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Hepatitis E

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Abstract

Hepatitis E is inflammation of the liver caused by infection with the hepatitis E virus.[1][2] It is one of five known human hepatitis viruses: A, B, C, D, and E. HEV is a positive-sense, single-stranded, nonenveloped, RNA icosahedral virus. HEV has mainly a fecal-oral transmission route.[3][4][5] Infection with this virus was first documented in 1955 during an outbreak in New Delhi, India[6]. A preventive vaccine (HEV 239) is approved for use in China.[7]

Although hepatitis E often causes an acute and self-limiting infection (the viral infection is temporary and the individual recovers) with low death rates in the western world, it bears a high risk of developing chronic hepatitis in people with a weakened immune system with substantially higher death rates. Organ transplant recipients who receive medications to weaken the immune system and prevent organ rejection are thought to be the main population at risk for chronic hepatitis E.[8].

Hepatitis E infection has a clinical course comparable to hepatitis A, but in pregnant women, the disease is more often severe and is associated with a clinical syndrome called fulminant liver failure. Pregnant women, especially those in the third trimester, have a higher rate of death from the disease of around 20%.[9][10][4] In total there are 8 genotypes; genotypes 3 and 4 cause chronic hepatitis in the immunosuppressed.[11][12] Hepatitis E incidence in 2017 was more than 19 million.[13]

Signs and symptoms

Acute infection

The incubation period of hepatitis E varies from 3 to 8 weeks. After a short prodromal phase symptoms lasting from days to weeks follow. They may include jaundice, fatigue, and nausea, though the majority of HEV infections are asymptomatic. The symptomatic phase coincides with elevated hepatic aminotransferase levels.[14][15]

Viral RNA becomes detectable in stool and blood serum during the incubation period. Serum IgM and IgG antibodies against HEV appear just before the 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.[4][14]

Chronic infection

While usually an acute disease, in immunocompromised subjects—particularly in solid organ transplant patients—hepatitis E may cause a chronic infection.[16] Occasionally this may cause a life threatening complication such as fulminant liver failure or liver cirrhosis.[17][18]

Other organs

Infection with hepatitis E virus can also lead to problems in other organs. For some of these reported conditions the relationship is tenuous, but for several neurological and blood conditions the relationship appears causal:[19][20][21][22]

- Acute pancreatitis
- Neurological complications include Guillain-Barré syndrome (acute limb weakness due to nerve involvement), neuralgic amyotrophy (arm and shoulder weakness, also known as Parsonage-Turner syndrome), acute transverse myelitis and acute meningoencephalitis.
- Glomerulonephritis with nephrotic syndrome and/or cryoglobulinemia
- Mixed cryoglobulinemia, where antibodies in the bloodstream react inappropriately at low temperatures
- Severe thrombocytopenia (low platelet count in the blood) which confers a risk of dangerous bleeding

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Infection in pregnancy

Pregnant women show a more severe course of infection than other populations. Mortality rates of 20% to 25% and hepatic failure have been reported from outbreaks of genotype 1 and 2 HEV in developing countries. Besides signs of an acute infections, adverse maternal and fetal outcomes may include preterm delivery, abortion, stillbirth, and intrauterine fetal and neonatal death.[23][9][24]

The pathologic and biologic mechanisms behind the adverse outcomes of pregnancy infections remain largely unclear so far. Mainly, increased viral replication and influence of hormonal changes on the immune system have been discussed lately.[25] Furthermore, studies showing evidence for viral replication in the placenta or reporting the full viral life cycle in placental-derived cells in vitro implicate the human placenta as site of extra-hepatic replication.[26]

Virology

Classification

HEV is classified into the family Hepeviridae, which is divided in two genera, Orthohepevirus (all mammalian and avian HEV isolates) and Piscihepevirus (cutthroat trout HEV).[25] Only one serotype of the virus is known, and classification is based on the nucleotide sequences of the genome.[27] Genotype 1 has been classified into five subtypes[28], genotype 2 into two subtypes[28]pg 10, and genotypes 3 and 4 have been divided into 10[29] and seven subtypes [29]. Additionally there are genotypes 5, 6, 7 and 8.[12] Rat HEV was first isolated from Norway rats in Germany[30] , a 2018 CDC article indicated the detection of rat HEV RNA in a transplant recipient.[31]

Distribution

- **Genotype 1** has been isolated from tropical and several subtropical countries in Asia and Africa.[32]
- **Genotype 2** has been isolated from Mexico, Nigeria, and Chad.[33]
- **Genotype 3** has been isolated almost worldwide including Asia, Europe, Oceania, and North and South America.[34]
- **Genotype 4** appears to be limited to Asia and indigenous cases from Europe.[32][35][36]

Genotypes 1 and 2 are restricted to humans and often associated with large outbreaks and epidemics in developing countries with poor sanitation conditions.[32] Genotypes 3 and 4 infect humans, pigs, and other animal species and have been responsible for sporadic cases of hepatitis E in both developing and industrialized countries.[37][38]

In the United Kingdom, the Department for Environment, Food and Rural Affairs said that the number of human hepatitis E cases increased by 39% between 2011 and 2012.[39]

