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Management of Recurrent HCV and HBV Infections after Liver Transplantation

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1. Introduction

1.1 Hepatitis C

Sequels of chronic HCV infection such as end-stage liver cirrhosis and hepatocellular carcinoma (HCC) are the leading indications for liver transplantation (LT) in Europe and in the United States. According to the United Network for Organ Sharing (UNOS) database the proportion of transplants performed due to the decompensated cirrhosis secondary to hepatitis C infection slightly declined in the last few years from 34% in 2002 to 29% in 2007, but at the same time the increased number of candidates for LT with HCC was noted [*www.unos.org*]. This trend will be observed until year 2030. Generally, one third of LTs worldwide is performed in HCV-positive patients. Given that recurrence of HCV infection is almost universal and the natural history of HCV hepatitis in allograft is more rapid than in the immunocompetent patient, liver failure secondary to recurrent HCV infection has a significant impact on post-transplant survival and will soon become the most common cause of liver retransplantation. Organ shortage and increasing evidence of poorer outcome in retransplanted patients makes this procedure a controversial issue, not accepted in many centers. Therefore efforts of transplant physicians to manage recurrent HCV infection in order to optimize outcomes and to slow down the progression of HCV-related liver disease are the greatest challenge. Most widely explored areas of interest include timing and schedule of antiviral treatment, immunosuppression regimens and matching in donor and recipient-related factors influencing outcomes.

1.2 Natural history of HCV recurrence

Natural history of HCV infection in the immunocompetent host since the acute HCV infection until the end-stage liver cirrhosis and eventually hepatocellular carcinoma covers approximately 30 years of progressive fibrosis developing in liver parenchyma (Hu & Tong, 1999). After liver transplantation the chronic HCV disease, albeit not fully understood and highly variable in different recipients, seems to be far more aggressive and significantly impacts the overall poorer post-LT survival in comparison with HCV-negative patients. Liver transplantation performed in viremic recipients results in rapid allograft reinfection in nearly 100% of cases. In the anhepatic phase HCV viremia dramatically declines to the very low or even undetectable levels, but within a few days after transplantation increases to the

load 10 to 20-fold higher than pretransplant ones. That gives too narrow window of opportunity for any potential intervention such as passive immunization or preemptive antiviral treatment to make it effective. The higher the pretransplant viral load the bigger the chance for faster and more severe HCV reinfection. Immunosuppressive treatment is responsible for the weaker immune control of HCV infection and a distinct natural history in post-transplant setting. Typically viremia peaks 1–3 months after LT, clinically apparent acute hepatitis develops after a median time of 4 to 6 months in more than 60% of patients and almost 100% of recipients show histological evidence of chronic C hepatitis between 1 to 4 years after LT (Gane et al., 1996). Protocol liver biopsies performed every year after LT show progression of fibrosis in the reinfected liver rating from 0.3 to 0.6 points per year (Pelletier et al., 2000) whereas in the immunocompetent hosts it scores 0.1 to 0.2 points per year (Poynard et al., 1997). According to the accessible database the mean time between acute HCV reinfection and the decompensation of liver disease, presented as variceal bleeding, refractory ascites or encephalopathy, is approximately 9.5 years (Berenguer et al., 2000). Once decompensation of liver function is established, one year survival probability decreases dramatically below 50% and 3-year survival does not exceed 10% of recipients (Berenguer et al, 2000; Roche & Samuel, 2007). This is significantly inferior than survival in the immunocompetent patients. It is estimated that 20 to 30% of HCV-positive recipients will progress to the liver cirrhosis within five years after LT. A small proportion of patients (appr. 3%) will present with a particularly severe form of HCV recurrence known as fibrosing cholestatic hepatitis with a fatal outcome (or retransplantation) in the first year post-LT (Gane, 2008). According to the UNOS database 3-year survival after LT in HCV-positive recipients is inferior to the survival rate in the other etiologies (78% vs. 82%) and 5-year survival is also lower (56.7% vs. 65.6%, $p < 0.05$) (Forman et al., 2002). All the above mentioned data explain why liver disease secondary to HCV infection is currently one of the worst and most challenging indications for LT.

1.3 Factors influencing severity of recurrent HCV infection

To date a number of factors has been described as having potential influence on the natural history of post-transplant recurrent C hepatitis. This debate has a practical aspect since a few of them are modifiable by the transplant team, for example optimization of immunosuppression therapy, anti-HCV therapy prior to LT, aggressive and efficient treatment of post-transplant diabetes or the appropriate donor selection. These factors are routinely divided into four groups: donor, recipient, virus and transplant procedure related (Table 1).

In the era of organ shortage careful donor-recipient matching is not always possible and poses some controversy, but there is a growing evidence that donor related variables such as younger age (< 40 years), male sex and lack or minimal steatosis in the liver (in < 30% of hepatocytes) are associated with a significantly better survival and slower progression of chronic C hepatitis (Aytaman et al., 2010). Factors related to the transplant procedure with a potential influence on hepatitis C progression include prolonged cold ischemia time, treatment of acute rejection episodes within the first months of LT, acute CMV infection post-LT, type of immunosuppressive regimen and type of liver transplantation (deceased-donor vs. living-donor LT). Initially, there was some concern that HCV recurrence was more severe with live donor transplant, but a growing experience did not confirm these findings (Gallegos-Orozco et al., 2009).

Donor factors	<ul style="list-style-type: none"> • older age (> 40 years) • female sex (?) • hepatocyte steatosis > 30% • donation after cardiac death • living donation (?)
Recipient factors	<ul style="list-style-type: none"> • female sex • concomitant HIV infection • diabetes mellitus pre- and post-LT • African American race • higher BMI (?)
Virus-related factors	<ul style="list-style-type: none"> • higher pre-LT viral load • HCV genotype (?) • number of quasispecies
Transplant procedure-related factors	<ul style="list-style-type: none"> • prolonged cold ischemia time • type of CNI (?) • immunosuppressive protocol without AZA and steroids (?) • treatment of ACR • acute CMV infection

Table 1. Predictors of severe HCV recurrence. BMI- body mass index, CNI - calcineurin inhibitor, ACR - acute cellular rejection, LT - liver transplantation, AZA - azathioprine, CMV - cytomegalovirus

Among the baseline viral characteristics some relationship was noted between genotype 1 of the virus and the patient and graft survival, but the predominance of genotype 1 among transplanted patients can be explained by the worse antiviral treatment results before and after transplantation in comparison with other genotypes, therefore negative impact of genotype 1 on the severity of HCV recurrence was not clearly determined. It was already mentioned that high pretransplant viremia, but also persistence of the same HCV variants are responsible for more severe picture of acute HCV reinfection and more progressive course of chronic HCV disease (Berenguer, 2003).

