Costs and Efficacy of "On Demand" Low-dose Immunoprophylaxis in HBV Transplanted Patients: Experience in the Romanian Program of Liver Transplantation

Speranța Iacob[1], Doina Hrehoreț[2], Emil Matei[2], Bogdan Dorobanțu[2], Eliza Gangone[2], Liana Gheorghe[1], Irinel Popescu[2]

1) Center of Gastroenterology and Hepatology, 2) Center of General Surgery and Liver Transplantation, Fundeni Clinical Institute, Bucharest, Romania

Abstract

Background. HBV in liver transplant (LT) patients is associated with good outcomes and the challenges are primarily focused around optimizing prophylactic regimens with hepatitis B immune globulin (HBIG) and minimizing related costs. **Aim**. To identify recurrence rates in patients transplanted for HBV or HBV+HDV infection in whom a combined "on demand" low-dose HBIG was used, maintaining low anti-HBs titres (not below 50 IU/L). **Methods.** Medical records of 42 patients transplanted for HBV or HBV+HDV induced cirrhosis between April 2000 and September 2007 at Fundeni Clinical Institute were analyzed. Patients received immunoprophylaxis with lamivudine and HBIG (10,000 IU within anhepatic phase and daily within the first postoperative week, followed by 2,500 IU on demand). HBV recurrence rates and survival during follow-up were evaluated using the Kaplan Meier method. **Results**. HBV recurrence rate was 4.8% after a median of 1.8 years. Three year patient survival rate was 70%. None of the patients died due to liver failure related to HBV recurrence. Using our "on demand" low-dose administration of HBIG, the total mean cost for HBIG and lamivudine for patient per month of survival was 598.3 Eur. The projected monthly cost for the "ideal" schedule/patient was 2,017 Eur. **Conclusion**. Individualization of immunoprophylaxis after LT for HBV related disease according to the lowest protective anti-HBs titers in combination with lamivudine is probably the best approach for non-replicative pre-LT patients in terms of costs and efficacy.

Key words

Cost-efficacy – hepatitis B virus – immunoprophylaxis – liver transplantation.

Received: 18.07.2008 Accepted: 08.10.2008
J Gastrointestin Liver Dis
December 2008 Vol.17 No 4, 383-388
Address for correspondence: Speranta Iacob, M.D
Center of Gastroenterology & Hepatology, Fundeni Clinical Institute
Sos. Fundeni no 258
Bucharest, Romania
E-mail: speranta.iacob@icfundeni.ro

Introduction

Hepatitis B virus (HBV) infection was previously considered a contraindication to liver transplantation (LT) since the risk of HBV reinfection was 80-90%, and fewer than half of the patients survived two years post-LT due to the severe clinical consequence of fibrosing cholestatic hepatitis [1, 2]. However, chronic infection with HBV is estimated to affect 300-400 million persons and each year over 1 million people die from HBV-related cirrhosis and hepatocellular carcinoma (HCC) [3]. This is the main indication of LT in regions with intermediate and high prevalence of HBV (≥ 2%), like Asia, Middle East, Africa, South America and Mediterranean countries. In Romania, the preliminary results of a nationwide cross-sectional survey showed an HBV infection prevalence of 5.2% in general population in 2008 (data yet unpublished). In 2005, our group found HBV infection (mono and coinfection) to be responsible for 44% of end-stage liver diseases in patients awaiting LT [4] compared to 4.8% hepatitis B patients on the Organ Procurement and Transplantation Network waitlist included between 1994 to 2006 [5].

Post-LT prophylaxis of HBV patients with hepatitis B immune globulin (HBIG) and with oral nucleotide and nucleoside therapy such as lamivudine and adefovir dipivoxil have greatly decreased the recurrence rate to <10% after 1-2 years and have made LT survival for hepatitis B comparable to that of other causes of liver disease [6, 7]. Nowadays, HBV in transplant patients is associated with good outcomes and the challenges are primarily focused around optimizing prophylactic regimens with HBIG and minimizing related costs. HBIG is an expensive therapy, and there are wide practice variations at different institutions, because no clear guidelines exist on the dosage and schedule of this prophylaxis. There were initial studies suggesting that anti-HBs antibody titers should be maintained to ≈500 IU/L, mainly in patients with active viral replication [8, 9] and to 100-150 IU/L in patients with negative HBV DNA at LT [7].

