Netherlands
The Journal of Medicine

REVIEW

Liver transplantation: an update

R.C. Verdonk[1*], A.P. van den Berg[1], M.J.H. Slooff[2], R.J. Porte[2], E.B. Haagsma[1], on behalf of the Liver Transplant Group Groningen

Departments of [1]Gastroenterology & Hepatology, and [2]Hepatobiliary Surgery & Liver Transplantation, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [*]corresponding author: tel.: +31 (0)50-361 61 61, fax: +31 (0)50-361 31 51, e-mail: r.c.verdonk@int.umcg.nl

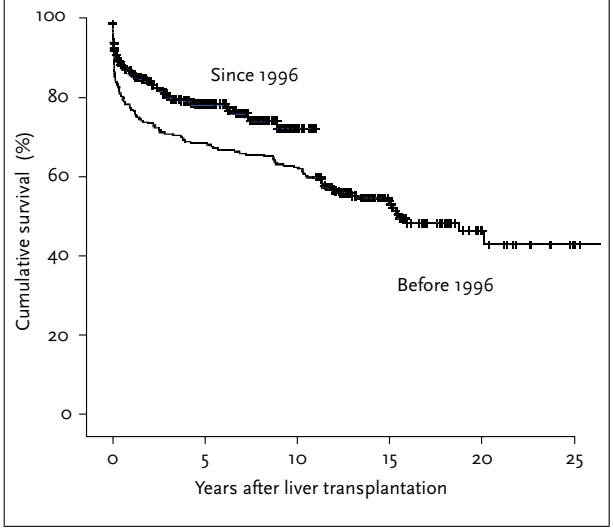
ABSTRACT

Liver transplantation has been an accepted treatment for end-stage liver disease since the 1980s. Currently it is a highly successful treatment for this indication. The aim of this review is to give a general update on recent developments in the field of liver transplantation. In the last decades considerable progress has been made in the care of liver transplant candidates and recipients. At present the one- and five-year patient survival rates are approximately 85 and 75%. The indications for liver transplantation are shifting and the number of absolute contraindications is decreasing. In the coming years, an increase in the number of transplant candidates can be expected. An important problem is the shortage of donor organs, for which many solutions are being explored. A recently introduced method for recipient selection is the MELD score using simple laboratory measurements. Perioperative care at the present time is characterised by a high degree of standardisation and rapidly declining blood loss during transplantation. Long-term care includes awareness and management of recurrent disease. Important causes of morbidity and mortality such as *de novo* malignancies and cardiovascular disease should be adequately screened for and managed. With the increasing success of liver transplantation, physicians should aim at reaching a normal life expectancy and quality of life for transplant recipients.

INTRODUCTION

The first report on attempts to transplant a liver in humans was by Starzl in 1963.[1] In the following years liver transplantation developed from an experimental operation with very high mortality rates into a standardised procedure with rapidly decreasing perioperative mortality. This ultimately led to a statement from the National Institute of Health (NIH) in 1983 declaring liver transplantation as an accepted therapy for end-stage liver disease.[2] Currently, liver transplantation is the treatment of choice for acute and chronic liver failure. Survival is excellent on both the short and long term, with patient survival rates of approximately 85% one year after surgery and 75% five years after transplantation (source: www.eltr.org). Survival figures from our centre are shown in *figure 1*. As can be seen in the figure, survival has improved markedly over recent decades. The two lines represent the survival of patients before and after the median date of our transplant programme. The first liver transplantation in the Netherlands was performed in Arnhem in the 1960s. The procedure, however, was not part of a formal transplant programme. Liver transplantation was first performed in Groningen in 1979. The University Hospital Groningen (currently University Medical Centre Groningen) pioneered

Figure 1. *Patient survival after adult liver transplantation at the University Medical Centre Groningen: before (n=247) and since 1996 (n=325)*



this treatment in Europe with a few other centres. The final NIH declaration was based partly on data from the Groningen programme. Currently, three university medical centres are performing liver transplantations in the Netherlands: Rotterdam, Leiden and Groningen. There is a shared protocol for indication and selection of patients. In the recent decades there have been important developments in patient selection, perioperative care, and long-term follow-up of liver transplant recipients. The aim of this review is to give an update on the present state of liver transplantation in adults, and to highlight some recent developments on indications for transplantation, patient selection, perioperative care, immunosuppression and long-term management of liver transplant recipients.

