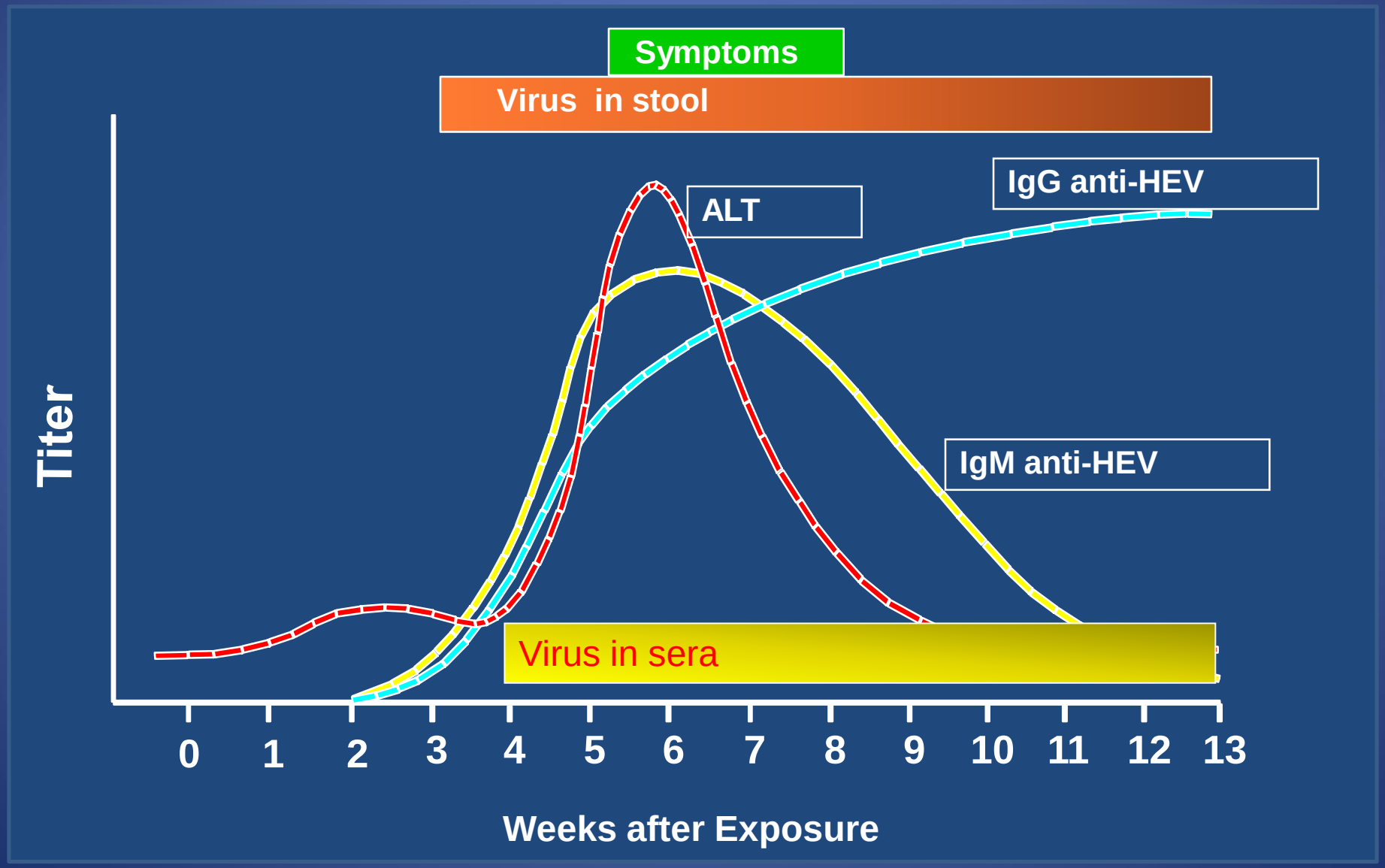
Extrahepatic Manifestations

- Thrombocytopenia, hemolysis, and aplastic anemia
- Acute thyroiditis
- Membranous glomerulonephritis
- Henoch-Schonlein Purpura.
- Acute pancreatitis
- Neurologic disorder:
  - Acute transverse myelitis,
  - Acute meningoencephalitis,
  - Aseptic meningitis,
  - Neuralgic amyotrophy,
  - Pseudotumor cerebri,
  - Bilateral pyramidal syndrome,
  - Guillain–Barré syndrome,
  - Cranial nerve palsies,
  - Peripheral neuropathy

HEV - Typical Clinical/Serological Course



HEV in Immunosuppressed Host
CHRONIC Clinical/Serological Course



Diagnosis: Virologic

Blood

- Short Window of Viremia

Stool

- Longer period of shedding
- Generally not available

Tests for HEV

Serologic

- **HEV IgG EIA** (last up to 14 years)
- **HEV IgM EIA** (last 4-5 months)