The aim of this study was to identify recurrence rates in patients transplanted for HBV or HBV and hepatitis D virus

(HDV) infection in whom a combined "on demand" low-dose HBIG was used. We also compared the cost-effectiveness of this regimen with an "ideal" high dose HBIG administration. A secondary aim was to identify factors associated with HDV presence as well as with patient survival after LT.

Patients and methods

Study population

A retrospective study was conducted, gathering data from medical records of 42 patients transplanted for HBV or HBV+HDV induced cirrhosis between April 2000 and December 2007 in the Center of General Surgery and Liver Transplantation at Fundeni Clinical Institute and followed for at least 6 months from inclusion of the last patient. All patients were hepatitis B surface antigen (HBsAg) positive and had pretransplant evaluation of the HBV DNA (Amplicor, Hoffmann-La Roche®, Basel, Switzerland; detection limit: 200 copies/mL), HBeAg, anti-HBe, anti-HBc IgM and IgG, anti-HBs, anti-HDV antibody (Ab) IgG, using an ELISA (qualitative enzyme immunoassay) test. Exclusion criteria were: fulminant liver failure due to acute HBV infection; coinfection with hepatitis C virus or HIV; posttransplantation acquired HBV infection; livers from donors with positive viral markers. Indications for LT were either end-stage cirrhosis or cirrhosis with hepatocellular carcinoma (HCC). It should be noted that the model for end stage liver disease (MELD) score was calculated retrospectively for patients transplanted before February 2002 using values of preoperative total bilirubin, serum creatinine and international normalized ratio. For patients with HCC, the MELD score was not assigned to be 20 or 24 [10] as proposed by the United Network for Organ Sharing, but calculated as usually. The allocation of MELD score to patients with HCC was introduced for the first time in the Eurotransplant International Foundation Organ Procurement System in 2006 [11].

This retrospective study was approved by our institutional review board. This study complies with the standards of the Declaration of Helsinki and current ethical guidelines. All patients signed an inform consent at inclusion on waiting list for LT and before LT.

Definitions of outcome measures

The main outcome was occurrence of recurrent HBV infection. Recurrent HBV was defined as the reappearance of HBsAg in serum after its initial disappearance post-LT. Serum HBsAg, HBV DNA, as well as the titer of anti-HBs [AXSYM MEIA (microparticle enzyme immunoassay) technology, Abbott Laboratories, Germany] were tested monthly during the first 6 months and than at every regular visit (2 to 3 months). In case of HBsAg recurrence or increase of the liver enzymes, serum HBV DNA was determined and was considered negative if <200 copies/mL.

A secondary outcome was overall patient survival, considered until death (hepatic or nonhepatic causes) of the recipient. All patients were followed-up until death or the end of the observation period.

Post-LT treatment and HBV immunoprophylaxis

Maintenance immunosuppression regimens consisted of either a triple-drug regimen that included cyclosporine (Neoral®, Novartis) or tacrolimus (Prograf®, Astellas Pharma Inc.), mycophenolate mofetil (Cell Cept®, Hoffman-La Roche), and corticosteroids (medrol), or dual immunosuppression based on cyclosporine or tacrolimus. Medrol was discontinued at 3 to 6 months. Liver biopsies were performed whenever clinically indicated by an elevation in serum liver enzyme levels. Therapy of acute cellular rejection episodes consisted of 1000 mg methyl-prednisolone for 3 days.

The patients were divided into two groups according to presence or absence of HDV, but protocol for HBIG administration was identical. All patients included in our study received 10,000 units HBIG during the anhepatic phase and every day during first postoperative week, followed by 2,500 UI HBIG (IVHEBEX®, 5,000 IU/100 mL, LFB-Biomedicaments, France) "on demand" according to anti-HBs level (lower than 50 IU/L). All patients received lamivudine 100 or 200 mg/day as prophylaxis after LT. Patients with positive HBV DNA pre-LT, with positive HBe antigen at LT and patients with HCC received 200 mg/day lamivudine within the first year post-LT. Cost-effectiveness was defined as the cost (in Eur) of HBIG prophylaxis plus cost of lamivudine needed to prevent HBV recurrence post-LT. In Romania, the cost of 5,000 IU IVHEBEX is 1.865 Eur and the price for lamivudine (100 mg/day) for a month is 76 Eur. We calculated for each patient the price for an "ideal" HBV immunoprophylaxis comprising 10,000 IU HBIG in the anhepatic phase followed by 10,000 IU HBIG daily within the first postoperative week and than 10,000 IU HBIG every 8 weeks in association with 100 mg lamivudine daily.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or medians. Categorical data were expressed as proportion of the subjects with a specific feature. Student t-test was used to compare continuous variables. The chi-squared test was used to compare qualitative variables. HBV recurrence rates, survival during follow-up and survival of patients according to different variables were evaluated using the Kaplan Meier method. Survival curves were compared using the log rank test. To identify potential predictors of patient death failure, univariate and multivariate Cox's proportional hazards regression model was used. All tests were two sided and a p value <0.05 was considered to indicate statistical significance. SPSS 13.0 statistical software (SPSS Company, Chicago, Ill) was used to analyze the relevant data.

