SUMMARY

Liver transplantation is an excellent treatment for hepatitis B virus infected patients who have acute or chronic liver failure and/or primary liver cancer. Advances in antiviral prophylaxis prevent clinically significant graft re-infection for the majority of patients. Graft and patient survival has improved significantly during the past decade, and results of transplantation for hepatitis B virus are now superior to those achieved for most other indications. In particular, the availability of lamivudine and adefovir have transformed outcome.

The addition of lamivudine to passive immunoprophylaxis with hepatitis B virus immunoglobulin prevents re-infection in most cases. Adefovir should be added to this combination when the patient develops lamivudine resistance before transplantation. The significance of serum hepatitis B virus DNA positivity in the absence of circulating hepatitis B surface antigen is uncertain. Hepatitis B virus infection of the graft can be observed when prophylaxis is inadequate, when the donor liver contains latent hepatitis B virus infection (so-called de novo infection from the hepatitis B virus core antibody positive donor), and when the donor is exposed to third party infection (sexual or nosocomial transmission).

Established hepatitis B virus graft infection is a good indication for combination nucleoside analogue therapy. Combination therapy can achieve sustained suppression of viral replication, and hepatitis B e antigen and hepatitis B surface antigen clearance can also be observed.
INTRODUCTION

Globally and annually, hepatitis B virus (HBV) infection causes twice the number of deaths than can be attributed to hepatitis C virus (HCV) infection. World Health Organisation (WHO) estimates for the year 2000 were that more than 600 000 deaths could be attributed to HBV infection, including nearly 400 000 deaths from primary hepatocellular cancer (HCC). However, the greatest burden of HBV infection is in countries and regions of the world that have little or no access to liver transplantation (LT). Thus, the prevalence of HBV infection remains fairly low in affluent countries, and HBV is not a leading indication for LT. In the UK for instance, HBV is the indication for LT in approximately 5% of cases. That figure has been fairly constant during the last decade, but may increase as a consequence of migration to the UK of people from countries of high HBV prevalence. Indeed, many transplanted HBV patients were/are first generation migrants from high to low HBV prevalence countries.

Liver transplantation for HBV should be discussed in a historical perspective. The results of LT for HBV have improved significantly during the past 2 decades. That improvement reflects the better outcome experienced by LT recipients in general, but also the significant and stepwise refinements made in antiviral prophylaxis and treatment of HBV infection. In particular, the recent introduction of nucleoside analogues as component(s) of prophylaxis, and the use of these drugs alone or in combination for treatment of established graft infection, have transformed the outcome of LT for HBV. As a consequence, few if any grafts should succumb to HBV-inflicted damage. HBV infection, not long ago perceived as a marginal indication for LT, is now considered an excellent indication for LT. Superior graft and patient survival is anticipated.

MANAGEMENT OF CHRONIC HBV INFECTION (INCLUDING CIRRHOSIS) AND SELECTION OF PATIENTS FOR LT

Hepatitis B virus infection is frequently diagnosed during the phase of chronic hepatitis before the development of cirrhosis. In the context of significant viral replication, reflected by the serum HBV titre, antiviral therapy should be given. Successful and prolonged inhibition of viral replication can prevent or delay progression to cirrhosis, thus preventing the development of liver failure and reducing the risk for HCC. Recent and ongoing developments with nucleoside analogues and new interferons, given as combination antiviral therapy, give optimism that complications of chronic HBV infection may be preventable. Unfortunately, chronic hepatitis is frequently asymptomatic, and many infected patients present after development of cirrhosis. Some are diagnosed at the time of presentation with hepatic decompensation or with symptoms of advanced HCC. A number of published series described the beneficial effect of viral suppression by lamivudine or adefovir for patients with advanced cirrhosis. Consistent observations included the normalization of laboratory parameters and co-incident improvement of symptoms of liver failure.

