

# THE CURRENT STATUS OF SMALL BOWEL TRANSPLANTATION IN THE UK AND INTERNATIONALLY

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Small intestinal transplantation should now be routinely considered for patients with irreversible intestinal failure and complications of parenteral nutrition (PN). Although technically possible for a century,<sup>1</sup> and attempted in humans for more than 40 years,<sup>2</sup> immunological graft intolerance presented an impenetrable barrier to successful engraftment until the development of the powerful calcineurin inhibitor immunosuppressive agents in the late 1970s. Their subsequent clinical use over the past 17 years has transformed small intestinal transplantation from a position of predictable failure to predominant success and routine clinical reality for a select group of patients

One year graft survivals for solid organs are now excellent and have been improving steadily since the introduction of ciclosporin to routine clinical practice in the early 1980s.<sup>3–4</sup> In contrast, survival values for small intestinal transplantation have been slow to improve although are now comparable with those for lung, and the latest published values for one year survival approximate those for liver and kidney (table 1) Why then has progress with intestinal transplantation been so much more difficult?

## A BRIEF HISTORY OF SMALL INTESTINAL TRANSPLANTATION

The technical feasibility of the procedure has been established for a century<sup>1</sup> but immunological feasibility was far more difficult to establish. The high density of lymphoid tissue and the large mucosal surface area of the small intestine expressing class 2 major histocompatibility antigens fuels the mutual intolerance between graft and host. As a hollow organ whose lumen is colonised by a multitude of bacteria and other micro-organisms, it behaves as a potent vector of infection to the host, a problem that is made worse by the precarious barrier from the lumen provided by the thin and vulnerable monolayer of mucosal epithelium. Here then is the fine balance between immunosuppression and infection that has bedevilled its transplantation and led to failure in so many early attempts.<sup>2</sup>

Following early transplantation attempts, deaths were most commonly a consequence of acute graft rejection and subsequent sepsis associated multiorgan failure.<sup>5–6</sup> This scenario was not improved even with the introduction of combination therapy with azathioprine, prednisolone, and antilymphocyte globulin.<sup>7–8</sup> More powerful immunosuppression was needed and the target of most of the early research.

The introduction of ciclosporin in 1978 by Calne and colleagues<sup>3–4</sup> both accelerated progress in solid organ transplantation and rekindled interest in intestinal grafts. Success in this new ciclosporin era led to the transition from success in animals to the first long term success in humans. In 1988 Grant and colleagues<sup>8</sup> reported a patient with short gut syndrome following mesenteric infarction who had undergone combined liver and small intestine transplantation and remained alive one year after the procedure. Other groups soon reported similar experiences.<sup>8–10–11</sup> Even though the barrier of chronic rejection was soon evident, the achievement of medium term survival was heralded as a defining moment.

The introduction of tacrolimus, a potent new calcineurin inhibitor, marked the next major step in allowing clinical intestinal transplantation to become a reality. Early rejection was then superseded by infection as the main cause of death,<sup>12</sup> indicating the need to refine the target of immunological suppression to reduce infection while avoiding rejection. Another adverse effect of heavy immunosuppression appeared to be a substantial increase in the incidence of chronic rejection,<sup>13</sup> and the near total loss of progressive tolerance that had allowed low dose maintenance immunosuppression or immunosuppression free management in a proportion of the earlier procedures.<sup>14–15</sup>

A possible explanation for the divergent frequencies of acute and chronic rejection and the potential key to tolerance with minimal immunosuppression came from the report by Starzl *et al* that long term tolerance was associated with donor and host leucocyte chimerism.<sup>15–16</sup> This apparent engagement of donor and host leucocytes seemed pivotal to long term tolerance but

