

# An updated approach to viral hepatitis E

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## ABSTRACT

Viral hepatitis E (VHE) is considered to be the most common acute viral hepatitis worldwide. Since the 1980s, VHE has been reported in developing countries. Although VHE is not a reportable disease in many developed countries, it is evidently on the rise even in these countries [1]. In Europe, VHE is no longer an imported disease and efforts have been made to map VHE cases in both humans and animals to be able to update the recommendations for VHE prevention, risk assessment for blood product and organ

transplants recipients, prevention strategies for severe and chronic VHE, and laboratory test algorithms.

## KEYWORDS:

acute viral hepatitis E – chronic viral hepatitis E – extrahepatic manifestations – blood derivatives – organ transplantations – prevention

## SOUHRN

### Mandáková Z.: Novinky v přístupu k virové hepatitidě E

Virová hepatitida E (VHE) je považována za nejčastější akutní onemocnění virovou hepatitidou na světě. Od 80. let 20. století byl popisován výskyt VHE v rozvojových zemích. Přestože hlášení výskytu VHE není v mnoha rozvinutých zemích povinné, je v současnosti zřejmé, že výskyt tohoto onemocnění narůstá a je i v těchto zemích významný [1]. VHE v Evropě není již delší dobu jen importované onemocnění, proto je v současné době na evropské úrovni snaha o zmapování výskytu onemocnění u lidí i zvířat, aby bylo možné vytvořit aktuální doporučení pro prevenci onemocně-

ní, stanovit riziko pro příjemce krevních derivátů a transplantované, stanovit strategii prevence závažných a chronických průběhů VHE a vytvořit doporučení laboratorních vyšetřovacích postupů.

## KLÍČOVÁ SLOVA:

virová hepatitida E akutní – virová hepatitida E chronická – extrahepatální manifestace – krevní deriváty – transplantace orgánů – prevence

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The causative agent for viral hepatitis E is the hepatitis E virus, the sole member of the genus *Hepevirus* in the family *Hepeviridae*. The virus was isolated in 1990, when it was also named and classified. Genotypes 1 and 2 are able to cause disease in humans only, while genotypes 3 and 4 infect both humans and animals (farm pigs, wild deer, wild boar, shellfish, and rodents), and genotype 5 has only been reported in birds [2]. In developing countries, the virus is spread via the faecal-oral route, primarily through contaminated water in areas with low hygiene standards. The infection is most often caused by genotypes 1 (South-East Asia and a large part of Africa) and 2 (Mexico and some parts of Africa). In developed countries, VHE is a food-borne infection linked to the consumption of pork and game meat. Genotype 3 has been detected in pork products in Europe (genotypes

3e, 3f, and 3g in the Czech Republic) [3, 4], the USA, and Japan. Even in industrialized countries, infection can be transmitted through contaminated water and food which came into contact with it (seafood or strawberries). This route of transmission has not yet been reported in the Czech Republic. Person-to-person transmission is also likely to occur through the faecal-oral route, and secondary transmission has been reported in households during epidemics. Studies focused on genetic relatedness between animal and human isolates from the same geographic area have confirmed that VHE is a zoonosis. The infectious period is not known. HEV can be detected in the stool 14 days before jaundice appears and around four weeks after the consumption of contaminated food or water. Moreover, the infection can be passed on through infected blood products, and HEV transmission has also

## KRÁTKÉ SDĚLENÍ

been reported in a recipient of an HEV-positive organ transplant [2, 6]. As pointed out by Soňa Fraňková from the Institute of Clinical and Experimental Medicine in Prague, MD who has long been involved in this issue, 12 organ transplant recipients with VHE were treated at the Institute in the last four years. Ten of these patients developed acute infection and two chronic infection. One of the latter patients was a heart transplant recipient and the other was a liver transplant recipient. They were both diagnosed with VHE when presenting with symptoms of decompensated cirrhosis. The suspected mode of transmission was the ingestion of meat products. No case of HEV transmission through blood transfusion has been reported to date. Routine testing of organ transplants or blood transfusion products has not been performed so far, but some West European countries plan to do so in 2016.