Results

Cohort characteristics

Patients' characteristics are shown in Table I.

All patients received tacrolimus (73.8%) plus steroids or cyclosporine (26.2%) plus steroids. Forty one patients received additionally mycophenolate mofetil and one patient daclizumab (Zenapax®, Hoffman-La Roche). No patient received anti-CD3 monoclonal antibody or antithymocyte globulin.

Table I. Patients characteristics

Variable	Patients (n=42)
Mean age at LT (years)	47.2 ± 8.05
Gender (men/ women)	27 (64.3%)/ 15 (35.7%)
Pre-LT HCC	9 (21.4%)
MELD score	17.6 ± 3.6
Child-Pugh class (B/ C)	25 (59.5%)/ 17 (40.5%)
Living donor LT	6 (14.3%)
HBV DNA undetectable at LT	41 (97.6%)
Negative HBeAg at LT	39 (92.8%)
HBV + HDV coinfection	29 (69%)

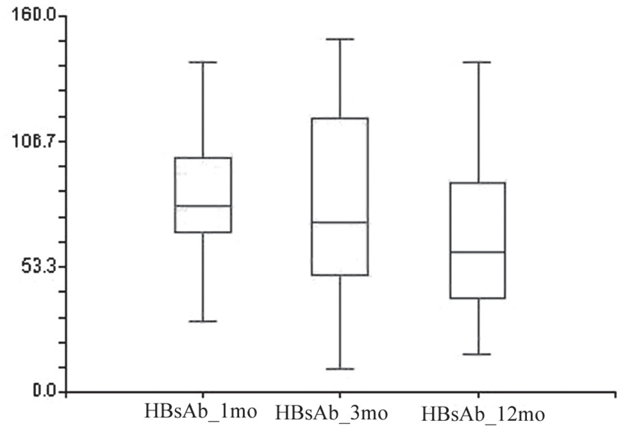

Fig 1. Plasma anti-HBs titres at 1, 3 and 12 months post-transplantation

Only one patient had a positive, but very low viral load at time of LT (232 copies/mL) and he did not receive lamivudine pre-LT. Eight patients received lamivudine prior to LT (between 3 to 12 months) because they had positive viral loads (range 11,200 – 560,000 copies/mL). All of them had undetectable HBV DNA in the day of transplantation. Three patients out of 29 with HBV and HDV coinfection had positive HBV DNA (232 – 50,600 copies/mL), two of them receiving lamivudine prior to LT. HBe antigen was positive at the moment of LT in 3 patients, two of them with HDV coinfection. None of the patients developed evidence of antiviral resistance during lamivudine treatment at pre or post-LT follow-up.

HBV recurrence

HBV recurrence rate (positivity of HBsAg after initial negativity) was 4.8% after a median of 1.8 years. Both patients had HBV+HDV coinfection, negative pre-LT HBV DNA and negative HBeAg. None had received lamivudine therapy prior to LT. At recurrence time, anti-HBs levels were low in both patients (10 IU/L and 2 IU/L, respectively) and both had positive viral loads (4,820 copies/mL and 2,000 copies/mL, respectively). The remaining 40 patients remained seronegative both for HBsAg and HBV DNA throughout the follow-up. The median serum anti-HBs level was 213 IU/L (range 30-1,200 IU/L) at 1 month posttransplantation, 112.9 IU/L (range 15-300 IU/L) at 3 months, and 63.6 IU/L (range 16-110 IU/L) at 12 months (Fig 1).