The potential for resolution of liver failure during HBV suppression with lamivudine created two challenges for the treating physician. The first challenge was the need to distinguish, at an early stage of management, those patients with liver decompensation that would or would not resolve during antiviral treatment. Improvement is observed during the first 3–6 months of treatment, and sustained for as long as suppression of viral replication is maintained. Patients with more severe decompensation at presentation are prone to die during short-term observation, and less likely to rally as a benefit of viral suppression. Large recipient waiting lists and long waiting times enabled patients to segregate into those that would improve substantially as a benefit of antiviral therapy, and those that would die despite viral suppression during short-term follow up. Short waiting times did not permit that segregation. Thus, patients with more severe disease at presentation were saved by early transplantation. However, many patients were transplanted despite the potential for recovery without transplantation. That dilemma persists despite the advances in antiviral repertoire and protocols.

A second challenge was posed by the almost inevitable eventual selection of lamivudine-resistant HBV during prolonged treatment with that drug. It was recognized that the emergence of drug-resistance before LT caused two problems. Some patients decompensated when HBV replication returned to pretreatment levels. Also, the merits of lamivudine [either alone or in combination with HBV immunoglobulin (HBIG)] as prophylaxis against graft infection were compromised when serum titres rose before LT to pretreatment levels. Thus, lamivudine treatment provided a window of opportunity for LT after improvement of
liver function but before the emergence of drug resistance. The problem for the clinician was, of course, that it was impossible to gauge the width of that window. For a given patient, the duration of treatment before emergence of resistance could not be accurately predicted. That uncertainty needed reconciliation with the uncertainties of waiting list management. This dilemma troubled physicians after the availability of lamivudine and before ready access to adefovir, during the period 1995–2000 (approximately). The use of adefovir for treatment of lamivudine-resistant HBV made possible the prolonged suppression of HBV with attendant clinical benefit for the cirrhotic patient. Also, as will be discussed in a later section of this review, the addition of adefovir for lamivudine-resistant HBV before transplantation provides excellent prophylaxis against post-LT graft infection.

In conclusion, the prognosis of chronic HBV infection is being transformed by developments in antiviral therapy. It appears that sustained suppression of viral replication can be achieved for the majority of patients with available drugs. For the patient treated before the development of cirrhosis, cirrhosis and its complications should be prevented. For the patients with well-compensated cirrhosis, sustained suppression should prevent hepatic decompensation and reduce the risk for development of HCC. For the patient with hepatic decompensation in the context of viral replication, antivirals may restore a well-compensated cirrhosis and prevent need for transplantation. The net effect may be to decrease the number of patients with decompensated HBV undergoing LT. Of course, despite the beneficial impact on risk for HCC, surveillance for HCC will be essential. Many may develop HCC during prolonged follow-up. It seems probable that the net effect will be that future cohorts transplanted for chronic HBV will be somewhat older and more likely to be transplanted for HCC than for decompensated cirrhosis.

**MANAGEMENT OF FULMINANT HBV AND SELECTION OF PATIENTS FOR LT**

Fulminant HBV is a rare disease, principally affecting adults. Sexual transmission is probably the most common route of acquisition, although a substantial proportion is infected by injecting drug use. Selection of patients with fulminant HBV for LT first requires an assessment of prognosis for survival with conservative management. LT is appropriate treatment if the prognosis for survival is substantially enhanced by LT. In addition, the likelihood of compliance with post-LT care needs to be considered. For instance, fulminant HBV occurring in the context of chaotic drug use might be more appropriately managed without LT. Under these circumstances, and despite the urgency, it seems appropriate to set equivalent standards to those that are posed for patients with substance abuse that suffer with HCV or alcohol-associated liver failure. Most clinicians agree that active intravenous drug use is an absolute contraindication to LT. In our experience, post-LT compliance with follow-up has been extremely poor by those patients transplanted for acute HBV in the context of injecting drug use.

The possible role for antiviral treatment for patients with fulminant HBV remains uncertain. Recently published series confirm that serum HBV titres are quite high (frequently in excess of 1 million genomic copies/mL serum) at the time of presentation with acute and fulminant infection. Although not shown by prospective controlled clinical trials, published data imply that prompt antiviral treatment with lamivudine may be beneficial. For instance, Schmilovitz-Weiss et al. reported their experience with the management of 15 consecutive cases of severe acute hepatitis B infection, including five patients with hepatic encephalopathy. The mean serum titre for the cohort at presentation was greater than $10^7$ copies/mL, and all were treated with lamivudine. Thirteen survived without the need for transplantation. Thus, there may be a rationale for antiviral therapy at the time of presentation, before the availability of serum HBV DNA measurements. For those patients with fulminant HBV that proceed to LT, the contribution of a short period of pre-LT lamivudine to success of post-LT prophylaxis is unknown.