The incubation period of VHE is 15–64 days. The disease has a similar course as viral hepatitis A – a short prodromal phase is followed by the development of clinical symptoms including jaundice that lasts several days to weeks. VHE caused by genotype 1 or 2, frequent in developing countries, is typically characterized by jaundice and is more common in adolescents and young adults. VHE in the third trimester of pregnancy is associated with a high case fatality rate (20%). Progression to chronicity has not been reported for these genotypes. Genotypes 3 and 4 cause endemic food-borne disease, with sporadic jaundice, in developed countries. In immunocompetent persons, acute VHE is mostly asymptomatic and self-limited, with no health consequences. VHE affects predominantly seniors and the elderly. Few severe extrahepatic manifestations of either acute or chronic VHE, i. e. neurological complications (Guillain-Barré syndrome, polyradiculopathy, bilateral brachial neuritis, encephalitis, or proximal myopathy) and kidney disease have been reported. In immunosuppressed persons, VHE can progress to chronicity [1, 6, 7]. In the Czech, no extrahepatic manifestations have been documented in either immunosuppressed or immunocompetent persons.

The diagnosis of VHE is based on serological tests (detection of anti-HEV IgM and anti-HEV IgG antibodies) that differ in specificity and sensitivity and on PCR for direct detection of viral RNA in the serum and stool. Since immunosuppressed patients may not produce enough antibodies, PCR diagnosis should be used as early as possible [5].

Most HEV infections only require symptomatic treatment. Patients with an underlying liver disease who are at risk of a severe course of VHE may benefit from ribavirin therapy. Antivirals are also recommended in immunosuppressed patients with chronic VHE. Reduced immunosuppression needs to be considered in transplant recipients prior to the institution of therapy for VHE, as it has been reported to result in the elimination of HEV in as many as 30% of patients [1].

In the Czech Republic, VHE was first diagnosed in a traveller to India in 1996. Since then, a clear increase in reported cases of VHE has been observed – see Figure 1 (source: EPIDAT) [10].

The number of imported cases has been relatively stable and low. In 1996–2014, 129 imported cases of VHE were diagnosed: of these, 59 were linked to travel to Asia, 20 to travel to Americas, Africa, and Australia, and 50 (38%) to travel to European countries. Therefore, an important increase can be seen in cases acquired in the Czech Republic or during travel to European countries. It can be assumed that local cases of VHE may have been under-reported in the past, as VHE testing was only performed in travellers with suspected VHE after their return from high-risk foreign countries.

Similarly to other European countries, in the Czech Republic, the older age groups are more affected – see Figure 2 (source EPIDAT). Men are more often diagnosed with VHE than women and account for 63.7% of the study cohort. VHE cases are unevenly distributed across the Czech Republic, with the most afflicted areas being the Ústí nad Labem Region, Central Bohemian Region, Hradec Králové Region, Prague, and South Moravian Region. More cases are reported between January and May than in other months of the year [9, 10].

Although the detection of HEV in foods is not routinely feasible in practice, the virus is known to be fully inactivated at temperatures above 70 °C; therefore HEV infection is preventable by the safe handling of pork and game meat which should never be undercooked.

Since 2012, a vaccine against VHE has been registered in China, but its efficacy against genotype 3, found in Europe, is yet to be determined [8].