The hottest debate concerns influence of immunosuppressive drugs on the evolution of HCV infection, two issues being discussed the most: how to optimally handle corticosteroids and which calcineurin inhibitor has an advantage in HCV-positive recipients. Some transplant centers favor corticosteroid-sparing regimens whereas in the others low-dose steroid maintenance is preferred over steroids avoidance or early withdrawal. The clear benefit of one of these approaches was not concluded. The most notable influence of corticosteroids on HCV infection is seen in the case of acute cellular rejection (ACR) treatment. It was proved that pulses of methylprednisolone commonly used for such treatment are associated with a transient increase in HCV-RNA concentration of 4- to 100-fold (Gane et al., 1996). While episodes of ACR treated with steroid pulses are associated with decreased mortality in HCV-negative patients, in the group of HCV infected recipients the relative risk of mortality or graft loss increases almost three times ($p=0.04$) and is even higher when ACR is steroid refractory. Therefore, in HCV-positive recipients empiric treatment of presumed rejection episodes without histological confirmation should be avoided to avert unnecessary exposure to corticosteroids. In contrast with convincing

association of steroid pulses with increased severity of HCV recurrence, detrimental effect of low-dose steroids versus no steroids is less obvious and requires further observations. According to the study of Manousou P. et al., lack of steroids in the immunosuppressive protocol was an independent factor affecting fibrosis (Manousou et al., 2009). Some authors suggest that a low maintenance dose of prednisone (usually 5mg daily) has no deleterious effect on HCV infection, but instead, is associated with better LT outcome, while early withdrawal of steroids (3 months beyond LT) can be detrimental and should be avoided. Some other researchers favor complete avoidance of steroids in HCV infected recipients undergoing LT. Maintenance of a low-dose and no steroids options are currently best supported.

Another hot topic is a choice of calcineurin inhibitor (CNI) in HCV-positive recipients. This discussion was initiated by the clinical observation that results of LT for cirrhosis type C in the last two decades of twentieth century did not differ from results of LTs performed for other etiologies, whereas nowadays they are clearly inferior in patients with HCV infection (Forman et al., 2002; Berenguer, 2005). One of the possible explanations was introduction of more potent immunosuppressive drugs such as tacrolimus or mycophenolate mofetil which practically replaced cyclosporine and azathioprine in the immunosuppression protocols used for liver transplant patients. The role of cyclosporine in the post-transplant recurrent C hepatitis is a subject of controversy. This drug is known as having an inhibiting effect on HCV replication *in vitro* (Watashi et al., 2003). It was also used in combination with interferon alpha-2b to treat chronic HCV infection and proved to be significantly more effective than interferon monotherapy (Inoue et al., 2003). For anti-HCV effect some authors combined cyclosporine A with interferon to treat established HCV-related graft disease (Inoue & Yoshida, 2005). Conflicting results regarding effects of CNI on HCV recurrence may be explained by the previous study design (mostly retrospective), small groups of patients, the lack of histological examinations, variety of confounding factors and multitude of immunosuppressive protocols. However, in the prospective randomized trial and in metaanalysis that were aimed to compare influence of tacrolimus and cyclosporine on HCV recurrence, no difference in the outcome was demonstrated (Berenguer et al., 2006a; Berenguer, 2007). It was concluded that the course of recurrent HCV hepatitis is not related to the CNI used after LT. Similar observation was made in HCV-positive patients with the end-stage renal disease subjected for kidney transplantation (Kahraman et al., 2011). The only difference noted by Berenguer et al. was the shorter time between LT and recurrent acute C hepatitis in tacrolimus treated patients (59 days vs. 92 days, $p=0.02$). On the other hand, introduction of tacrolimus improved results of LT (Cholongitas et al., 2011). Used in HCV-negative liver recipients, TAC is associated with fewer rejection episodes and significantly better survival. It cannot be ruled out that this effect is counterbalanced by anti-HCV effect of cyclosporine in HCV-infected recipients, therefore none of CNIs is favored in this specific group of patients.

Another type of immunosuppressive drugs that exert a specific antiviral effect on *Flaviviridae* is a group of antimetabolites such as azathioprine (AZA) and mycophenolate mofetil (MMF). As immunosuppressants they arrest T-cell proliferation by inhibiting inosine monophosphate dehydrogenase and by the same mechanism exert an anti-HCV effect (like ribavirin). AZA is one of the oldest immunosuppressive drugs, commonly used in combination with cyclosporine and steroids, but it was substituted a decade ago by more

potent MMF. However, the role of MMF in HCV-infected liver recipients is controversial. Addition of an effective immunosuppressive drug with antiviral properties to the immunosuppression protocol seemed very attractive. Some authors demonstrated that MMF not only improved allograft function but was also associated with reduction of HCV viral load and delayed histological recurrence. In a study of Fasola et al., it was shown that high doses of MMF efficiently reduced HCV-RNA concentration and liver fibrosis one year post-transplant, but after 2 years the extent of fibrosis did not differ along all studied groups (Fasola et al., 2002). Other groups demonstrated no superiority of MMF over AZA in decreasing HCV viremia, histological slow down and better survival. Moreover, it was reported that AZA decreased replication of flaviviruses 10 times more effectively than MMF and was as potent as ribavirin in HCV inhibition in a replicon model (Stangl et al., 2004). Lately, use of AZA in liver transplant recipient, chronically infected with HCV, was reevaluated. It was concluded that MMF shows little, if any, clinical benefit in LT versus AZA and that HCV recurrence was less severe in patients treated with AZA in contrast to MMF (Germani et al., 2009). Further randomized controlled trials are warranted to solve this issue.

mTOR inhibitors such as sirolimus and everolimus are not licensed in liver transplantation. Sirolimus, however, due to its antifibrotic, antiproliferative and renal sparing properties has been recently used by some transplant teams with encouraging results (Harper et al., 2011). Different mode of action by inhibiting proangiogenic factors (i.e. VEGF, vascular endothelial growth factor) is associated with a decreased risk of cancer recurrence or *de novo* development. The main indications for sirolimus in liver recipients are CNI nephrotoxicity, hepatocellular carcinoma (as an indication for LT, *de novo* or recurrent) and fibrosis related to chronic HCV infection. Some authors suggest conversion from CNI to sirolimus-based immune suppression in case of fibrosis progression > 2. Further trials are necessary to confirm the beneficial role of sirolimus in this indication.

In conclusion, the best immunosuppressive regimen for recurrent C hepatitis is not known. Despite some reports on beneficial effect of cyclosporine in this setting, the type of CNI does not seem to matter (Berenguer, 2011), and tacrolimus remains the major immunosuppressant in the protocol. Temporary conversion to CsA is suggested during antiviral treatment to combine cyclosporine with interferon and ribavirin. As soon as fibrosis progresses to the moderate-severe stages, switching to sirolimus-based suppression can be considered, but currently this is an off-label approach. A role of MMF in the HCV recurrence is unclear. As grafted liver usually does not require very potent immunosuppression, replacement of MMF by AZA is feasible and recommended. As far as steroids are considered, steroid-free protocols or low-dose maintenance steroids seem to be the best option.