False (+) in EBV and AIH

- HEV serotyping
- HEV ELISPOT

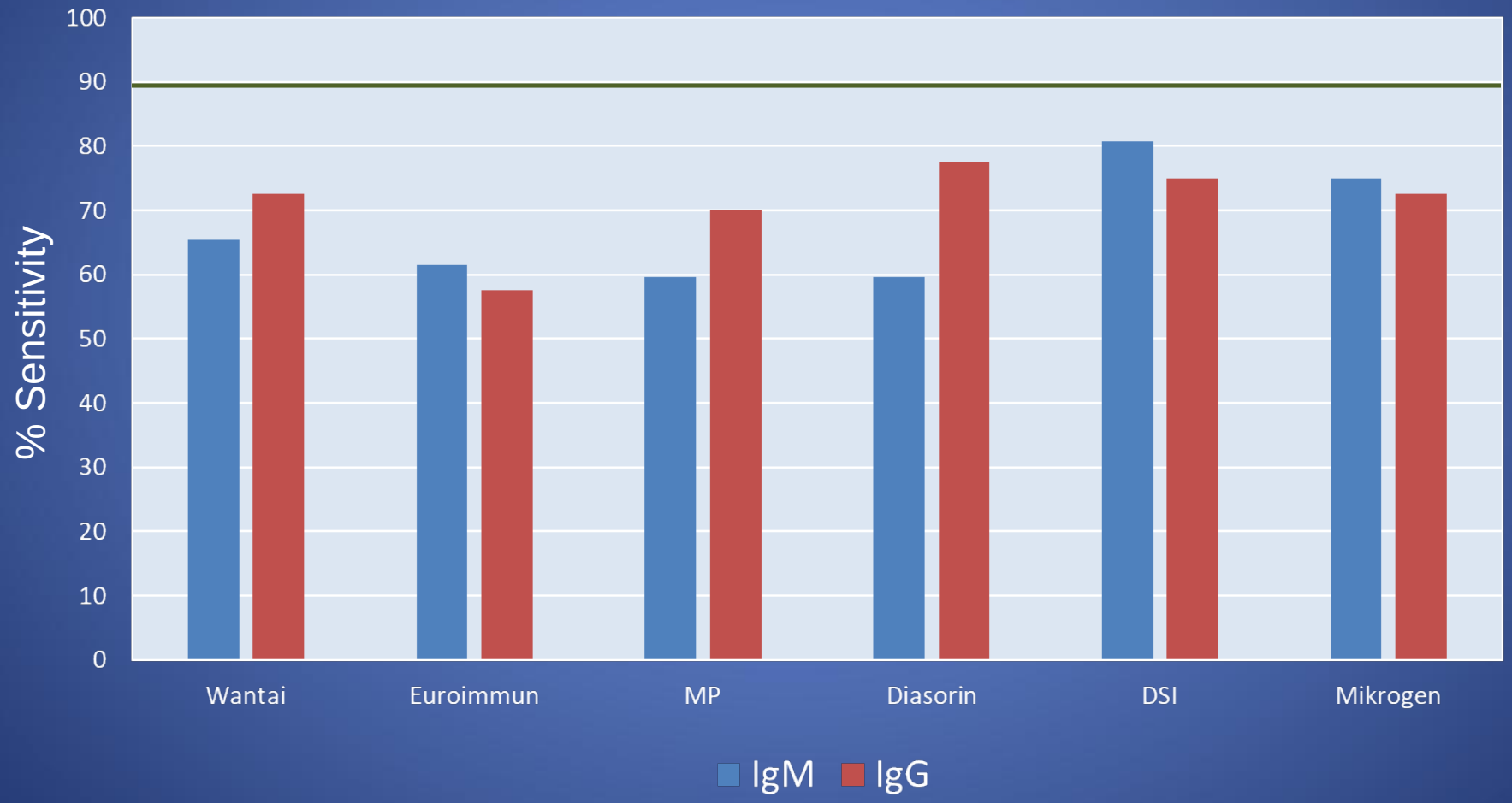
Virologic- Serum/Plasma or Stool

- Nested PCR
- **Real-time PCR** (found in serum 2-6 weeks after infection; lasts 2-4 weeks); in chronic HEV persists for years until cured.
- HEV Antigen Testing (may persist positive after viral clearance)

HEV IgM Assays

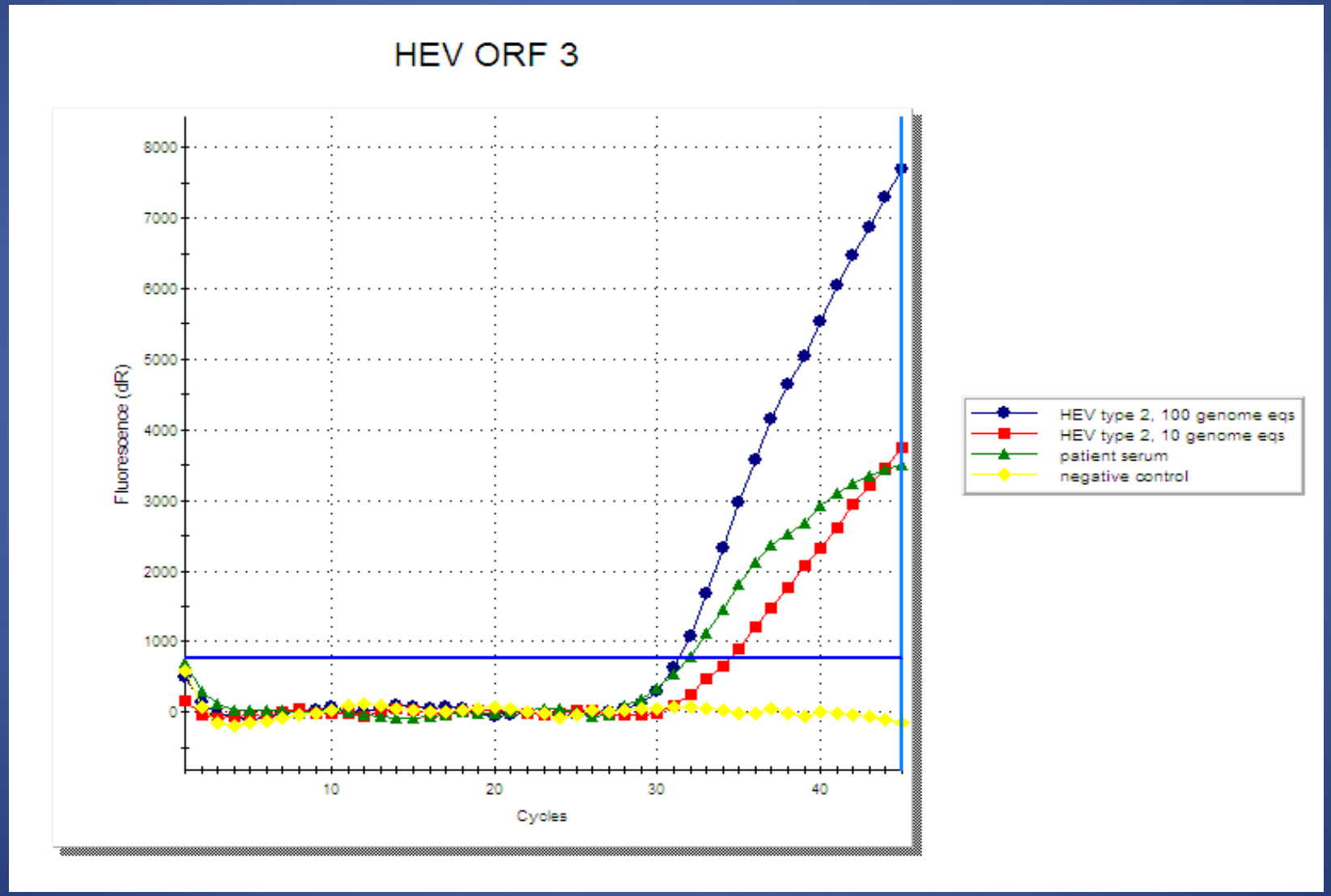
NAME/ MANUFACTURER	TYPE	ANTIGEN	FDA APPROVED
HEV IgM ELISA/WANTAI	U-chain Capture	ORF-2 GENOTYPE 4	NO
recomWell HEV IgM/Mikrogen	Indirect	ORF-3, GENOTYPE 1,2,3	NO
HEV IgM, ELISA 3.0/ MP	Indirect	ORF-2 GENOTYPE 1 (Chinese)	NO
Assure HEV IgM Rapid/MP	Reverse flow immunochemistry	ORF-2, GENOTYPE 1	NO
Anti-HEV ELISA/Euroimmune	Indirect	ORF-2 GENOTYPE 3 (US)	NO
EIAgen HEV/Adaltis	Capture	ORF-2/3 All GENOTYPES	NO

