JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2024.91300
J Inonu Liver Transpl Inst 2024;2(1):1–5

Review

Liver Transplantation Management from Anti HBc Positive Donors to HBV Negative Recipients in Liver Transplantation

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Abstract

Anti HBc + people are in the marginal donor group. It is considered as a donor source, especially in places where Hepatitis B is endemic. In endemic areas, 21.4% of donors are HBcAb positive. In regions where HBV is not endemic, it is 4.75%-7%. Anti-HBc is a 'non-neutralizing' antibody that does not provide immune protection. In other words, it is 'serological scar', that is the evidence of previous exposure to HBV). De novo hepatitis may develop in liver transplants from anti-HBc positive donors. The most important factors for de novo hepatitis are the presence or absence of anti-HBc and anti-HBs positivity. If both antibodies are positive, the risk of denovo hepatitis is least and if both antibodies are negative, it is highest. High genetic barrier antivirals alone are recommended for the treatment and prophylaxis of developing de novo hepatitis. Hepatitis B immune globulin has no place in de novo treatment and prevention.

Keywords: Anti HBc positise donors, liver transplantation, HBV negative recipient

Please cite this article as "Bilgic Y. Liver Transplantation Management from Anti HBc Positive Donors to HBV Negative Recipients in Liver Transplantation. J Inonu Liver Transpl Inst 2024;2(1):1–5".

Isolated anti-HBc positivity can be seen in the following situations:[1,2]

- False positivity (1-2%) caused by substances in the IgM structure that disappear as a result of the use of reducing substances such as dithiothreitol, cysteine, sodium metasulphite, or due to diagnostic systems,
- In acute infections, the window period in which HBsAg disappears but anti-HBs has not yet formed,
- Chronic infections in which HBsAg is undetectable,
- A defect in the humoral response to HBV antigens or the inability to produce anti-HBs, which is especially common in diabetics and kidney patients,
- Anti-HBs disappears over time,
- Viral infections which share antigenic determinants with HBcAg (such as HCV),
- Infections caused by mutant strains,
- Passive transfer of anti-HBc from mother to baby or from person to person as a result of blood transfusion.

Anti-HBc+ status can be seen both after acute infection and chronic infection.[3]

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Submitted Date: 03.04.2024 **Revised Date:** 18.04.2024 **Accepted Date:** 17.05.2024 **Available Online Date:** 13.06.2014

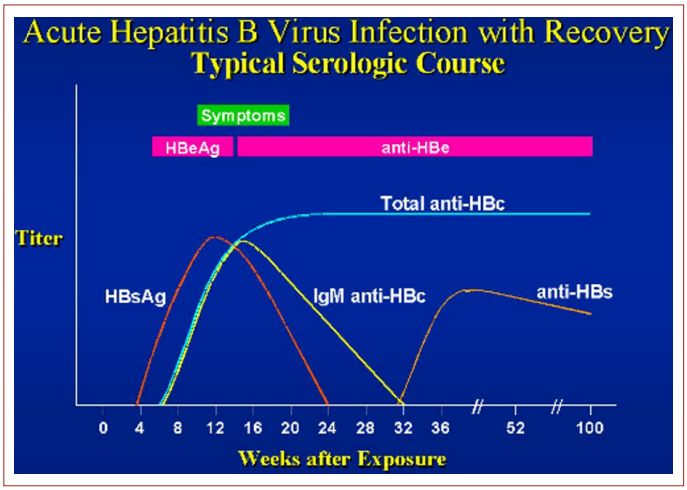

Figure 1. Acute infection.

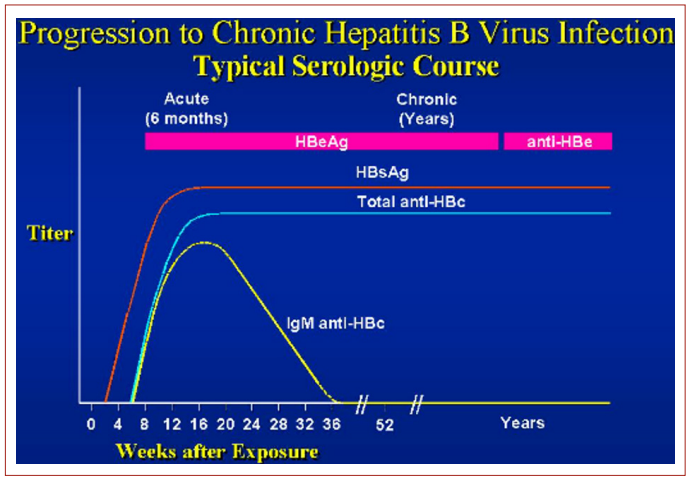

Figure 2. Chronic infection.