Transmission

Hepatitis E is widespread in Southeast Asia, northern and central Africa, India, and Central America.[40] It is spread mainly by the fecal-oral route due to fecal contamination of water supplies or food; person-to-person transmission is uncommon.[41] Genotypes 1 and 2 cause outbreaks, while the other genotypes cause sporadic cases.[42]

As mentioned, the incubation period following exposure to the hepatitis E virus ranges from 3 to 8 weeks, with a mean of 40 days.[41] Outbreaks of epidemic hepatitis E most commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies.[43] Major outbreaks have occurred in New Delhi, India (30,000 cases in 1955–1956),[44] Burma (20,000 cases in 1976–1977),[45] Kashmir, India (52,000 cases in 1978),[46] Kanpur, India (79,000 cases in 1991),[44] and China (100,000 cases between 1986 and 1988).[47] According to Rein et al., HEV genotypes 1 and 2 caused some 20.1 million Hepatitis E infections, along with 3.4 million cases of symptomatic disease, and 70,000 deaths in 2005; however the aforementioned paper did not estimate the burden of genotypes 3 and 4.[48]

According to the Department for Environment, Food and Rural Affairs, evidence indicated the increase in hepatitis E in the U.K. was due to food-borne zoonoses, citing a study that found in the U.K. that 10% of pork

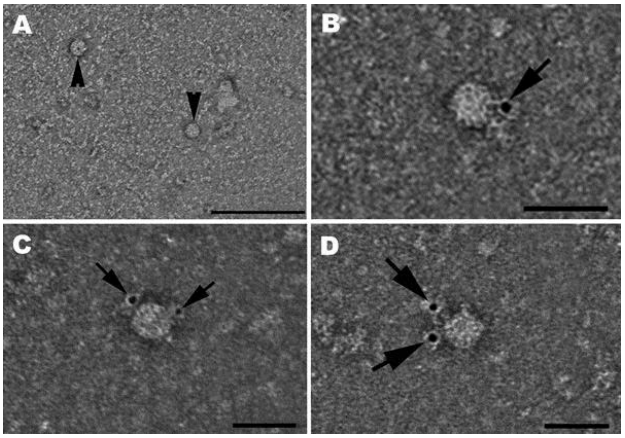

Figure 1 | Hepatitis E virus in pork liver sausage (the arrows in panel A point to the virion, those in B, C & D point to bound gold nanoparticles used in virus detection)
Alessandra Berto, et al, CDC U.S. public domain.

sausages contained the Hepatitis E virus. Some research suggests that food must reach a temperature of 70 °C for 20 minutes to eliminate the risk of infection. The Animal Health and Veterinary Laboratories Agency discovered hepatitis E in almost half of all pigs in Scotland.[39]

Hepatitis E infection appeared to be more common in people on hemodialysis, although the specific risk factors for transmission are not clear.[49]

Animal reservoir

The disease is thought to be a zoonosis in that animals are thought to be the source. Both deer and swine have been implicated.[50] Domestic animals have been reported as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs.[51] 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.[52] The rate of transmission to humans by this route and the public health importance of this are, however, still unclear.[53]

A number of other small mammals have been identified as potential reservoirs: the lesser bandicoot rat (*Bandicota bengalensis*), the black rat (*Rattus rattus brunneusculus*) and the Asian house shrew (*Suncus murinus*). A new virus designated rat hepatitis E virus has been isolated.[54]

Genomics

Main article: Hepatitis E Virus

HEV has three open reading frames (ORFs) encoding two polyproteins (O1 and O2 protein). ORF2 encodes three capsid proteins whereas O1 encodes seven fragments involved in viral replication, among others.[55][56][57]

The smallest ORF of the HEV genome, ORF3 is translated from a subgenomic RNA into O3, a protein of 113–115 amino acids. ORF3 is proposed to play critical roles in immune evasion by HEV. Previous studies showed that ORF3 is bound to viral particles found in patient sera and produced in cell culture. Although in cultured cells ORF3 has not appeared essential for HEV RNA replication, viral assembly, or infection, it is required for particle release. [58]

Virus lifecycle

The lifecycle of hepatitis E virus is unknown; the capsid protein obtains viral entry by binding to a cellular receptor. ORF2 (c-terminal) moderates viral entry by binding to HSC70.[59][60]

Geldanamycin blocks the transport of HEV239 capsid protein, but not the binding/entry of the truncated capsid protein, which indicates that HSP90 plays an important part in HEV transport.[59]

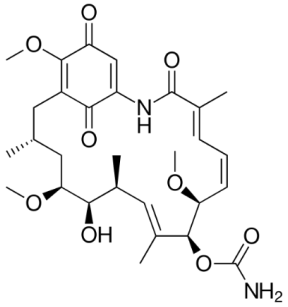

Figure 2 | Geldanamycin
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Diagnosis

In terms of the diagnosis of hepatitis E, only a laboratory test that confirms antibodies present for HEV RNA or HEV can be trusted as conclusive for the virus in any individual tested for it.[10][61] In the United States no serologic tests for diagnosis of HEV infection have ever been authorized by the Food and Drug Administration.[10] The World Health Organization has developed an international standard strain for detection and quantification of HEV RNA.[62]

Virological markers

Assuming that vaccination has not occurred:

