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Review

Changes in the relationship between hepatitis B virus and liver transplantation in the last decades

Hepatit B virus enfeksiyonu nedenli karaciğer nakillerde son yıllardaki değişim

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Abstract

In the last decade, both hepatitis B virus (HBV) prevalence and mortality related to HBV infection have decreased promptly. Worldwide HBV vaccination programs, precautions against HBV transmission and effective anti-viral drugs on market play crucial role for this encouraging result. Besides stopping or reversing the hepato-fibrogenesis induced by HBV infection, fighting against HBV related acute severe hepatitis are also improved recently. HBV associated cirrhosis is still the major cause of LTx, particularly in developing countries,whereas in developed countries, the rate of LTx due to HBV induced cirrhosis has declined over time. With the expanding use of NUCs before LTx, and the use of NUCs and HBIg even after LTx, HBV recurrence after LTx is no longer an important reason for graft loss or patient death. However, this positive impact is not yet reflecting survival, probably because of increasing recipient and donor ages. On the other hand, in the era of Milan criteria, overall hepatocellular carcinoma (HCC) survival has so increased that the number of transplanted HCC cases has almost doubled. However tumor recurrence is still the major cause of death, and treatment is still problematic.

Keywords: hepatitis B virus; acute or chronic infection; cirrhosis; hepatocellular carcinoma; liver transplantation; vaccine; anti-viral drugs

Öz

Hepatit B virus (HBV) enfeksiyonu prevelansındaki ve HBV ilişkili mortalitesindeki azalma son yıllarda oldukça dikkat çekicidir. Dünya çapında yaygın olarak uygulanan HBV aşı programları ve HBV'ye karşı kullanımda olan anti-viral ilaçların etkinliği bu başarıda başat rol oynamaktadır. HBV ile mücadelede, sadece HBV'ye bağlı karaciğer fibrozunun ilerlemesi veya geriye döndürülmesi değil, aynı zamanda HBV ilişkili şiddetli akut hepatit tablosunun tedavisinde güzel sonuçlar alınmaktadır. Gelişmekte olan ülkelerde HBV ilişkili siroz karaciğer nakli konusunda halen esas sebep iken, gelişmiş ülkelerde zaman içinde HBV nedenli karaciğer nakil sıklıkları ciddi oranda düşüş göstermiştir. Anti-viral ilaçların karaciğer nakli öncesi etkin kullanımı, HBIg tedavisinin nakil sonrasında yaygın olarak kullanımı sayesinde karaciğer nakli sonrası HBV nüksü, mortalite ve greft kaybı konusunda eskisi kadar sorun olmaktan çıkmıştır. Bu başarının nakil sonrası sürviler üzerine bariz bir yansıması henüz olmamıştır. Buradaki esas sebep ise, alıcı ve verici yaşının son yıllarda önemli oranda artış göstermesi olarak gösterilmektedir. Ekolarak, Milan kriterlerinin yaygın olarak klinik pratiğe girmesiyle karaciğer nakli yapılan hepatosellüler kanser (HCC) hasta sayısı da neredeyse ikiye katlamıştır. Ancak, HCC rekürrensi, nakil sonrası en önemli ölüm nedeni olarak devam etmektedir.

Anahtar Kelimeler: hepatit B virus; akut ve kronik HBV enfeksiyonu; siroz; hepatosellüler kanser; karaciğer nakli; aşı; anti-viral ilaçlar

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Introduction

What has changed in overall HBV epidemiology in the last decade?

Hepatitis B virus (HBV) is the smallest DNA virus infecting human beings.It is estimated that almost 2 billion people have been exposed to the virus and that nearly 350 million people worldwide are chronically infected[1, 2]. The routes of transmission vary from one geographic area to another (mainly vertical transmission among the poor, mostly horizontal transmission in intermediate economic populations, andsexual or percutaneous route in wealthy populations) [3, 4]. The route of transmission and the prevalence of HBV may also vary according to the availability of health resources in different countries [5]. It is also important to obtain exact data on HBV epidemiology in order to organize health plans in each country. Routine neonatal vaccination programs against HBV have become important health precautions, particularly in undeveloped countries. In countries where sanitation is poor, HBV is endemic and the most frequent route of HBV transmission is vertical. On the other hand, vaccination against HBV for the population at risk seems to be feasible in countries where HBV is rare [3, 4]. Indeed, routine vaccination against HBV for neonates and for people at risk is the main program accepted by many countries.