1.4 Treatment of recurrent HCV infection

Because many of the above mentioned strategies aiming to slow down progression of post-transplant HCV disease fail, the best option is to introduce anti-HCV treatment in order to attempt eradication of the virus prior to LT or after surgery to prevent recurrence or liver damage. Three approaches are possible: pre-transplant anti-viral therapy, early post-LT treatment (preemptive or in the acute phase) and treatment of the established disease. Each strategy has its pros and cons (Table 2), but the overall outcomes are rather disappointing.

There are several reasons for worse results in transplant patients in comparison with the non-transplant setting: history of unsuccessful antiviral treatment pre-LT, predominance of genotype 1 patients, significant increase in viral load following transplantation, concomitant immunosuppressive treatment, frequent dose reductions due to numerous side effects, mostly cytopenias and infections, frequent peritransplant renal impairment, limiting ribavirin dosing, and occasionally poor general status of the patient.

Firm conclusions on the role of interferon and ribavirin in the transplant setting are hard to be driven from clinical studies due to many methodological limitations such as a small number of patients, mostly retrospective character of the trials, lack of randomization and control, differences in immunosuppressive protocols, variability in patient selection, different doses, schedules and types of anti-viral therapy, different study end-points and scarce number of control liver biopsies. Nevertheless, in a limited and carefully selected number of patients anti-viral treatment can be strongly considered and is currently recommended (Wiesner et al., 2003).

Timing of treatment	Advantage	Disadvantage
Pre-transplant	<ul style="list-style-type: none"> • Elimination of HCV recurrence • Stopping of disease progression • Stabilization of the general clinical status of the recipient 	<ul style="list-style-type: none"> • Poor tolerance • Risk of life-threatening decompensation • Very low SVR rate
Preemptive	<ul style="list-style-type: none"> • Treatment at the low HCV RNA level • Minimal or no disease in liver biopsy 	<ul style="list-style-type: none"> • Very low SVR rate • Poor tolerance • Higher risk of ACR and infection • Maximal immunosuppression
Established recurrent HCV disease	<ul style="list-style-type: none"> • Stable clinical status of the recipient • Lower doses of immunosuppression • Lower risk of ACR 	<ul style="list-style-type: none"> • More advanced disease in liver biopsy • High viral load • Low SVR rate

Table 2. Advantages and disadvantages of anti-HCV treatment in the transplant setting

1.4.1 Pre-transplant antiviral therapy

Treating patients on the waiting list is an attractive option, because there is a body of evidence that viral clearance at the time of transplantation can minimize the risk of recurrent HCV infection post-LT and improve outcomes. However, only few candidates are suitable for the treatment. In a vast majority signs and symptoms of liver decompensation (jaundice, variceal bleeding, encephalopathy, tense ascites) and cytopenias (platelet count below 50 000/ μ L, absolute neutrophil count < 1500/ μ L) are the most common exclusion criteria. Those who are eligible, constitute a difficult-to-treat group of patients usually requiring

frequent administration of hematopoietic growth factors or decompensating on the treatment with the necessity for urgent transplantation. Expert panel recommends that antiviral treatment is worth considering in clinically stable patients with MELD score < 18 or Child-Pugh score < 7 points (Wiesner et al., 2003). Careful monitoring by the experienced team and local donor availability are mandatory. A special group of HCV-positive patients listed for LT are transplant candidates with HCC. They are often upgraded on the waiting list not due to the impaired hepatic synthetic function, but the risk of cancer growth. As having a well-compensated cirrhosis they should be strongly considered for antiviral treatment.

Duration of the treatment is not clearly defined, because cirrhotic patients can become HCV-RNA negative with a delay (if at all) and LT is not a scheduled procedure (with the exception of living donor LT). Some authors suggest keeping patients on treatment until viral clearance is achieved and continue at least for three months before LT. To avoid serious side effects, a low maintenance dose or a low accelerating dose regimen (LADR) was proposed (Everson, 2000; Everson et al., 2005). LADR was initially based on the recombinant interferon which is no more used as a standard of care (SOC). Encouraging results have been achieved by Everson (overall sustained viral response in 24% of patients and no recurrence after LT in most cases), but other trials were far less enthusiastic (Forns et al., 2003; Martinez-Bauer et al., 2006). In a low maintenance dose regimen 1 MU of standard interferon and 400 mg of ribavirin daily have been used; in LADR interferon was given 3 times a week with a starting dose of 1 MU and ribavirin was administered daily with a starting dose of 200mg, both drugs being subsequently increased fortnightly to a standard dose of 3 x 3 MU of IFN weekly and 800 mg of RBV daily.

Although combination therapy with pegylated interferons (peg-IFN) and ribavirin has limited efficacy in patients with advanced fibrosis and cirrhosis, especially if decompensated, results with peg-IFN can be better in comparison with the standard formula. Based on the current literature patients with compensated cirrhosis receive SOC therapy with peg-IFN α in a routine dose of 1.5 μ g/kg weekly with RBV in a routine dose of 1000-1200 mg daily for genotype 1 and 4, and in a dose of 800-1000 mg for another genotypes. In decompensated cirrhosis patients are more likely to develop various side effects and they cannot tolerate SOC easily. The suggested dose in this setting appears to be 1 μ g/kg/week of peg-IFN and 10.6 mg/kg/daily of RBV. In case of cytopenias, dose reductions are recommended in the first instance. If this strategy fails, hematopoietic growth factors can be used. For neutropenia G-CSF may be considered in a starting dose of 480 μ g weekly, then adjusted according to the response rate to a maximum dose of 480 μ g 3 times a week. Once adequate neutrophil count is attained, IFN dose can be increased to the optimum level. EPO may be considered if hemoglobin falls below 8 g/dL or by 4 g/dL. The starting dose is 20.000 IU weekly to a maximum dose of 60.000 IU weekly or, according to another study suggesting lower dosing, 4.000 IU thrice weekly with increase upon the response.

Although decompensated cirrhosis is no more an absolute contraindication to antiviral treatment, it must be used with caution. A chance to achieve sustained viral response (SVR) is rather low and patients experience numerous side effects, including life-threatening complications such as sepsis and liver function deterioration. Patients must be closely monitored and treated in experienced transplant centers. Treatment indications should be

individualized and very sick patients should be ruled out. Still the ideal candidate for pre-LT treatment is a patient in Child-Pugh class A to B, or MELD below 18 points listed because of HCC or history of variceal bleeding. Hopefully, novel therapies with combination of direct antiviral agents (DAA) such as protease or polymerase inhibitors will be more beneficial in decompensated HCV-related cirrhosis.