- **Positive Anti-HEV-IgM**- with HEV-Ag and/or HEV-RNA *positive* indicates chronic infection, however if *negative* with Anti-HEV-Ag being 'positive' this indicates recent infection, if Anti-HEV-Ag is *negative* then there is cross reactivity.[20]
- **Negative Anti-HEV-IgM**- with HEV-Ag and/or HEV-RNA *positive* as well as Anti-HEV-Ag *positive* then it is acute infection, if the latter is *negative* then it is dependent on time taken for seroconversion. If HEV-Ag and/or HEV-RNA is *negative* with Anti-HEV-Ag being 'positive' it is a past infection, if the latter is *negative* then infection is not present.[20]

Prevention

Sanitation

Sanitation is the most important measure in prevention of hepatitis E; this consists of proper treatment and disposal of human waste, higher standards for public water supplies, improved personal hygiene procedures, and sanitary food preparation. Thus, prevention strategies of this disease are similar to those of many other diseases that plague developing nations.[41] Cooking

meat at 71 degrees Celsius for 5 minutes kills the Hepatitis E virus.[63]

Blood products

The amount of virus present in blood products required to cause transfunction-transmitted infection (TTI) appears variable. Transfusion transmission of Hepatitis E virus can be screened via minipool HEV NAT (Nucleic acid testing) screening.[64][65] NAT is a technique used to screen blood molecularly, when blood donations are received; it screens for TTI.[66]

Vaccines

A vaccine based on recombinant viral proteins was developed in the 1990s and tested in a high-risk population (in Nepal) in 2001.[67] The vaccine appeared to be effective and safe, but development was stopped for lack of profitability, since hepatitis E is rare in developed countries.[68] No hepatitis E vaccine is licensed for use in the United States.[10]

Although other HEV vaccine trials have been successful, these vaccines have not yet been produced or made available to susceptible populations. The exception is China; after more than a year of scrutiny and inspection by China's State Food and Drug Administration (SFDA), a hepatitis E vaccine developed by Chinese scientists was available at the end of 2012. The vaccine —called HEV 239 by its developer Xiamen Innovax Biotech— was approved for prevention of hepatitis E in 2012 by the Chinese Ministry of Science and Technology, following a controlled trial on 100,000+ people from Jiangsu Province where none of those vaccinated became infected during a 12-month period, compared to 15 in the group given placebo.[69] The first vaccine batches came out of Innovax' factory in late October 2012, to be sold to Chinese distributors.[68]

Due to the lack of evidence, WHO as of 2015 did not make a recommendation regarding routine use of the HEV 239 vaccine.[70] National authorities may however, decide to use the vaccine based on the local epidemiology.[70]

Treatment

In terms of treatment, ribavirin is not registered for hepatitis E treatment, though off-label experience for treating chronic hepatitis E with this compound exists. The use of low doses of ribavirin over a three-month period has been associated with viral clearance in about two-thirds of chronic cases. Other possible treatments include pegylated interferon or a combination of ribavirin and pegylated interferon. In general, chronic HEV infection is associated with immunosuppressive therapies, but remarkably little is known about how different immunosuppressants affect HEV infection. In individuals with solid-organ transplantation, viral clearance can be achieved by temporal reduction of the level of immunosuppression.[71][72]

Epidemiology

The hepatitis E virus causes around 20 million infections a year. These result in around three million acute illnesses and resulted in 44,000 deaths during 2015 [4]. Pregnant women are particularly at risk of complications due to HEV infection, who can develop an acute form of the disease that is fatal in 30% of cases or more. HEV is a major cause of illness and of death in the developing world and disproportionate cause of deaths among pregnant women. Hepatitis E is endemic in Central Asia, while Central America and the Middle East have reported outbreaks.[73][74] Increasingly, hepatitis E is being seen in developed nations, with reports in 2015 of 848 cases of hepatitis E virus infection in England and Wales.[75]

Recent outbreaks

In October 2007, an epidemic of hepatitis E occured in Kitgum District of northern Uganda. This outbreak progressed to become one of the largest known hepatitis E outbreaks in the world. By June 2009, it had resulted in illness in 10,196 persons and 160 deaths.[76]

In July 2012, an outbreak was reported in South Sudanese refugee camps in Maban County near the Sudan border. South Sudan's Ministry of Health reported over 400 cases and 16 fatalities as of September 13, 2012.[77]Progressing further, as of February 2, 2013, 88 died due to the outbreak. The medical charity Medecins Sans Frontieres said it treated almost 4,000 people.[78] In April 2014, an outbreak in the Biratnagar Municipality of Nepal resulted in infection of over 6,000 locals and at least 9 dead.[79]

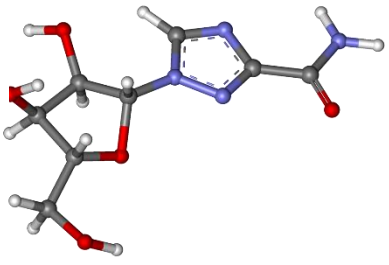

Figure 3 | Ribavirin
Marina Vladivostok, public domain

Figure 4 | Namibia, Africa
Vardion, CC by SA 3.0

An outbreak was reported in Namibia which is located in Africa, in January 2018, the total infected is reported as 490.[80] As of 14 April, 2019 according to the World Health Organization, there have been 5,014 cases and 42 deaths due to this Hepatitis E outbreak in the country of Namibia. The case fatality ratio for this outbreak is currently 0.8%.[81]