In recent years, some encouraging data related to routine vaccination against HBV has been reported. Declining HBV prevalence is evidencedbya reduction in acute HBV infection all over the world [6-8]. Studies investigating HBV seroprevalence in some specific groups (e.g. blood donors, pregnant women, soldiers and immigrants) showed that even though HBV is still epidemic in some parts of the world, the overall prevalence of HBV is steadily declining[1, 8, 9]. Guidelines recommend routine neonatal vaccination against HBV, givingimmunoglobulins against HBV (HBIG) to neonates of HBsAg positive mothers, and starting anti-viral medication inHBsAg positive mothers in the third trimester to reduce HBV DNA viral load [10, 11]. Anti-viral medication with lamivudin or tenofovir (both are class B in use during pregnancy) in the third trimester is suggested for a HBV viral load greater than 106 copies/mL, and this was shown to reduce the vertical transmission rate from 10% to 0% [12]. However, the main route of HBV transmission in wealthy countries is sexual contact or intravenous drug abuse under non-sterile conditions. After the emergence of the human immune deficiency virus (HIV) in developed countries, HBV related problems appeared with more serious disorders due to the same route of transmission of these two viruses [13]. Thus, health societiesinwealthy countries have sped up their work on protection from HBV and HIV co- or separatetransmission, and have tried to solve some serious conditions associated with the presence of HBV and HIV. HBV and HIV share the same transmission route from mother to neonates. Cesarean section is not helpful in preventing transmission from HBV positive mothers, but is for HIV positive cases.

In conclusion, with routine precautions against HBV applied in both developed and developing countries, HBV prevalence has declined all over the world in the last ten years.

Trends in the management of acute HBV infection

Spontaneous clearance of HBV after acute infection appears in only 10% of neonates [14]. Thus, protective measures for neonates from HBV transmission when born from HBV infected mothers are the most important part of the fight against HBV (Figure 1). On the other hand, acute HBV infection, diagnosed by the presence of HBsAg and IgM anti-HBc, resolves spontaneously in 95-99% of adult patients [15-18]. In this case, routine anti-viral treatment of acute HBV infection in adults is not feasible. However, the need for liver transplantation is estimated to be 1% [19]. The mortality rate is high in adult patients presenting with acute liver failure (ALF), characterized by the presence of rapid deterioration of transaminases, hepatic encephalopathy, and coagulopathy.

In case series studies with HBV induced ALF patients, survival rates varied between15.3% and 77.7%.If all of the published cases are taken into account, the mean survival rate without lamivudin therapy is nearly 45% [15, 20, 21]. In the era of liver transplantation (LTx), survival rates have increased to greater than 70% [22, 23]. Even though Kumar et al. determined that lamivudin is ineffective in preventing death, and Dao et al claimed that spontaneous survival was similar in both treated and untreated groups, the LTx free survival rates with NUCs therapy were shown to increase to 70- 100% [20, 21, 24-29] (Figure 2). Investigators concluded that initiation of lamivudin therapy may have been too late to rescue those patients presenting with a systemic inflammatory response (SIRS) [28]. The drawback of lactic acidosis risk under entecavir therapy, which was pointed out in HBV related cirrhosis patients, was not seen in ALF patients [20, 30].

Besides acute HBV infection, hepatic failure related to HBV reactivation with chronic HBV infection may lead to 30- 70% mortality [31]. Adding oral antiviral drugs in these patients has additional beneficial effects on survival [31, 32]. However, the mortality rate does not decrease to under 90% among those with >30 MELD scores, even with oral anti-viral drugs; in contrast

mortality rates declined to nearly 15% with <20 MELD scores [31]. Probably entecavir is not superior to lamivudine in treating acute severe reactivation of HBV infection; moreover, some reports revealed higher mortality rates in short term follow-up under entecavir therapy compared with lamivudin[32-34].

ALF accounted for 7% of all LTx in Europe from 1999- 2009, similar to the 8% for 1988- 2009, the same as in the US [35, 36]. And the number of LTx for HBV induced ALF among all ALF related LTx in Europe decreased from 17.9% to 13.2% in the periodsfrom 1988- 2003 and 2004- 2009, respectively.

Most Western countries have been able to succeed in finding deceased donors, in contrast to Eastern countries[37, 38]. After the first performed living donor LTx in Asia at the end of the 1990s, living donor LTx became the main source of liver for ALF related LTx in some countries, e.g. 62.5% in Turkey, 78.6-90.9% in Korea, 97.2% in Japan, and 80% in Hong Kong [36, 39-42]. The rate of ALF patients undergoing deceased LTx in Western countries was reported as 21- 93%; 0.1% living LTx were performed for the etiology of severe ALF before 1993, whereas it was 1.9% from 2004- 2009 overall in Europe [43]. In contrast, deceased LTx remains under 10% in most Asian countries [39, 41, 42,44]. Thus, the waiting list mortality has reached 60%, and therefore having a potential living donor has become a good positive predictor for ALF patients in Asian countries [39]. Investigators also showed that the number of living donor LTx peaked in the US in 2001, and started to decrease over the subsequent years [45-47]. The survival for deceased LTx is similar to living LTx in adults (63% vs 64% 5 year graft survival, respectively) [35].

In conclusion, probably due to the increase of preventive precautions and the marketing of effective anti-viral medications against HBV, the overall number and the necessity of LTx in HBV related severe ALF patients has decreased significantly in the last decade. We should also keep in mind that living LTx is a highly effective alternative to deceased LTx, particularly in countries in which the source of deceased organs is limited.

