Update on liver transplantation

Indications for liver transplant are expanding and most patients can expect a long-term successful outcome. Who should receive this life-saving gift and how should they be managed in an era of diminishing donors and increasing demand?

Liver transplantation is an established part of the management of chronic liver disease, acute liver failure, certain liver cancers and some metabolic conditions. Its marked success has had a number of consequences for case selection, organ allocation and surgical expertise. Immunosuppression has also developed and enabled long-term survival. This article outlines the areas of recent progress in liver transplantation and future developments and their potential impact.

Indications

Currently seven centres provide liver transplant services in the UK. Referrals have increased in number and quality as this treatment has become more successful, but there is still some way to go (Devlin and O'Grady, 1999). This article describes the process whereby potential liver transplant recipients are evaluated (*Figure 1*) and outlines the indications and their development in European liver transplantation practice (Hirschfield et al, 2009).

Figure 1. Patient journey through liver transplantation process from referral to post-transplant clinic.

Referral		
Assessment	Is liver transplantation indicated?	Objective evidence of liver failure
		Subjective symptoms
		Tumour
		Metabolic
	Is liver transplantation 'safe'?	Evidence of serious co-morbidity?
		Absent splanchnic circulation
		Uncontrolled immune deficiency
Multidisciplinary team meeting	Decision to accept onto waiting list	
Waiting list for liver transplantation	Approximately 15% die before transplantation	
	Continue to monitor for disease progression, e.g. hepatocellular cancer	
	Patients with advanced disease may be prioritized	
Liver transplantation operation	Surgical complications, e.g. biliary, arterial, venous	
	Medical complications: rejection, infection, immunosuppression	
Follow-up clinic	Drug monitoring, graft dysfunction	
	Monitor for disease recurrence	
	Monitor for cardiovascular risk factors, renal impairment, obesity etc	
	Screen for malignancy	

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Evaluation of patients pre-transplant

Referral

Acute liver failure is defined by the appearance of coagulopathy, encephalopathy and jaundice usually on a background of no previous liver disease and within a period of a few days to 26 weeks. All such patients should be discussed with a liver transplant unit. As patients with chronic liver disease deteriorate, the potential role of a liver transplant should be carefully considered. Over 6000 patients in the UK die every year with chronic liver disease, and only a fraction of those are seen or discussed with a liver transplantation unit, so a proportion of suitable patients may be missing out on a life-saving therapy.

As patients with chronic liver disease develop progressive jaundice, ascites (50% mortality within 12 months), variceal bleeding (60% survival at 12 months), encephalopathy and hepatorenal syndrome, whether such patients would benefit from liver transplantation and whether they are suitable candidates should be considered. Referral or discussion of such patients with the nearest liver transplant centre is appropriate and a decision that a patient is not suitable for transplant should be documented, along with the reasons for this decision.

The Model for End-stage Liver Disease score (United Network for Organ Sharing, 2009) was developed in the USA to try and predict mortality on a liver transplant waiting list and allow linking of organs to recipients to optimize outcomes and patient survival. UK Model for End-stage Liver Disease, its UK counterpart, incorporates serum sodium levels and gives a better prediction of likelihood of dying while on the waiting list for a liver transplant. *Figure 2* outlines the use of this score (Neuberger et al, 2008).

Transplant assessment

Liver transplant units consider two questions for all patients referred as potential liver transplantation recipients: is liver transplantation indicated and is it safe?

To answer these questions, each patient undergoes a variety of blood tests including blood-borne viruses, extensive cardiopulmonary testing and psychosocial evaluation. Anaesthetic, nursing and surgical assessment, and dietetic evaluation are routinely performed and further input from a substance misuse nurse may also be needed.

Listing meeting

Once the test results are known and the evaluations complete, the individual patient's case is presented at a multidisciplinary meeting where, assuming agreement is reached, the patient is accepted onto the transplant wait-

ing list. Those deemed unsuitable for liver transplantation are offered a second opinion in another unit.