**PROPHYLAXIS AGAINST GRAFT RE-INFECTION BY HBV**

The current impressive graft and patient survival figures for HBV transplanted patients are principally a reflection of improvements in antiviral prophylaxis. Without prophylaxis, clinically significant HBV recurred in the transplanted liver. In the context of immunosuppression, reinfection was usually associated with high serum titres and with hepatitis B e antigen (HBeAg)-positivity. The expression of disease ranged from subacute graft failure (sometimes with characteristic histological features known as ‘fibrosing cholestatic hepatitis’) to more conventional chronic...
hepatitis with progressive fibrosis leading to graft cirrhosis.

PASSIVE IMMUNOPROPHYLAXIS WITH HBIG

Early protocols for prevention of graft reinfection employed passive immunoprophylaxis with high titre HBIG. Short duration, low dose HBIG was of little benefit. Successful prophylaxis required the use of high dose HBIG administered indefinitely. Typical protocols commenced HBIG during the anhepatic phase of the transplant operation, gave repeated doses during the early postoperative period, and maintained serum anti-HBs titres above a predefined threshold by subsequent titrated intermittent administration. Samuel et al. clearly demonstrated that regular and sustained HBIG prophylaxis could achieve and maintain recipient serum hepatitis B surface antigen (HBsAg) negativity and prevent the development of clinically significant graft re-infection. HIG appeared to provide successful prophylaxis when transplantation was undertaken for patients with low pretransplant serum HBV titres (fulminant HBV, HBV/delta virus co-infection, and HBeAg negative chronic hepatitis). Inferior results were observed for patients who were HBeAg positive at the time of transplantation. Under this circumstance, graft reinfection was usually experienced. Typically, serum HBsAg became and remained positive during the first 6 months after transplantation. High serum titres of HBsAg and HBV DNA were rapidly achieved. Continued HBIG treatment did not restore serum HBV negativity. Actuarial serum HBsAg recurrence curves show that the majority of relapse was observed during the first two post-transplant years. Subsequent relapse was uncommon so long as HBIG administration continued. An interesting observation made during this era of HBIG usage was that the targeted antiviral activity of HBIG could select specific HBV species during failure of prophylaxis. Examination of paired pre- and post-LT specimens from patients who failed HBIG prophylaxis showed that the amino acid sequence of the HBsAg that emerged post-LT sometimes differed from the HBsAg that was present before transplantation. HBIG prophylaxis selected HBV species with changes in the principal ‘a’ antigenic determinant of the HBsAg. These ‘a determinant’ mutants should not be seen as the ‘cause’ of HBIG failure. Instead, they are simply the species most likely to emerge during inadequate HBIG prophylaxis. The dominant serum species would revert to ‘wild-type’ (the pre-LT species) following withdrawal of HBIG prophylaxis.

It seems unlikely that many, if any, transplant units continue to use HBIG alone for newly transplanted patients. However, many patients who were transplanted before the availability of nucleoside analogues continue to receive HBIG as single agent prophylaxis with low rates of serum HBsAg relapse during long-term follow up. As an alternative to sustained HBIG prophylaxis, many of those patients were converted to lamivudine monotherapy. A small randomized clinical trial showed that this was a viable alternative to ongoing HBIG. A small cohort of patients in Birmingham who were receiving HBIG as post-LT prophylaxis has been converted to lamivudine monotherapy without observing HBsAg relapse during follow up.