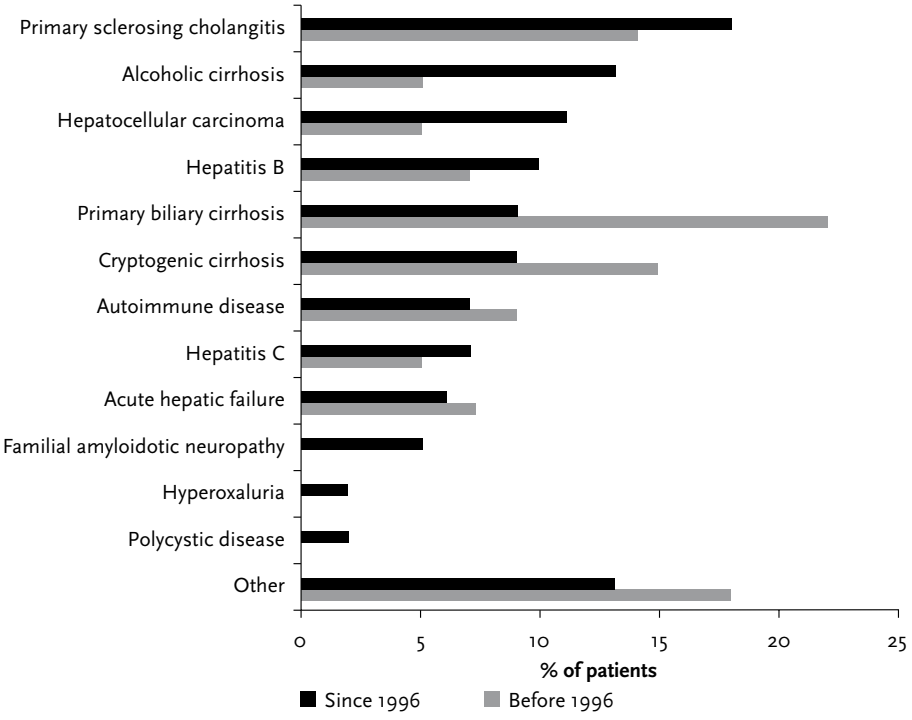
INDICATIONS AND CONTRAINDICATIONS FOR LIVER TRANSPLANTATION

The most important indications for liver transplantation in Europe are viral hepatitis (24%), alcoholic liver disease (20%), cholestatic liver diseases (18%) and hepatocellular carcinoma (10%) (source: www.eltr.org). The indications in our centre are shown in *figure 2*. Throughout the years, a changing pattern of indications has been recognised. The number of patients transplanted for hepatitis C cirrhosis and alcoholic cirrhosis is increasing, and the number of patients with immune diseases such as primary biliary cirrhosis is decreasing.

For alcoholic disease, the prerequisites for transplantation in most centres are alcohol abstinence for at least six months and active treatment for alcohol dependency. In general, treatment for hepatitis C virus infection is not effective in the advanced stage of cirrhosis, with the consequence that the infection recurs in the transplanted liver. This often results in a recurrence of chronic hepatitis and gradual progression to cirrhosis at 10 to 15 years after transplantation. Patients with hepatitis B cirrhosis and high hepatitis B viraemia were not eligible for transplantation in the past because of the high risk of recurrence after transplantation with consequent rapid graft loss. Since the availability of antiviral medication, high viraemia is treatable and transplantation has become a more realistic option with excellent graft and patient survival that is even superior to that of many other indications.[3] After transplantation, antiviral treatment, often including hepatitis B immunoglobulin, is continued to prevent recurrent infection.

About 10% of patients are transplanted because of acute liver failure. The main causes of acute liver failure are drug hepatotoxicity (mostly acetaminophen) and acute viral hepatitis. The waiting time for a donor liver and the threat of developing multiple organ failure and cerebral death during this time are of critical importance. The role of albumin and MARS dialysis (Molecular Adsorbent Recycling System) as a bridge to transplantation is under discussion and being investigated.[4]

Figure 2. *Changing indications for liver transplantation at the University Medical Centre Groningen: before (n=247) and since (n=325) 1996*



Primary hyperoxaluria is an inborn error of metabolism of the alanine:glyoxalate aminotransferase in the liver. The result is a systemic disease with loss of kidney function. Liver transplantation may halt further progression of the disease. Transplantation in an early stage may prevent the need for haemodialysis and kidney transplantation. At a later stage, when kidney failure has already developed, combined liver and kidney transplantation is the best option. Familial amyloidotic polyneuropathy is another example of a disease in which an inborn error of metabolism in the liver leads to systemic disease. In this case, mutant transthyretine production in the liver leads to amyloid depositions in the body. It is now known that in more advanced patients, cardiovascular amyloid may progress despite liver transplantation. Therefore, transplantation early in the course of disease now seems to be the best treatment option.[5]

Hepatocellular carcinoma is a well-recognised indication for transplantation when no other treatment options are available. Generally, only patients who meet the Milan criteria of a single tumour up to 5 cm or up to three tumours up to 3 cm, as determined by imaging studies,[6] are approved by the transplant organisations in most countries. Discussion at present focuses on expansion of these strict criteria, as on the one hand the removed liver often shows more tumour lesions than expected, and on the other hand patients with somewhat larger lesions often do well. In clinical practice, long waiting times for a suitable donor liver play an important negative role and strategies for downsizing or (temporary) control of the tumour are increasingly being used. Local ablative therapy, using radiofrequency ablation (RFA), is currently the preferred therapy in our centre in this situation.

Graft failure with the need for retransplantation accounts for an increasing number of transplantations. Shortly after transplantation. this mainly concerns primary nonfunction and hepatic artery thrombosis, later biliary complications and recurrent hepatitis C can become indications for retransplantation.

Although there is no formal age limit for liver transplantation, most centres rarely transplant patients over 65 years of age. It has been shown that older recipients (over 60 years) have a significantly reduced survival, mainly due to the high incidence of malignancies.[7,8]

Until recently, infection with the human immunodeficiency virus (HIV) was considered an absolute contraindication to liver transplantation. Many HIV infected patients, however, are co-infected with hepatitis B or C, and viral hepatitis and cirrhosis are a significant cause of mortality in these patients.[9,10] Also, the introduction of HAART (highly active antiretroviral therapy) has greatly improved survival in HIV-infected individuals. Currently, HIV infection is no longer an absolute contraindication for orthotopic liver transplantation (OLT), provided strict criteria for disease stage are fulfilled. Early results of OLT in HIV-positive patients are encouraging.[11,12]

Another development is the increasing number of patients transplanted with more than one organ. This can be done in patients with combined kidney/liver, intestine/liver or lung/liver failure.