Trends in the management of chronic HBV infection and cirrhosis

The natural course of chronic HBV ends with cirrhosis or hepatocellular carcinoma (HCC) in almost 20% of the patients without any specific treatment. Each year, almost 600,000 patients with chronic HBV infection are estimated to die due to the complications of the disease [48]. Progression of HCC from chronic HBV infection usually occurs after two to three decades of disease, and approximately 80% of HCC develop cirrhosis [49]. The economic burden of chronic HBV infection was estimated to be at least $1 billion worldwide and this amount is going to increase [50, 51]. Thus, data showing a nearly 50% decline in the numbers of HBV related cirrhosis on waiting lists for LTx is important [52].

The main goal of physicians should be to prevent the progression from fibrosis to cirrhosis, from compensated to decompensated cirrhosis, from cirrhosis to HCC, and of course to improve the survival rate of chronic HBV patients [48]. Moreover, a reversibility of cirrhosis has also been demonstrated by investigators. By using entecavir or tenofovir, the improvement in necro-inflammation scores was near 90%; at the end of five years oftreatment, 74% of the cirrhotic patients had no more cirrhosis [53, 54]. And lastly, preventing HBV infection recurrence in patients undergoing LTx is a targeted outcome.

Interferon (IFN) therapies (standard or pegylated), shown to be safe in compensated cirrhosis patients, is a choice for chronic HBV treatment in patients with limited indications [55, 56]. However, IFN usage was found to be related toan increased risk of hepatitis flares and some infectious complications in patients with decompensated cirrhosis [57, 58].

Even though recent guidelines recommend choosingnucleos(t)ide analogs (NUC) with a high genetic barrier against viral resistance in both chronic HBV and cirrhosis stages, most of the long term follow-up studies were performed with lamivudin[10, 11]. The clinical improvement related to hepatitis flare, hepatic decompensation and death was more prominent in patients with sustained virologic suppression [58, 59]. Histological improvement, regression of cirrhosis and decrease of fibrosis score were also found under NUCs with the help of follow-up liver biopsies at the end of 3- 5 years of therapy [54, 60-63].

In contrast to interferon, NUCs have also been found to be safe in decompensated cirrhosis [64-66]. It was shown repeatedly that in decompensated HBV patients all of the NUCs resulted in improvement of liver function tests, decreasing Child Pugh and MELD scores, mortality and need forLTx, even in patients already listed for LTx[53, 64, 66, 67]. Yao et al. showed that the LTx rate declined from 73.9% to 34.8% in lamivudin treated vs. non-treated groups, respectively [64] (Figure 2). A reduction in Child Pugh score (≥2 points) was observed in 26- 50% of the treated, decompensated HBV cirrhosis patients [48]. One year mortality or LTx rates appeared to be as low as 4-16% with NUC medications [48]. Due to the reverse effect of virologic resistance to NUCs, the authors suggested a preference forentecavir or tenofovir in decompensated HBV patients [10, 11]. However, reachingafast virologic response with a

combination of entecavir and tenofovir is not feasible in light of current data [48]. Lastly, the risk of lactic acidosis shown in cirrhosis patients with ≥20 MELD scores under entecavir therapy in one study from Germany was not supported by other investigators [30].

Cirrhosis is the most common reason for LTx in Europe [35]. Between 1988 and 2009, 52% of the patients who underwent LTx had cirrhosis, and 10% were chronic HBV patients (the rates revealed only HBV infection; if we add the co-infections with hepatitis C or hepatitis D, it reached 15% among all cirrhosis patients) [35]. The rates were found to be not greatly changed in comparing the periods from 1988-1998 and 1999-2009. However, even though the rate of cirrhosis among LTx indications has not changed in the last 10 years, Burra et al determined a significant change after an analysis of the rate of HBV cirrhosis related LTx before 1995 (1988- 1995), since we know the year of marketing of IFN was 1991, and for lamivudinwas 1998, compared with the data after 2006 (2006- 2010) [68]. Among all LTx indications, HBV cirrhosis declined from 24.4% in the years between 1988 and 1995 to 16.3% between 2006 and 2010. To separate the time period as done by Burra et al. seems to be more appropriatefor defining the impact of anti-viral medications against HBV, and also for determining trends related to HBV cirrhosis in the last decade [68].