HEV IgM Assay Comparison

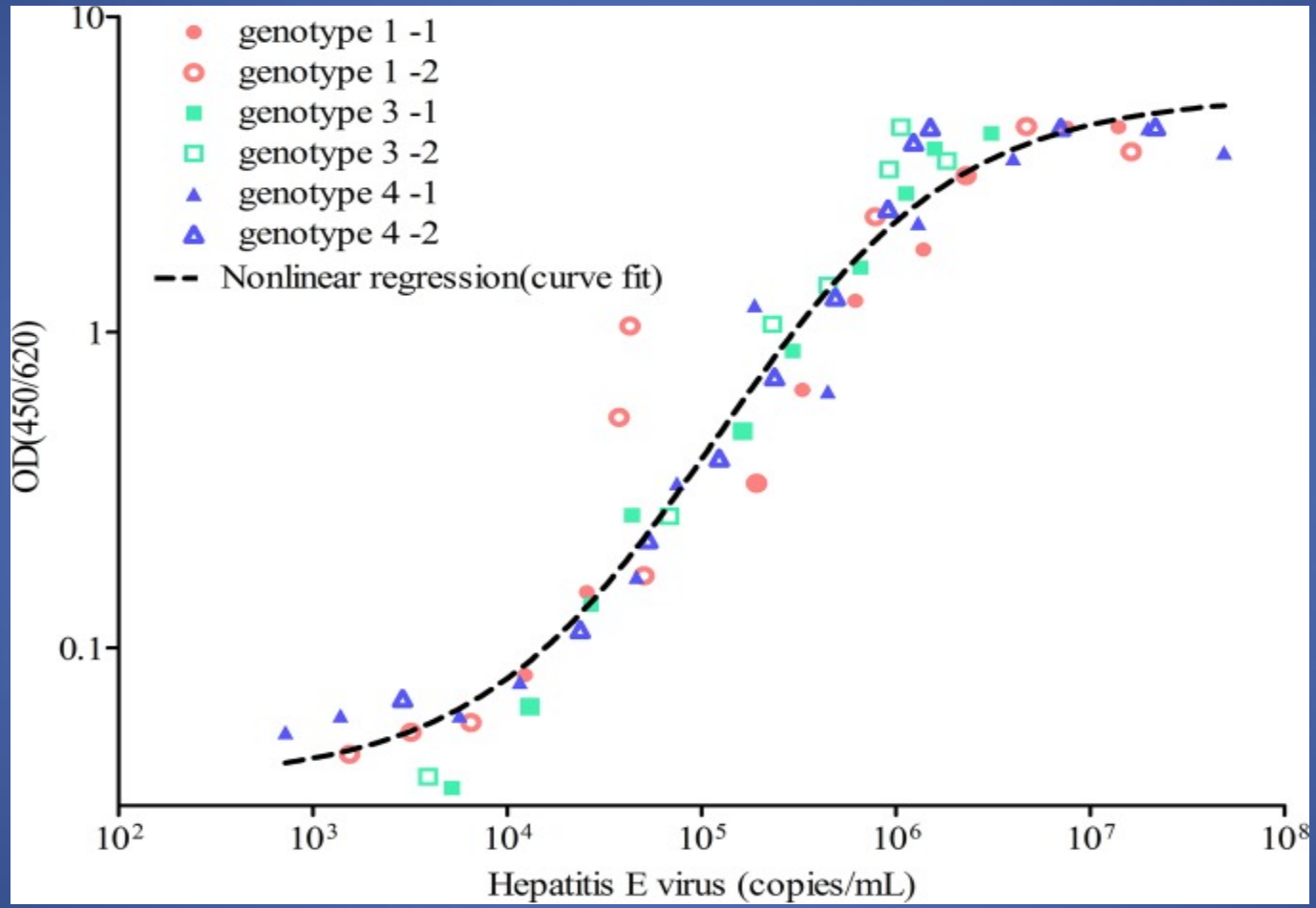


Avellon A et al, J MED VIROL, 2015

HEV Real Time PCR



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/10^6 cells
- **CHRONIC HEV INFECTION**
  - **HEV RNA detected twice over 3-6 months in stool or blood**

Anwar & Sherman, SCIENTIFIC AMERICAN GASTRO 2017
Sherman & Kottilil, Schiff Textbook of Liver Disease 2017
Sherman, UpToDate, Accessed 11/2019

EASL Diagnostic Guidelines

- "EASL recommends using a combination of serology and NAT testing to diagnose HEV infection" (A1)
  - "…the specificity of certain assays is not optimal and anti-HEV IgM on its own is not a sufficiently robust marker for diagnosis."
- "EASL recommends NAT testing to diagnose chronic HEV infection" (A1)

Table 3. Laboratory diagnosis of HEV infection.

