TOPIC HIGHLIGHT

Management of intestinal failure in inflammatory bowel disease: Small intestinal transplantation or home parenteral nutrition?

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Abstract

Inflammatory bowel disease and Crohn's disease in particular, is a common cause of intestinal failure. Current therapeutic options include home parenteral nutrition and intestinal transplantation. For most patients, home intravenous therapy including parenteral nutrition, with a good probability of long-term survival, is the favoured choice. However, in selected patients, with specific features that may shorten survival or complicate home parenteral nutrition, intestinal transplantation presents a viable alternative. We present survival, complications, quality of life and economic considerations that currently influence individualised decision-making between home parenteral nutrition and intestinal transplantation.

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Core tip: In this review we describe and compare the principal options for the management of intestinal failure in patients with inflammatory bowel disease: home parenteral nutrition and intestinal transplantation. We describe patient survival, complications and quality of life considerations that influence individualised decision-making between approaches. As survival from transplantation improves, decision-making is likely to change.

INTRODUCTION

Intestinal failure (IF) may result from obstruction, dysmotility, surgical resection, congenital defect or disease-associated loss of absorption[1]. It is characterized by the inability to maintain protein-energy, fluid, electrolyte and/or micronutrient balance[1]. Three categories exist: types 1, 2 and 3[2]. Type 1 generally occurs post-operatively and is self-limiting [such as a patient developing an ileus, requiring short-term parenteral nutritional (PN) support for days or even weeks]. Type 2 most commonly develops in individuals with sepsis following major intestinal resection. Patients require nutritional support for many weeks

or months, pending definitive surgery that may reverse dependency on PN. Type 3 is irreversible, for which long-term home parenteral nutrition (HPN) is required and is the focus of this article.

Intestinal failure in inflammatory bowel disease

Crohn's disease (CD) is most commonly associated with type 3 IF, but the overall incidence is low. The point prevalence of type 3 IF as a percentage of all causes in the United Kingdom in ulcerative colitis (UC) is 3% and 29% in CD[3]. UC is much less commonly associated with type 3 IF because the small intestine is uninvolved, although IF can still occur through complications arising from delayed colectomy in immunocompromised patients, early re-operation, or mesenteric infarction after colectomy.

When IF does occur in patients with CD, it is usually due to one of three reasons: as a result of complications of surgery for intra-abdominal sepsis, extensive primary small bowel disease impairing nutrient absorption, or uncomplicated sequential resection leading to a shortened small bowel. The first is the principal cause of IF in CD[4]. Following a first small bowel resection, the reported risk of IF in patients with CD at 5, 10, 15 and 20 years is 0.8%, 3.6%, 6.1% and 8.5% respectively[5]. Predisposing factors to type 3 IF in CD include younger age at diagnosis and (at first operation) stricturing disease or family history of inflammatory bowel disease[6]. In addition, the CD susceptibility gene nucleotide-binding oligomerization domain-containing protein 2 (NOD2) is associated with IF in patients without CD[7]. Whether this also applies to CD remains to be proven, despite established associations between NOD2 mutation and small bowel CD[8].

MANAGEMENT OPTIONS FOR INTESTINAL FAILIURE

Three options exist for the management of patients with type 3 IF: HPN, intestinal transplantation (ITx) and intestinal lengthening.

Home parenteral nutrition

HPN has formed the standard of care for managing patients with type 3 IF for several decades[9,10]. Early regimes were complicated, but solutions have evolved to mixed-nutrient, stable, "single" or "bipartite" bags, meeting a patient's tailored nutritional requirements[9,11]. These solutions can be delivered through long-term percutaneous intravenous catheters, specialised pumps and patients specially trained in self-administration, or specifically trained nursing staff. CD is the principal indication for HPN in the United Kingdom, although other disease aetiologies, such as cancer, form the principal indication in other countries[12-15].

Intestinal transplantation

The first human small bowel transplant was in 1964

but, like many early organ transplants, the graft failed to survive[16,17]. It was only after refinements in immunosuppression that ITx started to show promise, with the first successful small bowel (+ liver) transplant taking place in 1988, enabling the recipient to achieve nutritional autonomy[18]. With further advances in immunosuppression and operative techniques, the number of transplants performed annually rose until 2005, since when it has remained stable[19]. In the United Kingdom alone, the number of intestinal transplants has increased from single figures (2000-2008) to 14-22/year (2011-2013)[20]. Currently, 100 ITxs are performed per year in adults, primarily in North America and Europe; 65% of ITx transplants between 2006 and 2011 were indicated for short bowel syndrome (SBS), of which 13% were in patients with CD[19]. The number of transplants performed annually in other parts of the world, such as Asia and South America, is much lower, but gradually increasing[19]. In total, 20 ITxs were reported to have been performed in Japan between 1996-2010, while Australia and India have both recently reported their first cases[21-23]. To the best of our knowledge, there are no published reports of ITx in Africa.