The problem in HBV related LTx is the recurrence of HBV infection after LTx leading to a decline in survival of both the graft and the patient [68, 69]. Before effective prophylaxis, the recurrence rates of HBV after LTx was greater than 80%. It declined immediately after the introduction of routine use of hepatitis B immunoglobulin (HBIg) to less than 30%, and after the introduction of the combination of HBIg and NUCs, it declined to nearly 3% [5, 70-72].On the other hand, the authors claimed that entecavir and tenofovir, the high genetic barrier drugs against HBV infection, may be superior to lamivudine in terms of post-LTx prophylaxis for HBV. Cholangitas et al. showed that HBV recurrence was 6.1% under lamivudine and HBIg prophylaxis, whereas it declined to 1% with the use of entecavir/ tenofovir and HBIg[73]. Moreover, the results after discontinuation of HBIg in the entecavir/ tenofovir treated group were also similar toHBIg and lamivudine combination therapy. However, it was also shown that HBIg should be a part of HBV prophylaxis, even when entecavir or tenofoviris chosen [73]. The rate of death or graft loss related to HBV recurrence after LTx was 21.5% among all HBV recurrences from 1988-1995, and it dropped to 1.1% in the period from 2006- 2010 [68]. Patient survival after LTx then suddenly increased from 73% to 86% in 1 year, and from 63% to 78% in 5 years in the years 1988- 1995 and 1996- 2000, and the survival rates have had a plateau since then [68]. Investigators claimed that the main reasons for the plateau seen in recent decades were the improvements in prophylaxis against HBV, surgical techniques, immunosuppressive drugs, and post-op care, and the increasing ages of both donors and recipients[68, 74]. Donors over 60 years old increased from 1.8- 5% to 21- 30%, and for recipients from 3.3- 11% to 9.3- 22% in the last 20 years [35, 71,75]. Burro et al determined that both donor and recipient age were related to long and short term survival, whereas Yamashiki et al found recipient age to be similar, however donor age was related only to long term survival [68, 76].

Trends in the management of HBV related HCC

The incidence of HCC, the sixth most common cancer in the world, has increased in the last years, and this increase is estimated to continue in the next two decades [49, 77]. Chronic HBV infection is still the major risk factor for HCC in developing countries, while in contrast, chronic HCV infection and non-alcoholic steatohepatitis (NASH) are the two main risk factors in developed countries [49, 78]. The presence of chronic HBV infection raises the risk of HCC 100 fold compared to the healthy population, however not all of the chronic HBV or cirrhotic patients develop HCC. Persistence of HBeAg, and high HBV viral load, older age, male gender, presence of cirrhosis, HCV or HDV co-infection, family history of HCC, alcohol intake, smoking, and aflatoxin exposure are the risk factors for HBV related HCC [79-84].

Unfortunately, only 25% of HCC cases were diagnosed at an early stage for which curable treatment exists, and the 5 year survival is only 3% in symptomatic HCC patients [85]. Therefore, most HCC patients not suitable for surgery and local ablation therapies are candidates for palliative treatment with sorafenib, a multikinase inhibitor which targets the main signaling pathways of HCC, transarterial chemoembolization and radiotherapy appliedwith Yttrium-90 microspheres. Transarterial chemoembolization (TACE) is the only alternative for non-metastatic and non-invasive tumors; sorafenib is for advanced HCC withextrahepatic tumor spread and/ or vascular invasion. Both agents were proven to increase survival [86]. Surgical resection, liver transplantation and local ablative therapies (e.g. radiofrequency ablation (RFI) and percutaneous ethanol injection (PEI)) are the most frequently used curative treatments for HCC [87]. Surgical resection in selected cases has the best survival rates in HCC patients compared to other therapies (70-90% 5 year survival rate). Lack of cirrhosis or Child A cirrhosis, but without any findings

of portal hypertension and with a normal range of bilirubin in the serum, are favorable criteria for resection of HCC.

Probably the most cost-effective way to fight against the problem of HCC is in the prevention of HCC [88]. Apart from the other specific etiologies, in order to prevent HBV related HCC, we have two main options: first, nation-wide vaccination programs against HBV have already proven to be effective in reducing not only overall HBV prevalence, but also HBV related HCC (an almost 70% decline was reported from Taiwan) [88-90]. Second, anti-viral medications lead to a decrease in HBV viral load in the serum or increase the chance of seroconversion of HBsAg and HBeAg, which were all shown to be risk factors for HBV related HCC [88]. Studies revealed that among chronic HBV patients who were treated with IFN, and who reached a sustained virologic response and/ or biochemical improvement,there was a risk reduction for HCC [91, 92]. It was also pointed out that chronic HBV patients with maintained virologic suppression under NUCs showed a lower incidence of HCC compared with patients with no virologic response [93]. Not only lamivudine, but also tenofovir and entecavir may also decrease the rate of HCC, particularly in non-cirrhotic patients, however the rates are still higher than those in inactive healthy carriers [79, 94-96]. The exact impact of anti-viral drugs on HCC progression among cirrhotic patients is still controversial [96-98]. On the other hand, NUCs have beneficial effects on long-term survival even when used after curative treatment of HCC [99-101]. It is not widely accepted, but IFN may also be an alternative option to treat HBV patients after curative resection [102].

In the eighties, among all of the LTx, 12% were related to HCC; similarly, thiswas nearly 14.4% in the 2000s [35]. However, it was reported that the rate of HCC related LTx represents almost 40% of all transplanted patients [80]. Han et al found that almost half of the HBV patients undergoing LTx had HCC at the time of LTx[103]. Moreover, one fourth of all HCC patients received the diagnosis while on the waiting list or after explanting the liver [103]. With LTx, the etiology of HBV related decompensated cirrhosis dropped from 84.2% to 70.4%, whereas HBV related HCC increased from 15.8% to 29.6% in the periods of 1988- 1995 and 2006- 2010, respectively [68].

