**Table 2 | Trials of GLP-2 analogues in short bowel syndrome**

| Factor | Patient numbers | Design | SB length (cm), mean (range) | Outcomes ($P \geq 0.05$) | Reference |
|---|---|---|---|---|---|
| Teduglutide (0.05 mg/kg/day) | 86 | Multicentre double-blind parallel group study (24 weeks) | 76 (3–343) | Significantly more responders (>20% decrease in PN requirements) | 144 |
| Teduglutide (0.10 mg/kg/day or 0.05 mg/kg/day) | 83 | Multicentre double-blind parallel group study (24 weeks) | ND (6–200) | Significantly more responders in the 0.05 mg/kg/day group<br>No statistical improvement in 0.1 mg/kg/day group | 145 |
| Teduglutide (0.03/0.10/0.15 mg/kg/day) | 16 | Open multicentre safety study (21 days) | ND (40–150) | No adverse effects related to the drug | 146 |
| Synthetic GLP-2 (0.4 mg BD) | 8 | Open | ND (30–170) | Increased body weight and lean body mass compared with baseline | 147 |

containing a total of 79 patients.[148] This meta-analysis suggested a significant increases in weight (mean difference, 1.66; 95% CI, 0.69–2.63), lean body mass (mean difference, 1.93; 95% CI, 0.97–2.9), energy absorption (mean difference, 4.42; 95% CI, 0.26–8.58) and fat absorption (mean difference, 5.02; 95% CI, 0.21–9.82).[148] Adverse events including peripheral oedema (77%), arthralgia (10%) and carpel tunnel syndrome (32%) were reported. Overall, due to the limited numbers of patients assessed in each small RCT, the authors did not feel that there was adequate evidence to support the use of growth hormone for the indication of short bowel syndrome. There is also concern about a potential increased risk of colorectal cancer in patients receiving growth hormone, which may have limited further research.[149–150]

Perhaps the most promise currently rests with teduglutide, a long-acting GLP-2 analogue has recently received a licence for the treatment of short bowel syndrome from the European medicines agency (Revestive, Nycomed, Zurich, Switzerland) and the Food and Drugs Administration (Gattex, NPS Pharmaceuticals, Bedminster, USA). This has recently been assessed in two multinational double-blind parallel group studies.[144, 145] The first of these phase 3 studies assessed 83 patients on long-term HPN. This demonstrated that 16/35 (46%) patients receiving 0.05 mg/kg/day teduglutide showed $a > 20\%$ reduction in parenteral support over 24 weeks compared with 1/16 (6%) patients receiving placebo.[145] Three patients were weaned from parenteral support. Higher doses (0.1 mg/kg/day teduglutide) did not show a significant reduction in parenteral support, although this group did display a trend towards higher baseline parenteral volume, which may have biased the outcome. Teduglutide treatment (0.05 mg/kg/day) had no significant effect on body fat mass, but a modest increase in lean body mass as assessed by DEXA scanning.[145]

A further study then assessed teduglutide at a dose of 0.05 mg/kg/day in 86 patients over 24 weeks with aggressive reductions in parenteral support (10–30%) at two weekly intervals if urine volume increased by more than 10% from baseline.[144] This demonstrated both a statistically significant improvement in the primary end point, a >20% reduction in parenteral support ($P = 0.002$) as well as an increased plasma citrulline. The mean reduction in parenteral volumes achieved was 4.4 L in teduglutide-treated patients and 2.3 L in placebo-treated patients ($P < 0.001$).[144]

## Quality of life

Patients on long-term PN have been shown to have significantly lower SF36 QoL instrument scores than normal healthy controls.[83, 151] Many patients with IF may never eat or drink again without suffering severe abdominal discomfort and most need to infuse intravenous feed 5–7 nights per week. Thus, while long-term PN may offer many patients a lifeline, not determined dependency can have a detrimental effect on QoL. Enabling home administration of PN therapy and discharge from hospital HPN significantly reduces the cost of care[152] and can allow some patients to return to work.[153] Other factors demonstrating statistically significant effects on QoL include narcotic use, oral fluid volumes, nocturia, the presence of a

stoma, age and the number of infusions required per week.[16, 56, 154, 155] Thus, any reduction in the latter that may be afforded by the use of trophic factors will be welcomed.