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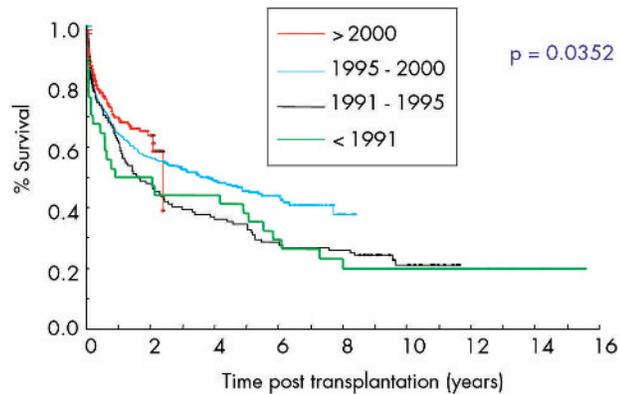
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vulnerable to ablation by the powerful new immunosuppressants.<sup>17</sup> Exhaustive deletion of helper and cytotoxic T cells<sup>18</sup> and preferential differentiation to suppressor and regulatory T cells following chronic exposure of host T cells to donor antigens presented in non-inflamed conditions after graft "healing-in" have been postulated as the mechanisms of long term tolerance.<sup>19, 20</sup>

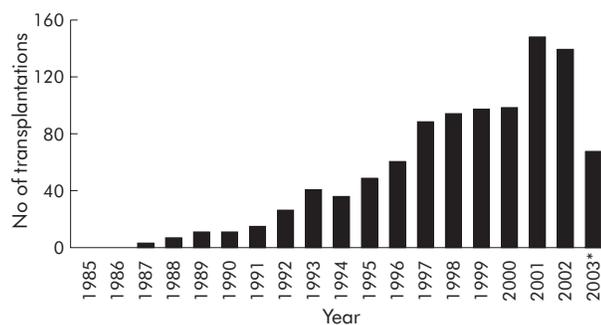
Monoclonal antibody therapy presented the potential to provide specific targeting of a wide range of immune mediators and, with the expected greater degree of selectivity, perhaps fewer problems with infection. It was postulated that preoperative induction with host lymphocyte depleting antibody might allow a more equitable engagement of graft with host and promote tolerance. Campath 1H, a monoclonal anti-CD 54 antibody which depletes both T and B cells<sup>19</sup> was used for a multivisceral transplantation in Cambridge UK in 1995. In combination with tacrolimus the level of immunosuppression was profound, leading to episodes of severe infection but subsequently the immunosuppression could be steadily reduced without evidence of rejection. Initially composite grafting was thought to be entirely responsible for this greater degree of immunological tolerance<sup>21</sup> but with the advancement of global experience and the benefits of a single international registry additional influence of the type and degree of immunosuppression on tolerance was appreciated.<sup>19</sup> Judicious immunosuppression with the aim of engaging graft and host in a manner that encourages tolerance with minimal immunosuppression has become the goal of modern transplantation immunosuppression.<sup>14, 19</sup> Facilitated by deployment of the more selective monoclonal antibody technology, inroads into maximising host tolerance to minimise immunosuppression are being made<sup>19</sup> and survival values are inexorably improving (fig 1).<sup>22</sup>

Immunological engagement and mutual tolerance is fundamental to successful long term engraftment.<sup>19</sup> Reliable achievement of this state of full or partial tolerance represents the next and perhaps last major barrier to the use of transplantation as first line treatment for intestinal failure.

The success of the tacrolimus era led to an exponential increase in transplantation procedures (fig 2) and centres are



**Figure 1** Survival of patients transplanted in different eras (from the International Registry<sup>22</sup>).



**Figure 2** Number of intestinal transplantations reported to the International Registry per year (from the Transplant Registry<sup>22</sup>). \*Data were acquired half way through 2003.

now established in more than 30 countries. The development of monoclonal antibody technology has further improved survival. Recent reports of over 90% one year survival rates<sup>23</sup> indicate the current incremental progression to a position that might eventually challenge PN as primary treatment for small intestinal failure. Such a broadening of the indications