Due to the shortage of donors, HCC patients were given 22 points over the MELD score to avoid the chance of dropping off the transplant list during the waiting time. It was estimated that a one year stay on the waiting list resulted in 40% of HCC patients losingLTx criteria [77, 86, 104]. Thus, as a bridge therapy to LTx, RF or TACE is performed on the tumor in order to prevent the progression of tumor size beyond the Milan criteria during the waiting time. Moreover, HCC patients responding to TACE therapy followed by LTx had a 90% 5 year survival compared with 35% who failed to respond to TACE therapy before LTx[105]. However, poor hepatic reserve appears to be a risk factor for TACE related mortality [106].

The 1 and 3 year survival rates of patients with HCC undergoing LTx were shown to increase from 65% to 89% and from 48% to 78% from 1988- 1995 to 2006- 2010, respectively [68, 80]. Even though there is a great improvement in the survival of HCC, the survival rates of HBV associated HCC are lower than those for HBV associated decompensated cirrhosis (84%, 68% vs. 83%, 78% in HCC vs. cirrhosis cases for 1 and 5 year patient survival, respectively) [68]. Nevertheless, some research studies have claimed that the overall survival of HCC related and HCC unrelated LTx are similar [80]. HBV recurrence is the major cause of death or graft loss after LTx, followed by tumor recurrence (26.3% and 20.7%, respectively) [68, 103]. It is important to note that none of the HCC diagnosed patients with explanted liver experienced HCC recurrence [103].

Even though HBV recurrence rates dropped from 18.7% to 3.6% from the years 1988- 1995 to 2006- 2010 (p value <0.001), the recurrence rates of HBV related HCC did not differ over time (30.9% and 36.1% for 1988- 1995 and 2006- 2010, p value 0.63) [68].

Tumor staging, tumor grading, moderate or poorly differentiated tumors, and the presence of vascular invasion, higher immunosuppressive levels or choice of mTOR- free inhibitors consisting of immunosuppressive regimes are the main risk factors of post LTx HCC recurrence (Table) [77]. Serum alpha-fetoprotein at the time of LTx may be a good predictor for HCC recurrence [103]. In the first years after LTx, the cancer incidence almost doubled and this was mainly attributed to the use of immunosuppressive drugs[107]. Even though the efficacy of treatment of recurrent HCC after LTx is controversial, all of the treatment options for advanced cirrhosis are on the table [77, 80,108]. Even LTx seems to be the most feasible therapy for recurrent HCC after LTx, though surgery alone or accompanied by radiofrequency ablation may be good options[108]. Patients treated with TAKE priortoLTx or suffering from arterial stenosis following LTx, may not be eligible for TAKE for recurrent HCC after LTx[108].

Conclusion

With routine precautions against HBV, both HBV prevalence and the rate of mortality, and the necessity of LTx related to HBV induced ALF have declined in the last decade. Early

initiation of NUCs, at least before the appearance of SIRS, in ALF cases seems to be important for preventing death. HBV associated cirrhosis is still the major cause of LTx, particularly in developing countries,whereas in developed countries, the rate of LTx due to HBV induced cirrhosis has declined over time. With the expanding use of NUCs before LTx, and the use of NUCs and HBIg even after LTx, HBV recurrence after LTx is no longer an important reason for graft loss or patient death. However, this positive impact is not yet reflectedin survival, probably because of increasing recipient and donor ages. On the other hand, in the era of Milan criteria, overall HCC survival has so increased that the number of transplanted HCC cases has almost doubled. However tumor recurrence is still the major cause of death, and treatment is still problematic.

Table 1. The risk factors of HCC recurrence following LTx-which performed fullfilling the Milan or University of San Fransisco (UCSF) criteria.

High Risk	Low Risk
Moderate or poor differentiation of tumor	mTOR inhibitör containing immuno-suppressive regime following LTx
Micro-vascular invasion of tumor	HCC diagnosed in the explanted liver
High serum AFP level at the time of LTx	Good response to pre-LT local ablative treatments
High immuno-suppressive level in serum following LTx	

