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BAPEN Symposium 4 on 'Managing complications in long-term parenteral nutrition'

Is intestinal transplantation now an alternative to home parenteral nutrition?

Stephen J. Middleton

Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University, Cambridge CB2 0QQ, UK

Patients with irreversible intestinal failure and complications of parenteral nutrition should now be routinely considered for small intestine transplantation. Despite attempts for >40 years immunological graft intolerance presented an impenetrable barrier to successful engraftment until the development in the late 1970s of the powerful calcineurin-inhibitor immuno-suppressive agents. Their use over the last 17 years has led to small intestinal transplantation being generally considered as a routine option for patients with irreversible intestinal failure and failing parenteral nutrition. The 1-year patient survival rates (%) are now excellent for renal (95), liver (78), heart (82) and lung (75) transplantation. In contrast, survival rates for small intestinal transplantation have been slow to improve, although they are now approaching those for lung and liver transplantation (intestine 78%, intestine and liver 60%, multivisceral 66%), and well-performing centres report recent 1-year graft survival rates as high as 92%. Patient 5-year survival (%) has also improved (intestine alone 50, intestine and liver 50 and multivisceral 62) and compares increasingly favourably with renal (85), liver (67), heart (67) and lung (46). Currently, small intestinal transplantation is reserved for patients with irreversible small intestinal failure who have a poor prognosis on parenteral nutrition. However, as 5-year patient survival following intestinal transplantation approaches that for parenteral nutrition there will be increasing pressure to offer this modality of treatment as an alternative to parenteral nutrition, especially for those patients who have a poor quality of life as a result of parenteral nutrition.

Parenteral nutrition: Small intestinal transplantation: Risk assessment: Survival: Intestinal failure

The short answer to this now frequently-asked question is yes, but only for certain patients in certain circumstances. Perhaps as a consequence of the exponential rise in the sophistication of medical treatments, patients with cata-strophic loss of the small intestine, at least in the devel-oped countries, are no longer treated in a palliative manner and are now offered salvage surgery and parenteral nutrition (PN) as a routine. The main concern in the art of intravenous feeding is getting the simple aspects con-sistently correct and paying attention to detail. It is a highly-skilled practice and is well established in the UK because of a relatively small number of dedicated clinicians. It is not, however, easily accessed by some patients in geographically-remote regions, and this lack of accessibility is currently the subject of much interest and debate. When used prudently and with care PN allows patients to have a good quality and length of life (Baxter *et al*. 2006). Given this good profile of PN, why take the added risks of small intestinal transplantation (SIT)? From the patient's perspective life without dependency on the intravenous infusion of water and nutrients, often daily over 8 h, is very attractive as it opens up many life

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Abbreviations: PN, parenteral nutrition; SIT, small intestinal transplantation.
Corresponding author: Dr Stephen J. Middleton, fax +44 1767 677810, email stephen.middleton@talk21.com

Table 1. Survival of patients according to primary disease and mechanism of intestinal failure subgroups (data from Lloyd *et al.* 2006)

Subgroup	Survival rate (%)		Hazard ratio	95% CI
	5 year	10 year		
Primary disease				
Crohn's disease	88	88	1	
Mesenteric infarction	80	80	1·40	0·52, 3·76
Pseudo-obstruction	70	54	2·32	0·93, 5·79
Radiation enteritis	51	51	4·00	1·67, 9·56
Systemic sclerosis	30	30	5·94	2·29, 15·4
Active neoplasia	14	N/A	23·1	8·23, 64·9
Parenteral nutrition*	73	71	N/A	
Mode of intestinal failure				
Enterocutaneous fistula and short bowel syndrome	85	85	0·40	0·16, 1·02
Short bowel syndrome	84	84	0·28	0·14, 0·57
Enterocutaneous fistula	65	N/A	0·85	0·25, 2·92
Dysmotility	53	48	1	
Intestinal obstruction	50	50	1·71	0·79, 3·72

N/A, not available.
*From Howard & Malone (1996).