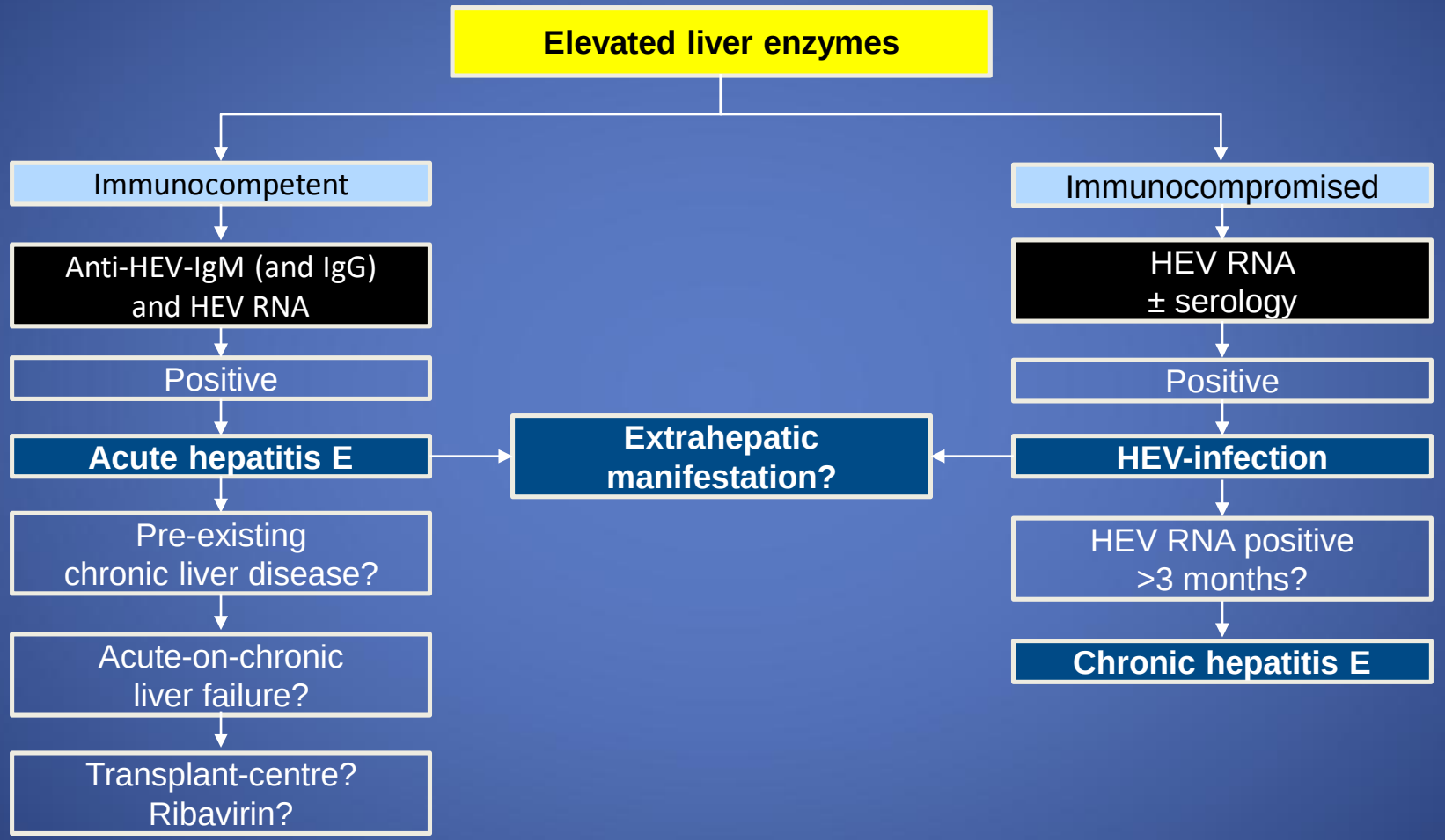
Infection status	Positive markers
Current infection - acute	• HEV RNA • HEV RNA + anti-HEV IgM • HEV RNA + anti-HEV IgG* • HEV RNA + anti-HEV IgM + anti-HEV IgG • Anti-HEV IgM + anti-HEV IgG (rising) • HEV antigen
Current infection - chronic	• HEV RNA (± anti-HEV) ≥3 months • HEV antigen
Past infection	• Anti-HEV IgG

*Patients with re-infection are typically anti-HEV IgM negative, but IgG and PCR positive. HEV, hepatitis E virus.

EASL Clinical Practice Guidelines on Hepatitis E Infection, J HEPATOL, 2018

Diagnostic algorithm for HEV infection

EASL 2018



Serology and NAT testing are best used in combination, as a negative PCR does not exclude acute infection; serology is sometimes negative in immunosuppressed patients with chronic infection

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Broadening testing for HEV

EASL 2018

- Previously, only patients travelling to areas in Africa and Africa hyperendemic for HEV GT 1 or 2 were considered for testing
  - Now know that most HEV infection is locally acquired
- All patients presenting with hepatitis should be tested*
  - Irrespective of travel history

Immunological status	Patients who should be tested for HEV
Immunocompetent	• **Any patient with biochemical evidence of hepatitis*** • **Suspected drug-induced liver injury*** • Decompensated chronic liver disease† • Neuralgic amyotrophy† • Guillain–Barré syndrome† • Encephalitis† • Patients with unexplained acute neurology and raised ALT‡
Immunocompromised (developed countries)	• As above • Persistently abnormal ALT§

*Grade of evidence A, Grade of recommendation 1; †Testing should be done at disease onset, irrespective of ALT results; ‡Testing should be done at disease onset if ALT is abnormal; §If ALT is above the limit of normal on more than one occasion

EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Clinical Outcomes

	ACUTE DISEASE	CHRONIC DISEASE	MORTALITY
Immunocompetent	YES	NO	LOW
Pregnancy	YES	NO	VARIABLE
Chronic Liver Disease	YES	NO	HIGH
Immunosuppressed -HIV -Post-Transplant -Cancer Chemotx	YES	YES	VARIABLE