**Table 1** Patient and graft survival of patients receiving small intestinal and solid organ grafts

Graft type	1 year survival (%)		3 year survival (%)		5 year survival (%)	
	Patient	Graft	Patient	Graft	Patient	Graft
Kidney <sup>68</sup> 1990-1999	94	83	90	73	85	65
Liver <sup>69</sup> 1994-2003*	78	73	72	67	67	62
Heart <sup>70</sup> 1990-2002	82	80	72	70	67	66
Lung <sup>71</sup> 1990-2002	75	75	59	59	46	46
Intestine <sup>32</sup> 1985-2004	72	64	57	42	47	35
Intestine <sup>32</sup> 1999-2004	78	65	62	50	50**	35**
Int and liver <sup>32</sup> 1985-2004	58	56	46	44	41	39
Int and liver <sup>32</sup> 1999-2004	60	58	50	45	50**	45**
MultiV <sup>32</sup> 1985-2004	58	58	50	45	50	40
MultiV <sup>62</sup> 1999-2004	66	62	62	58	62**	50**
Well performing individual centres						
Sudan et al <sup>62</sup> Intestine (2000)	93	71				
Goulet et al <sup>64</sup> Intestine and liver (1999)	80	80				
Pinna et al <sup>63</sup> Multivisceral (2000)	70	60				
Fishbein et al <sup>63</sup> Intestinal (2002)	92	92				
Parenteral nutrition <sup>72</sup> (1990-1996)	90				75	

Int, intestine; MultiV, multivisceral.

\*Data given for first transplantation only. All other data include a small number of repeat transplantations (heart and lung 2%, intestine 7%) which are associated with a poorer outcome.

\*\*Four year survival values are given.

Data in italics are most appropriate for comparison. Data, including during the early development of intestinal transplantation, are also given.

**Table 2** Indications for referral of adults to an intestinal failure centre

Complications of parenteral nutrition
(1) Impaired venous access
– Venous occlusion of one or more neck sites of central venous access (jugular or subclavian)
(2) Line related sepsis
– Two or more line changes in a year as a consequence of line related sepsis.
– One episode of life threatening line related sepsis (that is, cardiovascular shock).
– One episode of fungal line infection.
(3) Parenteral nutrition related liver disease.

already practised sporadically in some centres will generate the next quantum increase in small intestinal transplantation.

## INDICATIONS FOR SMALL INTESTINAL TRANSPLANTATION

### Patient selection

For the majority of patients, small intestinal transplantation is indicated only when irreversible small intestinal failure coexists with failure of PN. The main causes of PN failure are loss of venous access due to venous thrombosis, PN related liver disease, and recurrent line related sepsis.<sup>24–26</sup> A global consensus for indications has yet to be published but is likely to be broadly in line with the healthcare finance administration of North American policy decision.<sup>27</sup> Patients with significant complications of PN (table 2) should be discussed with an intestinal failure centre where they can be evaluated and PN optimised prior to referral to a transplantation centre if required.

Patients with more advanced disease with one or less PN intravenous neck access sites but patent femoral veins, less than three PN intravenous neck vein access sites without bilateral femoral access, or severe liver dysfunction should be assessed by a transplant centre. Frequently recurrent line infections represent the indication in the majority of the other candidates. Evisceration during removal of large desmoid tumours, along with a few highly selected patients with malignant disease, may be considered suitable (table 3)

The incidence of severe PN related liver disease has been reported to affect as many as 15% of patients after one year<sup>28</sup> and 50% of patients after five years. Although the latter

report included patients with chronic hepatitis C and B infection it was based on data acquired from a central government coordinated data bank and has the advantage of better representing the entire population of patients on PN than single centre studies.<sup>29</sup> This frequency of liver disease together with venous occlusion and infection would be expected to result in a considerable demand for small intestinal transplantation in the UK. The number of patients on PN in the UK has been steadily increasing, numbering approximately 500 in 2003.<sup>30</sup> However, in the UK patients are rarely referred for consideration and only 14 adult transplantations have been undertaken over the last 15 years.

### TIMING REFERRAL

Timely referral for assessment is essential to allow optimisation of physical and psychological factors and should be at a stage when central venous access is adequate for surgery and management of postoperative complications which may include renal replacement therapy. Patients referred to an intestinal failure centre can then be followed closely and familiarised with the options for treatment in the event of further deterioration. Patients who have lost all venous access in the neck and are receiving PN via the femoral vein are at a considerable disadvantage. Not only are they more prone to line infections<sup>26</sup> but if composite grafting of two or more organs is to be considered central venous access above the hepatic veins will be necessary. Time should be available to minimise comorbidity, particularly that which might increase the likelihood of postoperative complications, such as chronic infections which may be the focus of serious postoperative infections during immunosuppression. Mental health problems can present a threat to patients of similar severity to physical disease and should not be underestimated or overlooked.<sup>31</sup>

Patients who are well enough to be admitted for transplantation from home have a significantly better prognosis than those who are medically unstable and require hospitalisation during the pretransplant period.<sup>32</sup> This underscores the importance of preoperative preparation and timing intervention which requires fine judgement to find the window of opportunity that avoids inappropriate intervention without allowing the patient's condition to deteriorate to a point that excludes transplantation or makes it unduly hazardous.