LAMIVUDINE AS SINGLE-AGENT PROPHYLAXIS

The significant failure rate of HBIG inspired new approaches to prophylaxis. There was a perceived rationale for the use of lamivudine in this setting. HBIG failure was principally experienced by patients who had high serum HBV titres at time of transplantation. Lamivudine had been shown to reduce serum titres by at least 2 logs. Therefore, the next strategy was to use lamivudine to lower serum titres before transplantation, and to continue lamivudine to maintain viral inhibition post-LT (Figure 1). It should be remembered that these studies were designed and commenced recruitment before the first description of HBV lamivudine resistance. Indeed, HBV lamivudine resistance was first described in exactly this setting. That was a female patient who was HBeAg positive with high serum HBV titres before commencement of lamivudine (Figure 2). Lamivudine effected a significant decline in serum HBV titre before transplantation, and ongoing decline was observed during the first 6 months post-LT. Thereafter, serum HBV DNA titre rose rapidly to achieve pre-LT, pretreatment levels despite ongoing lamivudine treatment. The rise in serum HBsAg titre was delayed and observed by routine HBsAg assays after the serum HBV titre had risen to greater than 4log_{10} copies/mL. This patient subsequently developed subacute liver failure and died. That was in 1995, before the availability of adefovir for treatment of lamivudine-resistant HBV. From the Birmingham Liver Unit during that phase of lamivudine monoprophylaxis, three patients experienced graft
reinfection with lamivudine-resistant HBV, and all died as a direct consequence. Important lessons were learnt from the combined European and North American experience with lamivudine as single agent prophylaxis. The actuarial serum HBsAg recurrence curves looked very similar to those generated by studies of HBlg prophylaxis. HBsAg relapse was most likely to be observed for those patients with high
levels of HBV before lamivudine treatment and at time of LT. A period of serum HBsAg negativity was observed for the majority of patients post-LT. Failure of prophylaxis was invariably associated with emergence of lamivudine-resistant HBV during the first 2 years post-LT. For those that did not experience HBsAg relapse during this early post-LT period, subsequent relapse is unlikely during prolonged follow-up. In the experience of the Liver Unit in Birmingham, a cohort of 12 patients underwent transplantation with lamivudine monoprophylaxis. Three of 12 experienced relapse with lamivudine-resistant HBV during the first post-LT year (all died), and the remaining nine patients are alive without serum HBsAg relapse during a median follow up of 10 years (range 9–12 years). Thus, lamivudine monoprophylaxis, given before and indefinitely following transplantation, can provide safe and effective protection against significant graft HBV reinfection for a large proportion of patients. For patients with high pre-LT serum titres, neither lamivudine nor HB Ig as single agents could prevent graft re-infection. The published experience with lamivudine as single agent prophylaxis is not large. The pitfalls were soon exposed, and the majority of units probably shifted quite quickly from either HB Ig or lamivudine as single agents to prophylaxis that combined the two products. It is possible that some units persist with lamivudine as a single agent. That approach might reflect the difficulty experienced in some parts of the world with procurement of HB Ig, and also the confidence in adefovir as a salvage for those patients who relapse with lamivudine-resistant infection.

COMBINATION OF LAMIVUDINE AND HBIG FOR PROPHYLAXIS

This was the logical next step, and has proven extremely successful. The typical protocol commences lamivudine before transplantation, then lamivudine and HB Ig after LT (Figure 3). Most units adopt protocols for HB Ig administration that are identical or similar to those used during the era of HB Ig monoprophylaxis. Applying these protocols, serum HBsAg relapse is infrequently observed. When observed, failure is classically associated with the emergence of lamivudine resistant HBV. Frequently, that reflected a prolonged duration of lamivudine treatment with selection of resistant species before LT. Thus, close surveillance with repeated serum HBV DNA measurements must be the rule for listed patients who are receiving lamivudine monotherapy before LT. A significant rise of serum HBV DNA titre during this period requires immediate commencement of adefovir. As antiviral therapy of patients with HBV cirrhosis becomes more routine, an increasing proportion of patients will come to transplantation taking the combination of lamivudine and adefovir. As discussed earlier, many will have excellent liver function and the indication for LT may be primary liver cancer. The need for HB Ig post-LT, when viral suppression has been achieved with the combination of lamivudine and adefovir pre-LT, is not known. To date, HBV resistance to the combination of lamivudine and adefovir has not been reported. If this clean record for the nucleoside combination is sustained,
then the addition of HBIg post-LT may not be necessary. At present, however, triple prophylaxis with lamivudine and adefovir and HBIg should be sustained post-LT. HBsAg recurrence should be seldom observed if this approach to prophylaxis is employed. In the experience of the Birmingham Liver Unit, combination lamivudine and HBIg prophylaxis has been used for 49 consecutively transplanted HBV patients since 1997. Five required addition of adefovir before LT for treatment of lamivudine resistance. Double or triple agent prophylaxis has been maintained post-LT for all patients. HBsAg relapse has not been observed.