History

The most recent common ancestor of hepatitis E evolved between 536 and 1344 years ago.[82] It diverged into two clades — an anthropotropic form and an enzootic form — which subsequently evolved into genotypes 1 and 2 and genotypes 3 and 4, respectively.[83]

Genotypes 1, 3, and 4 all increased their effective population sizes in the 20th century.[82] The population size of genotype 1 increased noticeably in the last 30–35 years. Genotypes 3 and 4 population sizes began to increase in the late 19th century up to 1940–1945. Genotype 3 underwent a subsequent increase in population size until the 1960s. Since 1990, both genotypes' population sizes have been reduced back to levels last seen in the 19th century. The overall mutation rate for the genome has been estimated at roughly 1.4×10^{-3} substitutions/site/year.[82]

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References

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1. "Hepatitis E: Background, Etiopathophysiology, Epidemiology". *medscape.com*. Medscape. 13 March 2019.
2. Kamar, Nassim; Dalton, Harry R.; Abravanel, Florence; Izopet, Jacques (2014). "Hepatitis E Virus Infection". *Clinical Microbiology Reviews* **27** (1): 116–138. doi:10.1128/CMR.00057-13. ISSN 0893-8512. PMID 24396139. PMC 3910910.
3. "What is hepatitis?". *www.who.int. WHO. Retrieved 17 April2019.*
4. "Hepatitis E". *www.who.int. WHO. Retrieved 17 April 2019.*
5. Weston, Debbie; Burgess, Alison; Roberts, Sue (2016). *Infection Prevention and Control at a Glance.* John Wiley & Sons. p. 12. ISBN 9781118973554.
6. Kumar, Subrat; Subhadra, Subhra; Singh, Bhupinder; Panda, B.K. (April 2013). "Hepatitis E virus: the current scenario" (in English). *International Journal of Infectious Diseases* **17** (4): e228–e233. doi:10.1016/j.ijid.2012.11.026. ISSN 1201-9712. PMID 23313154.
7. Li, Shao-Wei; Zhao, Qinjian; Wu, Ting; Chen, Shu; Zhang, Jun; Xia, Ning-Shao (2015-02-25). "The development of a recombinant hepatitis E vaccine HEV 239". *Human Vaccines & Immunotherapeutics* **11** (4): 908–914. doi:10.1080/21645515.2015.1008870. ISSN 2164-5515. PMID 25714510. PMC 4514148.
8. Zhou X, de Man RA, de Knegt RJ, Metselaar HJ, Peppelenbosch MP, Pan Q.; De Man; De Knegt; Metselaar; Peppelenbosch; Pan (2013). "Epidemiology and management of chronic hepatitis E infection in solid organ transplantation: a comprehensive literature review". *Rev Med Virol.* **23** (5): 295–304. doi:10.1002/rmv.1751. PMID 23813631.
9. Patra, Sharda; Kumar, Ashish; Trivedi, Shubha Sagar; Puri, Manju; Sarin, Shiv Kumar (2007-07-03). "Maternal and Fetal Outcomes in Pregnant Women with Acute Hepatitis E Virus Infection" (in en). *Annals of Internal Medicine* **147** (1): 28. doi:10.7326/0003-4819-147-1-200707030-00005. ISSN 0003-4819. PMID 17606958.
10. "Hepatitis E Questions and Answers for Health Professionals". *www.cdc.gov*. CDC. 13 June 2018.
11. Dalton, Harry R.; Kamar, Nassim; Baylis, Sally A.; Moradpour, Darius; Wedemeyer, Heiner; Negro, Francesco (June 2018). "EASL Clinical Practice Guidelines on hepatitis E virus infection". *Journal of Hepatology* **68** (6): 1256–1271. doi:10.1016/j.jhep.2018.03.005. PMID 29609832.