1.4.2 Early post-transplant antiviral treatment

1.4.2.1 Pros and cons of preemptive therapy

Similarly to the idea of treating decompensated cirrhosis, early post-LT anti-HCV treatment has a theoretical rationale. It is well documented that the lower the HCV viremia, the more effective the antiviral therapy. Also treatment of acute hepatitis C gives extremely favorable results with almost 90% chance for viral clearance. However, transition of experience from immunocompetent patients onto the post-transplant setting is not possible due to several reasons. Indeed, HCV-RNA level rapidly decreases after reperfusion, but within one-two weeks reaches pretransplant load and tends to increase by 1 to 2 logs thereafter. Hence, time for antiviral intervention, optimal at the lowest viremia, is very narrow and falls to the moment of greatest clinical instability of the recipient (renal impairment, risk of rejection, risk of bacterial infection related to the surgical procedure, deep cytopenias, etc.). During early post-LT period patients are under the strongest immunosuppression and cannot spontaneously clear the virus as it happens in a significant proportion of immunocompetent patients with the acute C hepatitis. Moreover, immunological responses to HCV that were unable to clear the virus in the past, remain the same. These factors make early post-transplant anti-viral treatment a mission almost impossible. No more than two third of liver recipients are eligible for early treatment, but even if they start therapy, dose reductions as well as rate of discontinuation are very high (Sheiner et al., 1998; Verna & Brown, 2008).

1.4.2.2 Treatment regimes

Experience with interferon monotherapy, either standard or pegylated, is scarce and disappointing. Patients were started on therapy at a mean time of 2-3 weeks post LT. Results obtained with standard interferon did not show any SVR cases (Sheiner et al., 1998; Singh et al., 1998). According to Singh et al. prophylactic treatment with IFN did not have any influence on the severity of recurrent C hepatitis, whereas in the study of Sheiner et al. treated patients less frequently developed recurrent hepatitis on liver biopsy or had abnormal liver tests. In both studies discontinuation rate was high and IFN did not influence patient and graft survival. There was the only one well designed trial published to date with peg-IFN alone given prophylactically. According to Chalasani et al., SVR was a rare event (8% of treated patients vs. no treatment), but discontinuation from the study, rejection episodes, adverse events and life threatening complications were similar in both groups. One third of treated patients were withdrawn from the study (Chalasani et al., 2005).

Slightly better results were obtained using combined non-pegylated or pegylated IFN with ribavirin. In a study of Mazzaferro et al., SVR was achieved in 33.3% of patients treated with IFN and RBV in comparison with 13% of SVR in patients on IFN alone (Mazzaferro et al., 2003). Interestingly, those who cleared the virus, did not show recurrent hepatitis C. Less encouraging effects were shown by Terrault. Only 11% obtained SVR and there was no

difference in the frequency of recurrent hepatitis between responders and non-responders (Terrault, 2003). In the latter trial therapy was initiated a bit later – within 6 weeks post LT – and almost 50% of recipients did not meet inclusion criteria. Only minority (23%) received a full-dose RBV, haemolytic anemia being the main reason for significant dose reduction or discontinuation, what may explain worse results. Experience with pegylated IFN in combination with RBV in preemptive anti-HCV treatment is very limited and further studies are necessary to draw conclusions.

Given that early post-LT antiviral treatment is not efficacious and requires further studying, the expert panel consensus conference recommends that it should be limited to rapidly progressing recurrent C hepatitis and *de novo* acute C hepatitis in recipients who received grafts from HCV-positive donors (Wiesner et al., 2003).

1.4.2.3 Immunoprophylaxis

Another strategy that theoretically could be implemented in the early post-transplant period is immune globulin prophylaxis to prevent HCV recurrence similarly to highly successful use of hyperimmune anti-HBV globulin (HBIG). Farci et al., demonstrated the existence of neutralizing anti-HCV antibodies, at least in the animal model (Farci et al., 1996), and Krawczynski K. showed that hyperactive anti-HCV globulin can delay hepatitis C onset in chimpanzees (Krawczynski, 1999). It was also shown that HBIG used in liver recipients before 1990, hence before HCV discovery, also reduced graft reinfection with HCV and recurrent C hepatitis in patients coinfecting with HBV and HCV (Feray et al., 1998). These results suggested that at that time HBIG possibly contained antibodies with the anti-HCV properties. Unfortunately, clinical trials with high doses of human hepatitis C antibody enriched immune globulin product (Civacir) failed to prove any beneficial effects in HCV-positive recipients in terms of HCV suppression (Davis et al., 2005) and this strategy has been abandoned. There are several reasons for failure including unclear neutralizing properties of HCV antibodies, high genetic variability of HCV allowing easy escape from immune control and lack of small animal models to test various antibody preparations.

1.4.3 Treatment of established recurrent HCV hepatitis

Treating significant HCV recurrence that has been confirmed in liver biopsy is currently the best option to manage post-LT HCV infection. With the exception of fibrosing cholestatic hepatitis (FCH) antiviral treatment should be initiated after the first year of transplantation. Decrease in the doses of immunosuppressive drugs result in the lower HCV-RNA levels and better tolerance. Patients become clinically stable and have fewer contraindications for IFN and RBV. This strategy requires ease in performing protocol or clinically driven liver biopsies with repeated frequency, or implementation of reliable non-invasive methods to detect liver fibrosis. Current policy is to treat well established HCV recurrence defined by grade 3 or 4 of inflammation or by at least grade 2 of fibrosis. In such way patients with mild and non-progressing disease avoid unnecessary treatment, related drug toxicities and possible serious complications. Despite these issues, study results show that the efficacy of anti-HCV therapy in transplant setting is poor and SVR can be achieved in around 20% of treated patients (Samuel et al., 2003). In randomized controlled trials and in trials with pegylated interferon SVR seems to be higher and reaches rates of 38-50% (Berenguer et al. 2006b). The target dose of peg-IFN is 1.5 µg/kg/week for α-2b and 180µg/week for α-2a in

combination with ribavirin in a standard dose of 800–1200 mg/kg daily (or at least 10.6mg/kg/day). Duration of treatment is 48 weeks, but in previous relapsers or non-responders can be extended to 72 weeks or longer provided that there is an early viral response (EVR) at the end of the third month. Only a small proportion of patients are able to continue therapy without initial dose reductions and/or discontinuation mostly due to severe anemia or another cytopenia. The best predictors of SVR are non-1 genotype, achievement of viral clearance after 3 months of therapy, good compliance (>80% of IFN and >80% of RBV received) and less advanced fibrosis. EVR seems to have the strongest impact on treatment outcome. The most important concern regarding antiviral treatment in transplant setting is an increased risk of either acute or chronic rejection. Treatment of ACR episode requires otherwise unwanted high doses of steroids, and chronic rejection may lead to retransplantation. Recent studies suggest that ACR develops due to decreasing levels of immunosuppressive drugs after viral clearance and subsequent improvement of hepatic microsomal function. Reported rejection rates vary in respect to the study design, being lower in randomized controlled trials (0-5%) [Chalasan et al., 2005; Samuel et al., 2003] and as high as 35% in uncontrolled trials (Dumortier et al., 2004; Sharma et al., 2007; Stravitz et al., 2004). Berenguer M et al. reported trend towards higher rejection rate on pegylated IFN in comparison with standard treatment (Berenguer et al., 2006b). Also *de novo* autoimmune hepatitis due to immunomodulatory properties of IFN and RBV may develop in 0.4 to 3.4 % of treated patients (Selzner et al., 2011).