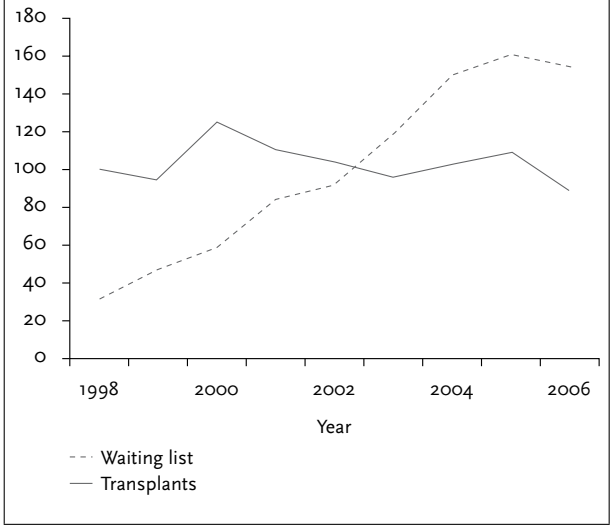
In general, the past few years are characterised by an increasingly shorter list of absolute contraindications and a growing list of indications for liver transplantation.

SELECTION OF DONOR AND RECIPIENT

Changing donor characteristics

Worldwide, physicians are struggling with waiting list mortality and an increasing demand for donor livers. This situation is also present in the Netherlands as can be seen in *figure 3*. This has led to expanded criteria for donor livers, accepting organs from 'compromised donors'. Where in previous decades many donors were young people dying of traumatic brain injury, currently over one third of donors are over 50 years of age.[13] To expand the donor pool, livers with steatosis and livers from donors with malignancies or prolonged ICU stay are being used with variable success rates.[14] The use of non-heart-beating donors (donation after cardiac death) may be a substantial source of donor organs. Transplantation using these grafts is unfortunately accompanied by increased rates of biliary strictures and early graft failure, leading to the need for retransplantation.[15,16] One way to improve the outcome of transplantation with organs from compromised donors is the use of better preservation solutions or

Figure 3. *Waiting list and number of liver transplants performed in the Netherlands from 1998-2006 (Source: Annual reports. Nederlandse Transplantatie Stichting)*



machine perfusion of the liver, providing hypothermic or possibly normothermic organ perfusion. These techniques are currently being tested for their value in clinical transplantation.[17]

Besides stretching donor criteria, other techniques have been used to expand the donor pool. For example, in some cases donor livers can be split into a right and left liver graft, with the potential to provide two patients with a donor organ.[18,19] It should be noted, however, that partial liver grafts generally perform worse than whole liver grafts.[20] Another option is to re-use the liver from patients undergoing liver transplantation for metabolic diseases such as familial amyloidotic polyneuropathy to transplant patients with cirrhotic liver disease.[21]

Live donor liver transplantation

A revolutionary way to expand the donor pool has been the use of partial liver grafts from live donors: live donor liver transplantation (LDLT). This procedure was pioneered in the late 1980s in children[22] and subsequently developed into a practice used worldwide. LDLT is currently commonly performed in the United States, Europe and especially Asia, where whole liver grafts are rarely used. Reports on significant donor morbidity and mortality have, however, tempered initial enthusiasm. In 2006, 4% of liver transplantations in the USA were performed using a graft from a living donor (source: www.unos.org). In the Netherlands, live-donor liver transplantation has been performed in adults (Rotterdam) and children (Groningen) since 2004. In 2006 three LDLT procedures have been performed in the Netherlands (source: annual report Nederlandse Transplantatie Stichting 2006). Whether LDLT will be of growing importance in the Netherlands remains to be seen, and is also dependent on for example the effects of the MELD score on waiting list mortality and public opinion on LDLT.

Although all the attempts to increase the donor pool mentioned above are worth pursuing, probably none of them will prove sufficient to increase the number of donor livers. In addition, grafts from marginal donors and split livers most likely have a negative influence on recipient outcome. A potential method to minimise this influence may be to better match donor and recipient characteristics.[23] Another possible solution may lie in changing legal issues regarding donorship and public awareness campaigns increasing the number of organ donors.

The MELD score for organ allocation

The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Germany, Luxemburg, the Netherlands, Slovenia and Croatia (candidate member). An important development in the allocation of donor organs has been the introduction of the MELD score (Model for End-stage Liver Disease).[24] Originally developed to calculate the risk for survival after placement of a TIPS (transjugular intrahepatic portosystemic shunt), the MELD score proved to be a predictor of survival in various liver diseases. The score is obtained by a mathematical calculation using three widely available laboratory variables: international normalised ratio (INR), serum creatinine and serum bilirubin (MELD = 9.57 x $\log_e$ (creatinine) + 3.78 x $\log_e$ (total bilirubin) + 11.2 x $\log_e$ (INR) + 6.43).