At present, three types of graft transplants are performed: isolated intestinal, combined liver-intestinal and multivisceral transplantation. Combined liver-intestinal grafts include intestine, duodenum, liver and pancreas. Multivisceral grafts include intestine, stomach, duodenum, pancreas, possibly liver and colon, or other organs. At present, isolated small intestinal transplants are the commonest, although abdominal wall transplantation is increasingly combined with intestinal transplantation and provides a readily accessible marker for rejection[19,24].

Currently, the choice between HPN and ITx as primary therapeutic options for patients with type 3 IF is principally driven by predicted survival outcome. Thus, HPN, with its superior long-term survival, remains the first-line management option for most patients with type 3 IF, with ITx being reserved primarily for those with HPN-associated complications and/or high risk of death from their underlying disease (Table 1). However, if transplant experience and survival continues to improve, other factors, such as patients' quality of life (QoL), will enter decision-making when balancing HPN against ITx.

Intestinal lengthening

Intestinal lengthening procedures involve the lengthways division of a dilated small intestine and subsequent end-to-end anastomosis ("Bianchi procedure") or sequential zig-zag stapling of a dilated small intestine (serial transverse enteroplasty or "STEP procedure")[25-28]. Lengthening techniques were pioneered in children with SBS, and have rarely been performed in adults, although recent European and American experience suggests they may be a viable treatment option for SBS. However, as only one series has reported their use in 2 patients with CD, lengthening procedures will not be discussed further in this review[29]. Instead, this review will focus on the choice between HPN and ITx in patients with type 3 IF.

Table 1 Intestinal transplantation indications[53,57,92,94]	
North American	**European**
Indications	Indication
Failure of home parenteral nutrition (HPN)	Irreversible, benign, chronic intestinal failure with no possibility of bowel rehabilitation associated with life threatening complications of HPN
Impending or overt liver failure	
Central venous thrombosis of ≥ 2 central veins	Individual case-by-case decision for all patients
Frequent and severe central venous catheter-related sepsis	
Frequent episodes of severe dehydration despite intravenous fluids in addition to HPN	Non-indications
	High risk of death due to underlying disease
High risk of death attributable to the underlying disease	
Intra-abdominal invasive desmoids tumour	Chronic dehydration
Congenital mucosal disorders	
Ultra-short bowel syndrome	Significantly impaired quality of life
Intestinal failure with high morbidity and low acceptance of HPN	
Need for frequent hospitalisation, narcotic addiction or inability to function	
Patient's unwillingness to accept long-term HPN	

PATIENT SURVIVAL

Survival on home parenteral nutrition

HPN series provide survival information, although series (Table 2) excluding cancer as a primary disease indication clearly have more relevance to IBD and ITx[14,30-32]. Of the latter, one series (1986-2001; *n* = 40) reported 1-, 3- and 5 year probability survivals on HPN of 97%, 82% and 67%[31]. Another study (1990-2006; *n* = 268) excluding malignancy, but only including patients with SBS, reported 1-, 5- and 10-year actuarial HPN survivals of 94%, 70% and 52%[30]. However, as 46% regained nutritional independence, most within 1 year, and only 6% had CD, this study does not represent ITx candidates or most patients with CD needing intravenous nutritional support. Indeed another study (1979-2003; *n* = 188), including 7% with malignancy (4% active neoplasia; 3% desmoid), showed that patients with CD on HPN (*n* = 60) had a better 5-year probability survival than all other patients (87% *vs* 77%)[33]. This is further supported by a review of case series, which reported the 10-year survival rate for patients with CD to be 88% in comparison to 62% for SBS due to other causes and 60% for pseudo-obstruction[34]. Thus, in general, patients with CD have the best probability of surviving long-term on HPN, which may reflect their age or limited co-morbidity (compared, for example, with those with SBS from mesenteric infarction). However, not all patients with CD have similar chances of long-term survival, as generic series show that having < 50 cm of remaining small bowel (RR = 7.7) or an end-enterostomy (RR = 6.2) are associated with worse survival[35,36].

