

E型肝炎

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Hepatitis E Virus



Hepatitis E virus

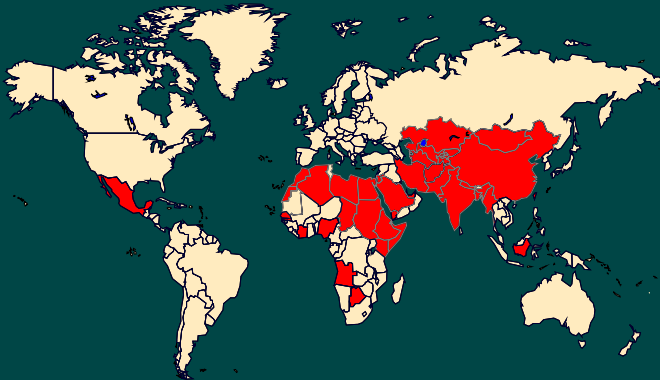
- HEV is a positive-sense single-stranded RNA icosahedral virus with a 7.5 kilobases genome
- HEV has a fecal-oral transmission route. Infection with this virus was first documented in 1955 during an outbreak in New Delhi, India

Molecular biology

- Small non-enveloped virus
 - Hepeviridae family
 - Caliciviridae family (prior classification)

Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in
> 25% of Sporadic Non-ABC Hepatitis



HEV Classification

- Serotype classification
 - Only one type
- Genotype classification
 - genotype 1 : 5 subtypes, age 15-35 y/o, mortality 1%
 - genotype 2 : 2 subtypes
 - genotype 3 : 10 subtypes, age > 60 y/o, mortality 5-10%
 - genotype 4 : 7 subtypes, age > 60 y/o, mortality 5-10%

HEV Distribution

- **Genotype 1 & 2**
 - restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions
 - Genotype 1 : tropical and subtropical countries in Asia and Africa
 - Genotype 2 : Mexico, Nigeria, and Chad
- **Genotype 3 & 4**
 - infect humans, pigs and other animal species and have been responsible for sporadic cases of hepatitis E in both developing and industrialized countries
 - Genotype 3 : worldwide
 - Genotype 4 : Asia
- In the UK, the number of human hepatitis E cases increased by 39% between 2011 and 2012

HEV Transmission

- Prevalent in most developing countries
- Common in any country with a hot climate
 - Widespread in Southeast Asia, northern and central Africa, India, and Central America.
- Spread mainly by the fecal-oral route due to fecal contamination of water supplies or food
- Person-to-person transmission is uncommon

Transmission

- Fecal-oral transmission
 - due to fecal contamination of water supplies or food
- Person-to-person transmission is uncommon
- Incubation period
 - 3-8 weeks, with a mean of 40 days
- Outbreaks
 - commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies
 - New Delhi, India, 30,000 cases, 1955–1956
 - Burma, 20,000 cases, 1976-1977
 - Kashmir, India, 52,000 cases, 1978
 - Kanpur, India, 79,000 cases, 1991
 - China, 100,000 cases, 1986-1988

Transmission of HEV in UK

- Food-borne zoonoses
 - 10% of pork sausages on sale in the UK contained the virus.
 - food must reach a temperature of 70°C for 20 minutes to eliminate the risk of infection
- Hepatitis E in 49% of pigs in Scotland

Animal Health and Veterinary Laboratories Agency

Animal reservoir: I

- Domestic animals
 - HEV infection rates > 95% among domestic pigs.
 - Replicative virus has been found in the small intestine, lymph nodes, colon and liver of experimentally infected pigs
 - Transmission after consumption of wild boar meat and uncooked deer meat has been reported as well. The rate of transmission to humans by this route and the public health importance of this are, however, still unclear
- Small mammals:
 - lesser bandicoot rat , black rat, Asian house shrew
 - A new virus rat hepatitis E virus has been isolated

Animal reservoir: II

- Rabbit hepatitis E virus
 - 2014 American rabbit vendors study
 - 40% HEV seropositive for Supplier A (conventional rabbit farm)
 - 50% HEV seropositive for Supplier B (SPF research rabbits)
 - Population at risk
 - Laboratory animal care personnel, researchers, and support staff
- Avian virus has been described that is associated with hepatitis-splenomegaly syndrome in chickens
 - This virus is genetically and antigenically related to mammalian HEV, and probably represents a new genus in the family