12. Sridhar, Siddharth; Teng, Jade L. L.; Chiu, Tsz-Ho; Lau, Susanna K. P.; Woo, Patrick C. Y. (20 April 2017). "Hepatitis E Virus Genotypes and Evolution: Emergence of Camel Hepatitis E Variants". *International Journal of Molecular Sciences* **18** (4): 869. doi:10.3390/ijms18040869. ISSN 1422-0067. PMID 28425927. PMC 5412450.
13. GBD 2017 Disease Injury Incidence Prevalence Collaborators (10 November 2018). "Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017". *Lancet (London, England)* **392**(10159): 1789–1858. doi:10.1016/S0140-6736(18)32279-7. ISSN 1474-547X. PMID 30496104. PMC 6227754.
14. Hoofnagle, J. H.; Nelson, K. E.; Purcell, R. H. (2012). "Hepatitis E". *New England Journal of Medicine* **367** (13): 1237–1244. doi:10.1056/NEJMra1204512. PMID 23013075.
15. "Facts about hepatitis E". *ecdc.europa.eu*. European Centre for Disease Prevention and Control. Retrieved 17 April 2019.
16. Bonnet, D.; Kamar, N.; Izopet, J.; Alric, L. (2012). "L'hépatite virale E : Une maladie émergente". *La Revue de Médecine Interne* **33** (6): 328–334. doi:10.1016/j.revmed.2012.01.017. PMID 22405325.
17. Behrendt, Patrick; Steinmann, Eike; Manns, Michael P.; Wedemeyer, Heiner (2014-12-01). "The impact of hepatitis E in the liver transplant setting". *Journal of Hepatology* **61** (6): 1418–1429. doi:10.1016/j.jhep.2014.08.047. PMID 25195557.
18. Kamar, Nassim; Pischke, Sven (7 May 2018). "Acute and Persistent Hepatitis E Virus Genotype 3 and 4 Infection: Clinical Features, Pathogenesis, and Treatment". *Cold Spring Harbor Perspectives in Medicine* **9** (7): a031872. doi:10.1101/cshperspect.a031872. ISSN 2157-1422. PMID 29735575.
19. Bazerbachi, F; Haffar, S; Garg, SK; Lake, JR (February 2016). "Extra-hepatic manifestations associated with hepatitis E virus infection: a comprehensive review of the literature.". *Gastroenterology Report* **4** (1): 1–15. doi:10.1093/gastro/gov042. PMID 26358655. PMC 4760069.
20. Rivero-Juárez, Antonio; Aguilera, Antonio; Avellón, Ana; García-Deltoro, Miguel; García, Federico; Gortazar, Christian; Granados, Rafael; Macías, Juan *et al.* (30 July 2018). "Executive summary: Consensus document of the diagnosis, management and prevention of infection with the hepatitis E virus: Study Group for Viral Hepatitis (GEHEP) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)". *Enfermedades Infecciosas y Microbiologia Clinica*. doi:10.1016/j.eimc.2018.06.014. ISSN 1578-1852. PMID 30072282.
21. Kamar, Nassim; Bendall, Richard P.; Peron, Jean Marie; Cintas, Pascal; Prudhomme, Laurent; Mansuy, Jean Michel; Rostaing, Lionel; Keane, Frances *et al.* (2011). "Hepatitis E virus and neurologic disorders". *Emerging Infectious Diseases* **17** (2): 173–179. doi:10.3201/eid1702.100856. ISSN 1080-6059. PMID 21291585. PMC 3298379.
22. Dalton, Harry R.; Kamar, Nassim; van Eijk, Jeroen J. J.; Mclean, Brendan N.; Cintas, Pascal; Bendall, Richard P.; Jacobs, Bart C. (29 December 2015). "Hepatitis E virus and neurological injury". *Nature Reviews Neurology* **12**