opportunities. However, from the clinician's point of view this optimism must be balanced against the associated dangers of the procedure and the clinician's need to help the patient take this often difficult and marginal choice. Currently, it is certainly not possible to advise all PN patients that SIT will improve their length of life; indeed, overall the opposite is probably the reality. If all those individuals currently on PN were transplanted there would be an overall reduction in longevity (Grant *et al.* 2005; Jones *et al.* 2005; Lloyd *et al.* 2006). However, certain patients would benefit, and not only experience a dramatic improvement in length of life but also a transformation in the quality of their lives (DiMartini *et al.* 1998; Rovera *et al.* 1998; Goulet *et al.* 1999; Cameron *et al.* 2002). There is also a financial consideration, it is less expensive to transplant patients with small intestinal failure (a 'one-off' cost of approximately £70 000) than to maintain them on PN (approximate cost of £40 000/year). The cost per 'quality of life' year gained has not been reported, although it would be difficult to apply, as there is considerable variation between patients. However, if evaluated this cost might provide another factor in favour of earlier transplantation.

The risks associated with SIT have thus far prevented it from being considered in general as a means of improving quality of life if a patient is on uncomplicated PN. However, complications of PN or complicated underlying gastrointestinal disease that severely impairs quality of life are already being considered as major factors in support of transplantation in certain centres (Abu-Elmagd *et al.* 1999).

Currently, however, failing PN remains the indication for SIT, with the aim of increasing longevity. Here then is the challenge, the identification of those patients likely to experience PN failure at a stage early enough to offer them a reasonable chance of surviving transplantation. This process requires the knowledge of the likely prognosis of patients at each stage of their decline on PN and the prognosis if they were to undergo SIT. The prognosis of patients on PN is related to their underlying condition and PN-related complications. Clearly, those patients with severe complications of PN, such as major loss of intravenous access, will do worse than those who are in better physical condition. The psychological condition is also of considerable importance. To further complicate this balance of risks the prognosis of SIT is continuously improving, currently quite steeply, thus constantly changing the optimal time for transplantation.

Reviews of several large series of patients on PN have been published and they report 1-year survival rates of 86% (Lloyd *et al.* 2006) and 91% (Messing *et al.* 1995) and a 5-year survival rate of 73% (Lloyd *et al.* 2006). However, when considering these data it should be taken into account that the indications for establishing patients on PN vary considerably between centres. For example, certain series include a large number of patients with malignant disease (Howard & Ashley, 2003; Winkler, 2005), whilst others almost entirely consist of patients with benign disease (Messing *et al.* 1995; Pironi *et al.* 2003). The lack of homogeneity within each group should also be recognised; patients on stable PN have a far better prognosis than those with failing venous access or progressive liver disease. It becomes apparent, therefore, that each patient on PN should be assessed according to their individual circumstances and this evaluation of their prognosis and quality of life should be compared with that expected with SIT, with full consideration of their co-morbidity. There is currently very little data available to make these judgements, although recently the large intestinal failure centres have begun to focus on this area (Lloyd *et al.* 2006).

There is better outcome data following SIT, and risk assessment for patients appears to be more straightforward. However, the pre-operative condition of patients has such a profound influence on their prognosis that it would be inappropriate for all patients to be ascribed the group survival. Patients with loss of all standard intravenous access, for example, have a poorer survival chance than those with well-preserved major venous access. Those patients with co-morbidities such as complicated diabetes and extensive vascular disease that may be associated with the underlying intestinal pathology might also be expected to have more complications of surgery.

Risk assessment of patients on parenteral nutrition

The prognosis of subgroups of patients on PN has recently been explored by Lloyd *et al.* (2006) in their extensive review of the UK referral centre at St Mark's Hospital (Harrow, London, UK) experience of patients on PN over a 20-year period. It is apparent that the primary-disease groups have markedly differing mortality rates (Table 1). This observation suggests that patients with primary diseases associated with poor prognosis might be more likely to benefit from transplantation. For example, patients with radiation enteritis and systemic sclerosis have a 5- and 10-year survival expectation similar to that for SIT. Patients with active neoplasia have the worst prognosis but

Table 2. Current indications for small intestinal transplantation in adults (Middleton & Jamieson, 2005)