Time on the waiting list is often protracted, with approximately 40% waiting longer than a year and relatively

**Table 3** Indications for referral of adults to an intestinal transplantation centre

(1) Complications of parenteral nutrition:
▶ Substantial venous occlusion with residual availability of:
– 2 or less major neck venous access sites with loss of one or more femoral sites or
– 1 or less major neck venous access site with both femoral sites available.
▶ Line related infection (events occurring despite review at an intestinal failure centre):
– recurrent episodes of severe line related sepsis requiring more than two line replacements in a year or
– recurrent fungal line related infections
▶ Parenteral nutrition related liver disease
– Impending or overt liver failure as indicated by portal hypertension, hepatic cirrhosis, or bridging fibrosis
(2) Requirement for extensive evisceration
▶ Desmoid tumours
– (malignant disease in very select circumstances, usually neuroendocrine or cholangiocarcinoma) (modified from Buchman and colleagues <sup>27</sup> )

longer if composite grafts are required.<sup>33</sup> Early referral before the patient develops severe irreversible liver disease may allow timely isolated small intestinal transplantation, avoiding the need for more complicated grafts.

As a hollow non-sterile organ the small intestine is very prone to damage, and cold ischaemia times must be minimised. Donor suitability is further restricted by accommodation of the graft within an often damaged peritoneal cavity. Late referral of patients and slow donor acquisition cause considerable waiting list mortality which has been reported to be as high as 50%.<sup>32–36</sup> Most of these deaths (two thirds) occur in infants who in particular should be referred or at least discussed with the appropriate transplant centre at an early stage. Discussion of full referral guidelines for children<sup>37–38</sup> are beyond the scope of this article. However, in general, intestinal disorders with a poor prognosis, PN related liver dysfunction, or protracted PN dependence in infants and children require prompt referral.

Occasionally PN fails because of frequent line infections. In most cases re-education and modification of line care can resolve the problem. However, for some these infections are frequent and recurrent<sup>39</sup> and in the event of serious life threatening infection, transplantation should be considered.

In the UK, Addenbrooke's Hospital in Cambridge and St James's hospital in Leeds are national centres for adult small intestinal transplantation, and St Mark's Hospital Northwick Park, London and The Hope hospital in Manchester are the national centres for intestinal failure. Referral of children should be made to the Birmingham Children's Hospital.

## IMMUNOSUPPRESSION

Current regimens are usually based on the powerful calcineurin inhibitor tacrolimus. The combination of tacrolimus and sirolimus does not have additional benefit over tacrolimus alone and current regimens are evolving away from combination maintenance therapy with adjunctive agents such as the antiproliferative agent mycophenolate mofetil,<sup>40</sup> the non-calcineurin immunosuppressant sirolimus,<sup>23</sup> or steroids, towards monotherapy with tacrolimus<sup>17</sup> or sirolimus<sup>41</sup> following induction with lymphocyte depleting antibodies such as antithymocyte globulin,<sup>17</sup> Campath 1H (alemtuzumab),<sup>24–42</sup> OKT3,<sup>13</sup> or with monoclonal anti-interleukin 2 (IL-2) receptor antibodies (daclizumab or basiliximab).<sup>43–47</sup> Antibody preconditioning seems to allow less potent subsequent maintenance immunosuppression and improved tolerance, allowing lower levels of tacrolimus.<sup>17</sup> Despite the use of lower levels of tacrolimus, monitoring of haematological and renal parameters remains important. Cardiomyopathy and neurological complications also continue to be considerations. Antibody therapies are occasionally associated with severe infusion related adverse reactions caused by hypersensitivity or profound cytotoxin release but in most cases they are well tolerated. There is an increasing trend to minimise the use of steroids although they remain part of most regimens. In addition, some have used donor bone marrow infusions<sup>48–49</sup> in an attempt to achieve better immunological engagement and improve subsequent long term tolerance, so reducing chronic rejection.<sup>14</sup> Lymphocyte depletion of the graft by *ex vivo* intestine irradiation<sup>49</sup> has shown promise but is limited by concerns related to graft radiation damage.

