

# CHANGES IN THE CLINICAL AND EPIDEMIOLOGICAL PROFILE OF ACUTE HEPATITIS B IN THE INFECTIOUS DISEASES HOSPITAL OF IASI IN THE LAST 15 YEARS

Andrei Vata<sup>1</sup>, Mihaela Catalina Luca<sup>1</sup>, Carmen Manciu<sup>1</sup>, Cristina Nicolau<sup>2</sup>,  
Luminita Gina Vata<sup>1</sup>, Carmen Mihaela Dorobat<sup>1</sup>

<sup>1</sup>University of Medicine and Pharmacy "Grigore T. Popa", Iasi

<sup>2</sup>Infectious Diseases Hospital, Iasi

## ABSTRACT

Changes in the viral subtypes, in hygienic measures and the effects of the national vaccination program are factors that can influence the epidemiological and clinical features of acute hepatitis B.

**Material and methods.** we retrospectively studied and compared two groups of patients diagnosed with acute hepatitis B in the Infectious Diseases Hospital of Iasi between 1997 and 2001 (group 1-582 cases) and between 2007 and 2011 (group 2-142 cases).

**Results.** Between the two intervals, the annual number of cases dropped by more than 4 times ( $p = 0.0006$ ), the mean age of the patients has significantly increased ( $p < 0.001$ ), as the proportion of those with rural origin ( $p = 0.003$ ). Risk factors for the transmission of HBV were identified more frequently in the first group ( $p = 0.04$ ). The maximum level of ALT has not changed, but a significant rise in the maximum level of total bilirubin was seen ( $p = 0.0004$ ). The second group had a higher proportion of severe ( $p = 0.01$ ) and prolonged ( $p = 0.04$ ) forms of disease. Antiviral therapy was more common in the second group ( $p < 0.001$ ), but the lethality was higher here too ( $p = 0.07$ ).

**Conclusions.** The clinical and epidemiological profile of acute hepatitis B has significantly changed in the last 15 years, the decrease in the annual number of cases being paralleled by an increase of severe or cholestatic forms of disease

**Key words:** incidence, clinical form, cytolysis

Acute hepatitis B incidence has decreased over the last years, both nationally (1) and internationally (2), due to the implementation of a newborn vaccination program, and to improved prevention measures of both horizontal and vertical virus transmission.

Our research aims to analyze how a set of epidemiological and clinical characteristics of acute hepatitis B have changed over the last 15 years in a regional infectious diseases hospital.

## MATERIAL AND METHODS

We conducted a retrospective and comparative study based on the medical records of two groups

of patients diagnosed with acute hepatitis B (AHB) in the "Sfânta Parascheva" Infectious Diseases Hospital of Iași, between 1997-2001 – 1<sup>st</sup> group (582 cases) and between 2007-2011 – 2<sup>nd</sup> group (142 cases).

The AHB diagnosis was set further to the detection of a severe hepatic cytolysis syndrome ( $ALT > 1000$  UI/l) and of the presence of IgM anti-HBc antibodies. Patients with IgM/IgG antibodies against hepatitis D virus were excluded.

Demographic (age, sex, origins), clinical (symptoms during the pre-jaundice period, jaundice severity), laboratory (cytolysis severity, cholestatic syndrome, viral markers) and therapeutic (use of antiviral medication) variables were analyzed.

Adresă de corespondență:

Andrei Vata, University of Medicine and Pharmacy "Grigore T. Popa", Str. Universității, Nr. 16, Iasi

The clinical forms in which the total serum bilirubin values remained below 30 mg/l throughout the disease were considered *anicteric*. The patients in whom the total serum bilirubin values ranged from 30 to 50 mg/l and who exhibited basic symptoms were considered to suffer from a *mild form* of the disease. The *moderate form* included patients with: total serum bilirubin values between 50 and 150 mg/l (50-100 mg/l in children), typical disease signs and symptoms and Quick's index above 50%. The *severe forms of disease* included patients with: total serum bilirubin above 150 mg/l (100 mg/l in children), Quick's index below 50%, pronounced signs and symptoms. The *fulminant cases* were those of patients with hepatic coma during the first 21 days of jaundice. The *prolonged forms* comprised the patients in whom the ALT and/or bilirubin values remained high for more than 21 days. The patients that exhibited bilirubin values superior to 150 mg/l for several consecutive days and then slowly descending bilirubin values were included in the *cholestatic form* of disease.

