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Hepatitis B Vaccination in Patients with Liver Cirrhosis Evaluated for Liver Transplantation – A Simple Intervention Ensures High Adherence

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Background: There is an unmet need to improve the HBV vaccination status in patients with chronic liver diseases. Primary care physicians and outpatient hepatologists often fail to vaccinate as recommended. Thus, new strategies to improve the HBV vaccination rate are required.

Material/Methods: This study was performed in a cohort of patients with chronic liver diseases evaluated for liver transplantation. Vaccination status was taken from the patients' vaccination cards. HBsAg-, anti-HBc-, and anti-HBs-negative individuals were vaccinated against HBV at hospital discharge, and subsequent outpatient completion of the standard vaccination protocol was recommended in detail in the discharge letter. At months 2 and 8, titer controls were performed, and completion of vaccination was evaluated.

Results: We prospectively recruited 37 patients. At baseline, the vaccination rate against HBV was 24% (N=9/37), and 3/9 HBV vaccinated patients presented with an anti-HBs-titer >10 IU/L. Thus, N=34 were vaccinated with Engerix® or Twinrix®. We evaluated 26/34 patients at month 2 and 10/26 again at month 8. The second vaccine dose was obtained by 21/26 (80%) of the patients seen at month 2, and 9/10 (90%) seen at month 8 obtained the third vaccine dose by primary care physicians or ambulant hepatologists. Only 2 patients presented with an anti-HBs-titer >10 IU/L at month 8.

Conclusions: Initiation of HBV vaccination during hospitalization and detailed recommendations on subsequent vaccinations in the discharge letter improve previously inadequate vaccination rates in the outpatient setting. Similar measures should be implemented at earlier time points of chronic liver diseases to achieve higher immune response rates.

MeSH Keywords: **End Stage Liver Disease • Hepatitis B Antibodies • Vaccination**

Abbreviations: **HBV** – hepatitis B virus; **HAV** – hepatitis A virus; **HCC** – hepatocellular carcinoma; **HBsAg** – HBV surface antigen; **anti-HBc** – IgG antibodies specific to the HBV core antigen; **anti-HBs** – IgG antibodies specific to the HBV surface antigen; **IgG** – Immunoglobulin G; **IU/L** – international units per liter; **LTX** – liver transplantation

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Background

Patients with liver cirrhosis have higher morbidity and fatality rates due to superimposed hepatitis B virus (HBV) infection than individuals without preexisting liver disease, including fulminant liver failure, and also have increased risk of hepatocellular carcinoma (HCC) [1–3]. In case of liver transplantation, post-transplant *de novo* HBV infection can lead to organ loss [4]. Thus, HBV vaccination is recommended for patients with chronic liver diseases and negative HBsAg, anti-HBc, and anti-HBs titers [5,6]. Vaccination should be performed at time points 0, week 4, and month 6 of the vaccination schedule. At 4–8 weeks after the last vaccination, the anti-HBs titer should be determined. Anti-HBs titers above 10 IU/l are considered to be protective against HBV infection [7].

Response rates to HBV vaccination decrease with disease progression and after liver transplantation, regardless of the applied vaccination protocol [8–12]. Therefore, vaccination should be administered at early stages of chronic liver diseases. However, most cases with chronic liver diseases are not vaccinated. The vaccination rate in patients in the USA with chronic liver diseases does not exceed 23–32%, and only 22% of hepatitis C-positive individuals are vaccinated against HBV [13,14]. Reasons for low vaccination rates are primary care physician inadequate knowledge [15], unjustified concerns [15] or noncompliance, and lack of motivation of hepatologists [16]. We therefore aimed to overcome these barriers in the outpatient setting by initiation of HBV vaccination prior to discharge of patients with liver cirrhosis hospitalized for evaluation for liver transplantation, and by giving detailed follow-up recommendations for further vaccinations in the discharge letter. These individuals undergo a structured follow-up program with close cooperation between outpatient physicians and our transplant center while on the transplant waiting list.