PROPHYLAXIS FOR HBV/HIV CO-INFECTED LT RECIPIENTS

This is an appropriate place to consider this special patient group. Typically, the co-infected patient will be receiving anti-retroviral treatment (HAART). For the co-infected patient HAART should include the combination of tenofovir and either lamivudine or emtricitabine. Those combinations have excellent anti-HBV activity, and the majority of treated patients have low or undetectable serum HBV DNA. They should continue these drugs (and the other components of their HAART) after LT, and should also receive HBIg prophylaxis. That should prevent HBV reactivation. Possibly, HBIg is superfluous, but there are insufficient published data to recommend that dual nucleoside therapy can provide adequate HBV prophylaxis without HBIg.

NEXT STEPS FOR PROPHYLAXIS

Hepatitis B virus recurrence should not be observed when patients and physicians comply with the current protocols. It would be good, however, to simplify the protocols without compromising efficacy. In particular, many patients and physicians would prefer to avoid or to minimize the use of HBIg. It is a good medical principal that repeated exposure to human blood products should be avoided. Also, many units titrate repeated intravenous HBIg administration according to measured serum anti-HBs levels that increases the cost of post-LT follow up. HBIg itself is usually quite expensive, although not necessarily less expensive than nucleoside therapy. The observation that a large proportion of patients do not relapse during lamivudine monotherapy prophylaxis implies that many patients are receiving HBIg without need. Buti et al. showed that HBIg can be withdrawn from combination prophylaxis in selected patients, and HBsAg recurrence was not observed during short-term follow up. Other than in the context of lamivudine resistance before LT, adefovir has yet to find a role for routine prophylaxis. Also, it is likely that other nucleosides will be used for prophylaxis and for treatment of HBV in the liver transplant setting. Protocols for prophylaxis will continue to evolve. Future protocols need to be compared with existing protocols, which are pretty safe, fairly expensive, but nearly 100% efficacious.

MANAGEMENT OF ESTABLISHED HBV GRAFT INFECTION

Hepatitis B virus ‘graft infection’ can be defined as sustained serum HBsAg positivity post-LT. This definition distinguishes clinically significant graft infection from serum HBV DNA positivity of uncertain clinical significance. For instance, Roche et al. examined with a sensitive polymerase chain reaction (PCR) assay the serum of patients who were maintained on HBIg prophylaxis for 10 years post-LT without serum HBsAg relapse. A significant proportion had detectable serum HBV DNA. Applying a sensitive PCR assay colleagues in Birmingham have been able to detect HBV DNA (in the context of sustained serum HBsAg negativity) in a high proportion of patients during long-term prophylaxis with lamivudine monoprophylaxis, with lamivudine/HBIg combination prophylaxis, and with lamivudine/adefovir/HBIg prophylaxis (D. Freshwater and P. Cane, unpublished observations). Although the clinical importance of these observations remains uncertain, it seems likely that serum DNA detection reflects persistent subclinical infection, which may be sensitive to changes in HBV prophylaxis or to modulation of immunosuppression.

Graft infection can be the consequence of one of three distinct processes. Graft infection can result from inadequate prophylaxis (re-infection by the recipient’s own HBV strain), from reactivation of donor HBV (so called de novo HBV), or from a third party (for example, sexual acquisition at some time post-LT).