Waiting list

The waiting time for liver transplantation recipients is a period of great uncertainty. Around 85% of patients accepted onto the waiting list will receive an organ; the remainder either die waiting or become so unwell that they aree deemed unlikely to survive the operation (van der Meulen et al, 2007). A few patients improve while waiting, most commonly alcoholic patients whose livers continued to recover despite them having completed the mandatory period of abstinence. The 'top band' system allows patients who deteriorate on the waiting list to be prioritized within or among participating units (three liver transplant centres in the north of England). These patients rank below the 'super-urgent' category but above general waiting list patients. However, as waiting lists grow in size there is a risk that only patients with advanced disease will receive transplants. The average wait is around 100 days, but there are great variations across blood groups (UK Transplant, 2009).

Transplant operation

Liver transplant surgery requires skilled anaesthesia to present and maintain a stable patient with organ failure through the period of hepatectomy, anhepatic phase and liver implantation. The surgery involves excision of the liver often on a background of severe portal hypertension, followed by implantation and careful vascular and biliary anastomoses. The main transplant-specific concerns during the early postoperative period relate to infection and organ rejection. Patients are managed in a multidisciplinary environment, requiring skilled input from dietetics, nursing staff and pharmacists.

Transplant clinic

Around 600 patients receive liver transplants in the UK each year. Over 90% survive the first year and 60% are alive at 10 years. The first few months after surgery often require the most input, with monitoring of drug levels and recovery. With time, rejection becomes less likely and the emphasis of the transplant clinic changes (see below).

Emerging indications

Over the last 20 years, the number of adults transplanted for cholestatic liver disease has steadily declined, mirrored by a rise in numbers transplanted for alcoholic liver disease and viral hepatitis, particularly hepatitis C. Liver cancer, which provided a ready supply of potential patients when the technique was being developed, now accounts for less than 1 in 10 of organs transplanted (European Liver Transplant Registry, 2009) (*Figure 3*).

Acute liver failure

Acute liver failure patients account for nearly 9% of transplant recipients. Paracetamol is the major contributor to this group in the UK where strict criteria exist to enable access to a country-wide donor pool (super-urgent waiting list) in recognition of the poor outcome if the wait for an organ is more than a few days. Paracetamol packaging was limited in 1998 in the UK to 8 g (16 tablets), which has reduced referral to liver transplantation units but appears not to have affected mortality rates (Morgan and Majeed, 2005). The lack of development of any effective liver support device to obviate the need for liver transplantation in this group is perhaps the most startling 'non-event' in hepatology practice.

Principles of selection to a waiting list	Selection is based on risk of death without a transplant
	Selection is based on ability of transplant to improve quality of life
	All cases on a waiting list should be reviewed regularly so they continue to meet criteria
	Criteria for removal from the list is agreed
Selection for super-urgent list	Ten categories allow access to the entire national pool for patients with acute liver failure
Selection for adult 'elective' waiting list	Category 1: 1-year liver disease mortality without liver transplant of > 9% based on UK Model for End-stage Liver Disease score >49
	Category 2: hepatocellular cancer – single lesion <5 cm in diameter or three or less lesions <3 cm in diameter
	Category 3: Variant syndromes – including diuretic-resistant ascites, hepatopulmonary syndrome, chronic encephalopathy, intractable pruritis
Allocation of donor organs	Maximize organ utility
	Reduce waiting list mortality
	Can an organ be split to service two recipients?
	Top band of patients at greatest risk of dying will be identified by UK Model for End-stage Liver Disease score
	Matching of donors and recipients based on need and donor issues (e.g. quality)

Figure 2. Summary of UK liver transplantation guidelines for selection and allocation. From Neuberger et al (2008).

Alcoholic liver disease

Alcoholic liver disease accounts for 18% of all transplants performed in Europe. The proportion of patients transplanted for this has steadily increased as their outcome is no worse than patients with non-alcoholic chronic liver disease. However, the effects of alcohol on other organs and general nutritional status may preclude safe transplantation. The general public is, at best, lukewarm in their support of liver transplantation for this indication, not least as a result of high-profile cases of recidivism post transplant (Neuberger, 2007). UK transplant centres all use a similar guideline requiring 6 months of absolute abstinence: this enables patients whose liver may recover without transplant the opportunity to do so, and allows identification of those who may relapse so that they can access appropriate help and support. The 6-month guideline does not predict post liver transplantation relapse, nor

does post liver transplantation relapse necessarily adversely affect graft or patient survival (Bathgate, 2006).