Patients with HBV monoinfection received lamivudine pre-LT in a significantly higher percent (80%) compared to HBV+HDV infection (21.1%, p=0.01). In the HBV group there was a tendency to a higher percentage of HCC patients - 38.5% vs 13.8% in the HDV group, but without statistical significance (p=0.07). The time to HBsAg negativity after LT was similar for the patients with and without HDV infection (p=0.43).

Overall posttransplant mortality

During the follow-up period, 12 (28.5%) patients died. Death was attributed to sepsis in 5 patients, hepatic artery thrombosis in 3 patients, intraoperative bleeding in one patient, cerebrovascular accident in one patient, myocardial infarction in one patient and de novo malignancy in one patient. The latter patient, with uterine and lung cancer had also HBV recurrence before occurrence of the malignancy. None of the patients died due to liver failure related to HBV recurrence. Three year patient survival rate was 70%. Median patient survival was not reached. The mean follow-up period for all recipients was 30.9 months.

Patient mortality after LT was predicted by severity of pre-LT liver disease: Child-Pugh class C (p=0.006) and MELD score >17 (p=0.007). None of these were independent predictors of death after LT. A higher pretransplant MELD score and Child-Pugh class C had not a negative prognostic value for posttransplant survival after excluding patients deceased within the first 3 months post-LT. Patient survival according to Child-Pugh class and MELD score is depicted in Figs 2 and 3. There was no difference between patient survival rates according to presence of HDV (p=0.38), or presence of HCC (p=0.39).

Cost-effectiveness

Using our "on demand" low-dose administration of HBIG, the total mean cost for HBIG and lamivudine (100 or 200 mg/day) for patient per month of survival was 598.3 Eur. The cost does not take into account the HBIG administered during the anhepatic phase. The projected monthly cost for the "ideal" schedule of HBIG and lamivudine (100 mg/day) for a patient was 2,017 Eur. This cost adds to the "ideal" calculated cost of the anhepatic phase and first posttransplant week (26,110 Eur/patient). This "on demand" schedule provides a greater than a 3 times cost-reduction compared to fixed, "ideal" dosage (p<0.0001).

Lamivudine given at a dose of 200 mg/day within the first year after LT was associated with less patient deaths (16% vs 47.1%, p=0.02). None of the patients with recurrent HBV had received 200 mg/day lamivudine after LT. This lamivudine dosage was administered in 27 patients (64.3%).

Discussion

Between April 2000 – December 2007, 32.06% of the

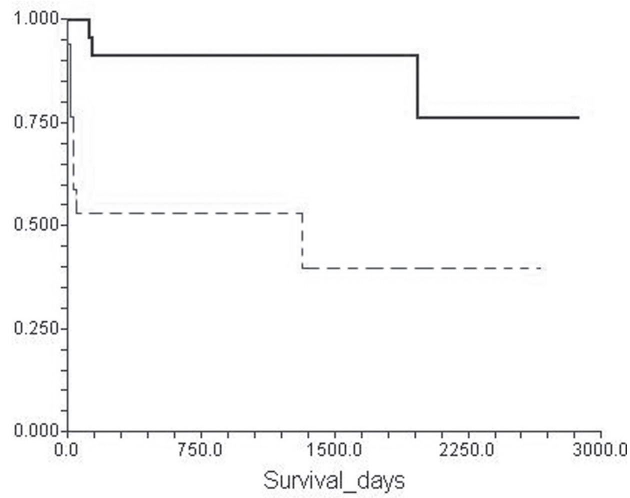

Fig 2. Patient survival according to Child-Pugh class C (dashed line) vs Child Pugh class B (continuous line) at LT (p=0.002, log rank test).

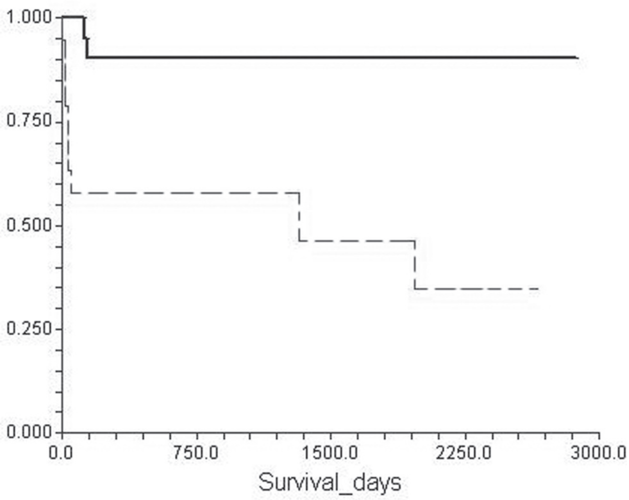

Fig 3. Patient survival according to MELD score >17 (dashed line) vs MELD score <17 (continuous line) at LT (p=0.001, log rank test).