The data were analyzed by means of multivariate statistical tests (t Student, Chi square, means, medians, 95% confidence intervals) calculated using Microsoft Excel and Analyze-It.  $p < 0.05$  was considered statistically significant.

## RESULTS

The annual number of AHB cases was found to have decreased almost constantly over the last 15 years, from 168 in 1997, to a minimum of 20 in 2008 (Figure 1).

The average number of hospitalized patients was 116.4 in the first group, and 4.1 times lower (28.4) in the 2<sup>nd</sup> group, the difference being statistically significant ( $p = 0.0006$ ).

The average age of the patients in the 1<sup>st</sup> group was 25.7 years (95%CI: 23.9-27.4), which is significantly lower ( $p < 0.0001$ ) than in the 2<sup>nd</sup> group – 35.1 years (95%CI: 30.6- 39.6).

As far as the sex ratio is concerned, the males prevailed in both groups, with a more pronounced predominance in the second group (average M/F ratio 1.4 vs. 2), which is close to the statistical significance threshold ( $p = 0.053$ ).

Most of the patients in both groups came from urban areas, yet significantly ( $p = 0.003$ ) more patients coming from rural areas were found in the second than in the first group (average R/U ratio 0.49 vs. 0.8).

HBV transmission risk factors were more commonly identified in the patients included in the 1<sup>st</sup> group (30.6%) as compared to the second group (16.2%) ( $p = 0.04$ ). Among these, in the second group, the following were found: unprotected sexual intercourse with partner suffering from chronic hepatitis B (6 cases), complex dental surgery (4 cases), surgical procedures (5 cases), recent tattoos/piercing (7 cases), iv drug use (1 case).

The dominant most common symptoms during the pre-jaundice period were of digestive nature in both groups (34.6% vs. 32.4%), and no significant differences between the frequencies of the other types of onset were reported (ANOVA  $F=0.77$ ,  $p = 0.4$ ) (Figure 2).

The pre-jaundice period duration ranged from 2 to 20 days in the 1<sup>st</sup> group, with an average of 5.72 days (CI 95% 5.150 - 6.414), whereas the average of the second group was 6.92 days (CI 95% 5.56 - 7.932); the difference was not significant ( $p = 0.3$ ).

The maximum values of the hepatic cytolysis syndrome during the disease acme (quantified by ALT measurements) were similar in both groups: the 1<sup>st</sup> group – 2416.4 (95%CI: 2128.9 - 2704.0),

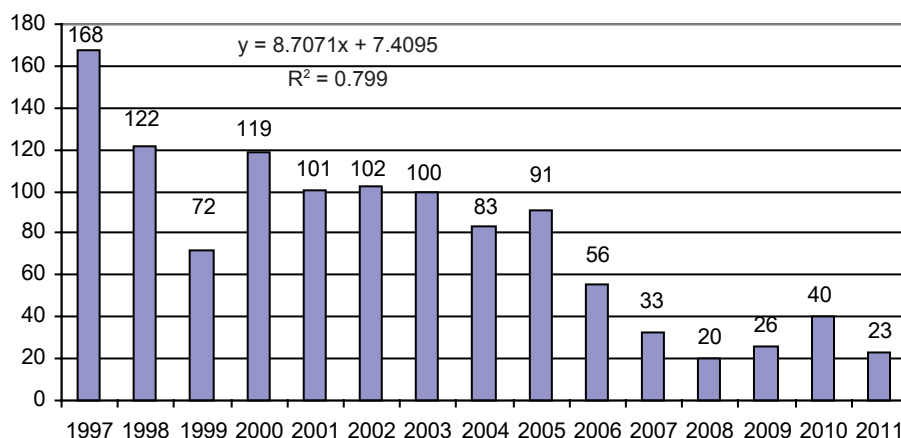
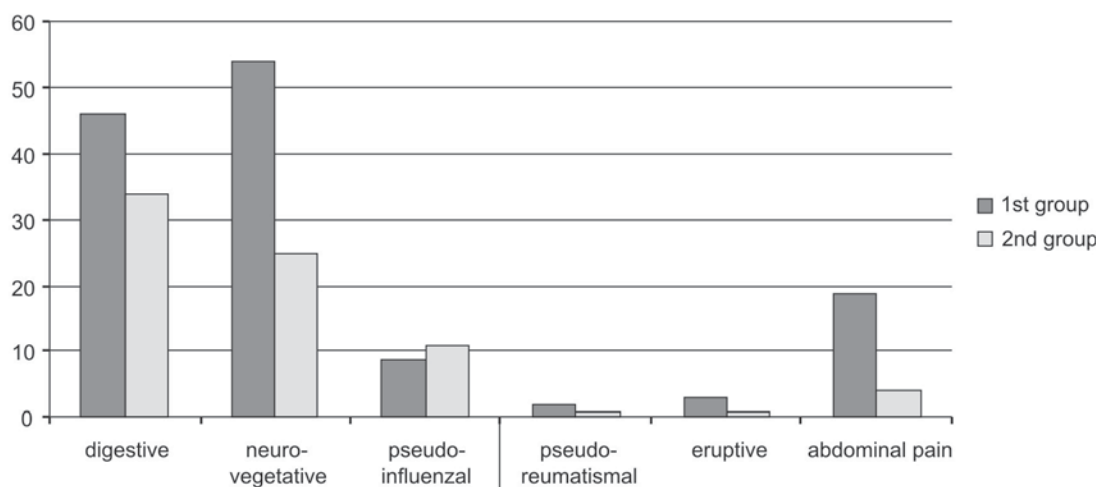