Hepatitis C

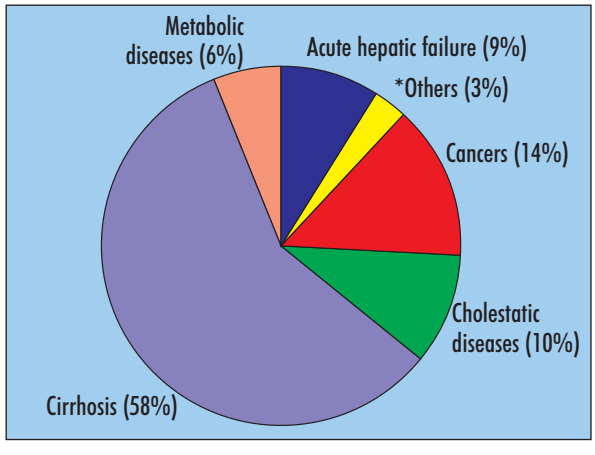
Hepatitis C (15% liver transplantation in Europe) is now the leading indication for liver transplantation in the USA. However, organ re-infection is universal, long-term survival is disappointing and re-graft outcomes for patient and organ are very poor compared to other indications for liver transplantation. Considerable effort has been made to identify factors that might account for this. Early graft dysfunction as a result of viral re-infection was often misrecognized as rejection and treated with high-dose steroids. It is now apparent that this was akin to pouring petrol on the fire and accounts for the severe and inexorable decline in such patients in the early days of transplantation for hepatitis C. Recipients of organs from older donors (>40 years) have a worse survival (Mutimer et al, 2006) which, in an era of an ageing donor pool, might increase the demand for live donor liver transplantation in the future. Some centres do not offer re-graft for hepatitis C patients, but with progress in histopathological interpretation and donor-specific factors, outcomes for this group of recipients are likely to improve and re-graft when necessary will not be an unreasonable option.

Hepatocellular cancer

Hepatocellular cancer accounted for nearly half the liver transplantations performed in Europe in the early period of liver transplantation development. Currently 9% of liver transplants in Europe have taken place for hepatocellular cancer as experience of tumour recurrence has accumulated. The first attempt to address this came from the Milan group who identified tumour size and volume with evidence of vascular invasion in a retrospective analysis (Mazzafero et al, 1996). Despite the flaws in this analysis, the absence of any alternative led to its adoption by many centres and the broadening of the criteria to a single lesion less than 6.5 cm or up to three lesions less than 4.5 cm with a total volume less than 8 cm has been hailed as an improvement (Said and Lucey, 2008).

However, these criteria remain radiology based, no tumour biology is taken into account and there are many anecdotal and case series reports of patients transplanted for larger tumours who do very well. The use of tumour down staging, to bring patients within transplant criteria, has been widely reported but not fully evaluated, and living donors have enabled patients outside of established criteria to have liver transplants. Live donation also reduces the time on the waiting list and may 'hide' the true nature of the hepatocellular cancer. Other tumours, such as cholangiocarcinoma, have poor outcomes and should only be considered in the setting of a clinical trial.

Figure 3. Primary disease leading to liver transplantation in Europe January 1998–December 2008. From European Liver Transplant Registry (2009). *Others: Budd Chiari = 675, benign liver tumours or polycystic diseases = 934, parasitic diseases = 67, other liver diseases = 533.



Human immunodeficiency virus

Before the advent of highly active anti-retroviral therapy (HAART) in the 1990s, human immunodeficiency virus (HIV) was an absolute contraindication to liver transplantation. The arrival of HAART altered the spectrum of HIV-related disease (Norris and Houlihan, 2008). The leading cause of death has become liver failure as a result of hepatitis C virus co-infection. The British HIV Association published guidelines for liver transplantation in HIV-positive individuals, which require a reconstituted immune system, i.e. CD4 count >200 cells/μl and absence of HIV viraemia (O'Grady et al, 2005). The presence of lymphoma, progressive multi-focal leukencephalopathy or visceral Kaposi's sarcoma are among absolute contraindications. The numbers of HIV-positive patients transplanted are small, but several studies have been published. One of the largest is the United Network for Organ Sharing (American) database, which showed a 2-year survival of 70% among 138 HIV-positive patients compared with 80% survival in the 30 520 HIV-negative patients. In the non-viral hepatitis-infected individuals, there was no significant difference between the two groups (Mindikoglu et al, 2008). Patients with HIV and hepatitis C virus co-infection seem to develop accelerated liver disease, so should be referred earlier for transplantation.