## SURGERY

The surgical procedure is usually technically demanding. Many of the patients who are candidates for small bowel transplantation will have a heavily scarred abdominal wall from multiple abdominal procedures and previous bowel resections, resulting in difficult access to a reduced volume abdominal cavity. At times this already difficult situation can be further compounded by portal hypertension as a result of concomitant liver disease. Selecting smaller size donors and thus smaller grafts to be transplanted will help with this issue but further graft size reduction may be necessary, and securing a satisfactory abdominal wall closure represents a substantial challenge. In many cases an end ileostomy will be appropriate and in the short term allows access for monitoring of the graft by repeated biopsies to look for evidence of rejection.

Isolated small bowel transplantation is in principle the simplest surgical procedure and offers a solution to the patient who has problems with venous access and no evidence of irreversible liver disease. It has the theoretical advantage that the graft can be removed if necessary and the patient returned to PN, although this frequently proves not to be the case due to sepsis and other postoperative complications. A graft is obtained from a cadaveric donor based on the superior mesenteric artery (SMA) with a narrow patch of aortic wall (a Carrel patch) and the superior mesenteric vein (SMV)/proximal portal vein (PV). The graft is placed in the abdominal cavity and revascularised by anastomosing the narrow patch of aortic wall around the orifice of the SMA with the front wall of the aorta in the recipient. The SMV/PV are anastomosed to either the right side of the recipient portal vein which can be approached just behind the bile duct above the upper border of the duodenum after mobilising the duodenum and head of pancreas, or more simply to the front surface of the inferior vena cava (IVC) at the same level as the anastomosis to the aorta. The former technique is more technically demanding but does offer restoration of physiological drainage of the gut via the portal system. In practice, the latter technique is technically easier and is seldom associated with major problems in terms of outcome.<sup>50</sup> Intestinal continuity is restored by performing a proximal anastomosis to the remaining recipient gut and a distal ileostomy fashioned. Grafts have also been obtained from living donors based on the distal SMA and SMV, removing approximately one third of the donor's small bowel and anastomosing the graft to the aorta and IVC in the same way as for a cadaveric graft.<sup>51</sup>

Combined liver and small bowel transplantation offers a treatment option in cases where there is irreversible liver damage and has been more commonly applied in paediatric cases, where PN related liver disease has been more of a problem than in the adult population. There are a number of technical issues with such procedures. Excision of the liver will leave any residual upper abdominal organs (usually stomach, duodenum, pancreas, and spleen) without any venous drainage unless the remaining native portal vein (which will have been divided in removing the diseased liver) is anastomosed to the cava to form a porta-caval shunt or "piggy backed" onto the portal vein of the liver/intestinal graft. The former usually offers the simplest option. Biliary drainage of the liver is restored either by a direct anastomosis to the remaining native bile duct or to a roux loop created from the transplanted bowel (identical to the biliary drainage

options in conventional liver transplantation). More recently a composite graft including the liver, intestine, duodenum, and head of pancreas (the pancreas being divided in the line of the portal vein/SMV) has been described which includes all of the donor bile duct and avoids the need for an additional biliary anastomosis and eliminates the risk of biliary leakage or anastomotic stricture.<sup>48</sup>

Vascular reconstruction for the graft in these cases will involve anastomosis of the caval venous outflow from the liver, either in the classical orthotopic liver transplant fashion or using a piggy back technique to the hepatic veins (or the more recently described technique of cavo-cavostomy) and an arterial anastomosis to the recipient aorta, usually involving a conduit of donor iliac artery or donor aorta anastomosed to a vascular patch from the donor, including the origins of the coeliac axis and SMA (which are closely related).

Multivisceral grafting offers an option in cases with large intra-abdominal desmoid tumours or other extensive disease processes which may necessitate excision of most or even all of the intra-abdominal organs.