1.5 Retransplantation in HCV recurrence

It is estimated that approximately 10% of HCV-positive transplant patients will require retransplantation (reLT) due to graft decompensation (Carrion et al., 2010). Similarly to the indications for the primary LT, hepatitis C may soon become the major indication for reLT. Many patients will not be able to survive until reLT is feasible as the mortality on the waiting list varies between 50 and 80%, and many transplant centers hesitate to retransplant patients with recurrent HCV disease due to inferior results of reLT in comparison with non-HCV candidates (Pelletier et al., 2005). However, there is no firm evidence that the unfavorable scenario after primary LT is going to repeat after reLT in every HCV-positive recipient. Moreover, other recent studies do not identify HCV recurrence as a predictor of increased mortality in comparison with other etiologies with the exception of reLT performed during the first year after primary LT (Ghobrial et al., 2002). Based on multivariate analysis it was shown that early reLT performed in HCV-positive patients is an independent predictor of mortality after reLT, indicating that severe hepatitis C recurrence (such as FCH or another reason for early graft dysfunction) should be a contraindication for retransplantation (Ghabril et al., 2008). Multiple prognostic scores were implemented to facilitate decisions which reLT would be unreasonable due to compromised graft and patient survival. Many of them are routinely used for urgent LT, and therefore are not appropriate for candidates with recurrent HCV disease who need an elective retransplantation. Prognostic criteria, traditionally used in patients with cirrhosis, such as MELD and Child-Pugh scores, turned out to be more accurate in the exclusion of high risk candidates. The ILTS expert panel concluded that bilirubin > 10mg/dL, creatinine > 2mg/dl (or EGFR < 40 ml/min), recipient age > 60 years, donor age > 40 years and early HCV-related cirrhosis (< 1 year post-LT) were the variables significantly associated with poorer outcome and with increased mortality (Wiesner et al., 2003). Lately, a MELD score >28 was

added to that list (Zimmerman & Ghobrial, 2005). With use of these prognostic measurements as screening tools survival in HCV-infected patients after reLT reached similar rates as survival in non-HCV patients.

2. Hepatitis B

Liver transplantation for hepatitis B is a true success story. In the early 1990s HBV infection was a relative contraindication for LT as the risk of recurrence was greater than 80% (depending on pre-transplant viral load) and the mortality rate was approximately 50% at 2 years. That was comparable with results of LT in malignancies (O'Grady et al., 1992). Introduction of effective immunoprophylaxis and very potent oral antivirals revolutionized this area in the last two decades and made HBV the best etiology for LT in terms of patient and graft survival (Lake et al., 2005). The number of LTs performed for this indication steadily declines in the Western countries due to effective vaccination program and good results of anti-HBV treatment, but in Asia the majority of patients undergoing LT still has HBV related end-stage liver disease or fulminant hepatitis. Overall, 5 to 10% of LTs worldwide are performed in HBsAg-positive patients (Terrault et al., 2005). By dint of long-term use of hepatitis B immune globulin (HBIG) combined with highly effective and well-tolerated nucleoside/nucleotide analogues (NUCs) HBV reinfection rate decreased below 10% (Angus et al., 2000; Marzano et al., 2001). Together with these favorable results there are, however, some concerns. According to current understanding of HBV pathogenesis complete withdrawal of reinfection prophylaxis is not feasible. Life-long prophylaxis makes LT for hepatitis B a very expensive procedure. Economical pressure stimulates studies on various alternatives which are cheaper and more convenient for the patient. Moreover, long-term use of HBIG is associated with some side-effects and the development of escape mutants in HBsAg region. Indefinite use of NUCs plus surface antigen mutations during long-term HBIG administration pose a great risk of multidrug resistance. Novel strategies need to be developed to optimize outcomes in this setting.

2.1 Pre-transplant HBV management

There are a few therapeutic options in chronic hepatitis B including indirectly acting interferons and directly acting anti-HBV molecules such as nucleotide/nucleoside analogues. Interferons were the first drugs used for this indication, but limited efficacy and poor tolerability in cirrhotic patients hampered successful management of HBV-related liver decompensation and preparation for LT for many years. Chronic HBV infection in the replicative phase was considered by many transplant teams a contraindication for transplantation because of a great risk of recurrence under immunosuppression. A turning point was discovery of the first potent viral polymerase inhibitor that allowed effective HBV suppression and clinical improvement, and in consequence permitted LT. Without LT survival in HBV-related decompensated cirrhosis is very poor and does not exceed 14% at 5 years (Zoulim et al., 2008). Independent factors associated with survival are hepatitis B e antigen (HBeAg) positivity, bilirubin level, age, transaminase activity, presence of oesophageal varices and Child-Pugh score (Zoulim et al. 2008). In another study in addition to age, bilirubin and HBeAg status, platelet count, albumin level and splenomegaly were found to be significantly related to survival. In patients with signs and symptoms of

decompensation (jaundice, increased bilirubin, low albumin level, low platelet count, prothrombin time prolongation), use of interferon alpha was associated with further deterioration and high risk of life-threatening flares in case of a minimal hepatic reserve. Its use was therefore restricted to experienced centers and was generally contraindicated. Notable improvement has been achieved in the recent years together with introduction of lamivudine (LAM), the first nucleoside analogue inhibiting HBV DNA polymerase, followed by the availability of new potent drugs with direct antiviral effect. In some patients excellent replication control and clinical stabilization allow removal from the waiting list. But these treatments do not eradicate HBV infection. HBV DNA polymerase can be suppressed and viremia effectively controlled only when patients take medications. As soon as treatment is stopped (or the patient is not compliant), the virus recurs in blood in most cases. That means the necessity for life-long treatment to maintain viral suppression and counteract decompensation.