Since December 2006, Eurotransplant has been allocating livers by means of the MELD score. The MELD score was first used in the USA. In the late 1990s, when waiting list mortality was rapidly increasing in the USA, a different way to allocate organs was needed. Till that time, organs were allocated on the basis of both the severity of the liver disease as well as time spent on the waiting list. The rationale behind using the MELD score is the 'sickest first' policy, in which not the time on the waiting list but the mortality risk determines to whom an organ is allocated.[25] After introduction of the MELD score in the USA waiting list mortality dropped substantially.[26] MELD score is not applied in patients with fulminant hepatic failure. Modifications in organ allocations purely based on MELD are used in patients with metabolic disease and hepatocellular carcinoma, since the MELD score does not adequately reflect disease severity in these patients.

DEVELOPMENTS IN PERIOPERATIVE CARE AND THE SURGICAL PROCEDURE

With the increasing number of liver transplantations performed, the surgical technique and perioperative care have developed towards standardised procedures and management. Two subjects will be discussed in more detail below: intraoperative blood loss and the surgical technique of the caval vein anastomosis.

Intraoperative blood loss

Blood loss during liver transplantation used to be one of the most important causes of perioperative death in the early days of transplantation. Although rarely so these days, increased blood loss and subsequent transfusions still contribute to postoperative infection,[27] mortality[28] and surgical reintervention.[29]

Interventions to reduce blood loss during OLT have been surgical, anaesthesiological and pharmacological.[30] An important surgical contribution to minimise blood loss has been the implementation of the piggy-back technique (see below). The anaesthesiologist has a crucial role in correcting coagulation abnormalities with blood products, preventing hypothermia, correcting acidosis and maintenance of a low central venous pressure ensuring a low pressure in the

hepatic veins, inferior vena cava, as well as the splanchnic venous circulation.[30] In recent years, many controversies have surrounded the use of pharmacological agents used to prevent or treat blood loss during OLT. Aprotinine, recombinant factor VIIa and tranxenamic acid have been most widely studied. In selected cases it appears that these agents can contribute to a reduction in the need for blood products.[31,32] With the use of the measures mentioned above, in our centre 40% of first adult liver transplantations are currently performed without any transfusion of red blood cells.[30] The reduction in blood loss has also led to the successful transplantation of livers in Jehovah's witnesses.[33] Also in our centre Jehovah's witnesses are no longer excluded from liver transplantation.

The caval vein anastomosis

Classically, the reimplantation of the donor liver in orthotopic liver transplantation is performed using an end-to-end anastomosis to re-attach the supra- and infra-hepatic vena cava of the donor and recipient. In recent years, the cava-sparing or piggy-back technique has become the standard. In this technique, the recipient's retrohepatic inferior vena cava remains intact. The inferior vena cava of the donor liver is sutured in an end-to-side or side-to-side fashion to the vena cava of the recipient (*figure 4*).[34,35] By using this technique, dissection of the retroperitoneum is avoided and only one caval anastomosis has to be made, resulting in less blood loss, a shorter anhepatic phase and less haemodynamic instability. The piggy-back technique has proven to be both safe and efficient.[36,37]

IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION

Solid organ transplantation was revolutionised by the introduction of cyclosporine as an immunosuppressant in the 1980s. After cyclosporine, a number of other drugs (tacrolimus, mycophenolate mofetil, sirolimus) were introduced expanding the possibilities for immunosuppression. Large series describing results from the previous years mention acute rejection in 40 to 60% of liver transplant patients.[38,39] More recent data from the USA for 2003 show acute rejection in as few as 18% of patients (www.unos.org). Moderate to severe acute rejection has been described in up to 15% of transplants.[38] The vast majority of patients can be treated satisfactorily with boluses of steroids. Chronic rejection is a rare event in liver transplantation, occurring in less than 5% of patients.[40] On the long term, graft loss due to either acute or chronic rejection occurs in approximately 1% of liver transplant recipients.[38,40]

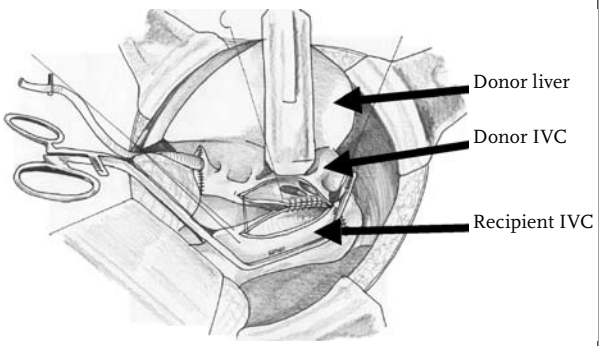
In the majority of liver transplant recipients, rejection is prevented by a combination of two or three different maintenance immunosuppressive drugs. The calcineurin inhibitors tacrolimus and cyclosporine are the mainstays of immunosuppression in liver transplantation. Over 95% of patients are discharged with a calcineurin inhibitor as a primary immunosuppressant, with tacrolimus being most frequently used (www.unos.org). In several analyses the superiority of tacrolimus over conventionally dosed cyclosporine with regards to the prevention of rejection has been shown.[39,41,42]

Steroids are still almost universally used after liver transplantation. There has been a trend towards a rapid steroid taper and steroid weaning shortly after transplantation.[43,44] Currently, in the USA most patients are discharged with steroids, which are subsequently weaned in the following months, and eventually completely stopped in over 50% of patients (www.unos.org).