### Survival

Retrospective cohorts from large European and North American centres have reported 5-year survival rates between 60% and 78% in unselected patients on PN (Table 3).[46, 48, 49, 83, 152, 156–158] Survival is principally determined by underlying disease; patients with inflammatory bowel disease for example demonstrate a high 5-year survival of 92%,[157] whereas patients with motility disorders have the poorest 5-year survival at 48%.[157] Multivariate analysis of survival data from single centres has also demonstrated lower survival rates in patients with end-enterostomies[156, 158] or a small bowel length of <50 cm.[156]

The survival of patients receiving PN for advanced malignancy is poor with median time to death of between 5 and 6.5 months.[14, 159] The majority of deaths from HPN (both malignant and nonmalignant) are related to the underlying disease with separate centres reporting only 9% of patients dying of HPN-related complications.[48, 157] Deaths related to the underlying disease tend to occur during the first 2 years of treatment, whereas HPN-related deaths often occur after this.[160]

## SURGICAL ALTERNATIVES TO LONG-TERM PN

### Intestinal transplantation

Three types of ITx are possible: isolated intestine, combined liver–intestine and multivisceral transplantation. Definitive indications for ITx are still an evolving area of debate, although criteria have been developed by the American Gastroenterology Association and the American Society for transplantation (Table 1).[161–163]

A recent prospective 5-year cross-sectional multicentre European study has further evaluated the role of ITx in 545 patients (73% adults) that were either deemed to be candidates or noncandidates for ITx based on current American criteria. The 5-year survival rate was 87% in noncandidates, 73% in candidates with HPN failure and 54% in intestinal recipients; in candidates, the HRs were increased in patients with desmoids or liver failure. In candidates with catheter-related complications or ultra-short bowel, the survival rate was 83% in those who remained on HPN and 78% after transplantation. The authors concluded that HPN was confirmed as the treatment of choice for IF and that HPN-associated liver disease and desmoids represented clear indications for a life-saving transplant. However, as the survival rate was 100% for patients in whom the transplant indication was low PN acceptance, the authors did not feel that poor QoL on HPN should form an indication for transplantation. Moreover, the authors felt that CVC complications and ultra-short bowel might be reasonable indications for a transplant in selected patients, pending future cost-utility and QoL studies. A caveat to this conclusion was raised in a subsequent editorial where it was noted that the survival in large volume USA transplant units may approach 75%, perhaps reflecting greater experience and/or the poor medical condition or late referral of transplanted patients within Europe.[164, 165]

As worldwide experience of ITx improves and immunosuppressive regimens evolve, there is no doubt that the indications for transplantation for patients with type

**Table 3 |** Reported survival outcomes in patients with nonmalignant disease on HPN

| Centre Location | Year | Number of patients | Patients with active cancer (%) | 1-year survival (%) | 5-year survival (%) | 10-year survival (%) | Reference |
|---|---|---|---|---|---|---|---|
| Belgium/France | 1995 | 217 | 0 (0) | 91 | 70 | NR | 156 |
| USA | 1999 | 225 | 39 (17) | NR | 60 | NR | 157 |
| Belgium/France* | 1999 | 124 | 0 (0) | NR | 49 | NR | 46 |
| Italy | 2003 | 40 | NR | 97 | 67 | NR | 83 |
| Italy | 2003 | 68 | 0 (0) | 95 | 79 | NR | 49 |
| UK | 2006 | 188 | 8 (4) | 86 | 73 | 71 | 48 |
| UK | 2012 | 547 | 18 (3) | 83 | 63 | 59 | 152 |
| France | 2012 | 268 | 0 (0) | 94 | 70 | 52 | 158 |

The percentages of patients treated for active cancer are shown. NR, not reported.

* Short bowel syndrome patients only.



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**Table 4 | Criteria for intestinal transplantation suggested by the AGA and American Society for Transplantation**

| |
|---|
| Failure of HPN |
| Impending, progressive or overt liver failure due to PN/IF-associated liver injury |
| CVC-related thrombosis of $\geq 2$ central veins |
| Frequent and severe CVC-related sepsis |
| High risk of death attributable to the underlying disease |
| Intra-abdominal invasive desmoid tumours |
| Congenital mucosal disorders |
| Ultra-short bowel syndrome |
| IF with high morbidity or low acceptance of PN |
| Need for frequent hospitalisation, narcotic dependency or inability to function |
| Patient's unwillingness to accept long term PN |

3 IF will increase. In the face of evolving and sometimes contentious indications, it is vital that all patients referred for transplantation should be carefully evaluated in a multidisciplinary setting that involves IF and transplant experts (Table 4).