MANAGEMENT OF GRAFT RE-INFECTION (FAILED PROPHYLAXIS)

As stated above, this is seldom observed with current prophylaxis protocols. Historically, the approach to management has depended upon the development and availability of nucleoside analogues. Cohorts of
patients who had failed HBIg prophylaxis were treated with lamivudine. No attempts were made to distinguish wild type from a determinant mutants at baseline, although the majority would have had wild-type dominance. Observations that had been made during the treatment of non-immunosuppressed HBV populations were reproduced in these post-LT studies. Virological response was associated with biochemical and clinical improvement, which were sustained until the emergence of lamivudine-resistant HBV. The majority of treated patients were HBeAg positive at baseline. A proportion underwent HBeAg seroconversion during treatment, and HBsAg clearance was also observed for a few.

The numbers of post-LT patients with lamivudine resistant HBV infection swelled during the late 1990s and early 21st century. They arose during lamivudine treatment of HBeAg failures or from failure of lamivudine or combination lamivudine/HBIg prophylaxis. Probably, the majority have now been treated to good effect with adefovir. Adefovir treatment of post-LT lamivudine-resistant infection achieves good viral suppression and clinical benefit. As observed for lamivudine resistant HBV, it is not surprising that adefovir-resistant HBV was first described in the post-LT setting. It was shown that adefovir-resistant HBV was susceptible to treatment with lamivudine. This and subsequent observations in the LT and non-LT settings confirm that adefovir and lamivudine are associated with distinct and different mutations in the HBV polymerase, thus providing a scientific rationale for the use of combination treatment. Therefore, it has probably achieved a consensus that lamivudine should be maintained after the introduction of adefovir for lamivudine-resistant infection, and the combination should be sustained indefinitely.

Tenofovir has also been used for the treatment of lamivudine-resistant infection post-LT. Neff et al. report success with tenofovir in the treatment of eight post-LT patients infected with lamivudine-resistant HBV. Excellent virological and clinical responses were observed. Tenofovir is presently undergoing controlled evaluation in large clinical trials of non-transplant patients with chronic HBV infection. It may emerge as a key player in the prevention and treatment of HBV in the LT setting.

In the management of immunosuppressed patients (perhaps in all patients) it is probably best to avoid resistance rather that to create a need to treat it. Thus, there is a persuasive argument to commence ab initio (and as soon as possible after diagnosis of HBV graft infection) the combination of lamivudine and adefovir. Available evidence suggests that the rate of treatment failure may be very low, thus avoiding the potentially harmful flares of hepatitis activity that can be observed during the emergence of drug resistance.

**RECOGNITION AND MANAGEMENT OF DONOR-ACQUIRED (DE NOVO) HBV GRAFT INFECTION**

People with past resolved HBV infection, signified by circulating antibody to the HBV core antigen (anti-HBc), may harbour latent HBV in the liver. HBV may reactivate from the liver of organ donors who are positive for anti-HBc (core antibody positive donors). This is referred to as de novo HBV infection. This phenomenon and the magnitude of the risk became clear during the 1990s. However, screening of liver donors for core antibody was not introduced into routine practice by many units/countries until quite recently. Thus, many LT patients have received livers from donors of unknown core antibody status. Occasionally, stored donor serum can be examined in retrospect to confirm that the donor was the likely source of HBV presenting post-LT. There may be a significant delay between date of LT and diagnosis of de novo HBV. Recently, the author diagnosed de novo HBV infection in a patient 8 years after LT (stored donor serum confirmed core antibody positivity). Conditions that favour the likelihood and timing of HBV emergence remain unknown. Of course, the exact timing of serological emergence can be difficult to identify. The majority of post-LT patients probably do not undergo regular and frequent screening for HBsAg. HBV is an important consideration in the differential diagnosis of all post-LT hepatitis.

It is now mandatory that organ donors are screened for anti-HBc. Core antibody positive donor livers can and should be used, not discarded. The ideal recipient is being transplanted for HBV and will receive appropriate prophylaxis to prevent graft re-infection by recipient strain. It seems very likely, and limited data confirm that combination prophylaxis prevents both recipient HBV re-infection and donor HBV reactivation. An interesting observation was made when HBV immune donor livers were transplanted into HBV patients who received lamivudine as monoprophylaxis. HBV antibody production was measured in recipient serum, presumably a consequence of stimulation of passenger HBV-specific donor lymphocytes by recipi-
ent HBsAg. High titres of anti-HBs were measured, although titres faded during the first post-transplant year, possibly reflecting the natural attrition of donor lymphoid cells. Thus, paradoxically, the core antibody positive donor liver has the potential to provide both protection (temporary neutralizing antibody production) and infection (at a later stage) by donor HBV!