Irreversible intestinal failure and:
  Failing venous access
    Loss of two or more neck veins
    Loss of one or more neck vein and one or more femoral vein
Severe recurrent line sepsis
Parenteral nutrition-related severe liver disease
Extensive evisceration (desmoids)

are unlikely to benefit from transplantation, as the natural history of their primary disease will in most cases not be altered, and under immunosuppressive treatment it might also be adversely affected. There are, however, several examples of patients with neoplasia being successfully transplanted, with subsequent cure of their malignancy and long-term survival (Moon *et al*. 2005). Here again, the individual assessment of each patient based on the precise nature of their circumstances is crucial.

Lloyd *et al*. (2006) have also described the prognosis of patients subgrouped in terms of their mechanism of intestinal failure (Table 1). Those patients with failure as a result of intestinal obstruction or dysmotility have the worst prognosis, which is similar to that expected following transplantation. For these patients additional factors such as PN-related poor quality of life might make them candidates for transplantation. Conversely, the survival of patients with short-bowel syndrome seems to be very good (75% at 10 years; Messing *et al*. 1999).

However, cause of death is commonly not a result of either intestinal failure or complication of PN, but is a consequence of the primary disease or related conditions, the progress of which will not be substantially altered by transplantation. Patients with Crohn's disease have a relatively favourable prognosis on PN, with 5-year survival rates of 80–90% (Messing *et al*. 1995; Vantini *et al*. 2004; Winkler, 2005). Conversely, the patients with systemic sclerosis have about a 6-fold greater risk than those with Crohn's disease, and an estimated 5-year survival of 33% (Lloyd *et al*. 2006), with death mainly caused by progression of the underlying disease. Radiation enteritis also has a rather poor outcome (Winkler, 2005), with an estimated survival chance of about 52% (Lloyd *et al*. 2006) and

half these deaths caused by recurrent malignancy. Pseudo-obstruction and mechanical obstruction have also been associated with poor survival (Messing *et al*. 1995; Winkler, 2005) and 5-year survival rates have recently been given as 70 and 50% respectively, whereas survival after mesenteric infarction has been found to be similar to that for Crohn's disease (Lloyd *et al*. 2006). Comparisons between studies are, however, restricted by demographic differences between study populations, such as the age distributions of the studied cohorts (Messing *et al*. 1999; Winkler, 2005). Distinct from many other disease subgroups, patients with dysmotility (from visceral myopathy or neuropathy) have a poor prognosis because of associated liver disease and involvement of other organs, sometimes resulting in multiorgan failure. Transplantation not only offers relief from multiorgan failure, but also resolution of the primary problem that is usually intrinsic to the removed organ and rarely recurs in the graft.

Although subgroups at high risk can be identified as target groups for potential transplantation, the fundamental indications for this procedure still apply (Table 2). Transplantation still cannot be considered as an alternative for patients on trouble-free PN. Candidates for transplantation are those with major complications of PN, such as failing line access and PN-related liver disease, whose primary disease is associated with a good prognosis. Clearly, those patients who have a progressive primary illness that will rapidly further deteriorate despite transplantation are not appropriate candidates. It is thus necessary to embrace a number of factors when evaluating the potential benefit of transplantation to the patient. These factors include the prognosis of the underlying disease process and other unrelated co-morbidity, the extent of PN-related complications and the patient's quality of life. These risks must then be weighed against those of transplantation surgery and subsequent immunosuppression. Only when this balance of risks favours transplantation and the overall surgical risks are reasonable should transplantation be considered.