LT were performed for HBV-related liver disease in our Center compared to 5.5% reported by Keeffe [12] from the United Network for Organ Sharing Database between 1987-1998 and 4% in 2007 in United States [13]. The number of American patients registered for LT for decompensated liver disease secondary to HBV has decreased by 37% since 2000, according to an epidemiological study presented by Kim et al [14], which is not the case in Romania. This is the reason why cheaper strategies to prevent HBV recurrence are warranted, especially in countries like ours with HBV intermediate prevalence, but high number of patients listed for LT due to end stage HBV liver disease. Long-term HBIG therapy places a huge economic burden on patients and on the health care system of Romania.

Our data are similar to the reported data from Southern Europe (Italy) in the 1970-1980s where HBV accounted for 30% of cirrhosis cases [15]. The proportion of HDV patients receiving transplants in Romania (69%) is even higher than the one reported in Italy 10 years ago (45%) [16]. This is in line with a previously published paper [17] suggesting that HDV-related cirrhosis in Romania is an aggressive disease with a median time to decompensation less than 2 years and a median survival less than 5 years, making these patients in need for LT. The severity of liver cirrhosis prior to LT was a negative prognostic factor for survival in our patients consistent with some studies [18, 19] and in contradiction with others [20, 21].

Our HBV study population was characterised by HBeAg negativity (92.8%) and undetectable (97.6%) or very low viral loads at LT. This was probably one of the reasons for a low recurrence rate in the presence of a low anti-HBs titre because there is a linear correlation between HBV recurrence and the replicative status at LT. HBV recurrence was present in 0–15% and 16–35% of patients transplanted for non-replicative and replicative HBV cirrhosis, respectively [7].

Another reason may be the high percentage of patients infected with HBV and HDV who are less at risk of HBsAg reappearance than patients infected with HBV alone, HDV having an inhibitory effect on HBV replication. The reported rate of HBsAg reappearance in patients with HBV+HDV cirrhosis was 50–60% in patients who did not receive long-term HBIG [22, 23] and 17% in those receiving long-term HBIG [24]. A recent retrospective study [25] showed absence of HBV recurrence in a cohort of HDV coinfected LT recipients under combined lamivudine and HBIG prophylaxis, as well as 38% lower requirements of HBIG as compared to HBIG monotherapy. Combined immunoprophylaxis is safe and cost-efficient, the regimen to be chosen also in patients with delta coinfection. Patients with HBV cirrhosis and HDV coinfection had significantly better survival rates after LT compared to patients with HBV alone [26], a fact that was not confirmed in our study.

Wild-type HBV infection has decreased greatly in Southern Europe in the last two decades to the advantage of infections sustained by the HBeAg negative variants of HBV [16], a feature of HBV infection present also in Romania nowadays. Post-LT survival rates, as well as the recurrence rate were significantly influenced by preoperative HBeAg status [26]. Patients in the positive HBeAg group showed a significantly higher recurrence rate than HBeAg negative patients (48% vs 21% at one year after LT), but this was not the case in our two patients with recurrent HBV.

HBV recurrence rate was found to be significantly higher (33-53%) in patients with HBV DNA ≥100,000 copies/mL than the rate of 4-7.5% found in patients with lower HBV DNA levels during both mono- or combined immunoprophylaxis [27]. In our study, none of the patients had a viral load ≥100,000 copies/mL at the time of surgery.

The ultimate goal of treatment in patients with HBV-induced cirrhosis is suppression of viral replication to undetectable HBV-DNA levels prior to and after LT to prevent infection of the newly transplanted liver. Most published data are available for therapy with lamivudine in pre- and post-transplant HBV patients. New oral treatments, such as entecavir, tenofovir and telbivudine, characterized by potent antiviral effects, good tolerability, improved histology, stable seroconversion, and minimal resistance, are available for non-transplant setting. There is an increasing need for individualization of therapy based on prior drug exposures, level of HBV DNA at time of transplantation and type of prophylaxis used. Combined HBIG and nucleos(t)ide analogue therapy has been widely adopted as the most effective treatment strategy against recurrent HBV disease after LT due to synergistic mechanisms of action that increase antiviral effect and reduce resistance [28, 29].

