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## Seroprevalence of anti-HEV IgG in 182 Polish patients

### Obecność przeciwciał anty-HEV IgG u 182 polskich pacjentów

#### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
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#### Summary

##### Introduction:

Hepatitis E virus (HEV) infection is an emergent disease in developed countries. HEV seroprevalence in such areas significantly exceeds values expected when one considers infection with this virus only as a problem restricted to classical endemic regions. To date, no related data are available in Poland. In this study we aimed to obtain HEV seroprevalence data and compare them with similar data for hepatitis A virus (HAV) in Polish patients.

##### Material/Methods:

From February 1st, 2013, to October 15th, 2013, we performed anti-HEV IgG (anti-HEV) tests (EIAgen HEV IgG Kit; Adaltis, Milano, Italy) in 182 patients (101 men and 81 women; 61 patients were HIV-positive) of one center in Poland, aged 19-85 (47.2±14.2 years).

##### Results:

We found a 15.9% seropositivity rate for anti-HEV (16.3% of the study population with an unequivocal test result) and 38.5% for anti-HAV. In 6 cases (3.4%), anti-HEV-positive persons had never travelled abroad. In contrast to HAV seroprevalence data, there was no significant difference in HEV seroprevalence between young adults (18-40 years) and older patients ( $p < 0.0001$  and  $p = 0.0967$ , respectively). Anti-HEV were found in 21.3% of HIV-infected individuals.

##### Conclusions:

HEV infection may occur in Poland. Anti-HAV seropositivity among Polish patients is significantly higher than anti-HEV. In contrast to HAV, HEV seroprevalence is similar in younger and older patients. The clinical course of HEV infection in Polish citizens seems to be largely asymptomatic. Polish HIV patients may be more commonly exposed to HEV than similar individuals from other countries.

##### Keywords:

**HEV • HAV • HIV • anti-HEV • anti-HAV • seroprevalence • hepatitis**

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**Abbreviations:** **Anti-HAV** – antibodies to hepatitis A virus, **anti-HBc** – antibodies to hepatitis B core antigen, **anti-HCV** – antibodies to hepatitis C virus, **anti-HEV** – antibodies to hepatitis E virus, **CHC** – chronic hepatitis C, **CMIA** – chemiluminescent microparticle immunoassay, **EIA** – enzyme immunoassay, **HAV** – hepatitis A virus, **HBsAg** – hepatitis B surface antigen, **HBV** – hepatitis B virus, **HCV** – hepatitis C virus, **HEV** – hepatitis E virus, **HIV** – human immunodeficiency virus, **IgG** – immunoglobulin G, **kb** – kilobase, **RNA** – ribonucleic acid, **s/co** – ratio of the sample optical density at 450 nm and the cut-off value.

## INTRODUCTION

Hepatitis E virus (HEV), one of the so-called primary hepatotropic viruses, was recognized as a separate cause of human disease in the early 1980s [1]. Its genome – single-stranded, positive-sense RNA of 7.2 kb in length – was cloned in the 1990s. In the beginning, the virus was provisionally classified within the Caliciviridae family, but eventually it was reclassified as the only member of the *Hepevirus* genus in the Hepeviridae family. The virus is icosahedral and nonenveloped.

HEV infection has worldwide distribution, but the genetic heterogeneity of the virus has an important impact on the epidemiology of hepatitis E in different geographical areas. Four genotypes involved in human infection and disease exist. They represent one serotype. HEV genotypes 1 and 2 are responsible for classic hepatitis E in highly endemic regions of Asia and Africa. Its prevalence is highest in geographical areas with a hot climate, unsatisfactory sanitation and a low level of personal hygiene. Genotype 3 is related to increasingly reported cases of the so-called autochthonous (locally acquired, that is, not related to travel abroad) hepatitis E in industrialized nations of Europe, North America, Australia and Japan. Numerous seroepidemiological surveys have been performed in the countries of Western Europe. Their results suggest that the anti-HEV IgG rate in blood donors ranges from 3.2% in western France and the Ile de France region [2], 4.7% in Scotland [7], 4.9% in southwest Switzerland [20], 6.8% in northern Germany [15], 16% in southwest England [9], 20.3% in Denmark [6] to 52.5% in the hyper-endemic region of southwest France [23] and, in the general population, from 1.9% in the Netherlands [30], 7.3% in Catalonia and Spain [4], 9.2% in Sweden [25], to 16.8% in Germany [10]. According to our knowledge, there have been no Polish reports on this issue to date. HEV genotype 4 has been identified mainly in Asia (China, Taiwan, Japan) and, recently, in France and Germany [14,34]. Infections with genotypes 3 and 4 are considered to be zoonoses. Although multiple animals can carry the virus, much attention is focused on swine as potentially the most important source of HEV in areas with high prevalence of these genotypes.