Organ availability, allocation and procurement

Over the last 10 years, the number of individuals waiting for liver transplantation has almost doubled while the actual number of liver transplants performed has fallen. This disparity would be even worse were it not for the surgical developments outlined below. Donor numbers in the UK are poor compared to many other European countries and attempts to improve this have so far been unsuccessful, with the inevitable consequence that a degree of resource rationing ensues.

In the UK, the liver transplantation community has tried to rationalize the selection and allocation process and involve the public in the process to enhance transparency

and 'fairness'. In 1996 guidelines were agreed among the transplant community, public and ethicists that:

- Donor organs are a national resource
- Patients should be selected for liver transplantation if their expected survival is less than 12 months or the liver disease gives them an unacceptable quality of life
- Patients who receive a graft should have a survival probability of 50% or more at 5 years (Neuberger and James, 1999).

The increasing scarcity of organs since these guidelines were drawn up has increased pressure on clinicians, resulting in further attempts to clarify the processes involved in case selection and organ allocation. In the UK this has been driven by the liver transplant community themselves supported by the NHS. The results of these deliberations were published in 2008 (Neuberger et al, 2008).

Surgical techniques

The success of liver transplantation has driven attempts to optimize the donor pool and develop new technologies (Petrowsky and Busuttil, 2009):

Split liver transplantation

Split liver transplantation is most commonly used to enable paediatric liver recipients to receive a left lateral segment and an adult to receive the remainder. A 'full' split divides the liver more equally for two adult recipients.

Living donor liver transplantation

Living donor liver transplantation involves resection of a partial graft from a healthy living donor and its transplantation into a recipient (Brown, 2008). The recipient receives a good quality graft, with minimal ischaemia time delivered at a known time, while the donor risks death (0.2–0.5%) and morbidity (15–40%). Outcomes are good for donor, recipient and graft (Olthoff et al, 2005).

Non-heart-beating donors

Non-heart-beating donor organs come from a donor who has had life support withdrawn after the multidisciplinary team has decided that further treatment is futile. Non-heart-beating donor organs have significantly enhanced the donor pool for kidney transplants (White and Prasad, 2006), but inferior graft survival and higher re-graft rates have been seen in liver transplantation.

Domino grafts

Livers from patients with diseases that are cured by liver transplantation, e.g. familial amyloid syndromes and certain metabolic disorders, can be used to benefit patients who may not receive an organ under usual circumstances (advanced liver cancer or recurrent primary disease) or who cannot wait for their turn on the waiting list.

Extended criteria grafts

Extended criteria grafts or marginal grafts are typically grafts that are associated with poor function and reduced survival. They include: older donors, donors post cardiac arrest, hepatitis C virus-infected donors, hepatitis B virus-infected donors, fatty livers and organs that have been cold stored for a long period (increased cold ischaemia time) (Reese et al, 2008).

Auxiliary liver transplant

Auxiliary liver transplant involves the resection of part of the native liver and the implantation of a donor graft, typically for patients with acute liver failure. Once the remnant liver recovers, immunosuppression is slowly withdrawn, the donor liver shrinks and the native liver regenerates (Lodge et al, 2008).

New technologies

Livers from pigs (xenotransplantation) could be genetically modified but they evince a rapid humoral rejection response and the discovery of porcine endogenous retrovirus has dampened enthusiasm for this technique.

Hepatocyte transplantation is an attractive option for metabolic conditions, whereby normal hepatocytes are injected into the portal vein and 'seed' in the liver. Stem cells derived from human bone marrow can mature in hepatocytes and human trials in liver disease are underway.

Immunosuppression

The discovery of the calcineurin inhibitor ciclosporin, was one of the milestones of liver transplantation. This drug in its current form (Neoral) and its 'sister' tacrolimus form the backbone of immunosuppression regimens across the world. *Figure 4* outlines standard immunosuppression protocols. Most patients in the UK receive a bolus dose of steroid at the time of transplantation and then a combination of oral calcineurin inhibitor plus an antimetabolite and a short course of steroids as maintenance. This triple combination reduces the incidence of acute cellular rejection to around one in three patients.