The estimated costs of HBIG administration in the United States is US$100,000 in the first year after LT and US$50,000 in each subsequent year (30). That is the reason why most countries look for alternatives to replace strategy using long term 10,000 IU HBIG IV to maintain anti-HBs >100-150 IU/L in HBV DNA negative patients or >500 IU/L in HBV DNA positive patients at LT [7]. A Chinese study [31] showed that a long-term use of lamivudine combined with low-dose (400-800 IU) intramuscular HBIG, according to the titer of anti-HBs was efficacious (a 2 year recurrence rate of 5.5%) and cost effective (an approximate cost of HBIG US$2,500-5,000 for the first year after LT) to prevent recurrent hepatitis B. Anyway they tried to maintain the anti-HBs titer >100 IU/L. Another study using “on demand” combined lamivudine and low-dose 2,000 IU HBIG given intravenously in order to maintain anti-HBs titers to 70 IU/L conferred adequate protection with significantly less antibody waste compared with fixed monthly schedules and with fewer yearly administrations [32]. This also resulted in remarkable cost reduction, but this was possible in patients at low risk of HBV recurrence (HBV DNA and HBeAg negative before and after LT). Another recent study [33], using very low doses (400-800 IU/month) of intramuscular HBIG plus lamivudine and having no target anti-HBs titres (but trying not to fell <50 IU/L), proved to provide safe and effective long-term prophylaxis against recurrent HBV at <10% the cost of the high-dose intravenous HBIG regimen. The actuarial risk of HBV recurrence in this latter study was 1% at 1 year and 4% at 5 years.

Our study is in line with these reports, using a threshold for anti-HBs titers not <50 IU/L after “on demand” administration of low-dose HBIG and was associated with a low HBV recurrence rate (<5%). Low risk HBV population (undetectable viral load, negative HBeAg, high proportion of HDV coinfection) and possibly the use of a higher dose of lamivudine may be responsible for our results (both efficacy and significant decrease of costs).

Although a drawback of our study is that it is a retrospective one, some study characteristics make the data reliable and therefore close to data that would result from a prospective study. We included a homogeneous population with non-replicative HBV cirrhosis prior to LT evaluated and then transplanted in a center with high level expertise in following such patients. The patients were followed up usually by the same physician during the postoperative course but the impossibility to administer HBIG at high dose (10,000 IU) every 6-8 weeks due to the lack of financial resources made the search for other criteria and limits of anti-HBs titers a necessity from the beginning of LT in Romania.

In **conclusion**, individualization of immunoprophylaxis after LT for HBV related disease according to the lowest protective anti-HBs titers in combination with lamivudine is probably the best approach for non-replicative pre-LT patients in terms of costs and efficacy.

Conflicts of interest

There are no conflicts of interest and no source of funding for this study. The patients received treatment through the National Insurance Agency Program for Liver Transplantation.

References

1. Berenguer M, Wright TL. Treatment of recurrence of hepatitis B in transplant patients. J Hepatol 2003; 39: S190-S193.
2. Schiff ER, Lai CL, Hadziyannis S, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 2003; 38: 1419-1427.
3. Alter M. Epidemiology of hepatitis B in Europe and worldwide. J Hepatol 2003; 39: S64-S69.
4. Gheorghe L, Popescu I, Iacob R, Iacob S, Gheorghe C. Predictors of death on the waiting list for liver transplantation characterized by a long waiting time. Transpl Int 2005; 18: 572-576.
5. www.optn.org. Accessed 6-Apr-2008
6. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of diseases following orthotopic liver transplantation. Am J Gastroenterol 2006; 101: 1370-1378.
7. Roche B, Samuel D. Liver transplantation for hepatitis B virus-related liver disease: indications, prevention of recurrence and results. J Hepatol 2003; 39: S181-S189.
8. Terrault NA, Zhou S, Combs C, et al. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. Hepatology 1996; 24: 1327-1333.
9. McGory RW, Ishitani MB, Oliveira WM, et al. Improved outcome of orthotopic liver transplantation for chronic hepatitis B cirrhosis with aggressive passive immunization. Transplantation 1996; 61: 1358-1364.
10. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907-1917.
11. Broelsch CE, Frilling A, Malago M. Should we expand the criteria for liver transplantation for hepatocellular carcinoma – Yes, of course! J Hepatol 2005; 43: 569-573.
12. Keeffe EB. Liver transplantation: current status and novel approaches to liver replacement. Gastroenterology 2001; 120: 749-762.
13. Mayo Clinic. Nationwide Decrease in the Need for Liver Transplant. Press release 31-Oct-2007. www.newswise.com. Accessed 6-Apr-2008
14. Kim WR, Benson J, Hindman A, Brosgart C, Fortner-Burton C. Decline in the need for liver transplantation for end stage liver disease secondary to hepatitis B in the US. Hepatology 2007; 46: 57A.
15. Bianchi P, Porro CB, Coltorti M, et al. Occurrence of Australia antigen in chronic hepatitis in Italy. Gastroenterology 1972; 63: 482-485.
16. Rosina F, Conoscitore P, Cuppone R, et al. Changing pattern of chronic hepatitis D in Southern Europe. Gastroenterology 1999;