The clinical spectrum of HEV infection ranges from an asymptomatic course to fulminant hepatitis. Moreover, the disease can be complicated with extrahepatic manifestations. Previous opinions on hepatitis E have also been revolutionized by a recent first report on the occurrence of the chronic form of HEV infection in solid-organ transplantation patients [19]. Since then, other groups of immunocompromised patients have been identified as endangered with such a form of HEV infection [11,24,32].

The aim of our study was to initially assess anti-HEV seroprevalence (proving past contact with HEV) in patients of the Department of Infectious Diseases in Poznan, western Poland, and the characteristics of HEV-seropositive persons in relation to HAV-seropositive study participants.

## MATERIAL AND METHODS

We prospectively evaluated 182 patients (101 men and 81 women), aged 19-85 (47.2±14.2 years; half of the patients were under 48 years), hospitalized for different reasons (infectious and non-infectious liver diseases, diarrheal illnesses, herpes zoster, HIV infection, meningitis and erysipelas) in the Department of Infectious Diseases of Jozef Strus Multidisciplinary Municipal Hospital in Poznan, Poland, for 9 months (from February 1st, 2013, to October 15th, 2013). The patients were mainly city and town inhabitants (72.5%), and a substantial majority of them were born (79.2%) and lived (94.5%) in the Wielkopolska (Greater Poland) Region, western Poland. Sixty-one patients (33.5%) were infected with HIV.

For anti-HEV IgG (anti-HEV) testing, we used the EIA-gen HEV IgG Kit (Adaltis, Milano, Italy), which is a third generation enzyme immunoassay test for the qualitative assessment of IgG antibodies to HEV in human plasma or sera. The results were considered positive when the ratio of the sample optical density at 450 nm and the cut-off (s/co) value was higher than 1.10 (accordingly to the manufacturer's recommendations). For anti-HAV IgG (anti-HAV) testing, we used the chemiluminescent microparticle immunoassay (CMIA, ARCHITECT HAVAb-IgG, Abbott Laboratories, Wiesbaden, Germany) for

the qualitative detection of IgG antibody to hepatitis A virus (HAV) in human serum or plasma. The results were considered positive when the signal to cut-off (s/co) value was equal to or higher than 1.0 (accordingly to the recommendations of the manufacturer).

The patients were also tested for HBsAg, anti-HBc total (anti-HBc) and anti-HCV (CMIA; ARCHITECT HBsAg Qualitative, Abbot Laboratories, Sligo, Ireland; ARCHITECT Anti-HBc II and ARCHITECT Anti-HCV, both Abbott Laboratories, Wiesbaden, Germany).

Additionally, we collected the patients' simple demographic (age, sex, level of education) and epidemiological (travel abroad, contact with farm animals, dietary habits, that is, consumption of raw meat and/or seafood) data. They were also interviewed for some clinical information, such as past icteric disease and, if available, its final diagnosis, vaccination against hepatitis A and details about the condition responsible for the current hospitalization.

All patients signed an informed consent. The study was approved by the Bioethics Committee of Poznan University of Medical Sciences (resolution number 819/13).