Survival following intestinal transplantation

Survival following ITx (Table 2) currently appears worse than for patients on HPN, with the American National Registry reporting 1-, 3- and 5 year survivals of 77%, 61% and 51% for all primary adult ITxs (1987-2009; *n* = 687)[37]. The trouble with direct comparisons with HPN survival data is, however, simple: the patient populations differ, since only a minority on HPN and predominantly those with established complications from HPN would be considered to be transplant candidates. Series highlight that graft and patient survival have improved considerably since earlier transplants; the American National Registry demonstrates a rise in 1-year survival from 69% in 1998 to 79% in 2007[38]. This improvement is particularly evident in centres performing larger case volumes; for example, 5-year survival in Pittsburgh improved from 40% in 1990-1994 to 68% in 2001-2003[19,39].

There are few survival data specific to adults with CD, with only one multi-centre series (1987-2009; *n* = 86) reporting 1-, 3- and 5 year survivals of 79%, 53% and 43% in patients with CD as the primary cause of IF[24]. As in other series, 5-year survival from more recent procedures (2001-2009) has increased (62% isolated ITx; 57% liver-ITx). Post-ITx survival in adults with CD therefore appears comparable to those of other diseases. As with all patients, negative predictors for post-ITx survival in CD include age > 40 years and hospitalization prior to ITx[24,37]. Furthermore, although the presence of NOD2 mutations are associated with an increased risk of rejection, graft loss and death in all patients post-ITx, this effect is not specific to CD[40].

HOME PARENTERAL NUTRITION COMPLICATIONS

Catheter-related complications

Complications (Table 3) including catheter-related blood stream infections (CRBSI) and central venous thrombosis (CVT) are a significant cause of morbidity in patients requiring HPN and form part of the indications for ITx (Table 1).

Reported rates of CRBSI vary from 0.1/1000-2.41/1000 catheter days[41-43]. Centre practices may influence rates; for example, increased use of lipid infusions or catheter use for infusions other than PN, are associated with an increase in CRBSI[44]. CD may also increase risk, with one series of patients with CD describing 57% of patients having at least one CRBSI within the 7.9 years follow-up, and another series comparing patients with and without CD, reporting an association between CD and infections, attributed to immunosuppression and/or genetic immunodeficiency[5,45]. Most CRBSI are bacterial (some are fungal) and remain a major concern, with between 4.5% and 16% of all HPN deaths attributed to CRBSI[35,36,46]. It

Table 2 Comparison of patient survival		1-yr	3-yr	5-yr	10-yr
Home parenteral nutrition	Series of 40 patients excluding malignancy (1986-2001)[31]	97%		82%	67%
	Series of 268 patients with SBS and excluding malignancy (1990-2006)[30]	94%		70%	52%
	Patients with Crohn's disease (CD) extracted from multiple series[34]				88%
	Series of 60 patients with CD (1979-2003)[33]			87%	
Intestinal transplantation	Series of 453 patients (1990-2008)[39]	85%		61%	42%
	Series of 687 patients (1987-2009)[37]	77%	61%	51%	
	Series of 86 patients with CD (1987-2009)[24]	79%	53%	43%	

Table 3 Potential complications of home parenteral nutrition and intestinal transplantation	
Home parenteral nutrition	Intestinal transplantation
Catheter-related blood stream infection	Allograft rejection
Catheter-related central venous thrombosis	Infection
Intestinal failure-associated liver disease	Graft *vs* host disease
	Post-transplant lymphoproliferative disease
	Renal failure
	Disease recurrence

is however clear that meticulous patient and carer training can achieve the very low CRBSI rates reported by some centres[41,43].

Catheter-related CVT is less common than CRBSI, with recent series reporting 0.06-0.16 episodes of CVT/1000 d PN[33,43,47]. Nevertheless, at one centre, the mean number of thrombosed central veins per patient at the point of ITx assessment, was 1.495[48]. In an older series of patients with CD on HPN (1987-2009; *n* = 86), 50% were reported to have exhausted vascular access[24]. This is clearly a concern for patients facing ITx, where vascular access is of paramount importance. CVT remains a prime consideration when determining an individual's referral for ITx assessment[48,49].