The major concern connected with prolonged HBV therapy is a risk of drug resistance. Knowledge of the past antiviral treatment (if relevant), baseline parameters and patterns of mutations conferring resistance is essential in the management of candidates for LT. Patients require careful monitoring and prompt interventions as soon as resistance emerges. Determination of pretreatment HBV-DNA level is obligatory, because this value will be used for further comparisons and treatment efficacy evaluation. Quantitative HBV-DNA testing should be repeated in three to six month intervals, preferably using the same diagnostic assay. Primary non-response to treatment is defined by HBV-DNA decrease below 1 log after 24 weeks of a given therapy. Patients with primary failure require prompt switch to an alternative treatment. Increase in serum HBV-DNA level by at least 1 log above nadir is defined as virological resistance (or viral breakthrough). This can be related to genotypic resistance which means emergence of amino acid substitutions in the reverse transcriptase region of HBV polymerase gene during treatment. Suspicion of mutations conferring resistance require confirmation with genotypic testing, especially as the main reason for viral breakthrough is medication non-compliance and should be considered in the first instance to avoid unnecessary modification in therapy. If the patient denies medication negligence, one of the tests for the detection of resistant mutants should be ordered and if antiviral resistance confirmed, a rescue therapy has to be implemented (Table 4). If it is not done in time, clinical (or biochemical) resistance, defined as a significant liver enzymes elevation on treatment, can occur within months to years after development of polymerase gene mutations. It can be potentially life-threatening in patients with decompensated cirrhosis, and should be strictly avoided.

A question is when and with which drug to initiate antiviral treatment in patients awaiting LT to avoid prolonged administration and development of drug resistance. There is a consensus panel agreement that each patient with HBV DNA > 2000 IU/mL is in danger of disease progression and HCC development, therefore requires antiviral treatment (Chen et al., 2006; Iloeje et al., 2006). It is especially relevant in patients with liver cirrhosis, as viral suppression may lead to significant clinical improvement and withdrawal from transplant waiting list. It is also commonly accepted that in decompensated cirrhosis any HBV viremia preceding transplantation is harmful and should be treated. If a patient is HBV DNA repeatedly negative by one of commercially available sensitive PCR assays, they can be commenced on antiviral therapy at the time of transplantation.

Therapeutic decision should be based on drug potency and high genetic barrier to resistance. Several oral NUCs with different antiviral properties are currently available and can be considered for treatment (Table 3).

Drug	Class	Resistance	Potency
Lamivudine	nucleoside	high	high in the first year of treatment
Adefovir	nucleotide	low	moderate
Telbivudine	nucleoside	medium	high in naïve patients
Entecavir	nucleoside	low	very high in naïve patients
Tenofovir	nucleotide	low	very high

Table 3. Antivirals against hepatitis B virus

Careful consideration of the past medical history, resistance pattern (if detected) and cross-resistance data is mandatory (Table 4). Lamivudine was the first NUC used in patients with decompensated cirrhosis, initially with a great success. It is a relatively cheap, very well tolerated and potent drug showing effective suppression of HBV viremia within a few weeks of treatment. It improves hepatic function in more than a half of patients with decompensated cirrhosis within the first year of treatment and is associated with better survival. Usual daily dose is 100–150 mg. A significant disadvantage is a low genetic barrier of resistance making long-term treatment with LAM impossible in a considerable number of patients. It was shown that drug-resistant mutants emerge in 20% of patients treated with LAM per year. Therapy with LAM requires frequent determinations of HBV viremia, preferably every three months, and prompt initiation of rescue therapy in case of genetic breakthrough (Table 4). LT performed in patients on lamivudine with LAM resistance mutations can give inferior results and should be avoided (Perillo et al., 2001).

Another disadvantage is cross-resistance with other NUCs, considerably limiting rescue treatment options. Albeit LAM provided an important progress in LT for hepatitis B, now it is not indicated as a first line therapy in decompensated cirrhosis type B. The same concerns telbivudine, another L-nucleoside, which is even more potent than LAM, but relatively quickly selects for mutations at the same sites as LAM and entecavir. For these reasons it is neither recommended as a first line therapy in cirrhotic patients nor as a rescue therapy in LAM or entecavir resistance.

Adefovir (ADV), a nucleotide analogue of adenosine monophosphate, is effective as a first line treatment of wild type HBV infection as well as a rescue therapy in LAM-resistant patients. It is a slowly acting molecule, and in some patients delayed decrease in viremia can be mistaken with a primary non response to treatment or with a breakthrough if the baseline HBV DNA level was not determined. Its use as a drug of choice in decompensated cirrhosis is limited due to a relatively weak inhibition of HBV DNA polymerase and slow viral suppression at the approved dose (10 mg daily). A potential nephrotoxicity also limits indication for ADV in patients with cirrhosis and concomitant renal insufficiency. Dose adjustment in case of renal impairment is necessary. Despite a few disadvantages, it was

discovered that ADV lacks cross-resistance with LAM and can be used as a rescue therapy in LAM-resistant patients. However, it was also reported that to avoid sequential resistance to ADV (resistance develops only if LAM is stopped), it is better to add ADV to LAM than to switch LAM on ADV (Villeneuve et al., 2003). In very sick patients who would not be able to tolerate hepatic flares related to the selection of resistant strains, the best option is to use *de novo* combination of LAM and ADV. In case of resistance to ADV (cumulative probability appr. 2% in 2 years), the best option is to add LAM, telbivudine or entecavir.

NUC	Primary antiviral resistant mutation	Preferred management
lamivudine	rtM204V/I rtA181T	<ul style="list-style-type: none"> • add adefovir • add or switch to tenofovir or tenofovir + emtricitabine
telbivudine	rtM204I	<ul style="list-style-type: none"> • add adefovir • add or switch to tenofovir or tenofovir + emtricitabine
adefovir	rtA181V/T rtN236T rtI233V*	<ul style="list-style-type: none"> • add or switch to entecavir • or tenofovir • or tenofovir + emtricitabine
entecavir	rtL180M and rtM204V plus rtI169T and rtM250V or rtT184G and rtS202I	<ul style="list-style-type: none"> • add or switch to tenofovir • or tenofovir + emtricitabine
tenofovir	none	?

*primary non-response

Table 4. HBV mutations associated with drug resistance and rescue treatment options

Entecavir, launched in 2005, is a very potent and well tolerated nucleoside analogue with a high genetic barrier of resistance. Used as a first line therapy in a daily dose of 0.5mg dramatically reduces HBV DNA viremia within a few weeks irrespectively on HBeAg status, and currently is a drug of choice in the naïve patients with decompensated HBV-related cirrhosis. Results obtained at 5 years of treatment showed practically negligible resistance rate (Colonno et al., 2006). However, in LAM-resistant patients the efficacy of entecavir is markedly reduced even at higher doses (1 mg daily), and resistance develops in more than one third of patients after 4-year treatment (Sherman et al., 2006). It can be explained by a selection of rtM204V/I mutants already being developed during LAM treatment and less susceptible to entecavir in comparison with wild-type HBV, and the emergence of another mutation at codons 184, 202 and 250 under entecavir pressure (Table 4). If at least three mutations develop together, a viral breakthrough occurs. Therefore, entecavir should not be used as a rescue therapy in LAM-resistant (or telbivudine-resistant) patients. Such sequence may select for multidrug resistant virus. In case of entecavir resistance the only possibility is to add (better than to switch on!) adefovir or tenofovir.