Besides the particularly commonly used calcineurin inhibitors and steroids, antimetabolites (azathioprine or mycophenolate mofetil (MMF)) are also frequently used. UNOS data show that 60% of patients are discharged from the hospital on one of the two agents, with MMF being more frequently used. MMF is as safe as azathioprine but more effective in preventing acute rejection.[45] An advantage of antimetabolites is their profile of side effects which is markedly different from calcineurin inhibitors, thus creating the possibility to reduce the calcineurin inhibitor dose and preventing or limiting side effects such as renal dysfunction, hypertension and hyperlipidaemia.

Drugs that are currently under investigation are the m-TOR inhibitor sirolimus and the related everolimus. Potential advantages of these drugs are their lack of nephrotoxicity and the antifibrotic and antineoplastic characteristics. Their clinical value still needs to be proven in larger studies, although present data show great potential.[46-49] In general, one can say that currently the most important challenge with regards to immunosuppression in liver transplantation is not to find drugs that are more powerful, but drugs that are less harmful. In the

Figure 4. *Piggy-back procedure*



Lateral view, showing a side-to-side anastomosis between the recipient and donor inferior vena cava (IVC) (Drawing by Dr. B. Nemes).

meantime, the present availability of a wide spectrum of effective and specific immunosuppressive drugs allows individualised selection of drugs, thereby limiting serious side effects.

BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION

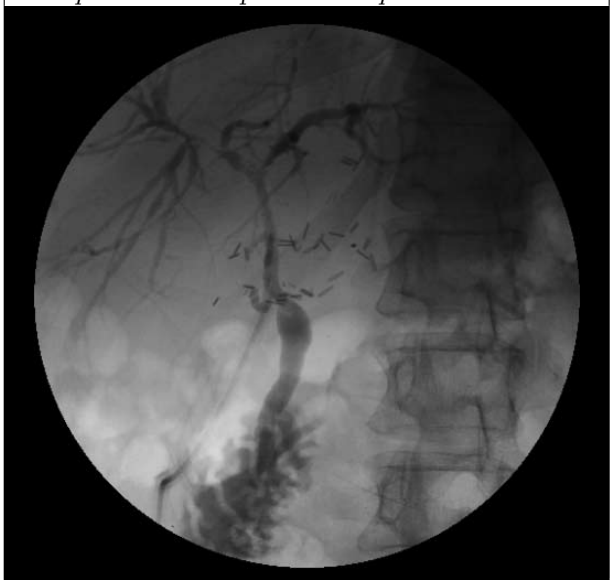
Since the early days of liver transplantation, biliary complications have been an important source of morbidity, and in severe cases even loss of the graft or mortality. Despite great improvements in both surgical and medical management of liver transplant recipients, biliary complications are still common, occurring in 6 to 35% of patients.[50] It appears that the biliary epithelium is much more susceptible to ischaemic injury than liver parenchyma and gross vascular structures.[51]

The biliary anastomosis in liver transplantation is most commonly performed making an end-to-end anastomosis of the donor and recipient common bile duct (choledocho-choledochostomy or duct-to-duct anastomosis). The remainder of transplants are performed using a roux-en-Y anastomosis (hepaticojejunostomy), especially when the recipient bile duct is too short or unsuitable, i.e. in patients with primary sclerosing cholangitis.

Of the biliary complications, leakage of bile and strictures of the biliary tree are most commonly encountered. Bile leakage is usually seen shortly after transplantation and occurs in 5 to 7% of patients.[50] It can occur at the site of the anastomosis, the cystic duct remnant or at the exit site of a biliary drain. The majority of cases can be successfully managed by placement of a stent through the sphincter of Oddi, reducing pressure in the common bile duct and preventing further leakage.[52,53]

Strictures of the biliary tree can be divided into anastomotic strictures (occurring at the site of the anastomosis of donor and recipients common bile duct) or nonanastomotic strictures (occurring elsewhere in the biliary system of the donor liver). Anastomotic strictures are usually due to fibrotic healing, and can be managed by ERCP in the vast majority of cases without any negative effects on the graft or patient survival.[54] Nonanastomotic strictures (NAS) are of a much more complex nature. They occur in approximately 15% of cases[55] and can present both early and late after transplantation. A radiological example of NAS is provided in *figure* 5. Their pathogenesis can be immunological, ischaemic or both.[56] In a number of patients, NAS are due to recurrent primary sclerosing cholangitis. In severe cases, NAS can lead to progressive destruction of the biliary tree, causing recurrent bacterial cholangitis, biliary fibrosis or even cirrhosis. Treatment can be attempted with multiple sessions of dilatation and stenting of stenotic areas. A considerable number of patients, however, will need a retransplantation.[57,58]

Figure 5. *Cholangiography via a biliary drain after liver transplantation, showing an example of nonanastomotic biliary strictures with predominantly hilar abnormalities*



LONG-TERM MANAGEMENT AND COMPLICATIONS AFTER LIVER TRANSPLANTATION

With increasing survival after liver transplantation, research nowadays focuses more and more on the long-term management of liver transplant recipients, up to decades after their transplantation. Late mortality after liver transplantation (occurring >1 year after initial surgery) can be divided into liver-related and liver-unrelated causes, with liver-unrelated causes being responsible for approximately 60% of late mortality.[59]

Liver-related causes of morbidity and mortality: recurrence of disease

Recurrence of hepatocellular carcinoma is especially common in patients with a poorly differentiated tumour or macroscopic vascular invasion.[60] Surgical treatment of recurrent disease should be considered, but outcome is almost universally dismal.[61]

Recurrence of autoimmune diseases in an organ from a donor is immunologically intriguing. Diagnosis can be difficult due to other potential causes for graft dysfunction. Recurrence of an early stage of primary biliary cirrhosis may occur in a majority of patients transplanted for this indication in the long term, but seldom leads to cirrhosis.[62] Recurrence of autoimmune hepatitis is seen in 22% of patients, and is treated as in nontransplant patients.[63] Recurrence of primary sclerosing cholangitis occurs in about 11% of patients;[63] diagnosis may be difficult because of overlap with nonanastomotic strictures from other causes.