Such grafts may involve a variety of organs, usually including the liver, stomach, pancreas, duodenum, and small bowel. The spleen is removed to avoid immunological sequelae and if necessary a kidney can also be included. The vascular reconstruction required will depend on the nature of the graft but can commonly be achieved by substitution of a segment of recipient IVC (if a kidney is also being included in the graft the cava draining the right renal vein can also be included) and a segment of donor aorta, including the coeliac axis and SMA (and if needed the right renal artery for an orthotopic kidney graft), or simply an aortic patch anastomosed to the front of the aorta for arterial inflow. Figure 3 illustrates such a case of our own where a patient with Gardner's syndrome complicated by extensive intra-abdominal desmoid disease required total exenteration (fig 3A). He received a graft consisting of stomach, liver, pancreas, small intestine, and a single kidney (graft shown in position in fig 3B). This patient died following head trauma five years after the procedure with a fully functioning graft.

## OUTCOME

### Patient and graft survival

Recent reports from certain centres are encouraging, with one year patient and graft survival rates for small intestine alone of approximately 90% and 80%,<sup>52, 53</sup> which are similar to those for children of 80% and 80%, respectively,<sup>54</sup> and comparable with those of solid organ transplantation (table 1) Combined international data indicate overall one year patient and graft survival of procedures undertaken since 2000 of approximately 70%, improving from about 50% in the early 1990s (fig 1).<sup>32</sup>

Longer term survival values, which include patients receiving earlier immunosuppression strategies, are poorer but in most cases preferable to continuation on failing PN. Patients receiving intestinal or composite grafts since 1999 are reported by the International Registry<sup>32</sup> to have one and five year graft and patient survival rates of approximately 60% and 45%, and 39% and 48%, respectively This is similar to the UK experience since 1995 of 57% and 43% respectively for both grafts and patients.<sup>31</sup>

The main reasons for graft loss in adults are rejection (48%), thrombosis/ischaemia (28%), and sepsis (12%). Infection is the main cause of death followed by rejection.<sup>32</sup>

### Quality of life

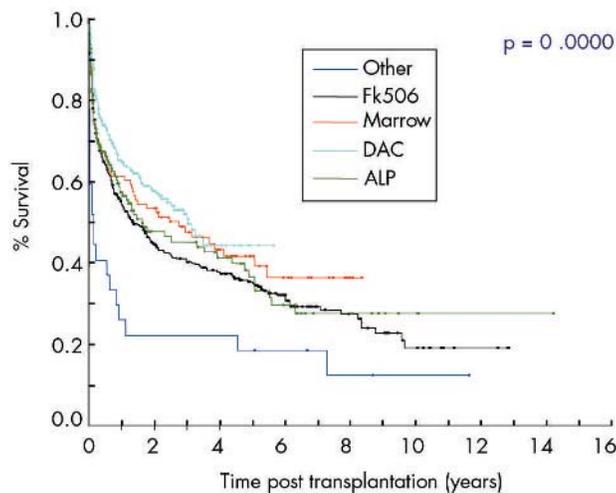
Several groups have reported an improvement in the quality of life following intestinal transplantation for patients who had complications of home parenteral nutrition (HPN) preoperatively.<sup>55, 56</sup> It also compares favourably with patients on stable HPN<sup>57</sup> and is better in transplanted patients than in patients who continue with frequent complications of PN.<sup>56</sup>

### Cost effectiveness

Although not extensively studied, the available evidence suggests that intestinal transplantation is less costly than HPN.<sup>58, 59</sup> The precise costs of HPN are case sensitive but are approximately £40 000 per patient per year. Patients with frequent complications will require greater health care provision with associated additional costs. On the other hand, the first and by far the most expensive year of intestinal transplantation costs is approximately £80 000 and



**Figure 3** Illustration of multivisceral transplantation. (A) Following preparation of the recipient for grafting. Clamps are shown on the inferior vena cava and oesophagus. All abnormal organs apart from the bladder have been excised. (B) Following grafting of the stomach, liver, pancreas, kidney, and small intestine. A stent was placed in the re-anastomosed ureter. A segment of iliac vein on the right has been replaced. Original water colours by Sir Roy Calne, with kind permission. This illustration originally appeared in Chan and colleagues.<sup>73</sup>