### STATISTICAL ANALYSIS

Nominal data of the patients' characteristics were compared with the test of proportions (comparing percentage ratios between two groups). Age as a numerical variable was compared using Student's t-test. The assumption that age follows a normal distribution was checked by the Shapiro-Wilk test, and homogeneity of variances was verified by Levene's test. Data were analyzed by the statistical package Statistica PL 10 (StatSoft, Inc). All tests were considered significant at  $p < 0.05$ .

### RESULTS

Anti-HEV were found in 29 patients (15.9%). In 4 of them (2.2%) the result was equivocal and they were excluded from further analysis of HEV-seropositivity issues. Anti-HAV were identified in 70 patients among 177 tested. Five persons reported vaccination against hepatitis A, but immunity was proven only in 3 such cases (these patients were excluded from further analysis of HAV-seropositivity issues), while 2 patients were seronegative. The final HAV seropositivity rate was 38.5%. When considering young adults (18-40 years) vs. older individuals, HAV seroprevalence was higher in the latter group (11.3% vs. 53.6%,  $p < 0.0001$ ). We failed to prove a similar relation of HEV seroprevalence with age (22.6% in young adults vs. 12.9%, in older patients;  $p = 0.0967$ ). The difference between the frequency of anti-HEV and anti-HAV positivity was statistically significant ( $p < 0.0001$ ) due to significantly higher HAV seroprevalence in individuals older than 50 years. Data describing the levels of seropositivity towards both viruses in relation to the age of patients are shown in Table 1.

**Table 1.** Anti-HEV and anti-HAV positivity depending on the age of patients

Age range [years]	Anti-HEV (+)*	Anti-HAV (+)**	p
18-30	7/25 (28.0%)	3/27 (11.1%)	0.1223
31-40	7/37 (18.9%)	4/35 (11.4%)	0.3763
41-50	6/31 (19.4%)	8/29 (27.6%)	0.4532
51-60	6/50 (12.0%)	27/49 (55.1%)	<0.0001
>60	3/35 (8.6%)	25/34 (73.5%)	<0.0001
Total	29/178 (16.3%)	67/174 (38.5%)	<0.0001

\* Patients with equivocal testing result were excluded from the analysis

\*\* There were no data available for 5 patients

Ratios of the sample optical density at 450 nm and the cut-off value (s/co) in anti-HEV-positive study patients were as follows: 1.20-2.00 in 9 cases (31%), 2.01-3.00 in 6 cases (21%), 3.01-4.00 in 3 cases (10.3%), 4.01-5.00 in 2 cases (7%), 5.01-6.00 in 3 cases (10.3%), 6.01-7.00 in 1 case (3%), 8.01-9.00 in 2 cases (7%) and >9.00 in 3 cases (10.3%).

The comparison taking into consideration both anti-HEV and anti-HAV status of patients in relation to different demographic, epidemiological and clinical variables is presented in Table 2.

As the data shown above suggest, anti-HAV-negative, anti-HEV-positive patients were significantly younger than people seropositive only for HAV ( $p < 0.0001$ ), but there was no mean age difference between them and double-negatives (HAV-, HEV-) ( $p = 0.5509$ ). The prevalence of a lower level of education (that is, elementary school or technical school vs. high school or university/college) among anti-HAV-positive, HEV-negative individuals was significantly higher when compared with HAV-negative, HEV-positive ( $p = 0.0163$ ) and HAV-negative, HEV-negative ( $p = 0.0001$ ) patients. It could not be ascribed only to older age of these (HAV+, HEV-) patients (mean age of 31 patients with a lower level of education was  $58.9 \pm 11.2$  years, and the same parameter value in 28 individuals with a higher level of education was  $53.9 \pm 11.0$  years,  $p = 0.0857$ ).

It is worth knowing that when prevalence of raw meat and/or seafood consumption was assessed in HAV-negative, HEV-positive vs. double-negative participants of the study, a trend toward higher prevalence of such behavior in the former group was observed (77.3% vs. 56.1%, respectively;  $p = 0.0711$ ).

Anti-HEV were positive in 6 out of 35 individuals (17.1%) in whom an unequivocal result of testing was obtained and who have never travelled abroad. Their more detailed characteristics are summarized in Table 3.