FIGURE 1. Annual number of AHB cases over the studied period



**FIGURE 2.** Types of clinical symptoms in the pre-jaundice period

and the 2<sup>nd</sup> group – 2653.5 UI/l (95% CI: 2301.3 – 3005.6). The difference was not statistically significant ( $p = 0.29$ ).

The average level of the maximum total serum bilirubin value was higher in the 2<sup>nd</sup> group - 175.6 mg/l (95%CI: 149.8-201.4) than in the 1<sup>st</sup> one - 129.5 mg/l (95%CI: 117.5 – 141.5), whereas the difference had statistical significance ( $p = 0.0005$ ).

The anicteric forms of the disease were more frequently diagnosed in the second group of patients – 12.7% against 7.2% in the 1<sup>st</sup> group, and the difference was close to the statistical significance threshold ( $p = 0.051$ ).

**TABLE 1.** Clinical forms distribution depending on severity, in the two groups

Groups	Clinical Forms							
	Mild (no)	%	Moderate (no)	%	Severe (no)	%	Fulminant (no)	%
1 <sup>st</sup> group	29	5.0	351	60.3	194	33.3	8	1.4
2 <sup>nd</sup> group	6	4.2	55	38.7	74	52.1	7	4.9

A comparative approach of the percentages of severe and fulminant forms in the two groups (Table 1) enabled us to note significantly higher occurrences in the 2<sup>nd</sup> than in the 1<sup>st</sup> group: 57% vs. 34.7% ( $p < 0.0001$ ).

As for disease duration, the forms prolonged by cytolysis occurred in similar percentages in the two groups: 14.9% vs. 15.5%; the difference was not statistically significant.

The cholestatic forms of the disease were significantly more common in the 2<sup>nd</sup> (19.7%) than in the 1<sup>st</sup> (8.7%) group, the difference having statistical significance ( $p = 0.0003$ ).

The frequency of AgHBs determination concomitantly with the IgM antiHBc antibodies in-

creased and reached 72.5% in the second group against only 28.1% in the first one. The number of acute AgHBs negative forms remained constant, being 3.6% (6/164) in the 1<sup>st</sup> group against 3.9% (4/103) in the 2<sup>nd</sup>,  $p = 0.81$ .

The percentage of patients that were administered antiviral therapy (lamivudine) during the acute stage was higher in the 2<sup>nd</sup> group (28.9%) than in the 1<sup>st</sup> one (3.4%),  $p < 0.0001$ .

3 deaths were reported in the 1<sup>st</sup> group (0.5% mortality rate) and 2 in the 2<sup>nd</sup> (1.4% mortality rate) due to AHB (fulminant forms), the difference not having statistical significance ( $p = 0.4$ ).

## DISCUSSIONS

Thanks to improved antiseptic measures, to a stricter control of transfusion products and vertical transmission, and to the large-scale implementation of an anti-hepatitis B virus vaccination program, the incidence rates of this infection has decreased considerably in most European countries in the last years (3).

From the viewpoint of AgHBs carriers prevalence, Romania is considered a moderately endemic country, as this percentage varied, according to Voiculescu (4), between 2.15% and 7.91% (mean value - 5.59%) in 2010. Whereas in 1989 the acute hepatitis B incidence was reported to be 43 cases/10<sup>5</sup> inhabitants, in 2004 it went down to 8.5 cases/10<sup>5</sup> inhabitants (1), and in 2010 it reached a level of 2.4 cases/10<sup>5</sup> inhabitants.