Stage 5: HBsAg Negative Phase[4]

In cases where HBsAg is negative, HBV DNA is positive in serum or liver parenchyma.

- HBsAg negative, anti HBc positive, anti HBs positive or negative in serum
- It is also called occult HBV infection.
- ALT levels are within normal limits and HBV DNA is undetectable.

Table 1. Incidence of de novo hepatitis B infection by recipient antibody status in patients receiving HBcAb- positive graft

	HBcAb (+) HBsAb (+) (n=24)	HBcAb (+) HBsAb (-) (n=6)	HBcAb (-) HBsAb (+) (n=6)	HBcAb (-) HBsAb (-) (n=4)	Total (n=40)
Recurrence	1 (4.2)	1 (16.7)	1 (16.7)	2 (50.0)	5 (12.5)
Nonrecurrence	23 (95.8)	5 (83.3)	5 (83.3)	2 (50.0)	35 (87.5)

Values are presented as number (%); HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody.

Table 2. Risk factors for de novo hepatitis B infection in recipients of HBcAb- positive graft

Veriable	Total (n=40)	Nonrecurrence (n=35)	Recurrence (n=5)	p
Donor				
Age	40.10±11.44	39.56±11.86	43.80±7.98	0.446
Male sex	28 (70.0)	26 (74.3)	2 (40.0)	0.125
HBsAb (+)	36 (90.0)	31 (88.6)	5 (100)	0.655
Recipient				
Age	50.12±10.68	51.37±10.49	41.40±8.14	0.049
Male sex	16 (40.0)	12 (34.3)	4 (80.0)	0.418
Alcohol: HCV: others	18 : 5 : 17	15 : 4 : 16	3 : 1 : 1	0.790
MELD	13.94±8.53	14.12±7.94	12.25±3.40	0.794
HBcAb (+)	30 (75.0)	28 (80.0)	2 (40.0)	0.096
HBsAb (+)	30 (75.0)	28 (80.0)	2 (40.0)	0.096
LDLT	30 (75.0)	26 (74.3)	4 (80.0)	0.633
Operative time (min)	1,093.6±446.7	1,114.8±237.6	1,080.0±423.6	0.806
Blood transfusion (unit)	6.9±4.4	9.6±5.1	4.3±5.1	0.106
Mortality	1 (2.5)	1 (2.9)	0 (0)	0.663
Survival time (mo)	43.73±35.03	40.19±32.37	66.4±46.75	0.121

Values are presented as mean±standard deviation or number (%); HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; hepatitis B surface antibody; BMI: body mass index; MELD: model for end- stage liver disease; LDLT: living donor liver transplantation.

- HBV DNA (ccc DNA) is frequently detected in the liver.
- If HBsAg loss occurred before the development of cirrhosis, the risk for cirrhosis, decompensation and HCC development is low.
- If cirrhosis developed before HBsAg loss, the risk of developing HCC remains the same.
- Immunosuppression may cause HBV reactivation in these patients.

Accurate measurement of ccc DNA can be achieved through droplet digital PCR (ddPCR) assays using hepatocyte samples obtained via liver biopsy. A new biomarker for Ccc DNA can be detected in serum HBV RNA, especially under NA treatment. In virally suppressed patients with low HBV DNA, HBV RNA level is an important marker to show ccc DNA level.[5]

This large cohort study described the long-term results of HBIG monotherapy preventing DNHB infection following liver transplantation using Anti-HBc antibody+ liver grafts in an area where hepatitis B virus is endemic. There is no advantage over monotherapy. Anti-HBc antibody negative recipients were more likely to develop new hepatitis B virus infection than Anti-HBc antibody positive recipients. High MELD score was significantly associated with DNHB virus infection.[6]

