# Abstract

**Background & Aims:** The incidence of locally acquired hepatitis E increased in recent years across Europe. There are only a few data on hepatitis E in Romania. The purpose of our research was to describe and compare hepatitis E and hepatitis A in adult patients.

**Methods:** We included all consecutive adult patients with hepatitis E (48) and hepatitis A (152) admitted in the Teaching Hospital of Infectious Diseases, Cluj-Napoca, Romania between January 2017 and August 2019.

**Results:** Hepatitis E incidence increased in 2018-2019 compared to 2017. The average age in hepatitis E patients was 50.6 versus 39.1 years in hepatitis A and two thirds of the patients in both groups were men. Compared to hepatitis A, patients with hepatitis E presented a milder course of disease with significantly less modified AST and ALT, bilirubin, prothrombin index and INR levels. We found a higher prevalence of comorbidities in hepatitis E patients adjusted for age & gender. Severe forms were found in 5 (3.3%) hepatitis A patients compared to 12 (25%) of hepatitis E patients, of which 3 died. Acute-on-chronic hepatitis E and immunosuppression were found in 6 and 5 patients, respectively.

**Conclusions:** Our study shows that hepatitis E incidence is increasing, being usually self-limited and milder compared to hepatitis A. Ribavirin treatment seems to be beneficial in patients with preexisting conditions.

# Keywords

hepatitis e, hepatitis a, ribavirin

# Background & Aims

Hepatitis E is an anthropozoonosis with typically mild evolution caused by the Hepatitis E virus (HEV), the *Hepeviridae* family, whose members infect humans and other mammals [1, 2]. Genotypes 3 and 4 are the most common in Europe, where the reservoir of infection is represented by asymptomatic but highly infectious pigs and wild boars (with reproductive index up to 8.8) [3–6].

Recent Romanian research found IgG HEV seroprevalence between 9.6% and 50% in farm, backyard pigs and wild boars, mostly genotype 3.

Romanian data on IgG HEV seroprevalence in humans is scarce: general population (5.9% - 28%), students and medical staff (12.5-13.98%) and patients with hepatitis B or C (12%). [7]

In Europe, transmission occurs through consumption of contaminated and undercooked pork or other meat products [8, 9] but other transmission routes have also been demonstrated (blood transfusions [10, 11]). Vegetable products are rarely associated with HEV in Europe, probably due to tight regulation of pig manure use in farming [8, 12]. Genotypes 3 and 4 may lead to chronic disease in immunocompromised patients [5, 13] yet, the majority of individuals are asymptomatic [14].

Genotypes 1 and 2 of HEV are obligate human pathogens that only cause acute disease and are more common in developing countries: Asia (genotype 1), Africa (genotype 2) and Central America (both), being transmitted through fecal-oral route and contaminated water [5].

The number of laboratory-confirmed cases increased across Europe since 2006 to even more cases than hepatitis A in Germany, UK and France [3] with an estimated two million locally acquired cases each year in Europe [5].

HEV infects the liver but may be present in other organs (brain, kidney, placenta) [15, 16] and HEV RNA becomes detectable in blood and feces after 2-3 weeks post-exposure and lasting 3-6 weeks. After an incubation of 15-60 days, liver enzymes, anti-HEV IgM and then anti-HEV IgG levels increase marking the clinical onset. Anti-HEV IgM antibodies may persist up to 1 year, anti-HEV IgG are long-lasting and in immunosuppressed patients, HEV RNA may be detectable for more than 6 months being considered chronic infection [5].

Risk factors for clinical manifestations include: male gender, age over 50 and preexisting liver disease [8, 17]. Acute-on-chronic liver failure has considerable fatality but benefits from antiviral treatment (ribavirin, interferon) [18, 19]. Occasionally, neurologic lesions in acute hepatitis E patients were reported and include: neuralgic amyotrophy, Bell palsy, Guillain-Barré syndrome, encephalitis and myelitis [20, 21]. Chronic cases (HEV RNA clearance failure after 6 months) have been reported in solid organ transplant recipients presenting long-lasting fatigue, elevated AST, ALT and γ-GT and sometimes negative anti-HEV IgM and IgG [13, 22, 23]. EASL recommends HEV testing in patients with the aforementioned pathologies, regardless of liver enzyme levels [5].

According to Romanian regulations, all confirmed and suspected cases of acute viral hepatitis (A to E) should be admitted and treated in an appropriate hospital.

Our objective was to describe all cases of HEV infection admitted in our hospital during the study period in comparison to all hepatitis A adult patients. We focused on patient characteristics that were available from our hospital’s electronic records.

# Methods

We performed a retrospective case-control study including all consecutive adult (>18 years old) hepatitis E and A cases registered in our hospital’s (The Teaching Hospital of Infectious Diseases of Cluj-Napoca, Romania) electronic database starting from 2017 January 1 until 2019 August 30. Our institution serves the Transylvania region, but most patients live in Cluj County. All clinical departments within our hospital were considered similar regarding diagnosis and management of patients.

Hepatitis A and E were diagnosed by qualitative anti-HAV and anti-HEV IgM respectively using *bioMérieux VIDAS® Hepatitis panel* electrochemiluminescence immunoassays from blood samples [24].

Among the 9 patients who received ribavirin, significant improvement was found in all cases; patients were either discharged at home or transferred to other departments for further care of their comorbidities. Acute-on-chronic liver failure was demonstrated in 3 of the treated cases, 5 other cases had immunologic deficiencies and another one presented with neurologic manifestations that triggered the search for hepatitis E infection.

The three deceased patients with acute-on-chronic end-stage liver disease with fulminant evolution and/or severe comorbidities did not receive etiologic treatment because of severe thrombocytopenia.

Only 5 hepatitis A cases (3.3%) developed severe disease with coagulation abnormalities and received plasma products, all with favorable outcome. Overall, more hepatitis E cases required additional treatment compared to hepatitis A despite apparent milder disease.

Our study had several limitations: Genotyping was not possible, we presumed that genotypes 3 and 4 are involved, as showed the studies performed in Romania and elsewhere in Europe [5]. No reliable data on our patient’s alimentary habits was available but the assumption is that pork products are responsible for most cases in a similar manner to other European countries [8]. Follow-up was not insured in all cases, which may have been valuable in measuring the rate of chronic HEV infection.

# Conclusions

An increased number of hepatitis E cases were admitted to our hospital in the last two years. Hepatitis E was generally milder than hepatitis A, more frequently found in older patients with preexisting conditions. Ribavirin treatment seems to be beneficial in patients with acute-on-chronic liver disease and immunosuppression.

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