Tenofovir alone or in combination with emtricitabine is a nucleotide analogue successfully used in HIV-positive patients. In HIV/HBV coinfection it also showed high potency against HBV virus. To date resistant strains have not been discovered. In comparison with ADV it is far more potent and can be used as a rescue therapy in the majority of resistance situations.

The daily dose is 300 mg. The drug is potentially nephrotoxic and should be used with caution in renal insufficiency. Tenofovir has been only recently registered in Europe to treat patients with chronic hepatitis B, therefore the experience in decompensated cirrhosis is very limited. Because of its excellent antiviral activity and lack of mutations associated with drug resistance it is reasonable to restrict its use to the patients who require rescue therapy and failed previous treatments.

In conclusion, the best option in treatment-naïve patients with decompensated HBV-related cirrhosis, especially if they await LT and will continue antiviral treatment after transplantation, is entecavir in a standard dose. In case of LAM-experienced patients, either with or without LAM-resistance, the best option is to add adefovir and to keep patients on the combination therapy until transplantation. To ensure ongoing viral susceptibility frequent, preferably in 3 month intervals, testing for HBV-DNA level is mandatory.

2.2 Prevention of HBV recurrence after LT

Two-three decades ago HBV recurrence after liver transplantation was very frequent. Although HBV replicates almost exclusively in hepatocytes, reinfection can be caused by the circulating HBV particles or, less frequently, by HBV harvested from peripheral blood mononuclear cells. A good evidence for that was a close relation of reinfection risk with the pre-transplant viral load. Viremic patients developed reinfection almost inevitably. The course of recurrent HBV hepatitis was accelerated in comparison with HBV infection in non-transplant setting resulting in liver failure and premature death in the majority of patients. It could be explained by high doses of steroids, routinely included to the immunosuppression protocol in all transplanted patients (there is a glucocorticoid-susceptible element in HBV genome), loss of immune control over HBV replication together with a potent immunosuppression and sudden availability of new hepatocytes for viral replication. Due to the very poor results, retransplantation for recurrent HBV infection was performed reluctantly and in many transplant centers was contraindicated. There was a new histological finding in recurrent HBV reinfection characterized by cholestasis, marked inflammation and fibrosis, described as fibrosing cholestatic hepatitis (FCH). This particular form of reinfection, believed to be a direct cytopathic effect of HBV on hepatocytes, resulted in rapid development of hepatic decompensation and death, usually within one year post-LT (Lau et al., 1992). Before implementation of successful strategies to prevent reinfection, it was reasonable to withdraw steroids from immune suppression in HBV-positive patients or maintain them at a low dose, and to reduce immunosuppression strength to the lowest possible levels. There was no evidence that any of CNI inhibitors had an advantage or disadvantage in this particular group of recipients by stimulating or suppressing HBV replication (McMillan et al., 1995). Neither it was confirmed for mycophenolate mofetil (Maes et al., 2001). Rather the overall potency compromising immune system mattered. New approaches were essential to change these disappointing results and to make transplantation of HBV-related end-stage liver disease an acceptable procedure.

The first change came together with the use of human immune globulin containing high titers of anti-HBsAg antibodies (HBIG) to neutralize circulating virions and to prevent virus entry to the hepatocytes. Different schedules were used (Table 5), but it was soon proved that HBIG started at the anhepatic phase in a dose of 10 000 IU followed by high doses during the first days after transplantation (10 000 IU daily for a week) and administered

long-term thereafter to maintain anti-HBs titer >100 IU/L was associated with a significant reduction risk of recurrence from 74 to 36% and far better prognosis (Samuel et al., 1993). The question arose why HBIG was not effective in all patients, but the answer is not entirely clear. Some centers tried to overcome this problem by administering larger and more frequent doses of HBIG in order to keep anti-HBs titer above 500 IU/L, but the costs of such approach were extremely high. Moreover, it was noticed that long-term use of HBIG results in selection of the escape mutants. Mutations occur in the coding region of 'a' determinant of the surface protein. In such cases vaccination failure is also present. Protective threshold of anti-HBs was not established. Some transplant teams preferred keeping anti-HBs at a level of 500 IU/L, whereas others accepted 300 IU/L or titers as low as 100 IU/L. A schedule of administration was either fixed (i.e. 2000 IU monthly or 5000 IU every second month) or individualized (on-demand) according to the anti-HBs titer. With HBIG monotherapy,

Type of HBIG	Lead-in dose	Maintenance dose	Recurrence
High-dose (iv.) HBIG	10 000 IU at LT followed by 10 000 IU daily for 7 days (80 000 IU in the first month)	10 000 IU monthly	0
	46 500 IU in the first month	5 000 IU monthly	4%
	40 000 IU in the first week	To keep anti-HBs > 500 IU/L for the second week and > 100 IU/L thereafter	9.5%, only in LAM-resistant patients
	10 000 IU daily until anti-HBs > 1000 IU/L	To keep anti-HBs > 100 IU/L	20%, only in LAM-resistant patients
	10 000 IU daily until HBsAg is cleared	To keep anti-HBs > 100 IU/L	8%, mostly in LAM-resistant patients
	80 000 IU in the first month	2 000 IU to keep anti-HBs > 100 IU/L	18%, only in LAM-resistant patients
Low-dose (im.) HBIG	800 IU at LT and daily for one week	800 IU monthly	3.1%
	80 000 IU iv. in the first week post-LT	1 200 IU monthly to keep > 100 IU/L	3.6%
	4 000 IU at LT and then 2 000 daily until anti-HBs > 200 IU/L	To keep anti-HBs > 100 IU/L	5.7%, only in LAM-resistant patients
	2 000 IU at LT and 800 IU daily for 6 days, weekly for 3 weeks	800 IU monthly	14%
	800 IU at LT and daily for 6 days	800 IU monthly	4%

Table 5. Different HBIG protocols and recurrence rate

however the recurrence rate was high when HBV DNA was detectable in blood at the time of transplantation. Lower recurrence was observed in negative HBV DNA patients, in the concomitant delta virus infection and in fulminant B hepatitis.