If a suitable HBV-positive donor is not available, the core antibody positive liver can be used for HBV-negative recipients. Recipient HBV immunity, both naturally acquired and vaccine-induced immunity, confers a degree of protection against de novo infection. However, one should not place complete reliance on recipient HBV immunity, and additional measures should be taken to prevent reactivation. Protocols employing either HBIg or lamivudine for prevention are probably equal and adequate. The long-term failure rate of such prophylaxis is not known, but is probably very low. For cost and simplicity, lamivudine may be preferable. Also, these protocols will probably prevent de novo infection in non-immune recipients. Thus, the core antibody positive liver should always find a grateful recipient.

De novo HBV infection should be treated according to recommendations made above for prophylaxis failure. The HBV species should be wild type and sensitive to nucleoside treatment. Again, there is a good argument for the ab initio use of combination nucleoside treatment (Figure 4).

HBV ACQUIRED BY OTHER MEANS

Liver transplantation recipients may be exposed to HBV by other means. Sexual and nosocomial acquisition of infection may occur. HBV infection needs to be considered in the differential diagnosis of post-LT hepatitis. In the context of immunosuppression, HBV chronicity rather than resolution is a more likely outcome. Combination nucleoside treatment should be given as soon as a diagnosis is established.

VACCINATION AGAINST HBV

All potential LT recipients should be screened for HBsAg and anti-HBs. HBsAg negative recipients without evidence of HBV immunity should undergo HBV vaccination. Unfortunately, vaccine response rates
appear poor in patients with advanced liver disease.\textsuperscript{36} Double-dose vaccination and newer HBV vaccines might be more successful.

Some investigators have evaluated the response to vaccination post-LT of patients who were transplanted for HBV liver disease and who were receiving post-LT prophylaxis. Various vaccines and strategies have been used. Careful monitoring and withdrawal of HBIG therapy is necessary for a vaccine response to be uncovered. Some investigators have induced in their patients quite good antibody production.\textsuperscript{37} Others report disappointing results.\textsuperscript{38} None have reported harmful consequences. A cohort of Birmingham Liver Unit patients, who were receiving long-term lamivudine monoprophylaxis post-LT, were vaccinated with a double dose of commercial vaccine (V. Lai, unpublished observations). These patients had no anti-HBs at baseline. A single patient developed low titre anti-HBs, which was not sustained. Nevertheless, attempts with vaccination to induce recipient production are worthy of further research.

**HBV AND LT, BEYOND 2005 (SUMMARY AND SPECULATION)**

Hepatitis B virus has become an excellent indication for LT. Graft and patient survival are superior to many other indications, and clearly superior to the results currently achieved for HCV. In many ways, transplantation for HCV in 2005 resembles the situation for HBV in 1990. Improvements in outcome of HBV recipients have been a consequence of improvements in HBV antiviral prophylaxis and treatment. Lamivudine gave a taste of success for the meal of HBV antivirals that is emerging. Combination antiviral therapy has the potential to suppress indefinitely HBV replication. Sustained viral suppression can prevent progression to liver failure and can reduce the risk for liver cancer. For those that require transplantation, compliance with antiviral protocols can prevent HBV recurrence. Recognition of the significance of donor core antibody positivity, and appropriate management of the recipient, should eventually eliminate de novo HBV infection. It seems appropriate to conclude with two notes of caution. The potential for HBV to reactivate from the liver of donors who have recovered from HBV with natural immunity, and the persistence and detection in serum of HBV DNA during long-term follow up of patients during successful prophylaxis, must remind us that HBV is controlled but never eliminated. The potential for reactivation during changes to prophylaxis and during changes in immunosuppression should be considered. The other development, which could spoil the party, would be the emergence during combination therapy of HBV species, which are resistant to both lamivudine and adefovir (or to other current or future combinations). It may be premature to have written with such confidence, but ongoing developments in antiviral therapy at least justify optimism!

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