It is of note that all these patients were born and lived in cities or towns of the Wielkopolska region.

In the case of HIV-negative patients, 95 of them (78.5%) were hospitalized because of liver disease and 26 (21.5%)



**Table 2.** Characteristics of patients depending on their anti-HAV (HAV) and anti-HEV (HEV) status (n=170\*)

Variable	HAV+, HEV+ n=7	HAV+, HEV- n=59	HAV-, HEV- n=82	HAV-, HEV+ n=22
Mean age±SD (range) [years]	51.6±18.0 (26-81)	56.5 <sup>a,b</sup> ±11.3 (27-85)	42.6 <sup>a</sup> ±13.0 (19-69)	40.8 <sup>b</sup> ±11.9 (23-64)
Male sex	4 (57.1%)	31 (52.5%)	46 (56.1%)	15 (68.2%)
Lower level of education	4 <sup>b</sup> (57.1%)	31 <sup>i,j</sup> (52.5%)	17 <sup>b,i</sup> (20.7%)	5 <sup>j</sup> (22.7%)
Direct contact with farm animals in lifetime	3 (42.9%)	34 (57.6%)	37 (45.1%)	10 (45.5%)
Travel abroad	4 (57.1%)	47 (79.7%)	65 (79.3%)	19 (86.4%)
Jaundice in history	2 (28.6%)	12 (20.3%)	8 (9.8%)	5 (22.7%)

\* 12 patients were excluded from the analysis, that is, 5 patients with no data available for anti-HAV, 4 patients with equivocal result of anti-HEV testing and 3 patients who were immunized for HAV through vaccination

a-j - Values followed by the same letters differ significantly at  $p < 0.05$

because of other causes. Anti-HEV were detected in 10 cases in the first group (out of 91, that is, 11%; in 4 hepatological patients, the HEV testing result was equivocal and they were excluded from this analysis) and 6 (23.1%) cases in the second group ( $p=0.1123$ ).

Data on coexistence of anti-HCV, HBV infection serological markers and anti-HEV in non-HIV individuals are shown in Table 4.

In HIV-infected participants of the study, anti-HEV were found in 13 cases (21.3%), and there was no difference in comparison with non-HIV patients (16 cases, 13.7%;  $p=0.1902$ ). Seropositivity towards HAV was significantly more frequent among non-HIV-infected individuals (46.1% vs. 23.7% in HIV-infected patients;  $p=0.0025$ ). Probably it was related mainly to the most important factor influencing immunity against hepatitis A, that is, older age of HIV-negative study participants (52.5±13.6 years vs. 38.0±9.6 years in persons with HIV infection;  $p<0.0001$ ).

In 6 anti-HAV-positive patients (8.6% of HAV-seropositive individuals; all these patients were anti-HEV-negative), a non-surgical icteric disease recognized as hepatitis A was reported in their medical histo-

ries. In other 4 cases, acute hepatitis B, acute hepatitis C, decompensation of liver cirrhosis and toxic liver injury were diagnosed as the cause of jaundice. In 3 cases (including one both anti-HAV and anti-HEV-positive), no data about the final cause of jaundice were available.

In 7 anti-HEV-positive patients (24.1% of HEV-seropositive persons; 2 individuals were also anti-HAV-positive), a non-surgical icteric disease was reported (Table 5). The identified causes of jaundice in these cases were: acute hepatitis B, decompensation of liver cirrhosis (2 cases), acute non-A non-B hepatitis and autoimmune hepatitis; no data existed for 2 cases (one such patient was seropositive for HAV). In all these cases, at least one serological marker of HAV, HBV or HCV infection was positive.