EXTRAHEPATIC MANIFESTATIONS

Pancreatitis

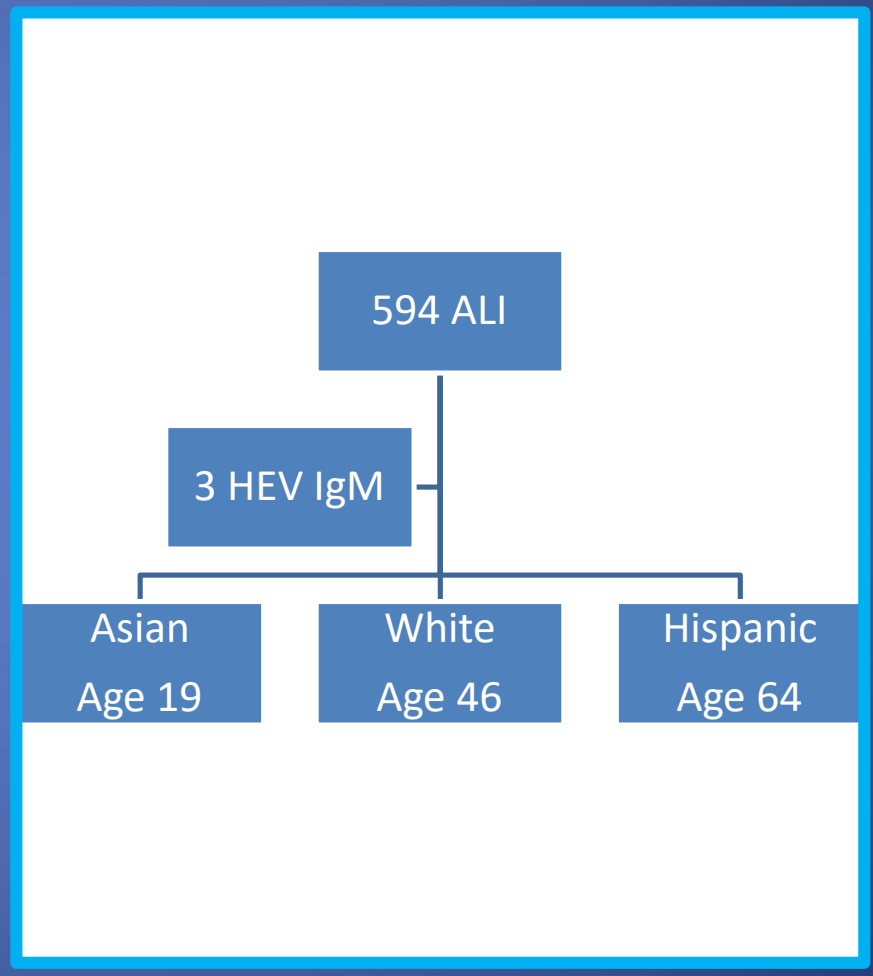
Guillain-Barre and other neurologic processes

Cryoglobulinemia, glomerulonephritis

Scham N et al, Infection 2014
Van den Berg B et al, Neurology, 2014
Fukae J et al, Neurol Sci 2016
Pischke S Et al, J HEPATOL, 2019
DelBello A et al, TRANS INFECT DIS, 2015

HEV in North American Acute Liver Injury

- Observation Acute Liver Failure Study Group
- N=594 cases of ALI (defined as INR>2 without HE)
- RESULTS
  - 9.7% HEV IgG positive
    - Older
    - Non-white
  - All HEV IgM Recovered
- Conclusion: Testing for acute HEV is indicated in patients with ALI



Fontana R et al, HEPATOLOGY, 2019, Abs 828

HEV Hospitalization

Query of National Inpatient Sample Database

N= 535 HEV-related hospitalization identified between 2012 and 2014

CHARACTERISTICS OF HOSPITALIZED PERSON

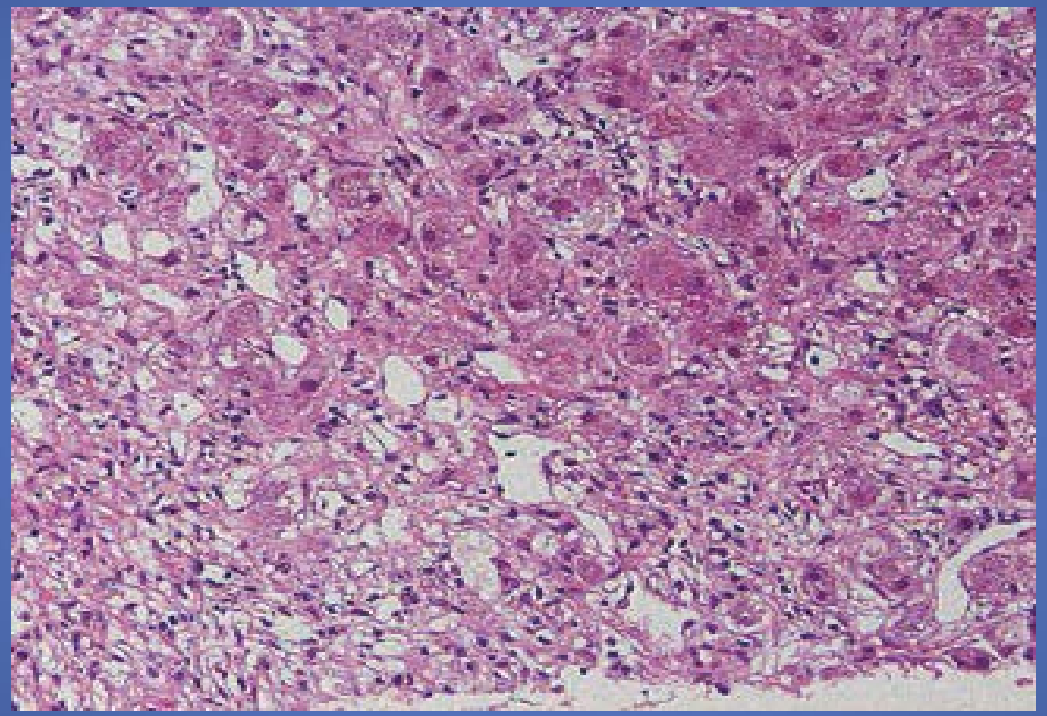
- Non-pregnant 88.9%
- Non-white 51.5%
- Peak Age 40-64 (49%)
- MORTALITY 1.9%
- More frequent in those with known cirrhosis, HBV, HIV and Crohn's Disease

Conclusion

- Mortality associated with HCV is low
- HEV should be considered in differential