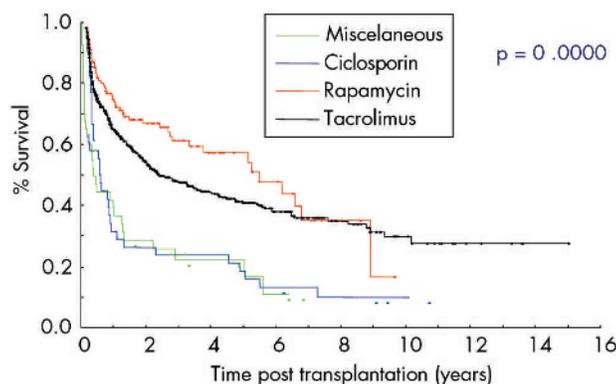


**Figure 4** Graft survival related to induction therapy (from the International Registry<sup>32</sup>). DAC, daclizumab; ALP, lymphocyte depleting antibodies; FK506, tacrolimus.

falls considerably in subsequent years. Cost effectiveness has not been formally compared with PN. However, when assessed by quality of life years, it might currently be expected to be better than patients with frequent complications of PN but inferior to those on stable HPN as the latter have a lower long term mortality.

#### Factors influencing outcome

Patients admitted for transplantation from their home have significantly better graft survival which underscores the need for good preoperative preparation to optimise patient health. Graft survival is also better in those who have received antibody induction therapy with lymphocyte depleting or anti-IL-2 receptor antibody (fig 4) and when the centre has had experience of more than nine procedures.<sup>32</sup> The highest success rates have been reported using antilymphocytic antibodies and post-transplantation tacrolimus monotherapy which is hoped to reduce postoperative immunosuppression related complications.<sup>17</sup> The type of maintenance immunosuppression also seems to influence patient and graft survival (fig 5). (Age)<sup>2</sup> is a significant risk associated continuous variable. Interestingly, the primary diagnosis, sex of the recipient, type of graft, retransplantation, portal venous



**Figure 5** Graft survival related to maintenance therapy (from the International Registry<sup>32</sup>).

drainage, and donor graft irradiation were not significant prognostic factors.<sup>32</sup>

#### Acute graft rejection

Until recently, acute host versus graft rejection was reported to affect between 50%<sup>32 54</sup> and 100%,<sup>52 54</sup> with most having averaged values for all types of graft between 70% and 80%.<sup>27</sup> However, novel regimens using antibody induction have seen the incidence fall, and Campath 1H (alemtuzimab) is associated with a particularly low rate of 20% in some series.<sup>22</sup> Composite grafts that include the liver tend to have a protective effect on acute intestinal rejection<sup>48</sup> and this may depend upon establishment of physiological perfusion preserving both arterial and portal venous blood flow. Prompt histological diagnosis<sup>60 61</sup> and treatment is usually effective to prevent severe rejection and graft loss but can be problematic when rejection is patchy.<sup>62</sup> Episodes are usually steroid responsive and can also be effectively treated with anti-lymphocyte antibodies such as OKT3.<sup>48</sup> A positive lymphocyte crossmatch is associated with a higher frequency of rejection whereas the degree of HLA mismatch is not. Most episodes of rejection occur within the first three months but can occur more than a year after transplantation.<sup>63</sup>

#### Graft versus host disease

The large quantity of lymphoid tissue present in the small intestine gave rise to early concerns that graft versus host disease would be a common problem. However, in practice, the incidence is far lower than expected, reportedly affecting between 5% and 16% of patients. The condition often manifests as a skin rash and is treated by increasing immunosuppression. However, occasionally it can be severe and may progress to multiorgan failure.<sup>32 48</sup>