## DISCUSSION

The results of this first prospective analysis of HEV seroprevalence in Polish patients suggest that HEV infection may be present in Poland (and more specifically, in the Wielkopolska Region) as an autochthonous problem, as it is in other industrialized countries. We found the presence of anti-HEV IgG (which can be regarded as proof

**Table 3.** Characteristics of anti-HEV-positive patients with no history of travel abroad (n=6)

Patient	Sex	Age	Cause of hospitalization	Identified cause of past jaundice	Anti-HEV (s/co)	Anti-HAV	HBsAg	Anti-HBc	Anti-HCV
1.	F	55	Liver cirrhosis, CHC	Cirrhosis decompensation	9.00	+	-	+	+
2.	M	81	Acute gastroenteritis	Not determined	2.31	+	-	nd	-
3.	M	52	HIV infection	Not determined	2.83	-	+	+	-
4.	F	40	Autoimmune hepatitis	Autoimmune hepatitis	3.07	-	-	-	-
5.	M	26	HIV infection	No jaundice in history	1.54	-	-	-	-
6.	M	42	HIV infection	No jaundice in history	1.89	+	-	-	-

CHC - chronic hepatitis C, s/co - ratio of the sample optical density at 450 nm and the cut-off value, nd - no data

**Table 4.** Anti-HCV, HBsAg, anti-HBc and anti-HEV testing results in patients not infected with HIV (n=121)

	Anti-HCV(+), n=72	HBsAg(+), n=7	Anti-HBc(+), n=30
Anti-HEV(+)	7 (10%*)	1 (16.7%*)	3 (10%*)
Anti-HEV equivocal	2*	1*	3*
Anti-HEV(-)	63	5	24
No data	-	-	27

\* Patients with equivocal anti-HEV testing were excluded from the analysis of HEV-seropositivity issues

**Table 5.** Anti-HEV-positive patients with non-surgical jaundice in medical history (n=7)

Patient	Sex	Age	Cause of hospitalization	Identified cause of past jaundice	Anti-HEV (s/co)	Anti-HAV	HBsAg	Anti-HBc	Anti-HCV
1.	F	48	Liver cirrhosis, CHC	Acute hepatitis B	2.10	-	-	+	+
2.	F	55	Liver cirrhosis, CHC	Liver cirrhosis decompensation	9.00	+	-	+	+
3.	M	81	Acute gastroenteritis	Not determined	2.31	+	-	nd	-
4.	M	52	HIV infection	Not determined	2.83	-	+	+	-
5.	F	40	Autoimmune hepatitis	Autoimmune hepatitis	3.07	-	-	-	-
6.	M	53	Liver cirrhosis, CHC	Liver cirrhosis decompensation	2.66	-	-	-	+
7.	F	64	Liver cirrhosis, CHC	Non-A, non-B hepatitis	1.95	-	-	-	+

CHC - chronic hepatitis C, s/co - ratio of the sample optical density at 450 nm and the cut-off value, nd - no data

of past infection with this hepatotropic virus) in 16.3% of the study population with an unequivocal test result. The prevalence of anti-HEV IgG in the participants of this study was similar to the result of a large analysis performed in inhabitants of our neighboring country, Germany (16.8%) [10].

However, the strongest argument for the occurrence of HEV infection in Poland is HEV seropositivity of 6 patients (3.4%) who have never travelled abroad (17.1% of all such individuals). For the remaining 23 anti-HEV-positive patients, it is difficult to speculate about the circumstances of their exposure to HEV infection, but it must be stressed that no person from this group experienced icteric disease after travelling abroad, and only 3 of them reported jaundice in the past.

Surprisingly, in contrast with other seroepidemiological studies [4,10], there was no difference in HEV seropositivity in young adults vs. older individuals. Moreover, a trend toward a more frequent presence of anti-HEV was observed in younger individuals. First, it may be only a random phenomenon related to a small number of the study participants. Second, perhaps HEV infection in Poland was initially restricted to limited groups of inhabitants of this country, and subsequently, because of unknown reasons, it became more prevalent, particularly among younger individuals. This subject requires larger studies performed on a higher number of Poles. HEV antibodies could also wane with time, assuming there were no recurrent contacts with the virus. Last but not least, some concern exists about the performance of

anti-HEV tests used in the present study, because no systematic analyses on this issue have been published. Of course, any combination of the factors discussed above could also occur. Additionally, no difference in HAV vs. HEV seroprevalence was noted among patients aged up to 50 years. This may reflect an approach to the situation observed in some countries of Western Europe (such as France and the United Kingdom), that is, more common occurrence of hepatitis E in comparison to hepatitis A in the populations of these countries [8,18].