(2): 77–85. doi:10.1038/nrneurol.2015.234. ISSN 1759-4766. PMID 26711839.
23. Kumar A., Beniwal M., Kar P., Sharma J.B., Murthy N.S. (2004). "Wiley Online Library". *International Journal of Gynecology & Obstetrics* **85** (3): 240–244. doi:10.1016/j.ijgo.2003.11.018. PMID 15145258.
24. Khuroo, Mohammad S.; Khuroo, Mehnaaz S.; Khuroo, Naira S. (20 September 2016). "Transmission of Hepatitis E Virus in Developing Countries". *Viruses* **8** (9): 253. doi:10.3390/v8090253. ISSN 1999-4915. PMID 27657112. PMC 5035967.
25. Pérez-Gracia, María Teresa; Suay-García, Beatriz; Mateos-Lindemann, María Luisa (20 March 2017). "Hepatitis E and pregnancy: current state". *Reviews in Medical Virology* **27**(3): e1929. doi:10.1002/rmv.1929. ISSN 1099-1654. PMID 28318080.
26. Bose, Purabi Deka; Das, Bhudev Chandra; Hazam, Rajib Kishore; Kumar, Ashok; Medhi, Subhash; Kar, Premashis (2014). "Evidence of extrahepatic replication of hepatitis E virus in human placenta". *Journal of General Virology* **95** (6): 1266–1271. doi:10.1099/vir.0.063602-0. PMID 24622580.
27. Pérez-Gracia, María Teresa; García, Mario; Suay, Beatriz; Mateos-Lindemann, María Luisa (2015-06-28). "Current Knowledge on Hepatitis E". *Journal of Clinical and Translational Hepatology* **3** (2): 117–126. doi:10.14218/JCTH.2015.00009. ISSN 2225-0719. PMID 26355220. PMC 4548356.
28. Wang, Youchun (2016). Hepatitis E Virus. *Springer. p. 75.* ISBN 9789402409420.
29. Boyer, Thomas D.; Manns, Michael Peter; Sanyal, Arun J.; Zakim, David (2012). Zakim and Boyer's Hepatology: A Textbook of Liver Disease. *Elsevier Health Sciences*. p. 609. ISBN 978-1437708813.
30. Johne, Reimar; Heckel, Gerald; Plenge-Bönig, Anita; Kindler, Eveline; Maresch, Christina; Reetz, Jochen; Schielke, Anika; Ulrich, Rainer G. (2010). "Novel hepatitis E virus genotype in Norway rats, Germany". *Emerging Infectious Diseases* **16**(9): 1452–1455. doi:10.3201/eid1609.100444. ISSN 1080-6059. PMID 20735931. PMC 3294985.
31. Sridhar, Siddharth; Yip, Cyril C.Y.; Wu, Shusheng; Cai, Jianpiao; Zhang, Anna Jin-Xia; Leung, Kit-Hang; Chung, Tom W.H.; Chan, Jasper F.W. *et al.* (December 2018). "Rat Hepatitis E Virus as Cause of Persistent Hepatitis after Liver Transplant" (in en-us). *Emerging Infectious Diseases* **24** (12): 2241–2250. doi:10.3201/eid2412.180937. PMID 30457530. PMC 6256372.
32. Song, Yoon-Jae (2010-11-01). "Studies of hepatitis E virus genotypes". *The Indian Journal of Medical Research* **132** (5): 487–488. ISSN 0971-5916. PMID 21149996. PMC 3028963.
33. Pelosi, E; Clarke, I (2008-11-07). "Hepatitis E: a complex and global disease". *Emerging Health Threats Journal* **1**: e8. doi:10.3134/ehtj.08.008. ISSN 1752-8550. PMID 22460217. PMC 3167588.
34. *Hepatitis E Vaccine Working Group (1 October 2014). Recommendations of HEV Working Group on the use of hepatitis E vaccine (PDF). www.who.int (Report). WHO.*
35. Guerrant, Richard L.; Walker, David H.; Weller, Peter F. (2011). Tropical Infectious Diseases: Principles, Pathogens and Practice. *Elsevier Health Sciences*. p. 424. ISBN 9781437737776.
36. Echevarría, José-Manuel (2014). "Autochthonous Hepatitis E Virus Infection in Europe: A Matter of Concern for Public Health?". *Journal of Clinical and Translational Hepatology* **2**(1): 7–14. doi:10.14218/JCTH.2013.00027. ISSN 2225-0719. PMID 26357613. PMC 4521255.
37. Meng, X. J. (2010-01-27). "Hepatitis E virus: Animal Reservoirs and Zoonotic Risk". *Veterinary Microbiology* **140**(3–4): 256–65. doi:10.1016/j.vetmic.2009.03.017. ISSN 0378-1135. PMID 19361937. PMC 2814965.
38. Woolson, K. L.; Forbes, A.; Vine, L.; Beynon, L.; McElhinney, L.; Panayi, V.; Hunter, J. G.; Madden, R. G. *et al.* (2014). "Extra-hepatic manifestations of autochthonous hepatitis E infection" (in en). *Alimentary Pharmacology & Therapeutics* **40**(11–12): 1282–1291. doi:10.1111/apt.12986. ISSN 1365-2036. PMID 25303615.
39. Doward, Jamie (21 September 2013). "Chefs fight for the right to serve their pork pink". *The Observer newspaper.*
40. Liu, Dongyou (2010-11-23). Molecular Detection of Human Viral Pathogens. *CRC Press*. p. 102. ISBN 9781439812372.
41. "Hepatitis E Fact sheet". *WHO.* Retrieved 17 April 2019.
42. Dai, Xing; Dong, Chen; Zhou, Zhenxian; Liang, Jiuhong; Dong, Min; Yang, Yan; Fu, Jianguang; Tian, Hua *et al.* (2013). "Hepatitis E Virus Genotype 4, Nanjing, China, 2001–2011". *Emerging Infectious Diseases* **19** (9): 1528–1530. doi:10.3201/eid1909.130013. ISSN 1080-6040. PMID 23965731. PMC 3810912.
43. Griffiths, Jeffrey; Maguire, James H.; Heggenhougen, Kristian; Quah, Stella R. (2010-03-09). *Public Health and Infectious Diseases.* Elsevier. ISBN 9780123815071.
44. Bitton, Gabriel (2005-05-27). *Wastewater Microbiology.* John Wiley & Sons. p. 132. ISBN 9780471717911.