Between 2000 and 2010, 71 anti-HBs antibody negative adult patients who received anti-HBc antibody positive grafts. Patients were divided into 3 groups: Group 1, good responders to active vaccination, patients with anti-HBs titer >1000 IU/L before transplantation and who didn't required prophylaxis after transplant (n=24); group 2, pretransplant active vaccinated patients but the level of anti-HBs antibody titer less than 1000 IU/L at transplantation time, who were administered lamivudine prophylaxis after transplantation at least 2 years, and who responded well to post-transplant active vaccination by maintaining their anti-HBs titers at > 100 IU/L (n=30); and group 3, patients with post-transplant anti-HBs<100 IU/L despite active vaccination who continued lamivudine lifelong (n=17). DNHB incidence was 17.6% and all DNHB occurred in group 3 patients with posttransplant level of anti-HBs <100 IU/L. No DNHB was occurred in patients with post-transplant anti-HBs levels >100 IU/L (p=0.001). Anti-HBs level >1000 IU/L before transplantation was significantly associated with early achievement and sustained post-transplantation level of anti-HBs >100 IU/L (p<0.001). Prevention of DNHB in LDLT patients can be achieved by active immunization in adults when the level of anti-HBs is kept above 100 IU/L after transplantation by active vaccination.[7]

Table 3. Characteristics of liver transplantation recipients who developed de novo hepatitis B infection, and treatment outcomes

No	Age	Sex	Diagnosis	At recurrence					Treatment			After treatment				
				ALT	HBsAg	HBsAb	HBeAb	DNA	DFS	Treatment	Duration (mo)	ALT	HBsAg	HBsAb	HBeAb	DNA
1	37	F	Wilson	23	74.10	-	957.7	1,091,234,112	119	No treatment	29	32	95,200	-	>4,000	1,038,348,586
2	46	M	Alcohol	33	72.90	-	77.3	28,279,990	28	Entecavir	71	53	311.3	-	-	-
3	43	M	Toxic	98	74.06	-	163.73	59,383	35	Entecavir HBIG	31	39	54.16	-	7.24	-
4	30	M	HCV	120	728.7	-	-	103,143,448	7	Entecavir HBIG	5	38	+	-	-	-
5	51	M	Alc	36	1.44	-	-	-	9	Entecavir	20	25	1,033	-	>4,000	-

HBcAb: hepatitis B surface antibody; DFS: disease- free survival; Wilson: Wilson disease; Toxic: toxic hepatitis; HBIG: hepatitis B immunoglobulin.

Table 4. Classification of De Novo HBV Infection Risk in Liver Transplants from Anti-HBc Positive Donors According to Hepatitis B Marker and Treatment Status of the Recipient.[10]

	Anti-HBc – Anti-HBs - Anti-HBc – Anti-HBs -	Anti-HBc + Anti-HBs - Anti-HBc + Anti-HBs -	Anti-HBc + Anti-HBs + Anti-HBc + Anti-HBs +	Anti-HBc – Anti-HBs + Anti-HBc – Anti-HBs +
In Those Not Receiving Prophylactic Treatment	>%40	%13	%2	%10
In Those Receiving Prophylactic Treatment	%12 High risk	%12 Moderate Risk	%12 Low Risk	%12 Moderate Risk

In a systematic review by Cholongitas et al on recipients of anti-HBc antibody positive liver grafts concluded that the highest risk rate of DNHI was among the recipients without HBV infection by 47.8%. In contrast, recipients with natural immunity had the lowest risk rate of DNHI by 1.4%–4.0%.[8]

In another article investigating the risk of developing DNHB virus infection in patients who received a graft from a donor with anti-HBc antibody positive the incidence of de novu hepatitis B was evaluated according to the anti-HBc and anti-HBs positivity or negativity of the recipient. De novo hepatitis developed in one of them. While the most risky group was the group in which both antibodies were negative, the risk was found to be lowest in the group in which both antibodies were positive. When the risk groups of patients who developed de novo hepatitis were examined, age, anti-HBc positivity and anti-Hbs positivity were found to be significant. Antivirals were started in patients who developed de novo hepatitis B. It was observed that HBsAg turned negative in all patients who developed de novo hepatitis after treatment.[9]

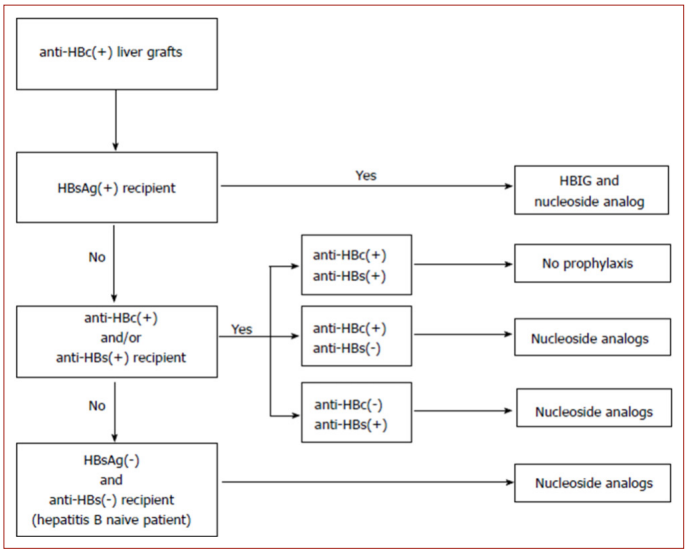

Figure 3. Treatment recommendations for recipients of anti-HBc positive donors.[8]