Material and Methods

The study was performed as a prospective, single-center trial at our liver transplant center between October 2015 and January 2017. We included 37 individuals with liver cirrhosis evaluated for liver transplantation. Baseline HBsAg, anti-HBc, anti-HBs, and anti-HAV were determined as part of the routine work-up for evaluation for liver transplantation. HBV vaccination status was taken from the patient vaccination card, which is a booklet used to document any vaccination administered since early childhood. Clinical characteristics (patient demography, etiology of liver cirrhosis, Child-Pugh score, and MELD score) were extracted from patient health records.

At hospital discharge, HBsAg-, anti-HBc-, and anti-HBs-negative (anti-HBs <10 IU/L) individuals were vaccinated with Engerix® or Twinrix®, depending on anti-HAV titer. Vaccine-naive patients received a 20-µg vaccine dose, while previously HBV-vaccinated anti-HBs-negative individuals received a 40-µg vaccine dose, as suggested for non-responders [11]. Subsequent outpatient completion of vaccination protocol was recommended in detail in the discharge letter (including timepoint, dose, and type of follow-up vaccines). At months 2 and 8, anti-HBs titer controls were performed, and completion of vaccination was evaluated at our outpatient transplant unit.

HBV vaccination was performed intramuscularly at the deltoid site with the licensed vaccines Engerix® (20 µg) or Twinrix® (20 µg). Anti-HBs serum titers were determined with the Architect® system (Abbott, Wiesbaden, Germany). Response to vaccine was defined by the presence of anti-HBs serum titers >10 IU/l.

The study was approved by the Ethics Committee of the University of Leipzig (ethics vote number 362-15-05102015). All patients provided written informed consent prior to any study-related procedure after the nature and possible consequences of the study had been fully explained. The study protocol is consistent with the ethics guidelines of the 1975 Declaration of Helsinki, as reflected by Ethics Committee approval.

Results

Baseline characteristics of the study population

During the study period, 89 individuals were listed for liver transplantation (Figure 1); 52 cases were not included in the study as they did not meet the inclusion criteria (i.e., anti-HBc-positive baseline status, acute liver failure without preexisting liver disease, patient refusal, and inability to give consent). Thus, the study population comprised 37 anti-HBc negative individuals (age 56.4±9.2 years, female 27%, alcoholic liver cirrhosis 54%, liver cirrhosis of other etiologies 22%, HCC 24%, Child-Pugh score A/B/C 16%/54%/30%, and MELD score 17.4±6.7). Patients included in the study did not differ from excluded cases regarding age and sex. However, excluded cases tended to have a higher Child-Pugh score (A/B/C 30%/30%/40%, p=0.081) and significantly higher MELD score (22.3±11.3, p=0.025) and varied in the etiology of cirrhosis (alcoholic liver cirrhosis 27%, HCC 13%, liver cirrhosis of other etiologies 60%, p=0.0031).

Baseline HBV vaccination status

At baseline, the vaccination rate against HBV was 24% (N=9/37). Anti-HBs-titer >10 IU/L was presented by 3/9 HBV vaccinated patients, 7/9 vaccinated patients received full HBV vaccination schedule prior to study inclusion (Twinrix® N=4, Engerix® N=2, Gen H-B-Vax-D N=1), and 2/9 received an incomplete