In the light of the reported severe extrahepatic complications, VHE testing should be part of the differential diagnosis of disease-

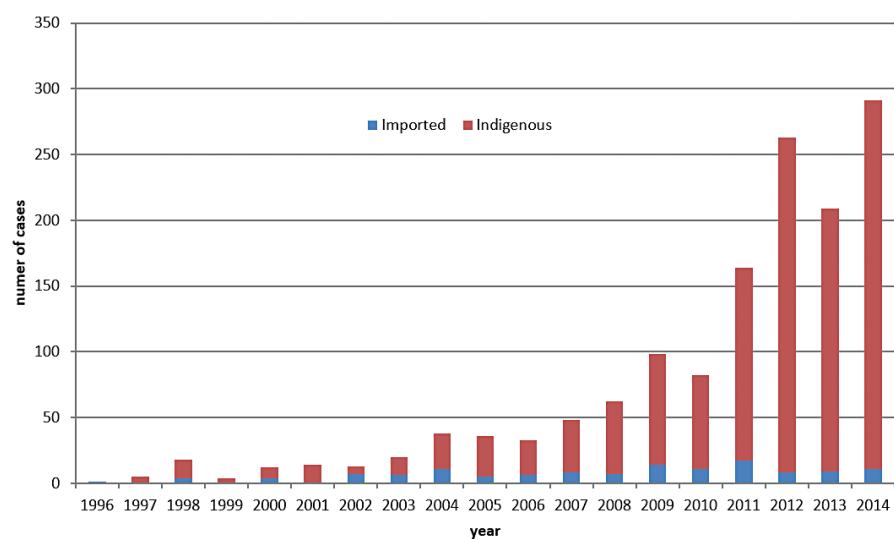
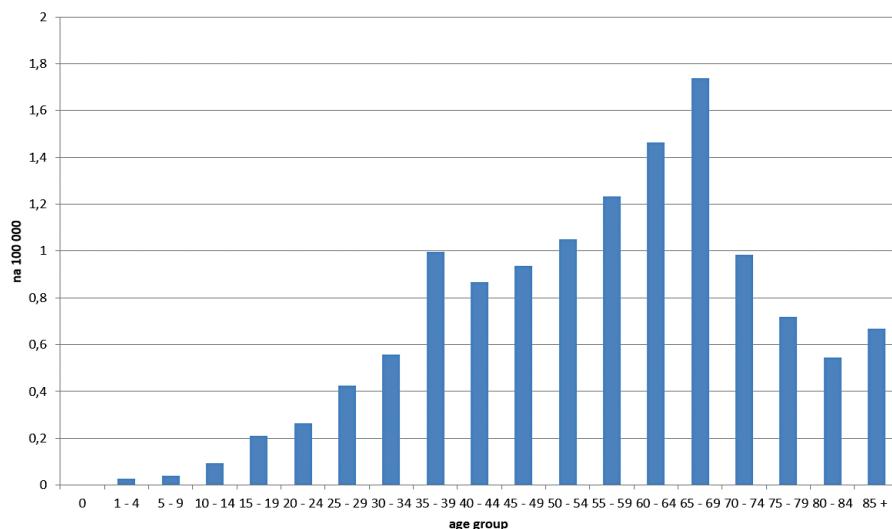


Fig 1. Absolute number of indigenous and imported VHE cases in the Czech Republic



**Fig 2. Average sickness rate/100 000 by age groups VHE in the Czech Republic**

es of unclear origin. Even if genotype 1 known to be the cause of a high case fatality rate in the third trimester of pregnancy is not present in Europe, VHE testing should be included in the differential diagnosis of unclear medical conditions in pregnancy.

Given the possible HEV transmission through blood products or organ transplants with subsequent development of acute hepatitis and its possible progression to chronicity, attention should be drawn to this issue, and recommendations for the prevention of HEV transmission through blood products and organ transplants should be formulated as soon as possible. According to the most recent guidelines from 2014 provided by the Society for Transfusion Medicine of the J. E. Purkyně Czech Medical Association in the Czech Republic, blood donation can be done one year after recovery from acute VHE provided that the donor is VHB and VHC negative [9].

To solve the problems related to VHE, funds need to be allocated to the area of diagnostic testing to make it possible to perform routine screening of blood and organ donors for HEV and to make HEV testing available to clinicians who, in cooperation with epidemiologists, thus will be able to proceed in line with the scientific evidence.

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