Recurrence of hepatitis C is almost universally seen. It usually presents gradually in the postoperative course, but the fact that it can also progress rapidly leading to liver failure (fibrosing cholestatic hepatitis) is a well-known entity. During recent years, however, improved survival of patients transplanted for hepatitis C has been seen, with a ten-year patient survival of approximately 60%.[64] Currently, the treatment of recurrent HCV in the transplanted liver is under investigation with some promising preliminary results.[65]

Liver-unrelated causes of morbidity and mortality

Major liver-unrelated contributors to morbidity and mortality in long-term survivors after liver transplantation are *de novo* malignancies, cardiovascular disease, renal insufficiency and osteoporosis.

Malignancies

De novo malignancy has an incidence of 5 to 16% in different series.[66] They significantly increase post-transplant mortality, with a calculated relative risk of cancer-related mortality of almost 3 compared with a nontransplant population.[8] The risk for skin cancer shows the most marked increase, but also noncutaneous, solid organ cancer is more common than in the general population.[8,67] Contributors to this increased risk are high-risk behaviour before transplantation (smoking, alcoholism) and the life-long use of immunosuppressive drugs. Consequently, post-transplant management should focus on the elimination of risk factors, as well as minimising the amount of immunosuppression. A screening protocol should be adopted for surveillance after liver transplantation, especially when the patient is a smoker, or has documented inflammatory bowel disease or previous skin cancer.

Cardiovascular disease

Almost all of the known risk factors for cardiovascular disease have an increased prevalence in liver transplant recipients: hypertension, diabetes, hyperlipidaemia occur in up to 75%, 15% and 40 to 60% of patients, respectively, long-term after transplantation.[68] Also obesity is an increasing problem after liver transplantation, reported to occur in 30 to 70% of patients.[69] This increase in risk factors is at least partly due to the continuous use of immunosuppressive drugs. This combined with the previously mentioned high-risk behaviour leads to a markedly increased risk for atherosclerosis and subsequent cardiovascular events.[70] The relative risk for cardiovascular mortality in the liver transplant population has been calculated to be approximately 2.6 compared with age-matched controls.[71] Vigorous screening for cardiovascular risk factors and aggressive management is justified in all liver transplant recipients.

Renal insufficiency

Impaired renal function before transplantation, chronic use of calcineurin inhibitors and hypertension probably all contribute to the increased risk for chronic renal disease after liver transplantation. The cumulative risk of renal failure has been described to be as high as 20% five years after transplantation.[72] Strenuous management of hypertension and withdrawal or reduction of calcineurin inhibitors should be considered in an early stage.[73]

Osteoporosis

The combination of low bone mineral density before transplantation due to hepatic osteodystrophy, malnutrition and inactivity and steroid use after transplantation puts the liver transplant recipient at increased risk for osteoporosis.[68]

In the earlier era of transplantation, osteoporotic fractures were a major cause of morbidity after liver transplantation. In the present era, with lower dosages of corticosteroids and the availability of bisphosphonates, we have the tools to prevent or treat bone disease both before and after transplantation.

CONCLUSION AND FUTURE PERSPECTIVES

Diseases of the liver are becoming increasingly common.[74] In the near future, hepatitis C related morbidity will increase.[75] With the worldwide epidemic of obesity, a vast increase in the number of patients with nonalcoholic fatty liver disease can be expected.[76] Treatments for end-stage liver disease other than transplantation, such as antifibrotic agents, hepatocyte transplantation and *ex-vivo* liver support systems, are very promising but currently lack the efficacy to delay or replace transplantation. Considering the above, liver transplantation will continue to be the standard of care for patients with end-stage liver disease in the next decades.

Liver transplantation has become an incredibly successful therapy for end-stage liver disease. With the enormous progress that has been made in the past decades, the focus of research and patient care in liver transplantation has shifted. In the future, strategies to stimulate a form of 'tolerance' for the transplanted organ will continue to be searched for, with some promising developments already on the horizon. A great problem is the donor shortage, for which a solution still needs to be found. With the increasing long-term survival of liver transplant recipients, the aim of current practice should be to gain a normal life expectancy and quality of life for these patients. Prevention and management of cardiovascular mortality and malignancies long-term after successful transplantation deserves full attention.