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References

1. A review of chronic hepatitis B epidemiology and management issues in selected countries in the Middle East. J Viral Hepat 2012. 19(1): p. 9-22.
2. Schweitzer, A., et al., Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet, 2015.
3. Locarnini, S., et al., Strategies to control hepatitis B: Public policy, epidemiology, vaccine and drugs. J Hepatol, 2015. 62(1 Suppl): p. S76-86.
4. Shepard, C.W., et al., Hepatitis B virus infection: epidemiology and vaccination. Epidemiol Rev, 2006. 28: p. 112-25.
5. Degertekin, H. and G. Gunes, Horizontal transmission of hepatitis B virus in Turkey. Public Health, 2008. 122(12): p. 1315-7.
6. Goyal, A. and J.M. Murray, The impact of vaccination and antiviral therapy on hepatitis B and hepatitis D epidemiology. PLoS One, 2014. 9(10): p. e110143.
7. Liang, X., et al., Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. Vaccine, 2009. 27(47): p. 6550-7.
8. Rantala, M. and M.J. van de Laar, Surveillance and epidemiology of hepatitis B and C in Europe - a review. Euro Surveill, 2008. 13(21).
9. Altinbas, S., M. Erdogan, and N. Danisman, The seroprevalences of HBs Ag and anti-HCV in pregnant women in Ankara. Arch Gynecol Obstet, 2010. 281(2): p. 371.
10. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol, 2012. 57(1): p. 167-85.
11. Lok, A.S. and B.J. McMahon, Chronic hepatitis B: update 2009. Hepatology, 2009. 50(3): p. 661-2.
12. Han, G.R., et al., A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. J Hepatol, 2011. 55(6): p. 1215-21.
13. Nunez, M., Routine hepatitis B virus DNA testing in human immunodeficiency virus-infected patients with positive hepatitis B core antibody but negative hepatitis B surface antigen is not justified by current evidence. Hepatology, 2010. 51(3): p. 1087-8.
14. McMahon, B.J., et al., Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis, 1985. 151(4): p. 599-603.
15. Tillmann, H.L., K. Zachou, and G.N. Dalekos, Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? Liver Int, 2012. 32(4): p. 544-53.
16. Kuruuzum, Z., et al., Rate of chronicity and time of disappearance of HBsAg following acute hepatitis B. Hepatogastroenterology, 2009. 56(90): p. 466-9.
17. Zhang, H.W., et al., Risk factors for acute hepatitis B and its progression to chronic hepatitis in Shanghai, China. Gut, 2008. 57(12): p. 1713-20.
18. Altinbas, A., et al., Spontaneous HBsAg seroconversion after severe flare of chronic hepatitis B infection. Ann Hepatol, 2010. 9(2): p. 194-7.
19. Cornberg, M., et al., Prophylaxis, diagnosis and therapy of hepatitis B virus (HBV) infection: the German guidelines for the management of HBV infection. Z Gastroenterol, 2007. 45(12): p. 1281-328.
20. Tillmann, H.L., et al., Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat, 2006. 13(4): p. 256-63.
21. Miyake, Y., et al., Lamivudine treatment improves the prognosis of fulminant hepatitis B. Intern Med, 2008. 47(14): p. 1293-9.

22. Hadem, J., et al., Etiologies and outcomes of acute liver failure in Germany. Clin Gastroenterol Hepatol, 2012. 10(6): p. 664-9 e2.
23. Fujiwara, K., et al., Fulminant hepatitis and late onset hepatic failure in Japan. Hepatol Res, 2008. 38(7): p. 646-57.
24. Kumar, M., et al., A randomized controlled trial of lamivudine to treat acute hepatitis B. Hepatology, 2007. 45(1): p. 97-101.
25. Torii, N., et al., Effectiveness and long-term outcome of lamivudine therapy for acute hepatitis B. Hepatol Res, 2002. 24(1): p. 34.
26. Kondili, L.A., H. Osman, and D. Mutimer, The use of lamivudine for patients with acute hepatitis B (a series of cases). J Viral Hepat, 2004. 11(5): p. 427-31.
27. Yu, J.W., et al., Lamivudine treatment is associated with improved survival in fulminant hepatitis B. Liver Int, 2011. 31(4): p. 499-506.
28. Yu, J.W., et al., The study of efficacy of lamivudine in patients with severe acute hepatitis B. Dig Dis Sci, 2010. 55(3): p. 775-83.
29. Dao, D.Y., et al., Use of nucleoside (tide) analogues in patients with hepatitis B-related acute liver failure. Dig Dis Sci, 2012. 57(5): p. 1349-57.
30. Lange, C.M., et al., Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology, 2009. 50(6): p. 2001-6.
31. Yuen, M.F., Anti-viral therapy in hepatitis B virus reactivation with acute-on-chronic liver failure. Hepatol Int, 2015. 9(3): p. 373-7.
32. Wong, V.W., et al., Entecavir treatment in patients with severe acute exacerbation of chronic hepatitis B. J Hepatol, 2011. 54(2): p. 236-42.
33. Chen, C.H., et al., Entecavir vs. lamivudine in chronic hepatitis B patients with severe acute exacerbation and hepatic decompensation. J Hepatol, 2014. 60(6): p. 1127-34.
34. Tsai, W.L., et al., Early entecavir treatment for chronic hepatitis B with severe acute exacerbation. Antimicrob Agents Chemother, 2014. 58(4): p. 1918-21.
35. Adam, R., et al., Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol, 2012. 57(3): p. 675-88.
36. Campsen, J., et al., Outcomes of living donor liver transplantation for acute liver failure: the adult-to-adult living donor liver transplantation cohort study. Liver Transpl, 2008. 14(9): p. 1273-80.
37. Ostapowicz, G., et al., Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med, 2002. 137(12): p. 947-54.
38. de Villa, V.H., C.M. Lo, and C.L. Chen, Ethics and rationale of living-donor liver transplantation in Asia. Transplantation, 2003. 75(3 Suppl): p. S2-5.
39. Liu, C.L., et al., Right-lobe live donor liver transplantation improves survival of patients with acute liver failure. Br J Surg, 2002. 89(3): p. 317-22.
40. Kayaalp, C., V. Ersan, and S. Yilmaz, Acute liver failure in Turkey: a systematic review. Turk J Gastroenterol, 2014. 25(1): p. 35-40.
41. Matsui, Y., et al., Living donor liver transplantation for fulminant hepatic failure. Hepatol Res, 2008. 38(10): p. 987-96.
42. Park, S.J., et al., Emergency adult-to-adult living-donor liver transplantation for acute liver failure in a hepatitis B virus endemic area. Hepatology, 2010. 51(3): p. 903-11.
43. Germani, G., et al., Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol, 2012. 57(2): p. 288-96.
44. Ikegami, T., et al., Living donor liver transplantation for acute liver failure: a 10-year experience in a single center. J Am Coll Surg, 2008. 206(3): p. 412-8.
45. Qiu, J., M. Ozawa, and P.I. Terasaki, Liver transplantation in the United States. Clin Transpl, 2005: p. 17-28.
46. Vagefi, P.A., et al., Use of living donor liver transplantation varies with the availability of deceased donor liver transplantation. Liver Transpl, 2012. 18(2): p. 160-5.
47. Carlisle, E.M. and G. Testa, Adult to adult living related liver transplantation: where do we currently stand? World J Gastroenterol, 2012. 18(46): p. 6729-36.
48. Mutimer, D.J. and A. Lok, Management of HBV- and HCV-induced end stage liver disease. Gut, 2012. 61 Suppl 1: p. i59-67.
49. Ertle, J., et al., Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. Int J Cancer, 2011. 128(10): p. 2436-43.
50. Altinbas, A., et al., Retrospective analysis of total direct medical costs associated with hepatitis B patients with oral antiviral versus pegylated interferon therapy in Turkey. J Viral Hepat, 2014. 21(11): p. 794-801.
51. Kim, W.R., Epidemiology of hepatitis B in the United States. Hepatology, 2009. 49(5 Suppl): p. S28-34.
52. Bernal, W., et al., Outcome after wait-listing for emergency liver transplantation in acute liver failure: a single centre experience. J Hepatol, 2009. 50(2): p. 306-13.
53. Liaw, Y.F., et al., Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology, 2011. 54(1): p. 91-100.
54. Marcellin, P., et al., Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet, 2013. 381(9865): p. 468-75.