The risks of intestinal transplant surgery

Survival following intestinal transplant surgery has considerably improved over the last decade. This improvement applies to intestinal grafting either alone, together with

Table 3. Patient and graft survival for patients receiving small intestinal and solid organ grafts

Graft type	Years	Reference	1 year		3 year		5 year	
			Patient	Graft	Patient	Graft	Patient	Graft
Kidney	1990–9	Morris *et al*. (1999)	94	83	90	73	85	65
Liver*	1994–2003	Jacob *et al*. (2004)	78	73	72	67	67	62
Heart	1990–2002	Taylor *et al*. (2004)	82	80	72	70	67	66
Lung	1990–2002	Trulock *et al*. (2004)	75	75	59	59	46	46
Intestine	1999–2004	Grant *et al*. (2005)	78	65	62	50	50†	35†
Intestine and liver	1999–2004	Grant *et al*. (2005)	60	58	50	45	50†	45†
Multivisceral	1999–2004	Grant *et al*. (2005)	66	62	62	58	62†	50†

*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.
†4-year survival rates given.

liver or as composite multivisceral grafting. Patient and graft survival are now similar to those for lung transplantation and are approaching those for heart and liver transplantations (Table 3). The main cause of transplant-related death is infection, which has become a greater problem than rejection following the introduction of powerful lymphocyte-depleting monoclonal antibodies such as Campath 1H (Tzakis *et al*. 2003; Middleton & Jamieson, 2005). To offset an augmented risk of infection, these new induction agents offer far lower rejection risks and seem to allow less powerful subsequent maintenance immunosuppression. These outcomes may be a consequence of better tolerance by the host of the graft, although the mechanism is not clear at present (Starzl *et al*. 2003).

Trends of small intestinal transplantation

Intestinal transplantation is now undertaken as part of a routine clinical service in approximately sixty countries, with about 150 procedures performed in total per year (Grant *et al*. 2005). Most patients undergoing this surgery will have had established irreversible intestinal failure and will have been maintained on PN, which could not be continued. In the early 1990s there were only four countries that had achieved successful engraftment (USA, Canada, Germany and the UK), but over the relatively short intervening period the procedure has become virtually global.

Despite providing a major contribution to the development of SIT, the UK has subsequently seen slow acquisition of this technique into the clinical arena. Fifteen procedures have been performed in the UK, of which there were six lone small intestine, five multivisceral grafts, two small intestine and liver, one small intestine and colon and one patient died before engraftment (Starzl *et al*. 1993). Survival rates are similar to the global experience, but the cohort of patients referred for consideration appears to be much smaller, with more advanced disease, than in countries such as the USA, Canada and Italy.

Developments with potential impact on small intestinal transplantation

The British Society for Parenteral and Enteral Nutrition maintains a comprehensive registry (British Artificial Nutrition Survey) of patients on PN (Glencorse *et al*. 2003). This registry allows review of the quality and accessibility of PN. The considerable geographical differences in the prevalence of PN, which tends to be most commonly employed near to intestinal failure centres, suggests inequality of access to PN. Correction of this situation might substantially increase the number of patients offered salvage surgery for intestinal catastrophe, such as superior mesenteric artery infarction, and consequently increase the number of patients on PN, some of whom may subsequently require transplantation.

New techniques such as the development of living related segmental intestinal transplantation (Benedetti *et al*. 2006) will allow more timely transplantation and have a high success rate, with latest reports of 1- and 3-year survival rates of 100 % and 82 % respectively.

Conclusion

SIT surgery has substantially improved over the last decade and now has a 5-year survival similar to lung transplantation and approaching that of liver and heart transplantations. The recent 1-year survival rates from well-performing centres are as high as 93 %. This procedure is now considered to be a routine clinical procedure in many countries and should always be considered for patients with irreversible intestinal failure who have complications of PN or other progressive co-morbidity that is potentially reversible by transplantation. Certain patient subgroups, according to the type of primary disease or mechanism of failure, can be targeted for close monitoring and earlier intervention. However, the risk assessment is complex and should be made by a multidisciplinary team composed of the many disciplines required to make a well-balanced recommendation about the likely benefits of surgery. For this purpose a national forum has been established by Addenbrooke's Hospital, Cambridge University, and St Mark's Hospital and Academic Institute. This forum convenes every 4 months and reviews new potential candidates, previously-transplanted patients and those who were thought to be unsuitable for transplantation. Clinicians wishing to refer patients to this forum are welcome to attend the meeting and present the patient or send the details to either Addenbrooke's or St Mark's. Those patients requiring optimisation of PN or complex intestinal failure should ideally be referred to St Mark's for evaluation before being assessed at Addenbrooke's, if they remain potential candidates for transplantation.

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