Intestinal failure-associated liver disease

Intestinal failure-associated liver disease (IFALD) in children can be graded as early/mild, established/moderate and late/severe based on biochemical, histological and clinical parameters[50]. With late disease, clinical and radiological signs of liver failure are accompanied by extensive hepatic fibrosis. IFALD incidence varies between centres, with one series reporting no patient with a bilirubin > 50, no decompensated liver disease or IFALD-related deaths in 107 HPN patients over a median of 40 mo (range: 4-252 mo)[51]. Meanwhile, at the other extreme, another series of 90 HPN patients (median HPN duration 49 mo, range: 6-198 mo) reported complicated liver disease (as defined by bilirubin > 60, decompensation or fibrosis/cirrhosis on biopsy) in 50% of patients at 6 years; there were 6 IFALD-related deaths in the latter series[52]. IFALD is associated with increased risk of death on HPN, but in light of its variable frequency, mortality also differs between centres (0%-22% of deaths)[51-53]. These differences may reflect differing HPN management decisions, leading to variable exposure to risk factors, such as excess calories (especially lipids), underlying diseases (*e.g.*, bacterial overgrowth in CD) and recurrent episodes of sep-

sis[51,52,54,55]. Careful PN lipid formulation certainly seems to have a role in prevention and treatment[51,52,56].

Given its association with death, IFALD is an indication for ITx in most countries[53,57]. Patients with impending (raised bilirubin, progressive thrombocytopenia, or splenomegaly) or overt liver failure (portal hypertension, hepatosplenomegaly, fibrosis, or cirrhosis) should be considered for ITx[53,57]. Traditionally, stratification of waiting times for liver-ITx was influenced by the model for end-stage liver disease (MELD), and paediatric version, pediatric end-stage liver disease. However, deaths on the waiting list in those awaiting combined liver-ITx were 8 times higher compared to liver alone[38]. As a result these scores were adjusted to incorporate a sliding scale of 10% mortality at 3 mo. Over time this has reduced time waiting for a transplant, increased the number of liver-ITx and narrowed the gap between the two groups in both paediatric and adult populations[58]. In addition, the MELD score and C-reactive protein have been shown to be independent predictors of survival in IF and may also be considered as reasons for early ITx assessment[59]. Future areas for research include algorithms that may predict risk of developing IFALD. In reality, whilst liver biopsy remains the gold standard for assessing hepatic disease, non-invasive markers, such as Fibroscan®, are gathering popularity. Rigorous data on its predictive value are needed. If a Fibroscan® score equated to a level of hepatic injury that in turn predicted the risk of IFALD, then there would be a strong argument for tailoring lipid exposure and total caloric intake to reduce this risk. As yet there is insufficient evidence to justify its use as a monitoring tool for patients on HPN.

Assessment tools

The Cambridge-Miami (CaMi) assessment tool has undergone preliminary validation to predict ITx outcome according to an individual's venous access and co-morbidity[48,49]. It was developed as a pre-operative scoring system to help quantify the likelihood of survival after isolated ITx or as a composite graft, to help assess patients. The score combines risk factors for early-, medium-, and long-term survival, including loss of venous access and impairment of organs or systems not corrected by transplantation, each scored 0-3. Initial validation examined the preoperative scores of 20 patients who had

received intestinal transplants either isolated or as part of a cluster graft, who had either been followed up postoperatively for at least 10 years, or died within 10 years and compared with their survivals. A CaMi score < 3 was associated with survival ≥ 3 years (12/12 patients) and > 3 with survival < 6 mo (4/4). It is simple, disease-specific and is undergoing prospective validation, but does not examine QoL.

INTESTINAL TRANSPLANTATION COMPLICATIONS

Post-ITx complications (Table 3) may result in graft failure or death. Graft failure leads to patients resuming HPN and the need to consider re-transplantation, which has a lower probability of success than the index transplant[37]. Graft failure is common, with reasons including allograft rejection, graft-*vs* host disease (GVHD), infection, posttransplant lymphoproliferative disorder (PTLD), primary non-function, or technical complications[39]. Most graft failure occurs within the first few years. The North American Registry reported graft failure rates at 0.5-, 1-, 3- and 5 years of 16%, 26%, 46% and 48%[60]. Graft survival in CD (2001-2009; *n* = 63) at 1-, 3- and 5 years is reported to be 90%, 65% and 52% for isolated-intestinal grafts and 65%, 57% and 57% for liver-intestinal grafts[24]. Notably, the reason why liver-ITx grafts in the latter series of CD patients fared worse than in patients with other primary disease remains unexplored.