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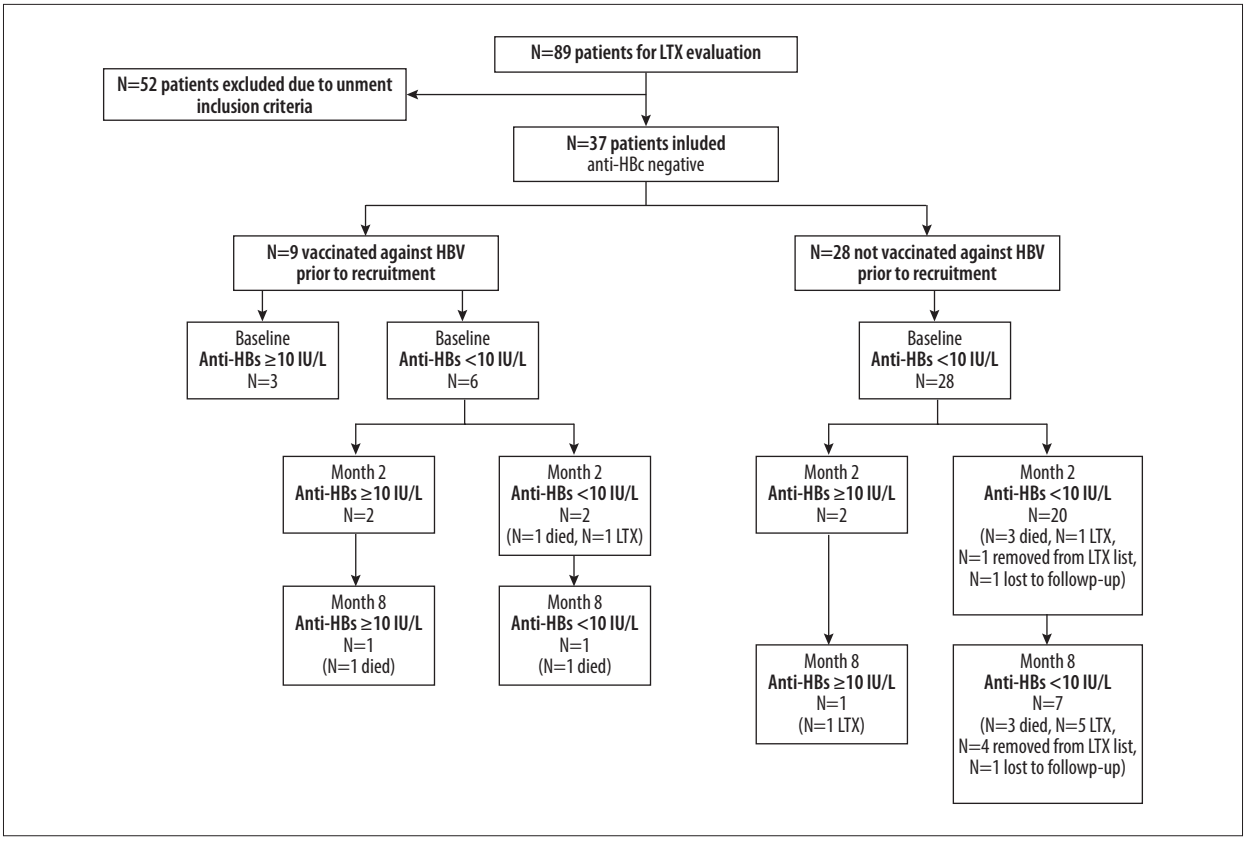

Figure 1. Flow chart of study population. LTX – liver transplantation.

schedule (2 doses of Twinrix®). The 3 patients with anti-HBs titer >10 IU/l at baseline were vaccinated as follows: 3 doses Engerix® N=1, 3 doses Twinrix® N=1, and 3 doses Twinrix® plus 1 dose Engerix® N=1.

Efficacy of HBV vaccination

HBsAg-, anti-HBc-, and anti-HBs-negative individuals (N=34) were vaccinated with Engerix® (N=15) or Twinrix® (N=19), depending on their anti-HAV titer. Previously HBV-vaccinated patients with negative anti-HBs titers (N=6) received a 40-µg vaccine dose. 26/34 patients were evaluated at month 2 (N=4 died, N=2 liver transplantation, N=1 removed from transplant list, N=1 lost to follow-up) and 10/26 again at month 8 (N=5 died, N=6 liver transplantation, N=4 removed from transplant list, N=1 lost to follow-up). Only 4/26 (15%) individuals presented with anti-HBs >10 IU/L at month 2; 2/4 of these individuals were vaccinated with a 40-µg vaccine dose. The positive anti-HBs titer was preserved in 2 of these cases at month 8. No individual with negative anti-HBs titer at week 8 developed a titer >10 IU/L at month 8. The response rate to HAV vaccination was 25%.