Recent trends in immunosuppression use suggest that tacrolimus does have some benefits, although opinions are not uniform (O'Grady et al, 2007). Steroids are usually tapered, and by 3 months post transplant have been stopped altogether. Dependence on calcineurin inhibitors is not without its drawbacks. While the calcineurin inhibitors are potent and provide excellent immune suppression, their side effects include nephrotoxicity, dyslipidaemia, hypertension and, particularly with tacrolimus, diabetes and neurotoxicity. When liver transplant patients are rou-

Figure 4. Standard immunosuppression protocols post liver transplant.

Induction	Intravenous steroids at surgery Consider monoclonal antibodies				
Maintenance	Tacrolimus or neoral	+	Azathioprine or mycophenolate mofetil	+	Corticosteroids (short period only)
Anti-rejection therapy	High dose corticosteroids				
	Monoclonal antibodies				

tinely surviving into their second decade post transplant, these cardiovascular and renal side effects become very significant. As the likelihood of rejection diminishes over time, the post transplant management of these patients focuses less on graft wellbeing and more on minimizing side effects of medication and looking for comorbidity.

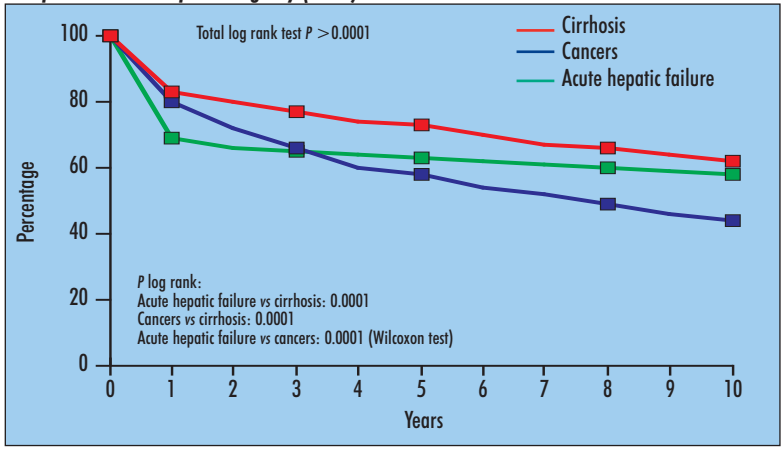
More recent immunosuppressants include sirolimus and everolimus. Experience with these drugs is limited, but sirolimus appears to have an antifibrotic and antiproliferative effect that makes it attractive for patients transplanted for cancer and perhaps also those who have developed fibrosis following transplant for hepatitis C. Its side effects include poor wound healing, hyperlipidaemia, nephrotic syndrome and perhaps a higher hepatic artery thrombosis rate. Its main attraction is its absence of effect on renal function, and sirolimus is often used as a renal-sparing agent when calcineurin inhibitor-related renal toxicity is seen.

Many liver transplantation recipients survive with minimization of their immunosuppression, and do not develop graft dysfunction, which is at odds with the experience of transplanting other organs. A review of this 'operational tolerance' described studies in immunosuppression withdrawal from 19 centres (Orlando et al, 2009). Of 223 patients who had no additional treatment, only 69 (30%) remained free of immunosuppression, while 51 (22%) had episodes of rejection. More worrying was the finding that rejection might occur at any time, even after a long period of established withdrawal of immunosuppression and that liver pathology was more alarming than biochemistry. Attempts to encourage tolerance with lymphocyte depletion, ursodeoxycholic acid, stem cell transplantation or donor bone marrow cell infusion have met with varying degrees of success. At present, data are too preliminary and outcomes too unpredictable to be able to recommend immunosuppression withdrawal outside of a carefully considered clinical trial.

Outcomes

The 1, 5 and 10-year survival rates for all liver transplantation based on the European Liver Transplant Registry results are 83%, 71% and 61% respectively (*Figure 5*). From the same database, it is clear that year of transplant is critical with distinct improvement in latter years. The 1-year survival in patients transplanted before 1985, 1985–9, 1990–4, 1995–9, 2000–4 and after 2004 were 34%, 64%, 79%, 81%, 84% and 85% respectively. It is expected that these improved 1-year survival data will translate into improved longer-term survival.

Figure 5. Patient survival according to the first disease January 1988–June 2008. From European Liver Transplant Registry (2009).