Allograft rejection
Rejection occurs *via* an immune-mediated response, which may be acute (cellular or vascular) or chronic[39]. Although the incidence of rejection has fallen with improvements to immunosuppressive regimes, it remains a common problem. While not all episodes of rejection result in graft loss, they are associated with substantial morbidity[39]. Acute cellular rejection has been reported to occur in 50%-75% intestinal transplants (1990-2008; *n* = 500) varying, with immunosuppressive regime, while acute vascular rejection occurred in 6% of isolated intestinal grafts (1990-2008; *n* = 215), of which 92% responded to treatment with anti-lymphocyte therapy[39]. Chronic rejection occurred in 15% of all grafts (1990-2008; *n* = 500), but as indicated above, liver-containing grafts showed a significantly better chance of avoiding rejection than liver-free grafts, presumably due to the transplanted liver's immune-protective properties[39,61]. In patients with CD, acute rejection has been reported to be the commonest cause of graft failure in the first 3 mo (33%), while chronic rejection was the commonest cause between 1-5 years (28%)[24].

Infection
Immunosuppression minimises rejection, but renders recipients vulnerable to environmental and donor infections, with resultant morbidity and mortality[62]. Infec-

tions are the second commonest cause of graft failure, accounting for 11% failures in a general ITx series (1990-2008) and 18% (1987-2009) in a CD ITx series[24,39].

In one study 100 infections were reported in 19 ITx recipients during a median 524 d (18 mo) follow-up, with 94% having at least one bacterial infection[63]. A larger study (1994-2001; *n* = 124) reported 2.6 episodes/patient[64]. Bacterial infections are commonest, representing 61% of infections in one series, with septicaemia in 15%[64]. However, the risk of fatal bacterial infections has declined following changes to immunosuppression regimes[39].

Viral infections, particularly cytomegalovirus (CMV) and Epstein Barr virus (EBV), are potent causes of post-ITx morbidity, but the risk is declining, with altered immunosuppression regimes, viral monitoring and prophylaxis, and the matching of CMV donor to recipient status[39,65,66]. In a recent series, (2001-2008; *n* = 322) 11% of ITx recipients were infected but none died[39].

Graft vs host disease
ITx recipients are at high risk of developing GVHD, with one centre (1994-2007; *n* = 241) reporting GVHD in 9% of recipients, with children being at greatest risk (12.4% *vs* 4.6% adults, *P* = 0.05)[67]. Isolated ITx have a lower risk than multivisceral grafts (4.4% *vs* 13.2%, *P* = 0.05). When GVHD does occur, it has a high mortality: in one series (1990-2008; *n* = 500), 18% of those affected died[39]. There are no data to show whether ITx recipients with CD as the primary disease have an altered incidence of GVHD.

Post-transplant lymphoproliferative disease
Immunosuppression increases the risk of malignancy (8.7 times higher than general population), with the commonest being PTLD, which is associated with 1% of graft failures (2001-2008) and a high mortality (29% affected died; 1990-1995)[39,68,69]. Recipients may be affected early or late following ITx, as shown by rates of 2.5%, 5.3%, 7.2%, 8.2% and 10.2% at 0.5-, 1-, 2-, 3- and 5 years post-ITx in one series (2005-2009)[60]. Risk factors include EBV infection, which is present in 97%, immunosuppression and splenectomy[39]. CD has not been investigated as a risk factor for PTLD.

Renal failure
Renal dysfunction is common in patients requiring HPN due to chronic dehydration from SBS and oxalate nephropathy, associated with jejuno-colonic anastomoses that are not uncommonly formed following CD resection. Although recurrent episodes of dehydration may be considered an indication for ITx, the actuarial incidence of significant renal dysfunction as a referral criterion for ITx (usually including multivisceral transplant) is uncommon[53].

The risk of chronic renal failure is higher following ITx than in patients remaining on HPN[70]. In the first year following ITx, 80% of adults experience an episode of acute kidney injury[71]. Isolated small intestinal recipi-

ents have a significant decline in renal function at 1 year, but multivisceral recipients do not, which may relate to their differing immunosuppressive regimes, since high dose tacrolimus is a risk factor[71-73]. At one centre, 9% of surviving adult recipients required renal replacement therapy during a median follow-up of 7.6 years, with 50% attending for dialysis and 50% undergoing renal transplant[74]. Furthermore, renal dysfunction at 1 year is a risk factor for mortality[72]. Whether or not patients with CD undergoing ITx have an increased risk of renal impairment due to oxalate exposure or other factors remains unexplored.