REFERENCES

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet 1963;117:659-76.
2. National Institutes of Health Consensus Development Conference Statement: liver transplantation--June 20-23, 1983. Hepatology 1984;4 (1 suppl):S107-10.
3. Kim WR, Poterucha JJ, Kremers WK, Ishitani MB, Dickson ER. Outcome of liver transplantation for hepatitis B in the United States. Liver Transpl 2004;10:968-74.
4. Liu JP, Gluud LL, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for liver failure. Cochrane Database Syst Rev 2004;(1):CD003628.
5. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation 2004;77:64-71.
6. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-9.
7. Collins BH, Pirsch JD, Becker YT, et al. Long-term results of liver transplantation in older patients 60 years of age and older. Transplantation 2000;70:780-3.
8. Herrero JI, Lorenzo M, Quiroga J, et al. De Novo neoplasia after liver transplantation: an analysis of risk factors and influence on survival. Liver Transpl 2005;11:89-97.
9. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. J Hepatol 2005;42:799-805.
10. Tatsunami S, Taki M, Shirahata A, Mimaya J, Yamada K. Increasing incidence of critical liver disease among causes of death in Japanese hemophiliacs with HIV-1. Acta Haematol 2004;111:181-4.
11. Castells L, Escartin A, Bilbao I, et al. Liver transplantation in HIV-HCV coinfected patients: a case-control study. Transplantation 2007;83:354-8.
12. Roland ME, Stock PG. Liver transplantation in HIV-infected recipients. Semin Liver Dis 2006;26:273-84.
13. Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? J Hepatol 2006;45:484-8.
14. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. Liver Transpl 2003;9:651-63.
15. Abt P, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. Transplantation 2003;75:1659-63.
16. Foley DP, Fernandez LA, Leverson G, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Ann Surg 2005;242:724-31.
17. Maathuis MH, Leuvenink HG, Ploeg RJ. Perspectives in organ preservation. Transplantation 2007 May 27;83(10):1289-98.
18. Cardillo M, De Fazio N, Pedotti P, et al. Split and whole liver transplantation outcomes: a comparative cohort study. Liver Transpl 2006;12:402-10.
19. Yersiz H, Renz JF, Farmer DG, Hisatake GM, McDiarmid SV, Busuttil RW. One hundred in situ split-liver transplantations: a single-center experience. Ann Surg 2003;238:496-505.
20. Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet 2006 Jan 21;367(9506):225-32.
21. Ericzon BG, Larsson M, Herlenius G, Wilczek HE. Report from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR) and the Domino Liver Transplant Registry (DLTR). Amyloid 2003;10(suppl 1):67-76.
22. Raia S, Nery JR, Mies S. Liver transplantation from live donors. Lancet 1989;2:497.
23. Burra P, Porte RJ. Should donors and recipients be matched in liver transplantation? J Hepatol 2006;45:488-94.
24. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864-71.
25. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007;45:797-805.
26. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 2003;124:91-6.
27. Gayowski T, Marino IR, Singh N, et al. Orthotopic liver transplantation in high-risk patients: risk factors associated with mortality and infectious morbidity. Transplantation 1998;65:499-504.
28. Mor E, Jennings L, Gonwa TA, et al. The impact of operative bleeding on outcome in transplantation of the liver. Surg Gynecol Obstet 1993;176:219-27.
29. Hendriks HG, van der Meer J, de Wolf JT, et al. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. Transpl Int 2005;17:673-9.
30. de Boer MT, Molenaar IQ, Hendriks HG, Slooff MJ, Porte RJ. Minimizing blood loss in liver transplantation: progress through research and evolution of techniques. Dig Surg 2005;22:265-75.
31. Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. Am J Transplant 2007;7:185-94.
32. Xia VW, Steadman RH. Antifibrinolytics in orthotopic liver transplantation: current status and controversies. Liver Transpl 2005;11:10-8.
33. Jabbour N, Gagandeep S, Mateo R, Sher L, Genyk Y, Selby R. Transfusion free surgery: single institution experience of 27 consecutive liver transplants in Jehovah's Witnesses. J Am Coll Surg 2005;201:412-7.
34. Polak WG, Miyamoto S, Nemes BA, et al. Sequential and simultaneous revascularization in adult orthotopic piggyback liver transplantation. Liver Transpl 2005;11:934-40.
35. Polak WG, Nemes BA, Miyamoto S, et al. End-to-side caval anastomosis in adult piggyback liver transplantation. Clin Transplant 2006;20:609-16.
36. Jovine E, Mazziotti A, Grazi GL, et al. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. Transpl Int 1997;10:109-12.
37. Miyamoto S, Polak WG, Geuken E, et al. Liver transplantation with preservation of the inferior vena cava. A comparison of conventional and piggyback techniques in adults. Clin Transplant 2004;18:686-93.
38. Demetris AJ, Ruppert K, Dvorchik I, et al. Real-time monitoring of acute liver-allograft rejection using the Banff schema. Transplantation 2002;74:1290-6.
39. Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus for liver transplanted patients. Cochrane Database Syst Rev 2006;(4):CD005161.
40. Jain A, Demetris AJ, Kashyap R, et al. Does tacrolimus offer virtual freedom from chronic rejection after primary liver transplantation? Risk and prognostic factors in 1,048 liver transplantations with a mean follow-up of 6 years. Liver Transpl 2001;7:623-30.
41. McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant 2006;6:1578-85.
42. O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. Lancet 2002;360:1119-25.
43. Pageaux GP, Calmus Y, Boillot O, et al. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. Liver Transpl 2004;10:1454-60.
44. Ringe B, Braun F, Schutz E, et al. A novel management strategy of steroid-free immunosuppression after liver transplantation: efficacy and safety of tacrolimus and mycophenolate mofetil. Transplantation 2001;71:508-15.
45. Wiesner R, Rabkin J, Klintmalm G, et al. A randomized double-blind comparative study of mycophenolate mofetil and azathioprine in combination with cyclosporine and corticosteroids in primary liver transplant recipients. Liver Transpl 2001;7:442-50.