High costs of HBIG, the necessity of frequent testing and inconvenient immune globulin administration led transplant centers to study some other options. Early results with lamivudine showing recurrence rate of 10% at the first year post-LT were very promising and gave hope to abandon costly immunoprophylaxis, but further observations were less enthusiastic, as 43-50% of patients developed recurrence within 3 years after LT largely due to cumulative LAM-resistance and high pre-transplant viral load [Mutimer et al., 1999; Perillo et al., 2001]. Because monotherapy either with HBIG or with LAM was not satisfactory, a combination of these two agents was soon proposed. As both drugs have different mode of action and exert additive prophylactic effect, it was quickly proved that such strategy is very effective and prevents HBV recurrence in more than 90% of recipients. Combination of LAM with intravenous high dose anti-HBV immune globulin (IV HBIG) is currently a standard of care in terms of anti-HBV prophylaxis. LAM can be replaced with another NUC (or combination of NUCs), usually the one that was started before transplantation. Some centers try to reduce IV HBIG use by switching on the intramuscular formula or by administering HBIG only when anti-HBs titer falls below 10 IU/L. The latter approach turned out to be safe and no recurrence was noted despite low cumulative dose of HBIG. The authors suggested that in the concomitant use of NUC it is not necessary to keep anti-HBs at higher levels (Takaki et al., 2007). Recent publication from Australia and New Zealand on the efficacy of low-dose IM HBIG in combination with LAM is very promising and supports efforts to reduce high costs of anti-HBV prophylaxis. IM HBIG is given at a dose of 800 IU daily for 7 days post-transplant and in a dose of 400-800 IU monthly thereafter. With this strategy the rate of recurrence was only 4% at 5 years (Gane et al., 2007). The authors suggest that in case of low risk of recurrence (HBV-DNA < 2 000-20 000 IU/mL at baseline, HDV coinfection, fulminant hepatitis) HBIG can be withdrawn within one-two years post-LT with NUC to be continued life-long. In high recurrence risk (HBV-DNA > 2 000-20 000 IU/mL before treatment commence, history of drug resistance) IM HBIG in combination with NUC should be administered indefinitely. According to Gane et al. IM HBIG can be possibly replaced by the combination of two potent analogues. Further studies on this issue are warranted.

Another strategy to provide an effective anti-HBV prophylaxis without immunoglobulin administration is a vaccination program. The idea was to start active immunization at an anti-HBs titer around 100 IU/mL hoping to maintain this level after indefinite HBIG withdrawal. First generation vaccines did not prove to be useful. Some success has been achieved with the pre-S vaccines in lamivudine treated recipients. In one series anti-HBs response was obtained in 50% of vaccinated, two third of whom managed to maintain titers (Lo et al., 2007). Spontaneous antibody production was also noted in a small number of patients and development of a novel vaccine that is able to sustain that production would be of great importance.

2.3 Management of *de novo* or recurrent HBV hepatitis

As it was already mentioned, in the absence of an effective prevention, recurrent B hepatitis, defined as detectable HBsAg in blood after LT, occurs in a substantial proportion of patients

preoperatively positive for HBsAg. In the nineties of the last century recurrence rate was reported to be as high as 70 to 90% among HBsAg-positive recipients (Lake & Wright, 1991). Nowadays these proportions are notably better and vary between 26 and 53%, possibly due to more accurate selection of HBV DNA negative candidates (Yeo et al., 2004). To a lesser extent HBsAg may reappear in circulation as a result of reactivation in patients with previously resolved infection, that is in HBsAg-negative but anti-HBc positive individuals. Berger et al. found reactivation in 0.9% of anti-HBc positive liver recipients, whereas other authors reported a bit higher risk of HBsAg reappearance reaching approximately 3% of transplant patients (Barclay et al., 2008). In addition to reactivation, *de novo* HBV infection following LT has been reported in HBsAg-negative individuals who received livers from anti-HBc-positive donors (Dickson et al., 1997; Prieto et al., 2001). Currently, livers from anti-HBc-positive donors can only be transplanted to the HBsAg-positive recipients or to the anti-HBc-positive recipients with high anti-HBs titers. The same applies to kidney donors and recipients. Anti-HBc-positive heart and lung donors do not pose a significant risk of HBV transmission. In most transplant centers there is a policy to administer pre-emptively one of the NUCs (usually lamivudine for at least one year post-LT) to the anti-HBc-positive recipient to prevent reactivation of an occult HBV infection. It is needless to say that harvesting organs from HBsAg-positive donors is not allowed.

However, post-LT HBV infection still occurs either as recurrent hepatitis B due to the unsuccessful prophylaxis or as *de novo* community acquired infection, but most frequently because of use of an organ from anti-HBc-positive/HBsAg-negative donor. In case of recurrent B hepatitis or newly acquired HBV infection recipients have to be treated promptly with one of the potent NUCs, preferably the one with high genetic barrier of resistance, i.e. entecavir or tenofovir (in LAM-experienced patients). Adefovir should be considered with caution as the potency of the drug is moderate and there are reports on nephrotoxicity. Antiviral therapy should be continued until the end-point is reached (preferably HBsAg loss and seroconversion to anti-HBs) or life-long. HBV-DNA level and aminotransferase activity should be monitored every 12 to 24 weeks to seek for primary non-response, partial virological response (HBV-DNA decrease >1 log but <2 logs without resistance) and virological breakthrough. In primary and partial non-response a rapid switch to another NUC is recommended. In case of genotypic resistance-related virological breakthrough (after excluding non-compliance) adding-on a second drug is the optimal strategy. Knowledge of cross-resistance patterns is obligatory (European Association for the Study of the Liver, 2009). Clinical experience with interferons in the recurrent or *de novo* hepatitis B in liver transplant recipients is scarce.

3. References

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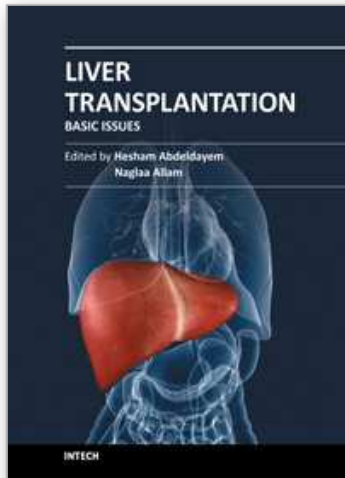
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Liver Transplantation - Basic Issues

Edited by Prof. Hesham Abdeldayem

ISBN 978-953-51-0016-4

Hard cover, 418 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Marta Wawrzynowicz-Syczewska (2012). Management of Recurrent HCV and HBV Infections after Liver Transplantation, Liver Transplantation - Basic Issues, Prof. Hesham Abdeldayem (Ed.), ISBN: 978-953-51-0016-4, InTech, Available from: <http://www.intechopen.com/books/liver-transplantation-basic-issues/management-of-recurrent-hcv-and-hbv-infections-after-liver-transplantation>

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