Disease recurrence

Patients may view ITx as a cure for CD and, theoretically, donor graft genetics may reduce the risk of CD recurrence. However, case reports describe 2 patients, transplanted in 1994, who later developed clinical and histological recurrence (7 mo and 8 years post-ITx)[75,76]. In another series, up to 19% of ITx survivors with initial CD had a recurrence suggested on routine histological assessment, but this did not affect graft function[74]. Similarly, another small study reported asymptomatic CD recurrence in 50% (2/4) of patients, which was evident only on mucosal biopsy specimens (granulomatous enteritis)[77]. Patients should therefore be advised that CD may reoccur in the grafted tissue, but that this may not manifest clinically, perhaps due to the effects of post-ITx immunosuppression.

QUALITY OF LIFE

Generic and disease-orientated tools exist for the assessment of QoL. Generic tools completed by patients on HPN and/or following ITx include the SF-36, Karnofsky performance score and QoL Inventory[74,78-80]. The value of generic tools, including EQ5D (EuroQol) which is used by National Institute of Clinical Excellence to calculate quality-adjusted life years, is that they are validated in many diseases, allowing comparisons with QoL in other chronic conditions, and in many languages[81]. Their disadvantage is that they give little weight to disease-specific factors, such as a stoma or need for parenteral fluids. Disease-orientated tools have been developed, including both the Short Bowel Syndrome-Quality of Life Scale for patients with SBS and the HPN-QoL, for patients with IF on HPN[82,83], which has been partially validated. An adapted version of the HPN-QoL has been used post-ITx[84].

Quality of life on home parenteral nutrition vs intestinal transplantation

The SF-36 and an adapted version of HPN-QoL have been used to compare patients on HPN and following ITx. One study using the adapted HPN-QoL, found ITx recipients scored statistically better for ability to holiday/travel, fatigue, gastrointestinal symptoms, stoma management/bowel movements and global health status/quality of life and non-significantly better for eating ability[84].

However, ITx recipients scored worse for sleeping pattern. Another study using SF-36, compared ITx recipients with patients stable on HPN and those with complicated IF on HPN, who were defined as those referred for ITx but who remained on HPN for whatever reason. Better QoL in ITx recipients and patients stable on HPN was reported than in those with complicated IF on HPN, suggesting that the benefit of ITx over HPN is limited to selected patients[85]. This is to be expected, since patients on stable HPN not being considered for ITx cannot reasonably be compared to ITx. Another study, limited by low numbers from a single centre in the comparator group, compared QoL in those transplanted with those on stable HPN and found no difference between pre-ITx and stable HPN, but a significantly higher QoL score post-ITx[78]. Since all these studies were small (*n* = 55, 22 and 59) and included patients who had undergone a variety of grafts for differing indications and at varying intervals, larger prospective assessments with disease specific tools are needed to confirm these findings, before QoL can be used to guide ITx decision-making. The optimal study would compare outcomes of those undergoing ITx for HPN failure compared to those with poor QoL at risk of HPN failure[78]. No studies have examined QoL pre- and post-ITx in patients with IBD.

ECONOMIC CONSIDERATIONS

Both HPN and ITx impose financial burdens on the healthcare system and the patient. HPN cost estimates differ between countries and health services. In North America, HPN is estimated to cost $64000/year[86]. In the United Kingdom, HPN costs £30-40000/year, for 5 d/wk if self-caring, or £55-65000/year if requiring nursing support[87]. ITx in the United Kingdom is estimated to cost £80000 in the first year, followed by £5000 annually. Thus, assuming no complications arise, ITx should be cost-effective after 2 years[88]. Another European group drew similar conclusions when they reported an initial HPN fee of €9006, followed by €63000 annually, compared to €73000 initially for ITx followed by €13000 annually[89].