Therefore, the 4.1 times decrease in the number of AHB cases diagnosed at the Infectious Diseases Hospital of Iași, which was noticed between the two 5-year time intervals under survey (namely 1997-2001 and 2007-2011), is in agreement with

the national decreasing trend. A similar annual number of cases to that recorded during our second interval (28.4) was reported by Daina et al. in Bihor County, in 2011 (5).

The considerably higher average age of the patients examined between 2007 and 2011 (35.1 vs. 25.7,  $p < 0.0001$ ) may be accounted for by the effects of the free compulsory newborn vaccination campaign started in 1995, which was later extended to include school children (1999), and 18-year olds (2004).

The masculine sex prevalence among acute hepatitis B patients has been noted by other authors as well (6, 7), and in our study it tended to be more pronounced in the second group of patients ( $p = 0.053$ ).

Although, just as in literature, the patients of urban extraction prevailed in both study groups, we found significantly ( $p = 0.003$ ) more rural patients involved in the second interval, possibly due to incomplete vaccine coverage or to failing preventive health education.

Due to the high concentration levels in the blood of patients suffering from chronic virus B infection, the sexual or blood-related virus transmission risk is high. The infection's transmission route could not be identified in most of the patients (especially in the second group). The most common risk factor for VBH transmission in the 2<sup>nd</sup> group was tattoos or piercings performed with non-sterile equipment (7 cases), followed by unprotected sexual intercourse with partners that later proved to be chronic virus carriers (6 cases). Nevertheless, acute infection also occurred in patients having undergone dental or surgical procedures that apparently observed all hygienic measures.

The beginning of the disease is usually the noisiest from the standpoint of clinical symptoms, the spectrum and frequency of which seem not to have significantly changed between the two time intervals under survey. The clinical manifestations of the pre-jaundice period were dominated mostly by dyspeptic or neuro-vegetative symptoms. Pseudo-influenzal and pseudo-rheumatismal symptoms were sometimes reported, and even a few cases (3 in the 1<sup>st</sup> group and 1 in the 2<sup>nd</sup>) with eruptive onset (Gianotti-Crosti syndrome).

The hepatic cytolysis syndrome is pronounced during acute hepatitis B, and it sometimes reaches impressive values (the maximum value recorded in

our group was 9200 UI/l), but is not usually indicative of the severity of the disease; the mean value of the maximum ALT recorded was similar in both groups (2416.4 vs. 2653.5 UI/l).

The total serum bilirubin value is generally correlated with the severity of the disease and it was significantly higher in the 2<sup>nd</sup> than in the 1<sup>st</sup> patients group (175.6 vs. 129.5 mg/l,  $p = 0.0003$ ). In addition to higher maximum values, the 2<sup>nd</sup> group patients also exhibited a slower decrease of these values, as the forms prolonged by cholestasis were significantly more frequent (19.7 vs. 8.7%,  $p = 0.0003$ ).

The drop in the number of cases reported over the last few years was accompanied by an increase in their severity, which is supported by the significant rise in the number of severe and fulminant clinical forms between the 1<sup>st</sup> and 2<sup>nd</sup> group (34.7 vs. 57%,  $p < 0.0001$ ).

The changes affecting the clinical spectrum of acute hepatitis B, materialized in more frequently occurring severe or cholestasis-prolonged forms in our region, over the last 15 years, are difficult to explain and they may suggest the involvement of new viral subtypes, as genotype or preC/C mutations.

The more severe clinical forms and improved lamivudine accessibility determined doctors to use this therapy significantly more frequently these last few years (28.9 vs. 3.4% of the patients). However, AHB mortality rates have not decreased between the two time intervals we researched, as they amounted to 0.5% in 1997 through 2001 and to 1.4 between 2007 and 2011. The small number of deaths made the difference not to have any statistical significance.

## CONCLUSIONS

The last 15 years have brought about considerable changes in the acute virus B hepatitis features in our region. Epidemiologically we have seen a 4.1 times decrease in the annual number of cases, a significant increase in the average age of the patients and in the number of patients from rural areas. From a clinical point of view we found a significant increase in the frequency of severe and cholestasis-prolonged forms. Therapeutically there was a more frequent use of antiviral therapy (lamivudine), which did not necessarily result into lower mortality rates.

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