45. Hubálek, Zdenek; Rudolf, Ivo (2010-11-25). *Microbial Zoonoses and Sapronoses.* Springer Science & Business Media. p. 189. ISBN 9789048196579.
46. Khuroo, Mohammad Sultan (2011-10-01). "Discovery of hepatitis E: The epidemic non-A, non-B hepatitis 30 years down the memory lane". *Virus Research*. Hepatitis E Viruses **161** (1): 3–14. doi:10.1016/j.virusres.2011.02.007. PMID 21320558.
47. Cowie, Benjamin C.; Adamopoulos, Jim; Carter, Karen; Kelly, Heath (2005-03-01). "Hepatitis E Infections, Victoria, Australia". *Emerging Infectious Diseases* **11** (3): 482–484. doi:10.3201/eid1103.040706. ISSN 1080-6040. PMID 15757573. PMC 3298235.
48. Rein, David B.; Stevens, Gretchen A.; Theaker, Jordan; Wittenborn, John S.; Wiersma, Steven T. (2012). "The global burden of hepatitis E virus genotypes 1 and 2 in 2005" (in en). *Hepatology* **55** (4): 988–997. doi:10.1002/hep.25505. ISSN 1527-3350.
49. Haffar, Samir; Bazerbachi, Fateh (2017-09-04). "Systematic review with meta-analysis: the association between hepatitis E seroprevalence and haemodialysis". *Aliment Pharmacol Ther***46** (9): 790–799. doi:10.1111/apt.14285. PMID 28869287.
50. Pavio, Nicole; Meng, Xiang-Jin; Renou, Christophe (2010-01-01). "Zoonotic hepatitis E: animal reservoirs and emerging risks". *Veterinary Research* **41** (6): 46. doi:10.1051/vetres/2010018. ISSN 0928-4249. PMID 20359452. PMC 2865210.
51. Satou K, Nishiura H; Nishiura (2007). "Transmission Dynamics of Hepatitis E Among Swine: Potential Impact upon Human Infection". *BMC Vet. Res.* **3**: 9. doi:10.1186/1746-6148-3-9. PMID 17493260. PMC 1885244.
52. "Hepatitis E Virus Transmission from Wild Boar Meat". *Emerging Infect. Dis.* **11** (12): 1958–60. 2005. doi:10.3201/eid1112.051041. PMID 16485490. PMC 3367655.
53. Kuniholm MH & Nelson KE (2008). "Of Organ Meats and Hepatitis E Virus: One Part of a Larger Puzzle Is Solved". *J Infect Dis* **198** (12): 1727–1728. doi:10.1086/593212. PMID 18983247.
54. Johne R, Plenge-Bönig A, Hess M, Ulrich RG, Reetz J, Schielke A; Plenge-Bönig; Hess; Ulrich; Reetz; Schielke (March 2010). "Detection of a novel hepatitis E-like virus in faeces of wild rats using a nested broad-spectrum RT-PCR". *J. Gen. Virol.* **91** (Pt 3): 750–8. doi:10.1099/vir.0.016584-0. PMID 19889929.
55. Balakrishnan, V.; Rajesh, G. (2016). *Practical Gastroenterology.* JP Medical Ltd. p. 195. ISBN 9789352501908. Retrieved 22 July 2019.
56. Cocquerel, Laurence; Dubuisson, Jean; Meuleman, Philip; d'Autume, Valentin de Masson; Farhat, Rayan; Aliouat-Denis, Cécile-Marie; Duvet, Sandrine; Saas, Laure *et al.* (18 April 2019). "New insights into the ORF2 capsid protein, a key player of the hepatitis E virus lifecycle" (in en). *Scientific Reports* **9**(1): 6243. doi:10.1038/s41598-019-42737-2. ISSN 2045-2322. PMID 31000788. PMC 6472401.
57. Ahmad, Imran; Holla, R. Prasida; Jameel, Shahid (October 2011). "Molecular Virology of Hepatitis E Virus". *Virus Research* **161** (1): 47–58. doi:10.1016/j.virusres.2011.02.011. ISSN 0168-1702. PMID 21345356. PMC 3130092.
58. Ding, Qiang; Heller, Brigitte; Capuccino, Juan M. V.; Song, Bokai; Nimgaonkar, Ila; Hrebikova, Gabriela; Contreras, Jorge E.; Ploss, Alexander (2017). "Hepatitis E virus ORF3 is a functional ion channel required for release of infectious particles". *Proceedings of the National Academy of Sciences of the United States of America* **114** (5): 1147–1152. doi:10.1073/pnas.1614955114. ISSN 1091-6490. PMID 28096411. PMC 5293053.
59. Cao, Dianjun; Meng, Xiang-Jin (2012-08-22). "Molecular biology and replication of hepatitis E virus" (in en). *Emerging Microbes & Infections* **1** (8): e17. doi:10.1038/emi.2012.7. PMID 26038426. PMC 3630916.
60. Tao, TS; Liu, Z; Ye, Q; Mata, DA; Li, K; Yin, C; Zhang, J; Tao, YJ (Aug 4, 2009). "Structure of the hepatitis E virus-like particle suggests mechanisms for virus assembly and receptor binding". *Proceedings of the National Academy of Sciences of the United States of America* **106** (31): 12992–7. doi:10.1073/pnas.0904848106. PMID 19622744. PMC 2722310.
61. Aggarwal, Rakesh (2 October 2012). "Diagnosis of hepatitis E" (in En). *Nature Reviews Gastroenterology & Hepatology* **10**(1): 24–33. doi:10.1038/nrgastro.2012.187. ISSN 1759-5045.subscription needed
62. Baylis, Sally A.; Blümel, Johannes; Mizusawa, Saeko; Matsubayashi, Keiji; Sakata, Hidekatsu; Okada, Yoshiaki; Nübling, C. Micha; Hanschmann, Kay-Martin O. (May 2013). "World Health Organization International Standard to Harmonize Assays for Detection of Hepatitis E Virus RNA". *Emerging Infectious Diseases* **19** (5): 729–735. doi:10.3201/eid1905.121845. ISSN 1080-6040. PMID 23647659. PMC 3647515.
63. "Hepatitis E Virus and Food". *www.fsai.ie*. Food Safety Authority of Ireland. 11 July 2017.