117: 161-166.
17 Gheorghe L, Iacob S, Simionov I, et al. Natural history of compensated viral B and D cirrhosis. Rom J Gastroenterol 2005; 14: 329-335.
18. Onaca NN, Levy MF, Sanchez EQ, et al. A correlation between the pretransplantation MELD score and mortality in the first two years after liver transplantation. Liver Transpl 2003; 9: 117-123.
19. Iacob S, Cicinnati VR, Hilgard P, et al. Predictors of graft and patient survival in hepatitis C virus (HCV) recipients: model to predict HCV cirrhosis after liver transplantation. Transplantation 2007; 84: 56-63.
20. Adler M, De Gendt E, Vereerstraeten P, et al. Value of the MELD score for the assessment of pre- and post–liver transplantation survival. Transplant Proc 2005; 37: 2863-2864.
21. Jacob M, Copley LP, Lewsey JD, et al. Pretransplant MELD score and post liver transplantation survival in the UK and Ireland. Liver Transpl 2004; 10: 903-907.
22. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. J Hepatol 1992; 14: 104-111.
23. Ottobrelli A, Marzano A, Smedile A, et al. Patterns of hepatitis delta virus reinfection and disease in liver transplantation. Gastroenterology 1991; 101: 1649-1655.
24. Samuel D, Muller R, Alexander G, et al. Liver transplantation in European patients with the hepatitis B surface antigen. N Engl J Med 1993; 329: 1842-1847.
25. Caccamo L, Agnelli F, Reggiani P, et al. Role of lamivudine in the posttransplant prophylaxis of chronic hepatitis B virus and hepatitis delta virus coinfection. Transplantation 2007; 83: 1341-1344.
26. Steinmuller T, Seehofer D, Rayes N, et al. Increasing applicability of liver transplantation for patients with hepatitis B–related liver disease. Hepatology 2002; 35: 1528-1535.
27. Marzano A, Gaia S, Ghisetti V, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transpl 2005; 11: 402-409.
28. Coffin CS, Terrault NA. Management of hepatitis B in liver transplant recipients. J Viral Hepat 2007; 14 (Suppl 1): 37-44.
29. Gish RG, McCashland T. Hepatitis B in liver transplant recipients. Liver Transpl 2006; 12 (11 Suppl 2): S54-64.
30. Dan YY, Wai CT, Yeoh KG, Lim SG. Prophylactic strategies for hepatitis B patients undergoing liver transplant: a cost-effectiveness analysis. Liver Transpl 2006; 12: 736-746.
31. Jiao ZY, Jiao Z. Prophylaxis of recurrent hepatitis b in Chinese patients after liver transplantation using lamivudine combined with hepatitis B immune globulin according to the titer of antibody to hepatitis B surface antigen. Transplant Proc 2007; 39: 1533-1536.
32. Di Paolo D, Tisone G, Piccolo P, Lenci I, Zazza S, Angelico M. Low-dose hepatitis B immunoglobulin given "on demand" in combination with lamivudine: a highly cost-effective approach to prevent recurrent hepatitis B virus infection in the long-term follow-up after liver transplantation. Transplantation 2004; 77: 1203-1208.
33. Gane EJ, Angus PW, Strasser S, et al. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology 2007; 132: 931-937.