Comparison suggests that grafts from living donors have similar or better outcomes than deceased donor grafts. Split grafts in children yield excellent results, but adults receiving splits have poorer graft outcomes in some series. Similarly, the results of larger series reporting the outcomes for recipients and grafts of extended criteria and non-heart beating donors suggest these types of graft are inferior. It is hoped that over time, outcomes for these less successful grafts will improve as data on appropriate recipients accumulate and surgical techniques mature.

Finally, examination of the recipient's primary diagnosis suggest that recipients transplanted for primary biliary cirrhosis have the best outcome (71% 10-year survival), viral hepatitis recipients have a 10-year survival of 61% and alcoholic liver disease is 56%. The advent of new antivirals for hepatitis B has moved outcomes for this condition closer to that of primary biliary cirrhosis, while accumulating experience of post-transplant management of hepatitis C has improved outcomes in recent years compared to those transplanted up to a decade ago.

Long-term management

Long-term management of patients who have had a liver transplant can be divided into liver-related issues, non-liver consequences and malignancy. Osteoporosis, a common consequence of chronic liver disease, deteriorates for the first 3–6 months post surgery and then begins to recover. Dual energy X-ray absorptiometry scanning helps to decide which patients need bisphosphonates.

Liver-related issues

The recurrence of certain diseases post liver transplant require careful observation. Hepatitis C, cholestatic liver diseases and autoimmune disease may recur (Mells and Neuberger, 2009). Pharmacological interventions may alter the progress of recurrent disease. In contrast, recurrent hepatocellular cancer has no effective treatment.

Non-liver-related issues

Cardiovascular risk factors are more prevalent in liver transplant recipients. By 5 years post liver transplantation nearly one in ten recipients will have had a cardiovascular 'event' and by 10 years this is one in four. Obesity (20–40% of recipients), hyperlipidaemia (up to 30%), hypertension (up to 85%) and diabetes (de novo in up to 30%) (Hirschfield et al, 2009) all contribute to a much increased risk of cardiovascular death in liver transplant recipients. Renal impairment results from calcineurin inhibitors and its associated hypertension. Up to 20% of American trans-

plant recipients are on dialysis or have had a renal transplant. Smokers should be encouraged to stop smoking.

Malignancy

Malignancies, including skin-related tumours and lymphoma (post transplant lymphoproliferative disorder), are more common post liver transplantation. Comparison with age and gender-matched controls show that the relative risk of cancer in liver transplant recipients is at least twice the normal risk. Routine post transplant care should include examination of sun-exposed skin for evidence of skin malignancies. Patients presenting with fevers and/or weight loss, even within the first few months of liver transplantation, should be carefully screened for post transplant lymphoproliferative disorder.

Infections

Cytomegalovirus infection, either as a de novo event or as a recrudescence of a chronic infection, can cause pyrexia of unknown origin, weight loss and neutropenia. Treatment usually involves reduction of immunosuppression and specific antivirals such as ganciclovir or foscarnet. Annual flu vaccination is recommended.

Conclusions

Over 90% of liver transplantation recipients will survive to the first anniversary of their transplant and over 60% will survive to their tenth anniversary. Indications have broadened and now incorporate HIV as well as the expanding number of patients with viral hepatitis and alcoholic liver disease. The undoubted success of the procedure has fuelled demand way beyond the current availability of organs, hence organ allocation has had to be scrutinized and revised to optimize benefit.

Surgical innovations are attempting to bridge the widening gap between supply and demand, but the impact so far has not been significant. Calcineurin inhibitor-based immunosuppression has extended the life of recipients and grafts and altered the emphasis in post transplant clinics from organ-centred review to the management of cardiovascular risk factors and careful screening for tumours. The last two decades have witnessed great success in liver transplantation, but to maintain the trajectory of this success requires a sustainable, sufficient supply of high quality organs. **BJHM**

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KEY POINTS

- The majority of transplant recipients will survive to 1 year and nearly three quarters will make it to 10 years.
- Successful outcomes inevitably result in expanding indications, but the donor pool is relatively static.
- Developments in organ allocation should reduce deaths on the waiting list, while surgical innovation may increase the donor pool.
- Long-term management of recipients should focus on minimizing cardiovascular and renal risk factors.