More frequent seropositivity towards HAV in comparison to HEV in older individuals can be easily explained by higher efficiency in person-to-person transmission of infection with the former virus, which is commonly known and, in our opinion, was facilitated by worse sanitary conditions in Poland in the past. We also postulate that a higher frequency of a lower level of education among anti-HAV-positive patients could be related to poor adherence to elementary hygiene rules, which resulted in greater exposure to HAV.

Non-surgical icteric disease was reported by about one-fourth of anti-HEV-positive patients and an even lower percentage of HAV seropositives. It is important that icteric hepatitis A was identified in only about 9% of individuals with the presence of anti-HAV. This value is similar to what we found in our previous HAV seroprevalence survey [3]. All these data suggest that an asymptomatic or paucisymptomatic course is the most common clinical scenario for both (HEV and HAV) infections in the Polish population. To support this contention for



infection with HEV, an investigation of a hepatitis E outbreak on a cruise ship can be cited [29]; in that report, two-thirds of passengers with serological evidence of recent contact with HEV had no symptoms related to infection with the virus. An even higher percentage (about 97%) of asymptomatic HEV seroconversions was suggested by a large HEV vaccine study from China [35].

We failed to observe more frequent contacts with farm animals in patients exposed to HEV. It should also be mentioned that a high percentage of these individuals (77%) reported consumption of raw meat and/or seafood. The comparison of such culinary preferences between anti-HEV-positive and double-negative patients did not reach statistical significance, but we think it was only due to the low number of study participants. Zoonotic HEV strain infections were linked to the consumption of undercooked or raw pork [18] and shellfish [29].

HEV seroprevalence among 61 HIV-infected individuals was similar to the value observed in other patients. According to our knowledge, no data have been published that prove HEV transmission through intravenous drug use or the sexual route, the two main modes of HIV transmission in adults. However, the prevalence of anti-HEV in our HIV patients was significantly higher when compared with data reported by four recent larger studies from Switzerland (2.6%) [21], Germany (4.9%) [26] and France (4.4-6.2%) [17,27]. The reason for such a different HEV seroprevalence pattern in Polish HIV-infected individuals is unknown.

Our analysis has some limitations. The main one is that HEV seroprevalence was tested only in a subset of patients hospitalized in the Department of Infectious Diseases, which means that the results of this study may not reflect appropriately the seropositivity level in the

whole Polish population. Another important limitation of the present study, which might have had an impact on the significance of the final results, is the small number of study participants, who were additionally mainly city or town inhabitants. To obtain more complete data on seroprevalence of HEV in the Wielkopolska Region and generally in the whole of Poland, the performance of large-scale studies on varied populations is needed. In addition, more profound analysis of unexplained hepatitis cases in Poland should be started in search of autochthonous HEV infections. To date, only two Polish original reports on hepatitis E describing seroprevalence [13] and an acute complicated hepatitis E case [12] are known to us, and both concern Indian students from Białystok, eastern Poland. As mentioned previously, the accuracy of the test used in this study was not compared with other tests searching for anti-HEV IgG antibodies. Nevertheless, the same anti-HEV kits were used in other seroprevalence studies [5,16,28]. Moreover, knowing the data on the sensitivity of different HEV IgG tests [22,31,33], it can be stated that we have underestimated rather than overestimated HEV seroprevalence in our analysis.

In conclusion, the results of the present study suggest that infection with HEV may occur in Poland – we identified 17.1% of HEV seropositives among individuals who have never travelled abroad. Anti-HAV positivity among Polish patients is significantly higher than anti-HEV. In contrast to HAV, HEV seroprevalence is similar in younger and older patients. The clinical course of hepatitis E virus infection in Polish citizens seems to be asymptomatic or paucisymptomatic in the majority of cases. Initial and limited data suggest that, for unknown reasons, Polish HIV patients may be more commonly exposed to HEV than similar individuals from other European countries.

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