55. Lau, G.K., et al., Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med, 2005. 352(26): p. 2682-95.
56. Marcellin, P., et al., Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med, 2004. 351(12): p. 1206-17.
57. Hoofnagle, J.H., et al., Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. Gastroenterology, 1993. 104(4): p. 1116-21.
58. Perrillo, R., et al., Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. Gastroenterology, 1995. 109(3): p. 908-16.
59. Lok, A.S., et al., Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology, 2003. 125(6): p. 1714-22.
60. Dienstag, J.L., et al., Histological outcome during long-term lamivudine therapy. Gastroenterology, 2003. 124(1): p. 105-17.
61. Hadziyannis, S.J., et al., Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology, 2006. 131(6): p. 1743-51.
62. Chang, T.T., et al., Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology, 2010. 52(3): p. 886-93.
63. Heathcote, E.J., et al., Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. Gastroenterology, 2011. 140(1): p. 132-43.
64. Yao, F.Y., et al., Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort. Hepatology, 2001. 34(2): p. 411-6.
65. Koklu, S., et al., Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol, 2013. 11(1): p. 88-94.
66. Liaw, Y.F., et al., Tenofovir disoproxil fumarate (TDF), emtricitabine/TDF, and entecavir in patients with decompensated chronic hepatitis B liver disease. Hepatology, 2011. 53(1): p. 62-72.
67. Shim, J.H., et al., Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol, 2010. 52(2): p. 176-82.
68. Burra, P., et al., Liver transplantation for HBV-related cirrhosis in Europe: an ELTR study on evolution and outcomes. J Hepatol, 2013. 58(2): p. 287-96.
69. Mascarenhas, R. and A. Gurakar, Recent advances in liver transplantation for the practicing gastroenterologist. Gastroenterol Hepatol (N Y), 2009. 5(6): p. 443-50.
70. Gane, E.J., et al., Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology, 2007. 132(3): p. 931-7.
71. Gane, E., Posttransplant prophylaxis strategies for hepatitis B. Am J Transplant, 2010. 10(8): p. 1721-2.
72. Perrillo, R., et al., Entecavir and hepatitis B immune globulin in patients undergoing liver transplantation for chronic hepatitis B. Liver Transpl, 2013. 19(8): p. 887-95.
73. Cholongitas, E. and G.V. Papatheodoridis, High genetic barrier nucleos(t)ide analogue(s) for prophylaxis from hepatitis B virus recurrence after liver transplantation: a systematic review. Am J Transplant, 2013. 13(2): p. 353-62.
74. Burroughs, A.K., et al., 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet, 2006. 367(9506): p. 225-32.
75. Karam, V., et al., Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. Transplantation, 2003. 75(12): p. 2167-73.
76. Yamashiki, N., et al., Outcomes after living donor liver transplantation for acute liver failure in Japan: results of a nationwide survey. Liver Transpl, 2012. 18(9): p. 1069-77.
77. Clavien, P.A., et al., Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol, 2012. 13(1): p. e11-22.
78. Yim, S.Y., et al., The management and prognosis of patients with hepatocellular carcinoma: what has changed in 20 years? Liver Int, 2015.
79. Kim, W.R., et al., Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer, 2015. 121(20): p. 3631-8.
80. Mancuso, A. and G. Perricone, Hepatocellular Carcinoma and Liver Transplantation: State of the Art. J Clin Transl Hepatol, 2014. 2(3): p. 176-81.
81. Kwon, H. and A.S. Lok, Does antiviral therapy prevent hepatocellular carcinoma? Antivir Ther, 2011. 16(6): p. 787-95.
82. Yang, H.I., et al., Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med, 2002. 347(3): p. 168-74.
83. Lee, M.H., et al., Prediction models of long-term cirrhosis and hepatocellular carcinoma risk in chronic hepatitis B patients: risk scores integrating host and virus profiles. Hepatology, 2013. 58(2): p. 546-54.