Enofe, HEPATOLOGY, 2019 Abs. 1044

HEV Acute on Chronic

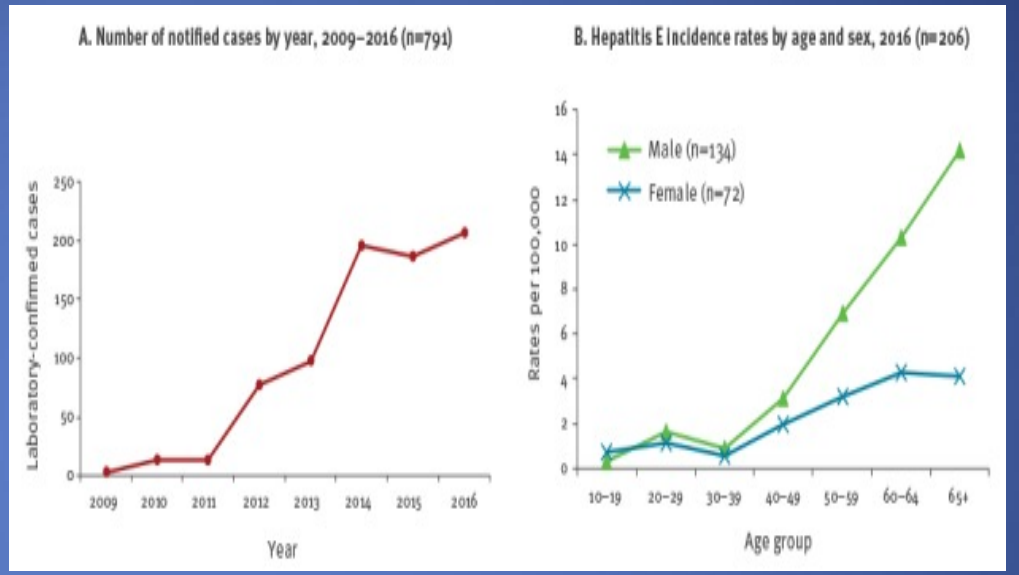


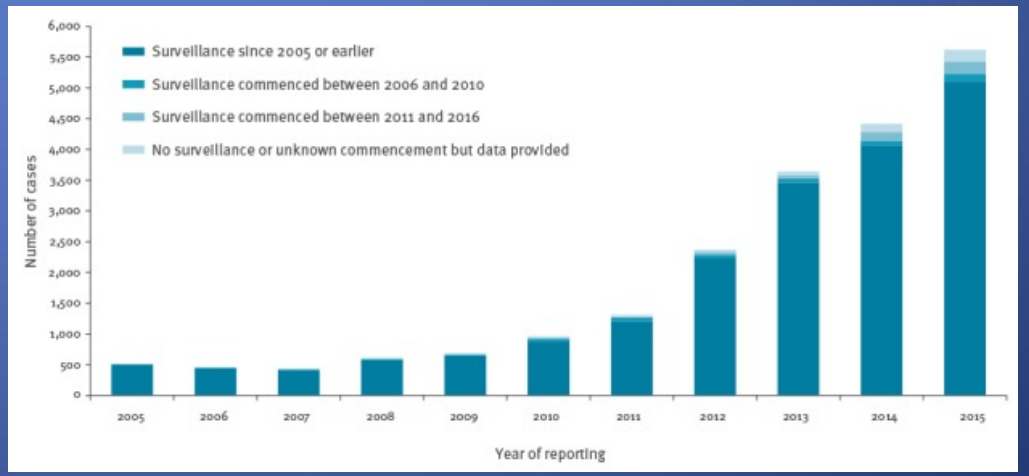
Sub-massive necrosis in cryptogenic cirrhosis patient
Associated with eating shellfish and/or pork

Inagaki Y et al, T J Exp Med, 2015

Rising Rates of HEV in Europe

- HEV in Blood Donors in Scotland
  - Dramatic Increases in viremia between 2009-2016
  - All genotype 3
- Similar increases seen in 22 European Union countries





Thom K et al, EURO SURVEILL, 2018
Aspinall EJ, EURO SURVEILL, 2017

HEV and Pregnancy

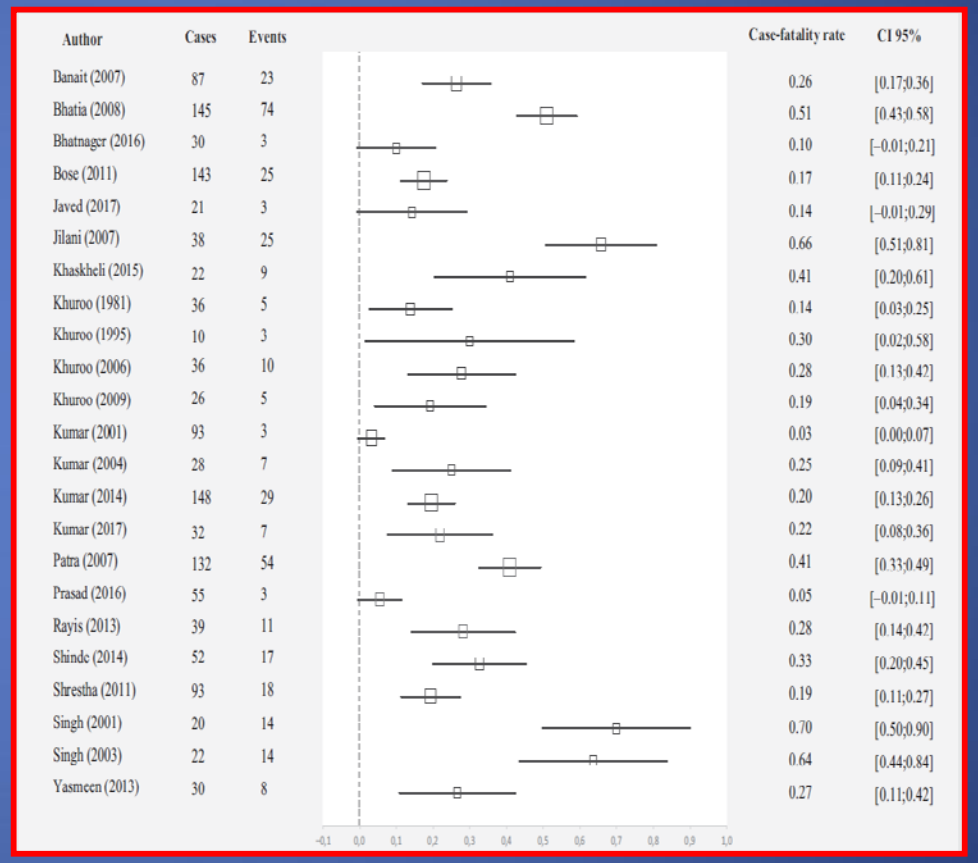
Maternal mortality High

- Cochrane Analysis
  - 26% (IQR 17-41%)
  - Hospitalization for ALF Bias

Low mortality in other places

REASON?