Outpatient completion of HBV vaccination

After detailed recommendation in the discharge letter, 21/26 (80%) of the patients seen at month 2 received the second vaccine dose, and 9/10 (90%) seen at month 8 received the third vaccine dose by primary care physicians or outpatient hepatologists.

Discussion

Vaccination against HBV is recommended for all HBsAg-, anti-HBc-, and anti-HBs-negative individuals with chronic liver diseases as early as possible in the course of the disease, when immune response is still functional [17,18]. The HBV vaccination rate of eligible patients with chronic hepatitis C infection has been proposed as a quality measure for medical treatment [14,19]. However, low adherence to vaccination guidelines by primary care physicians and outpatient hepatologists, despite official recommendations and education, impairs widespread vaccination uptake [20–22]. In our cohort, only 24% of patients with liver cirrhosis evaluated for liver transplantation were vaccinated against HBV at baseline. This number is similar [13,16,20,23,24] or slightly higher than that previously reported for patients with chronic liver diseases [25,26], and is

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far from optimal. Lack of awareness, force of habit, and not feeling responsible were identified as possible reasons why outpatient physicians did not to screen and vaccinate against HBV [27]. HBV vaccination recommendations of specialist physicians to primary care physicians are often poorly followed [28]. Use of health information technology, including reminder/recall interventions for primary care physicians, appeared to improve vaccination awareness [29]. However, these systems require the widespread use of electronic health records, which are not yet established in our health care system. The consultation of an infectious diseases specialist was shown to improve vaccination adherence in kidney transplant candidates, but may not be uniformly available [30].

Therefore, to overcome such hurdles, we not only recommended HBV vaccination to the patients and their primary care physicians, but already initiated HBV vaccination prior to discharge and provided a detailed follow-up schedule for further injections, including timepoint, dose, and type of follow-up vaccines, in the discharge letter. By this simple and inexpensive intervention, we achieved high adherence to the recommended HBV vaccination protocol, with subsequent HBV vaccinations in 80% of patients after the second and 90% after the third vaccine dose. This result is considerably higher than in end-stage renal disease patients listed for kidney transplantation, in whom vaccine recommendation only, but not initiation of HBV vaccination, was performed [31].

Thus, HBV vaccination of patients with chronic liver diseases should not solely rely on recommendations for the outpatient care sector, but rather should be already initiated during hospitalization before the patient is referred back to the primary care physician or outpatient hepatologist.

Anti-HBs seroconversion rates after vaccination in our study were lower than expected for patients with end-stage liver diseases [9,10,12]. Possible reasons are the high percentage of alcoholic liver cirrhosis (54%), the predominance of male patients (73%), and the rather old median age of the study population (56±9.2 years). These factors were found to impair response to HBV vaccination [32,33]. Despite low anti-HBs seroconversion rates, HBV vaccination should be advocated because it may provide protection through the clonal expansion of specific memory cells, even without producing high serum anti-HBs levels [34]. In patients on the waiting list for liver transplantation, HBV vaccination is a cheap and safe option to prevent *de novo* HBV infection before and after transplantation [35,36].

Several shortcomings of this study should be noted. It was conducted as a single-center trial with a limited number of patients. Only patients with end-stage liver diseases were included, whereas HBV vaccination should ideally be administered in early disease stages. Implications of the proposed procedure for patients with early-stage liver diseases who might be hospitalized for non-liver related reasons need to be evaluated. Time constraints and cost concerns were identified as additional reasons for ambulant physicians not to screen and vaccinate against HBV [15,27]. These issues are not targeted by the proposed procedure and require further attention.

Conclusions

In summary, initiation of HBV vaccination during hospitalization and detailed recommendations on subsequent vaccinations in the discharge letter improve previously inadequate vaccination rates in the outpatient setting. Similar measures should be implemented at earlier time points of chronic liver diseases to achieve higher immune response rates.

Conflict of interests

None.

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