84. Loomba, R., et al., Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol, 2013. 11(12): p. 1636-45 e1-3.
85. de Lope, C.R., et al., Management of HCC. J Hepatol, 2012. 56 Suppl 1: p. S75-87.
86. Forner, A., J.M. Llovet, and J. Bruix, Hepatocellular carcinoma. Lancet, 2012. 379(9822): p. 1245-55.
87. Chen, Q.W., et al., Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol, 2015.
88. Lok, A.S., Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma? J Gastroenterol Hepatol, 2011. 26(2): p. 221-7.
89. Leroy, V. and T. Asselah, Universal hepatitis B vaccination: the only way to eliminate hepatocellular carcinoma? J Hepatol, 2015.
90. Chang, M.H., et al., Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. J Natl Cancer Inst, 2009. 101(19): p. 1348-55.
91. Yang, Y.F., et al., Interferon therapy in chronic hepatitis B reduces progression to cirrhosis and hepatocellular carcinoma: a meta-analysis. J Viral Hepat, 2009. 16(4): p. 265-71.
92. Lin, S.M., et al., Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol, 2007. 46(1): p. 45-52.
93. Sung, J.J., et al., Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther, 2008. 28(9): p. 1067-77.
94. Idilman, R., et al., Long-term entecavir or tenofovir disoproxil fumarate therapy in treatment-naive chronic hepatitis B patients in the real-world setting. J Viral Hepat, 2015. 22(5): p. 504-10.
95. Hosaka, T., et al., Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology, 2013. 58(1): p. 98-107.
96. Cho, J.Y., et al., Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. Gut, 2014. 63(12): p. 1943-50.
97. Kim, S.S., et al., Effect of virological response to entecavir on the development of hepatocellular carcinoma in hepatitis B viral cirrhotic patients: comparison between compensated and decompensated cirrhosis. Am J Gastroenterol, 2014. 109(8): p. 1223-33.
98. Kurokawa, M., et al., Long-term effect of lamivudine treatment on the incidence of hepatocellular carcinoma in patients with hepatitis B virus infection. J Gastroenterol, 2012. 47(5): p. 577-85.
99. Liu, G.M., et al., Adjuvant antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after curative treatment: A systematic review and meta-analysis. Hepatol Res, 2015.
100. Sun, P., et al., Nucleot(s)ide analogues for hepatitis B virus-related hepatocellular carcinoma after curative treatment: a systematic review and meta-analysis. PLoS One, 2014. 9(7): p. e102761.
101. An, H.J., et al., Sustained low hepatitis B viral load predicts good outcome after curative resection in patients with hepatocellular carcinoma. J Gastroenterol Hepatol, 2010. 25(12): p. 1876-82.
102. Xu, J., et al., Effect of adjuvant interferon therapy on hepatitis b/c virus-related hepatocellular carcinoma after curative therapy - meta-analysis. Adv Clin Exp Med, 2015. 24(2): p. 331-40.
103. Han, S.H., et al., Clinical outcomes of liver transplantation for HBV-related hepatocellular carcinoma: data from the NIH HBV OLT study. Clin Transplant, 2011. 25(2): p. E152-62.
104. Poon, R.T., et al., Difference in tumor invasiveness in cirrhotic patients with hepatocellular carcinoma fulfilling the Milan criteria treated by resection and transplantation: impact on long-term survival. Ann Surg, 2007. 245(1): p. 51-8.
105. Otto, G., et al., Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. Liver Transpl, 2006. 12(8): p. 1260-7.
106. Garwood, E.R., et al., Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and synthetic hepatic dysfunction. Liver Transpl, 2013. 19(2): p. 164-73.
107. Collett, D., et al., Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant, 2010. 10(8): p. 1889-96.
108. Welker, M.W., et al., Recurrent hepatocellular carcinoma after liver transplantation - an emerging clinical challenge. Transpl Int, 2013. 26(2): p. 109-18.