- Genotype
- Epidemiology of exposure
- Host factors- Lower NK Count during pregnancy
- Poor Maternal and Birth Care



Author	Cases	Events	Case-fatality rate	CI 95%
Banait (2007)	87	23	0.26	[0.17;0.36]
Bhatia (2008)	145	74	0.51	[0.43;0.58]
Bhatnagar (2016)	30	3	0.10	[−0.01;0.21]
Bose (2011)	143	25	0.17	[0.11;0.24]
Javed (2017)	21	3	0.14	[−0.01;0.29]
Jilani (2007)	38	25	0.66	[0.51;0.81]
Khaskheli (2015)	22	9	0.41	[0.20;0.61]
Khuroo (1981)	36	5	0.14	[0.03;0.25]
Khuroo (1995)	10	3	0.30	[0.02;0.58]
Khuroo (2006)	36	10	0.28	[0.13;0.42]
Khuroo (2009)	26	5	0.19	[0.04;0.34]
Kumar (2001)	93	3	0.03	[0.00;0.07]
Kumar (2004)	28	7	0.25	[0.09;0.41]
Kumar (2014)	148	29	0.20	[0.13;0.26]
Kumar (2017)	32	7	0.22	[0.08;0.36]
Patra (2007)	132	54	0.41	[0.33;0.49]
Prasad (2016)	55	3	0.05	[−0.01;0.11]
Rayis (2013)	39	11	0.28	[0.14;0.42]
Shinde (2014)	52	17	0.33	[0.20;0.45]
Shrestha (2011)	93	18	0.19	[0.11;0.27]
Singh (2001)	20	14	0.70	[0.50;0.90]
Singh (2003)	22	14	0.64	[0.44;0.84]
Yasmeen (2013)	30	8	0.27	[0.11;0.42]

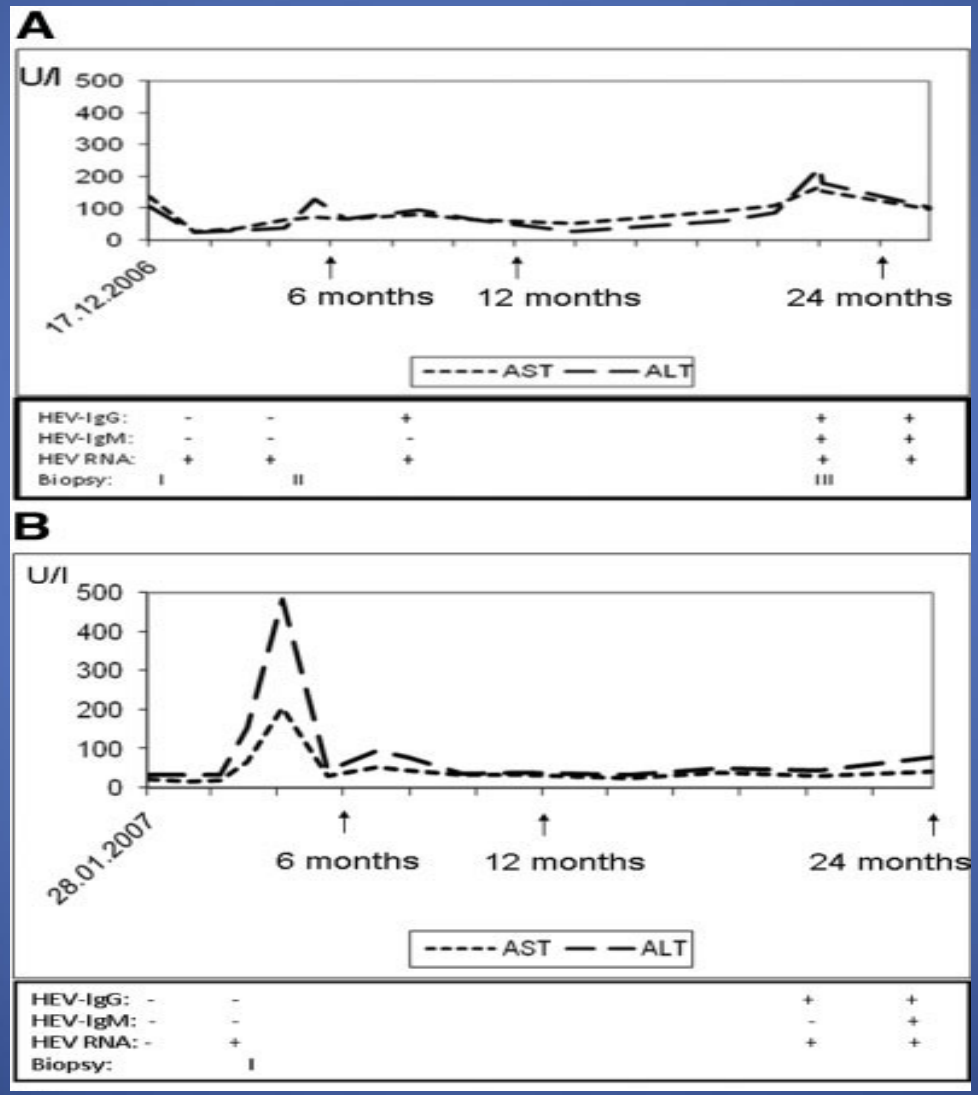
−0.1 0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Berglov A et al, J VIRAL HEP, 2019

