

# *Clinical Chemistry*

Trainee Council

## PEARLS OF LABORATORY MEDICINE

### *Hepatitis E*

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# Hepatitis E Virus (HEV)

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- Recognized as a new virus during outbreaks in India during the 1950s
  - Enterically-transmitted non-A, non-B hepatitis
  - Associated with contaminated water
- Viral particles isolated in 1983
- HEV cloned and sequenced in 1990
  - Family *Hepeviridae*, genus *Hepevirus*
  - Small (~30 nm) non-enveloped RNA virus
  - Targets hepatocytes and replicates in the cytoplasm
  - 7.2 kb genome with 3 open reading frames (ORF)

# HEV Viral Genome

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- ORF1—Nonstructural proteins for replication/processing
- ORF3—Small protein with strain to strain variability
- ORF2—Viral capsid

# Epidemiology

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## 4 mammalian genotypes with 2 patterns of illness

### ➤ Genotypes 1 and 2

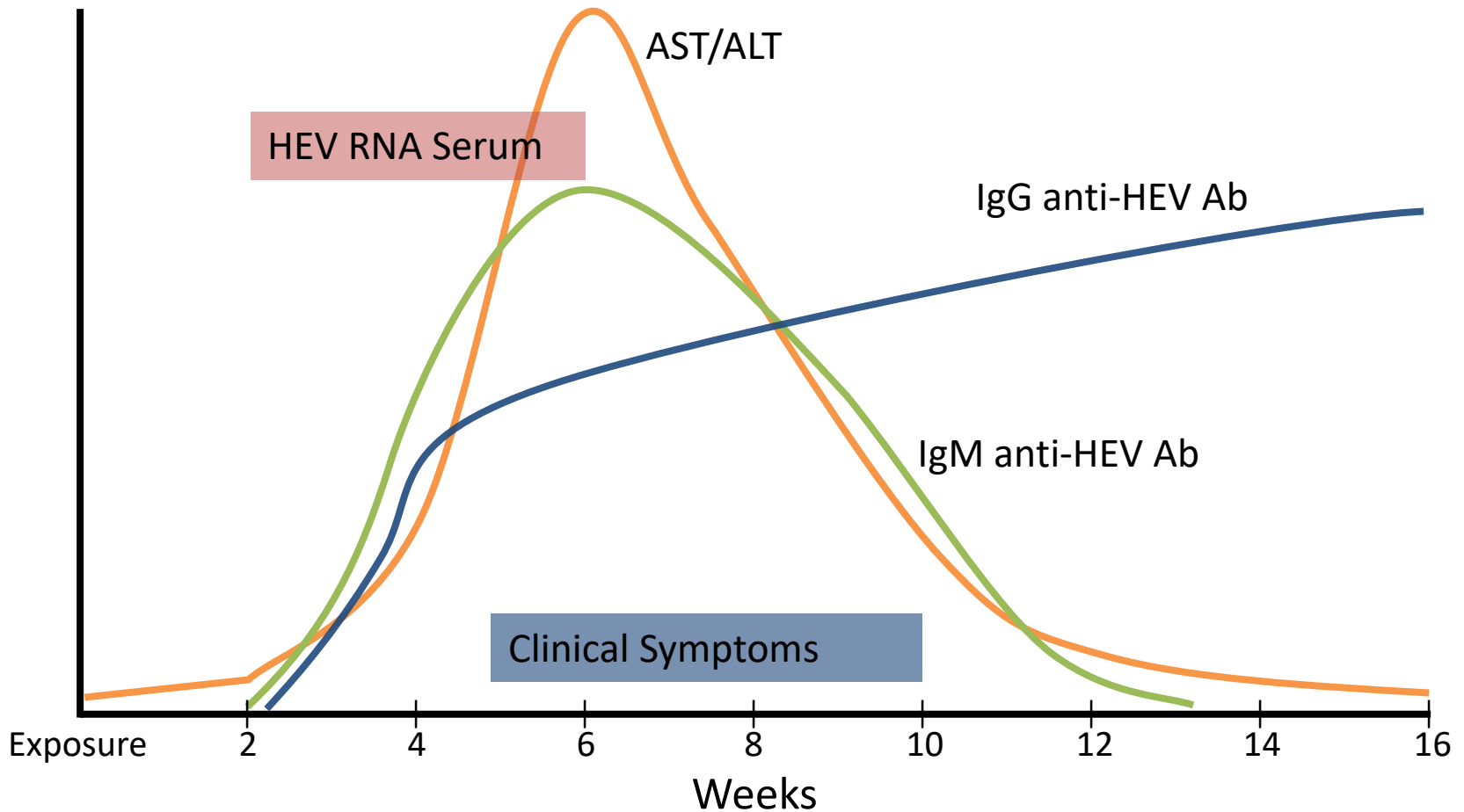
- Human viruses endemic to parts of Africa, Asia, Central, and South America
- >3 million cases/year worldwide
- Fecal-oral transmission, primarily waterborne
- Pregnant women have increased incidence and mortality