Treatment of de Novo Hepatitis;[8]

Cholongitas et al. In HBsAg negative recipients, de novo infection rates were determined as 2.6% in lamivudine only, 2.8% in combination of lamivudine and HBIG, and 19% in HBIG monoprophylaxis. In other words, NA treatment revealed that the rate of de novo hepatitis was significantly reduced. This study showed that treatment with NA is effective in preventing de novo hepatitis.

- HBIG+LAM combination compared to LAM monotherapy in HBV DNA(-) patients receiving HBcAb(+) liver grafts;
- LAM monotherapy has the same efficacy as HBIG+LAM combination therapy
- Entecavir and tenofovir monotherapy is safer
- Therefore, we recommend that clinicians administer nucleoside(t)ide analogs with lower resistance profiles to recipients of HBcAb(+) liver allografts without additional HBIG therapy.
- AASLD and EASL recommend monotherapy.

The role of Immunosuppressants used in the Development of de Novo Hepatitis

The immunosuppressive regimen using mTOR inhibitors after liver transplantation has been shown to generally reactivate HBV infection, as well as viral infections such as HCV, cytomegalovirus (CMV), HIV-1, human papillomavirus (HPV), and Epstein Barr.[11]

Survival in de Novo Hepatitis

The recipient survival at 5 years in patients who received a graft from a donor with Anti-HBc antibody positive was 97.5% while in patients with Anti-HBc abtibody negative was 89.7%. It shows that the survival rate does not differ significantly depending on the anti-HBc antibody status of the donor.[7]

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Badur S. Hepatit B virusu (HBV) moleküler viroloji ve serolojik tanı, s: 65-90. Kılıçturgay K (ed), Viral Hepatit 94. 1994, Viral Hepatitle Savaşım Derneği, İstanbul.
2. Mert A, Şentürk H, Süve İ ve ark. HBsAg ve anti-HBs negatif, anti-HBc pozitif olguların çeşitli yönlerden incelenmesi. Viral Hepatit Dergisi 1996;2:92-5.
3. Lok ASF. Uptodate, 2010, Clinical manifestaions and naturel history of hepatitis B virus infection.
4. Hepatitis B virus: Screening and diagnosis - UpToDate [Internet]. [a.yer 12 Nisan 2020]. Erişim adresi: https://www.uptodate.com/
5. Raimondo G, Allain J-P, Brunetto MR, Buendia M-A, Chen D-S, Colombo M, vd. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol 2008;49(4):652-7.
6. Jung HS, Choi Y, Yoon KC, Hong SY, Suh S, Hong K, Han ES, Lee JM, Hong SK, Yi NJ, Lee KW, Suh KS. Hepatitis B immunoglobulin prophylaxis for de novo hepatitis B infection in liver transplantation: a 30-year experience. Ann Transl Med 2022;10(5):243.
7. Wang SH, Loh PY, Lin TL, Lin LM, Li WF, Lin YH, Lin CC, Chen CL. Active immunization for prevention of De novo hepatitis B virus infection after adult living donor liver transplantation with a hepatitis B core antigen-positive graft. Liver Transpl 2017;23(10):1266-1272.
8. Cholongitas E, Papatheodoridis GV, Burroughs AK. Liver grafts from anti-hepatitis B core positive donors:a systematic review. J Hepatol 2010;52:272–9.
9. Han JH, Kim DG, Na GH, Kim EY, Lee SH, Hong TH, You YK, Choi JY, Yoon SK. De novo hepatitis B virus infection developing after liver transplantation using a graft positive for hepatitis B core antibody. Ann Surg Treat Res 2015;89(3):145-50.
10. Harputluoglu M, Cecen EM, Aladag M, Sarici KB, Caliskan AR, Erdogan MA, Saglam O, Yilmaz S. P-004. Retrospective Investigation of De novo hepatitis B infection in recipients after liver transplantation by anti-HBc positive donors. Turk J Gastroenterol 2019;30(supp1):S20.