Acute to Chronic HEV

- HIV
- Organ Transplantation
- Chemotherapy

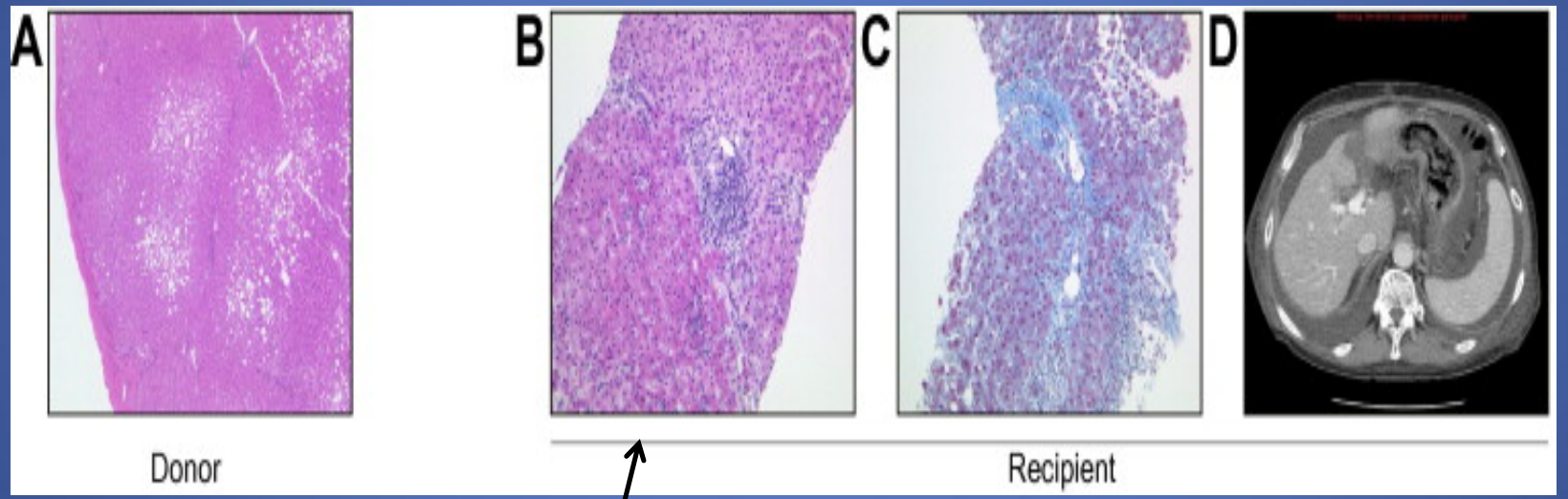
Chronic HEV Infection in Transplant Recipients



Pischke et. al. LIVER TRANSPLANTATION 2010

Rapid Disease Progression after OTLTx

1 Year Post-OTLTx

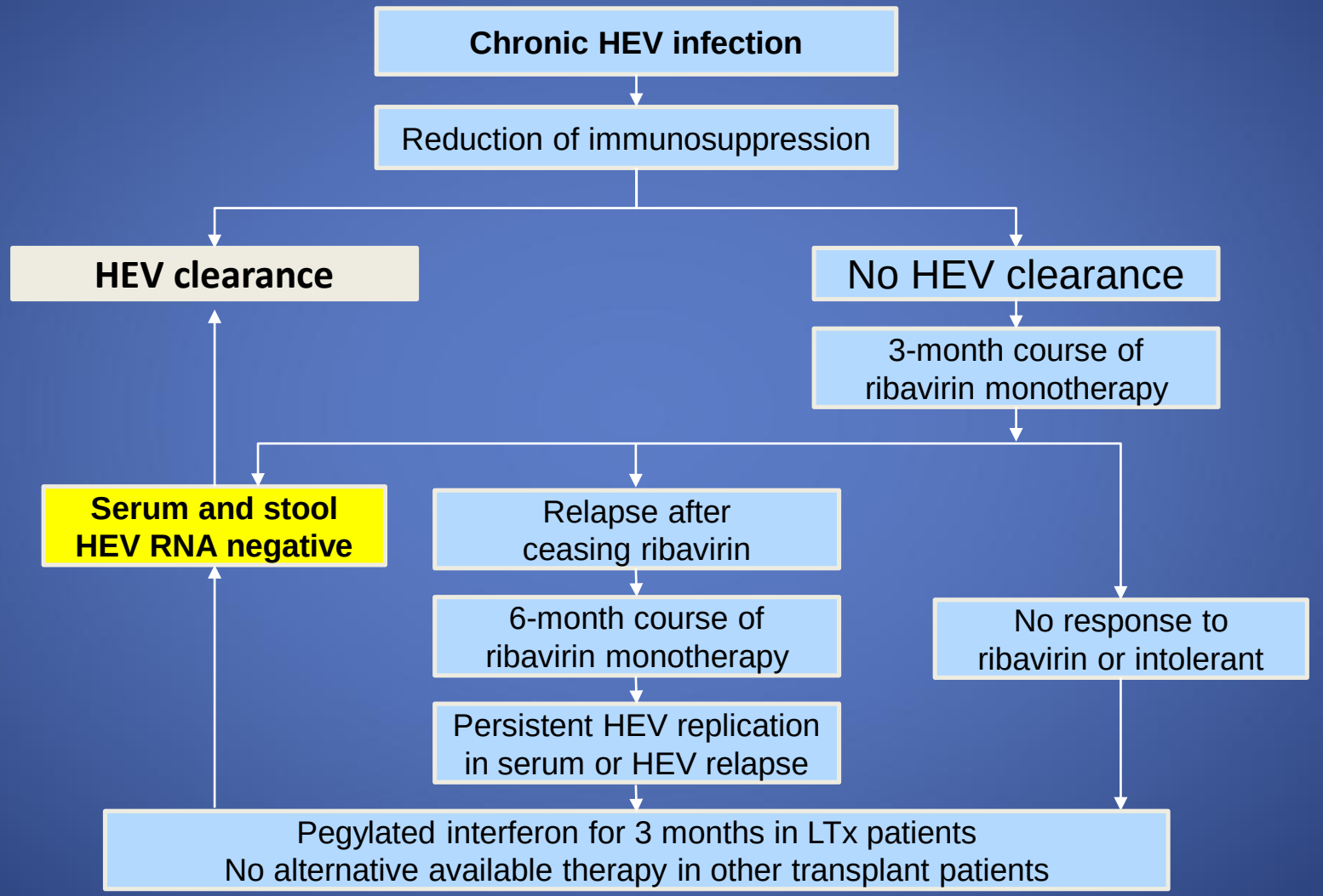


Attributed to Acute Rejection
150 Days Post-Tx

Schlosser et al., J HEPATOL 2012

Management of patients not clearing HEV infection

EASL 2018



EASL CPG HEV. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.005 [Epub ahead of print]

Conclusion

- ✓ HEV is a global problem
- ✓ Humans are both…
  - Primary Hosts (Genotype 1,2)
  - Apex Food Chain Hosts (all other genotypes)
- ✓ 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