### ➤ Genotypes 3 and 4

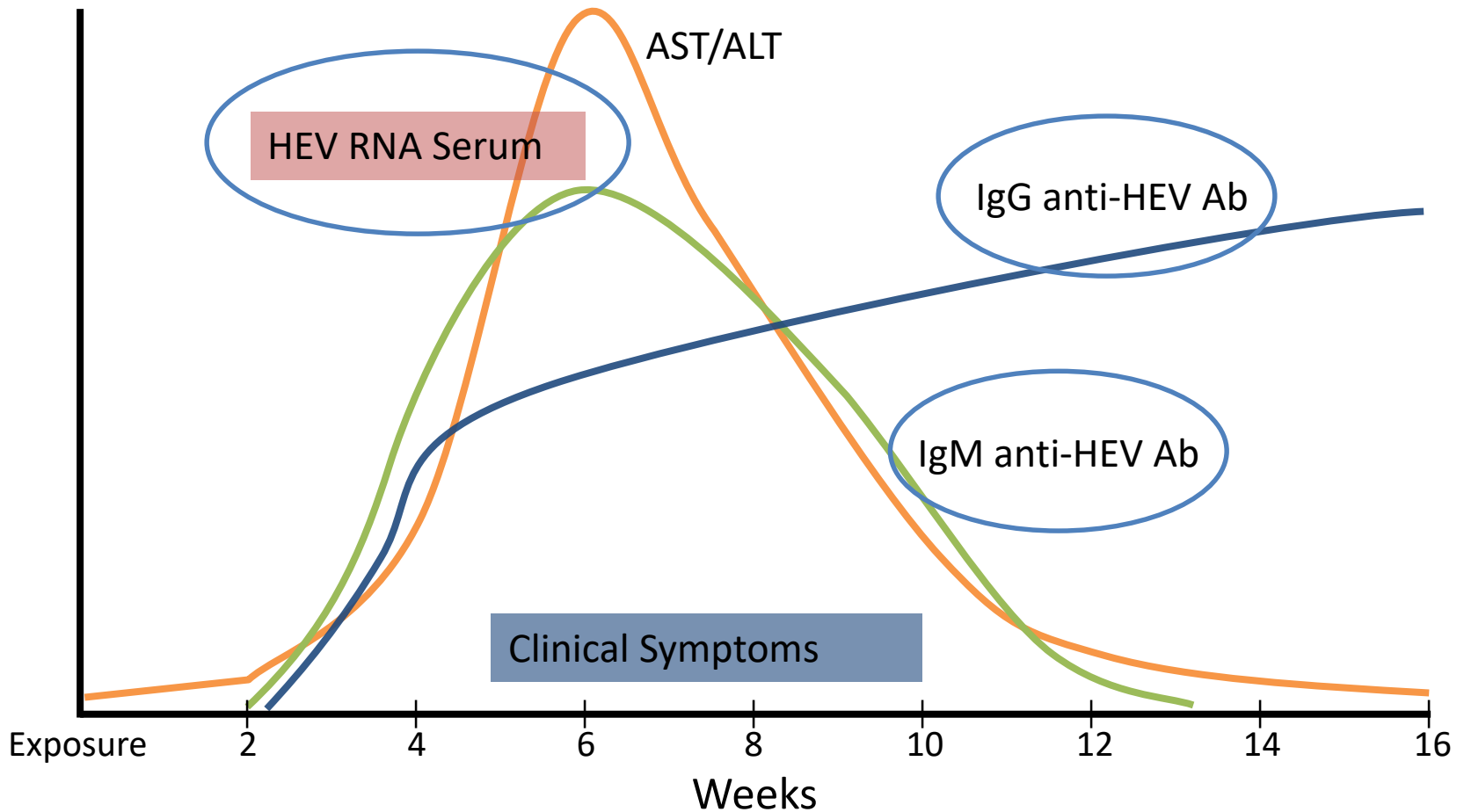
- Zoonotic viruses in the United States, Europe, parts of Asia
- Human infection from consumption of undercooked meat (pork, game, etc)
- Prevalence varies by region
- Incidence unknown
  - Subclinical course
  - Testing not performed
- No known difference for pregnant patients