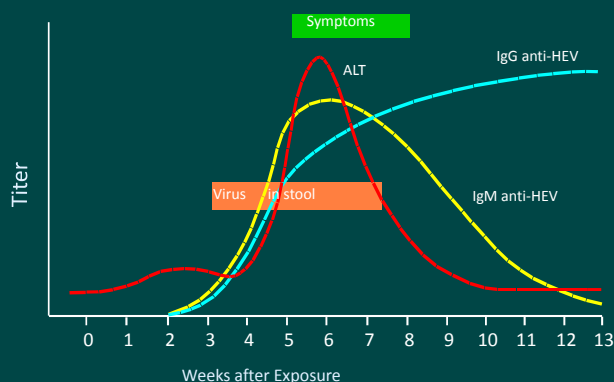
Acute infection

- Incubation period
 - 3 to 8 weeks
 - Viral RNA detectable in stool & serum
- Prodromal phase
 - days to weeks
 - jaundice, fatigue, and nausea
- Symptomatic phase
 - elevated hepatic aminotransferase levels.
- IgM and IgG appear just before onset of clinical symptoms
- Recovery leads to virus clearance from the blood, while the virus may persist in stool for much longer. Recovery is also marked by disappearance of IgM antibodies and increase of levels of IgG antibodies.

Chronic infection

- While usually an acute disease, in immunocompromised subjects—particularly in solid organ transplanted patients—hepatitis E may cause a chronic infection.
- Occasionally this may cause liver fibrosis and cirrhosis.

Hepatitis E Virus Infection Typical Serological Course



Hepatitis E – Clinical Features

Incubation period:	Average 40 days Range 15-60 days
Case-fatality rate:	Overall, 1%-3% Pregnant women, 15%-25%
Illness severity:	Increased with age
Chronic sequelae:	None identified

Epidemiology

- 20 million infections a year
 - 3 million acute illnesses
 - 57,000 deaths, 2010
- Risk group of acute infection
 - pregnant women : mortality rate 20%
 - Some indigenous people in some region

Hepatitis E – Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission
- U.S. cases usually have history of travel to HEV-endemic areas

Recent outbreaks

- 2004, sub-Saharan Africa
 - Chad, September 27, 1,442 cases/46 deaths
 - Sudan, September 28, 6,861 cases/87 deaths
- October, 2007 to June, 2009
 - Kitgum District of northern Uganda, >10,196 cases/160 deaths
- 2011
 - Tangail, a neighborhood of Dhaka, Bangladesh, minor outbreak
- June 2012
 - Ichalkaranji, Maharashtra, India, 3232 cases/18 died
- July 2012 to Feb 2013
 - South Sudanese refugee camps in Maban County, 4,000 cases/88 deaths
- April 2014
 - Biratnagar Municipality, Nepal, 6,000 cases/9 death

Prevention

Prevention and Control Measures for Travelers to HEV – Endemic Regions

- Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler
- IG prepared from donors in Western countries does not prevent infection
- Unknown efficacy of IG prepared from donors in endemic areas
- Future vaccine (?)

Sanitation

- Improving sanitation is the most important measure in prevention
 - proper treatment and disposal of human waste
 - higher standards for public water supplies
 - improved personal hygiene procedures
 - sanitary food preparation

Vaccines

- Recombinant viral proteins
 - developed in 1990s
 - tested in a high-risk population (military personnel of Nepal), 2001
 - vaccine appeared to be effective and safe
 - development was stopped for economic reasons
 - Since hepatitis E is rare in developed countries
 - There is no licensed hepatitis E vaccine for use in the US

HEV Vaccines in China

- Hecolin
 - HEV 239
 - Developer : Xiamen Innovax Biotech
 - Approved by SFDA, available in late October, 2012
 - phase 3 trial on 2 groups of 50,000 people each from Jiangsu during a 12-month period
 - Vaccinated : noninfected
 - Placebo : 15 infected

Treatment : I

- Supportive care
- Ribavirin
 - off-label experience for Tx chronic Hepatitis E
 - 600 to 800 mg per day for 3 months
 - viral clearance in 2/3 of chronic cases
- Peginterferon or ribavirin + peginterferon

Treatment : II

- Temporal reduction of immunosuppression
 - chronic HEV is associated with immunosuppressive Tx
 - little is known about how different immunosuppressants effect
 - In 1/3 with solid-organ transplantation viral clearance can be achieved by temporal reduction of the level of immunosuppression
- Calcineurin inhibitors (like cyclosporin) stimulate and mycophenolic acid inhibit replication of Hepatitis E Virus and this should be considered when physicians select immunosuppressive therapies for patients at risk for Hepatitis E, for instance recipients of organ transplantation

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