#### Chronic graft rejection

With the gradual reduction of acute rejection and better short term survival, chronic rejection has become a more significant problem and the main limitation to long term survival after the first year. It affects approximately 8% of grafts<sup>62</sup> and occurs insidiously, which often results in late diagnosis. The pathological changes of chronic rejection are seen in the deep layers of the gut wall and the gut vasculature, with relative mucosal sparing. Superficial biopsies obtained during endoscopic routine surveillance can miss these changes and full thickness biopsies are often required which further hampers the diagnosis. The clinical picture of chronic watery diarrhoea, weight loss, and chronic abdominal pain is the result of the underlying obliterative endarterectomy with neointimal hyperplasia that is the pathological hall mark of the condition.<sup>61</sup>

#### Postoperative infection

Clinical signs of impending sepsis in the postoperative period are often subtle but can proceed extremely rapidly, commonly making this the most challenging part of the procedure. Acute rejection can first manifest itself as infection caused by disruption of the mucosal barrier and bacterial translocation, leading to a complex clinical picture. Infection is now the most frequent cause of death<sup>32</sup> in contrast with the pre-tacrolimus era when rejection was predominant. Almost all patients experience at least one infection following transplantation.<sup>64</sup> Serious infections are most usually bacterial and commonly affect central venous lines, the lower respiratory tract, and the urinary system.

Intra-abdominal collections can also occur often as a consequence of intestinal bacterial translocation<sup>65</sup> or peritoneal contamination during surgery.<sup>64</sup>

Cytomegalovirus (CMV) infection affects up to one third of patients and is higher when grafts are CMV positive. Strategies to encourage tolerance and allow lower levels of immunosuppression will be important to reduce the incidence of CMV disease which is quite resistant to ganciclovir prophylaxis.<sup>66</sup>

### POTENTIAL DEMAND

The British artificial nutrition survey reported that the point prevalence of adults on HPN in 2002 was 465, which is part of an increasing trend from 206 in 1996, 306 in 1998, and 400 in 2000.<sup>30</sup> With greater awareness of the life saving potential of PN and a more interventional approach to conditions such as small intestinal infarction, this value is expected to continue to increase. The annual mortality statistics for England and Wales indicate that the death rate for small intestine catastrophe is 15, 95, and 800 and volvulus 12, 33, and 350 per 100 000 for ages up to 45, 60, and over 60 years, respectively.<sup>67</sup> Should more of these patients become established on PN the requirement for small intestinal transplantation would consequently increase. Additionally, further improvements in long term survival may soon see transplantation challenge PN as the treatment of choice for those patients who find that PN adversely affects their quality of life.

### THE FUTURE

As patient survival approaches that of PN the improved quality of life will make small intestinal transplantation an increasingly attractive prospect and eventually an alternative to PN. Certain centres are now offering carefully selected patients transplantation as an alternative to PN on this basis.<sup>58</sup> The ability to reliably achieve immunological tolerance is likely to be the key to improved long term survival.

### Summary

- ▶ Small intestinal transplantation should be considered routinely as an option for patients with irreversible small intestinal failure who have complications of parenteral nutrition.
- ▶ Patient and graft survival rates are now comparable with those of lung, and approaching those of liver and heart transplantation.
- ▶ Quality of life of patients following small intestinal transplantation is improved and similar to that of patients on stable uncomplicated home parenteral nutrition.
- ▶ The most recent results using more targeted immunosuppression with lymphocyte depleting antibodies and less potent maintenance immunosuppression indicate a further improvement in one year survival, reaching 90% in some centres.
- ▶ Small intestinal transplantation may become an alternative to parenteral nutrition for patients with irreversible small intestinal failure if the current trend of improvement in survival values continues.
- ▶ Patients with complications of parenteral nutrition should be referred to an intestinal failure or transplantation centre at an appropriate stage, as indicated in this article, before their deterioration substantially increases their surgical risk.

Strategies to increase residual intestinal function with the use of growth factors such as glucagon-like peptide-2<sup>74-75</sup> or engineer the growth of additional "intestinal" tissue with the capacity to digest and absorb nutrients<sup>76-77</sup> are being developed and may provide alternatives to transplantation in the future.

Progress with the development of small intestine transplantation in the UK has been impaired by the apparently low demand for the procedure. It is however probable that the actual requirement is much greater.

Small intestinal transplantation is now established as the favoured treatment option for patients with significant complications of PN. The timing of transplantation is critical and patients should be referred for assessment before debilitation and inadequate venous access substantially increases the associated risks.

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