64. Hillyer, Christopher D.; Shaz, Beth H.; Zimring, James C.; Abshire, Thomas C. (2009). *Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects.* Elsevier. p. 364. ISBN 9780080922300.
65. Dreier, Jens; Knabbe, Cornelius; Vollmer, Tanja (1 February 2018). "Transfusion-Transmitted Hepatitis E: NAT Screening of Blood Donations and Infectious Dose". *Frontiers in Medicine* **5**. doi:10.3389/fmed.2018.00005. ISSN 2296-858X. PMC 5799287.
66. Hans, Rekha; Marwaha, Neelam (2014). "Nucleic acid testing-benefits and constraints". *Asian Journal of Transfusion Science* **8** (1): 2–3. doi:10.4103/0973-6247.126679. ISSN 0973-6247. PMC 3943139.
67. "Safety and efficacy of a recombinant hepatitis E vaccine". *New England Journal of Medicine* **356** (9): 895–903. 2007. doi:10.1056/NEJMoa061847. PMID 17329696.
68. Park, S. B. (November 2012). "Hepatitis E vaccine debuts". *Nature* **491** (7422): 21–22. doi:10.1038/491021a. PMID 23128204.
69. Labrique, Alain B.; Sikder, Shegufta S.; Krain, Lisa J.; West, Keith P.; Christian, Parul; Rashid, Mahbubur; Nelson, Kenrad E. (2012-09-01). "Hepatitis E, a Vaccine-Preventable Cause of Maternal Deaths". *Emerging Infectious Diseases* **18** (9): 1401–1404. doi:10.3201/eid1809.120241. ISSN 1080-6040. PMID 22931753. PMC 3437697.
70. "Hepatitis E vaccine: WHO position paper, May 2015.". *Releve Epidemiologique Hebdomadaire* **90** (18): 185–200. 1 May 2015. PMID 25935931.
71. Hepatitis E Treatment & Management: Medical Management, Diet and Activity. 2019-05-30.
72. Kamar, Nassim; Izopet, Jacques; Tripon, Simona; Bismuth, Michael; Hillaire, Sophie; Dumortier, Jérôme; Radenne, Sylvie; Coilly, Audrey *et al.* (2014-03-20). "Ribavirin for Chronic Hepatitis E Virus Infection in Transplant Recipients". *New England Journal of Medicine* **370** (12): 1111–1120. doi:10.1056/NEJMoa1215246. ISSN 0028-4793. PMID 24645943.
73. Teshale, Eyasu H. (31 May 2017). "Hepatitis E - Infectious Diseases Related to Travel Chapter 3 - 2018 Yellow Book". *www.cdc.gov. CDC.*
74. Navaneethan, Udayakumar; Mohajer, Mayar Al; Shata, Mohamed T (2008-11-01). "Hepatitis E and Pregnancy- Understanding the pathogenesis". *Liver International : Official Journal of the International Association for the Study of the Liver* **28** (9): 1190–1199. doi:10.1111/j.1478-3231.2008.01840.x. ISSN 1478-3223. PMID 18662274. PMC 2575020.
75. "Common animal associated infections quarterly report (England and Wales) – fourth quarter 2015". *Assets.publishing.service.gov.uk* **10** (6). 12 February, 2016.
76. "Hepatitis E epidemic, Uganda". *Emerging Infect. Dis.* **16**(1): 126–9. January 2010. doi:10.3201/eid1601.090764. PMID 20031058. PMC 2874362.
77. Investigation of Hepatitis E Outbreak Among Refugees — Upper Nile, South Sudan, 2012-2013. *www.cdc.gov (Report).* **62**. CDC Morbidity and Mortality Weekly Report. 26 July 2013. pp. 581–586.
78. Hereward Holland (February 2, 2013). "Hepatitis outbreak kills 88 in South Sudan—aid agency". *Reuters.*
79. Sharma, Christopher (5 September 2014). "Nepal, hepatitis E epidemic: 9 dead and over 6 thousand infected". *www.asianews.it.*
80. "Hepatitis E cases in Namibia rise to 490". *www.xinhuanet.com.* Xinhua News. 28 January 2018.
81. *"Weekly bulletins on outbreaks and other emergencies"(PDF). World Health Organization. WHO.int. Retrieved 20 May2019.*
82. Khudyakov, Yury E.; Purdy, Michael A. (17 December 2010). "Evolutionary History and Population Dynamics of Hepatitis E Virus" (in en). *PLOS ONE* **5** (12): e14376. doi:10.1371/journal.pone.0014376. ISSN 1932-6203. PMID 21203540. PMC 3006657.
83. Mirazo S, Mir D, Bello G, Ramos N, Musto H, Arbiza J (2016). "New insights into the hepatitis E virus genotype 3 phylodynamics and evolutionary history". *Infect Genet Evol* **43**: 267–73. doi:10.1016/j.meegid.2016.06.003. PMID 27264728.

Further reading

- Parvez, Mohammad Khalid (2013-01-01). "Chronic hepatitis E infection: risks and controls". *Intervirology* **56** (4): 213–216. doi:10.1159/000349888. ISSN 1423-0100. PMID 23689166.
- *Aggarwa, Rakesh; Gandhi, Sanjay (December 2010). "A systematic review on prevalence of hepatitis E disease and seroprevalence of hepatitis E virus antibody" (PDF). World Health Organization. WHO/IVB/10.14.*