46. Levy G, Schmidli H, Punch J, et al. Safety, tolerability, and efficacy of everolimus in de novo liver transplant recipients: 12- and 36-month results. Liver Transpl 2006;12:1640-8.

47. Neuhaus P, Klupp J, Langrehr JM. mTOR inhibitors: an overview. Liver Transpl 2001;7:473-84.

48. Semela D, Piguet AC, Kolev M, et al. Vascular remodeling and antitumoral effects of mTOR inhibition in a rat model of hepatocellular carcinoma. J Hepatol 2007;46:840-8.

49. Zaghla H, Selby RR, Chan LS, et al. A comparison of sirolimus vs. calcineurin inhibitor-based immunosuppressive therapies in liver transplantation. Aliment Pharmacol Ther 2006;23:513-20.

50. Verdonk RC, Buis CI, Porte RJ, Haagsma EB. Biliary complications after liver transplantation: a review. Scand J Gastroenterol Suppl 2006;243;89-101.

51. Noack K, Bronk SF, Kato A, Gores GJ. The greater vulnerability of bile duct cells to reoxygenation injury than to anoxia. Implications for the pathogenesis of biliary strictures after liver transplantation. Transplantation 1993;56:495-500.

52. Morelli J, Mulcahy HE, Willner IR, et al. Endoscopic treatment of post-liver transplantation biliary leaks with stent placement across the leak site. Gastrointest Endosc 2001;54:471-5.

53. Saab S, Martin P, Soliman GY, et al. Endoscopic management of biliary leaks after T-tube removal in liver transplant recipients: nasobiliary drainage versus biliary stenting. Liver Transpl 2000;6:627-32.

54. Verdonk RC, Buis CI, Porte RJ, et al. Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transpl 2006;12:726-35.

55. Buis CI, Verdonk RC, van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 1: Radiological features and risk factors for early vs. Late presentation. Liver Transpl 2007;13:708-18.

56. Buis CI, Hoekstra H, Verdonk RC, Porte RJ. Causes and consequences of ischemic-type biliary lesions after liver transplantation. J Hepatobiliary Pancreat Surg 2006;13:517-24.

57. Guichelaar MM, Benson JT, Malinchoc M, Krom RA, Wiesner RH, Charlton MR. Risk factors for and clinical course of non-anastomotic biliary strictures after liver transplantation. Am J Transplant 2003;3:885-90.

58. Verdonk RC, Buis CI, van der Jagt EJ, et al. Nonanastomotic biliary strictures after liver transplantation, part 2: Management, outcome, and risk factors for disease progression. Liver Transpl 2007;13:725-32.

59. Pruthi J, Medkiff KA, Esrason KT, et al. Analysis of causes of death in liver transplant recipients who survived more than 3 years. Liver Transpl 2001;7:811-5.

60. Zavaglia C, De CL, Alberti AB, et al. Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. Am J Gastroenterol 2005;100:2708-16.

61. Roayaie S, Schwartz JD, Sung MW, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 2004;10:534-40.

62. Jacob DA, Neumann UP, Bahra M, et al. Long-term follow-up after recurrence of primary biliary cirrhosis after liver transplantation in 100 patients. Clin Transplant 2006;20:211-20.

63. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. Liver Transpl 2006;12:1813-24.

64. Belli LS, Burroughs AK, Burra P, et al. Liver transplantation for HCV cirrhosis: Improved survival in recent years and increased severity of recurrent disease in female recipients: Results of a long term retrospective study. Liver Transpl 2007;13:733-40.

65. Oton E, Barcena R, Moreno-Planas JM, et al. Hepatitis C recurrence after liver transplantation: Viral and histologic response to full-dose PEG-interferon and ribavirin. Am J Transplant 2006 ;6:2348-55.

66. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 2005;56:87-99.

67. Haagsma EB, Hagens VE, Schaapveld M, et al. Increased cancer risk after liver transplantation: a population-based study. J Hepatol 2001;34:84-91.

68. Sethi A, Stravitz RT. Review article: medical management of the liver transplant recipient - a primer for non-transplant doctors. Aliment Pharmacol Ther 2007;25:229-45.

69. Munoz SJ, Elgenaidi H. Cardiovascular risk factors after liver transplantation. Liver Transpl 2005;11(11 suppl 2):S52-6.

70. Neal DA, Tom BD, Luan J, et al. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? Transplantation 2004;77:93-9.

71. Johnston SD, Morris JK, Cramb R, Gunson BK, Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. Transplantation 2002;73:901-6.

72. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 2003;349:931-40.

73. Fairbanks KD, Eustace JA, Fine D, Thuluvath PJ. Renal function improves in liver transplant recipients when switched from a calcineurin inhibitor to sirolimus. Liver Transpl 2003;9:1079-85.

74. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet 2006;367:52-6.

75. Buti M, San MR, Brosa M, et al. Estimating the impact of hepatitis C virus therapy on future liver-related morbidity, mortality and costs related to chronic hepatitis C. J Hepatol 2005;42:639-45.

76. Haslam DW, James WP. Obesity. Lancet 2005;366:1197-209.