**Prior infection does not necessarily confer lifelong immunity**

# HEV Course of Illness



# HEV Course of Illness



# Whom To Test and Why

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## ➤ Immunosuppressed patients

- Documented chronic HEV in solid-organ transplant recipients and AIDS patients
- Intervention: reconstitute immune system for clearance of the virus

## ➤ Suspected Drug-Induced Liver Injury (DILI)

- A major cause of acute liver failure
- A diagnosis of exclusion
- Patients may be taken off of necessary medications if diagnosed incorrectly

# Basis for Testing

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- Immune electron microscopy studies demonstrate cross-reactivity among HEV virions from different geographic regions
- Recombinant peptides from ORF2 and ORF3 in a Mexican strain of HEV were shown to react with sera collected from outbreaks in Pakistan, Russia, and Somalia
- “Common” epitopes allowed for development of immunoassays that broadly react with antibodies to different strains of HEV



# Current Testing and Problems (USA)

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- Only Enzyme-Linked Immunosorbent Assay (ELISA) methods are available for clinical testing in the USA
- Problems with Testing
  - Lack of standardization
  - Testing in a low prevalence area

# Current Testing and Problems (USA)

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- Lack of standardization
  - None FDA-approved
  - Commercial vs. Lab Developed
    - Different antigens: recombinant vs. synthetic?
    - Positive cut-off value: set with different sample sera
  - Difficult to compare results

# Comparison of Immunoassays for IgM

Test	Sensitivity (95% CI)	Specificity (95% CI)
In-House 1	98% (88-99.9)	78.2% (72.1-83.2)
In-House 2	98% (88-99.9)	93% (88.7-95.8)
Immuno-Dx	82% (68.1-90.9)	91.2 (86.6-94.4)
MP Biomed	72% (57.2-83.3)	93% (88.2-95.5)
*Dx Systems	98% (88-99.9)	95.2%(91.3-97.4)
Mikrogen	92% (79.9-97.4)	95.6% (91.9-97.8)

Drobeniuc J, Meng J, Reuter G, et al. Serologic assays specific to immunoglobulin M antibodies against Hepatitis E virus: Pangenotypic evaluation of performances. Clin Infect Dis. 2010;51:e24-27.

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# Current Testing and Problems (USA)

## ➤ Low prevalence

- Ex.:10% Hepatitis E in 200 patients with acute hepatitis

	Positive	Negative	Total	
Test +	19	9	28	PPV=68%
Test -	1	171	172	NPV=99%
Total	20	180	200	
	Sens=98%	Spec=95%		

# Current Testing

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## ➤ PCR-based methods

- Testing for HEV RNA in blood is available in other countries
- Recommended for testing in immunosuppressed patients
  - May not mount appropriate antibody response
  - Monitoring chronicity
- In immunocompetent patients, viremia may be absent by the time of presentation
- Only available in research laboratories in the USA

# Points to Remember

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- Hepatitis E is an important cause of acute hepatitis worldwide
- “Locally acquired” Genotype 3 is now known to cause human disease in the United States and Europe
- Hepatitis E can progress to chronic hepatitis
- Hepatitis E should be ruled out before a diagnosis of drug-induced liver injury is made
- Current clinical testing in the US by immunoassay only
  - Needs standardization
  - Always order IgG and IgM simultaneously
- PCR important in immunocompromised patients

# References

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# Disclosures/Potential Conflicts of Interest

*Upon Pearl submission, the presenter completed the Clinical Chemistry disclosure form. Disclosures and/or potential conflicts of interest:*

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