HPN and ITx both affect an individual's economic situation. In some countries, patients are liable for a proportion of their healthcare cost, which places pressure on the patient to be in gainful employment. Assessment of employment status has been studied, but heterogeneity of the studies has produced variable data. For example, a recent review of QoL found that the employment rate after commencing HPN was 0%-52%[90]. In contrast, in the last 500 transplants from Pittsburgh, 31% of their 151 adult patients were in employment or education[39]. At a subsequent paper assessing long-term outcomes, of their surviving adult patients, 41 (35%) were in employment[74]. The only comparative study between HPN and ITx was a cross-sectional study, where demographic data in a QoL study reported 56% (6% unemployed) of ITx recipients in part or full-time employment, compared to 30% (52%

unemployed) of patients on HPN (P = 0.013)[84].

INDICATIONS FOR INTESTINAL TRANSPLANTATION

Decisions regarding the role of ITx *vs* HPN in type 3 IF necessarily consider many factors. Guidelines produced by the American Society of Transplantation (AST) (Table 1) are based on the premise that HPN still offers patients the best chance of long-term survival. Current guidelines therefore state that ITx should only be considered for patients with complications associated with HPN[57]. These vary, ranging from life-threatening IFALD, recurrent CRBSI or limited venous access from CVT. Notwithstanding limited evidence of benefit, QoL can be included in the decision-making process. Thus, of these indications, HPN failure is the commonest (62%), followed by risk of death from underlying disease (26%) and high morbidity IF or low acceptance of HPN (12%)[91]. More recent European guidelines suggest that indications for ITx should be restricted to complications associated with a higher mortality and do not support ITx for indications such as chronic dehydration or poor QoL[92]. Further to evaluate the indications, Pironi and colleagues recently carried out a multi-centre, 5-year prospective follow-up of 545 European patients with type 3 IF, stable on HPN; patients were divided into two groups based on their candidacy for ITx according to AST criteria (Table 1). Within these groups, only those with desmoids or IFALD were associated with an increased risk of death on HPN, leading the authors to suggest that early referral for ITx should be mandatory for patients with these conditions. By contrast, patients with central venous catheter (CVC) complications or ultra-short bowel did not have an increased risk of death on HPN. Since there was no difference in survival in these groups whether they were transplanted or not, the authors concluded that CVC complications and ultra-short bowel be considered indications for ITx on a case-by-case basis. Notably, no patient who was considered to be an ITx candidate as a result of poor QoL or chronic dehydration actually died whilst remaining on HPN. The authors therefore concluded that these complications should not be considered an indication for ITx. Relatively few patients of the entire cohort underwent a transplant (n = 22), with a 5-year mortality rate of 54%. All deaths in transplanted patients were related to the transplant itself or to complications resulting from immunosuppression.

After this paper the European Society of Parenteral and Enteral Nutrition suggested that – at least in Europe – indications for ITx should be restricted (summarised in Table 1). This conclusion has been questioned by North American colleagues among others, who highlighted that the relatively poor survival rate of transplanted European patients, compared to 75% 5-year survival in a larger (n = 182) North American series over the same period[93]. Indeed, it has been suggested that the poor European survival may relate to inadequate experience, since data

from the International Intestinal Transplant registry demonstrate improved graft survival in centres performing more cases[19,93]. This trans-Atlantic debate remains unresolved, with Pironi and colleagues pointing out that some European ITx candidates (catheter complications and ultra-short bowel) had comparable survival figures on HPN and post-ITx to those of equivalent Pittsburgh ITx recipients[93]. A key point when considering the risks and benefits of ITx *vs* HPN is that while ITx centre experience and/or outcomes may vary, the same is equally true of HPN experience and outcome. As earlier indicated, quality HPN outcomes such as the incidence of IFALD and catheter-related complications, vary appreciably between different HPN centres[34,36,42,51,52]. Consequently, while ITx survival is likely to continue to improve and indications for ITx will shift as experience evolves, it is also essential that patients with type 3 IF are managed in expert IF centres with optimal HPN quality outcomes[53].

CONCLUSION

Current management options for patients with irreversible IF secondary to IBD are HPN and ITx. For most patients, HPN has the more favourable survival and complication profile, but for selected patients, such as those with IFALD or specific catheter-related complications, ITx may offer better survival. As experience and outcomes in ITx improve, indications for ITx will no doubt widen. In the meantime, further work into tailoring the indications for ITx to individual patients will facilitate better selection. Since patients with CD have one of the better outcomes on HPN, the future use of tools such as CaMi, along with tailoring selection based on the predicted survival on HPN according to the primary disease aetiology, will facilitate patients' choice between ITx and HPN.

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