### Autologous gastrointestinal reconstruction

Intestinal lengthening procedures have been used for some time in children on HPN with promising results.[166–169] The two main surgical operations are the Bianchi and the serial transverse enteroplasty (STEP) procedure. The Bianchi procedure (Figure 2a) involves splitting the small bowel down the middle and anastomosing the two pieces end to end thus creating a smaller diameter, but longer length small bowel; this has allowed successful weaning of PN in children with short bowel syndrome.[166] The STEP procedure (Figure 2b) involves stapling dilated small intestine into smaller segments serially along the long axis of the bowel. Data supporting the use of these procedures in adults are sparse. The largest published series included both paediatric ($n$ = 50) and adult ($n$ = 14) patients undergoing intestinal lengthening procedures and that 69% of the patients in this series were able to wean HPN completely, although this did include eight patients who required ITx.[170] Recently, Yannam *et al.*[171] reported the results of intestinal lengthening procedures in adult patients, including 6 Bianchi and 15 STEP procedures: PN independence was achieved in 59% and a further 18% demonstrated improved enteral caloric intake.

## CONCLUSIONS

The use of long-term PN as a treatment for IF has evolved over the last half-century. It has allowed high

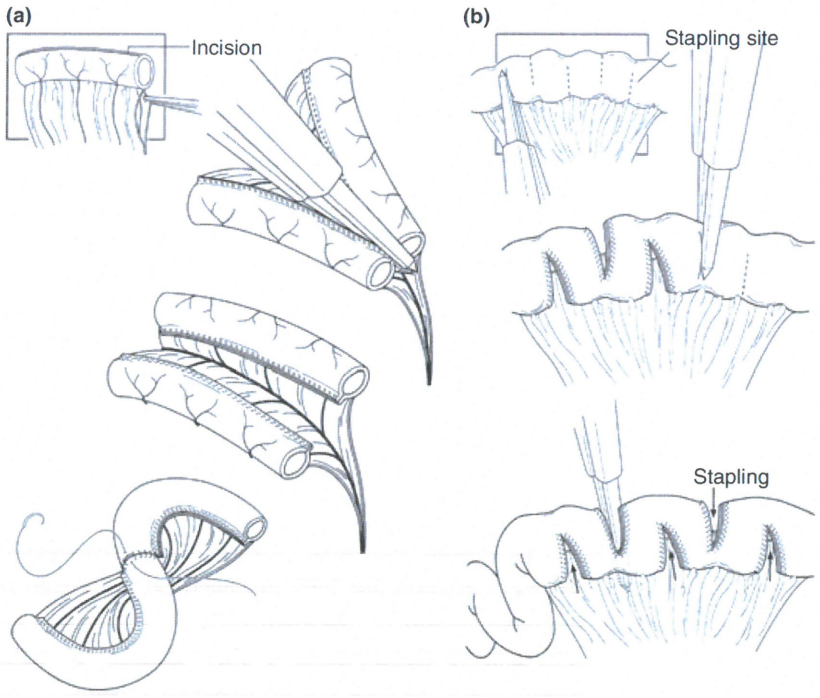


**Figure 2 |** Intestinal lengthening procedures. (a) Bianchi procedure. Reprinted with permission from Bianchi.[172] (b) Step transverse enteroplasty (STEP). Reprinted with permission from Kim *et al.*[173]

quality, low morbidity care that improves patients' survival, QoL and functioning. Fundamental to this is a patient-centred multidisciplinary team of IF doctors; reconstructive and transplant surgeons, specialist nurses, dieticians, pharmacists, psychologists and home-care PN providers. Engagement of patients, and where appropriate relatives, with structured training programmes enabling safe independent PN administration leads to lower health costs and improved QoL. Complications of treatment should be actively sought, assessed and treated. Teams should meet regularly to optimise PN regimens, assess health and psychosocial issues and identify potential candidates for alternative treatments. PN is likely to remain the bedrock of treatment for most patients with type 3 IF, although evolving modalities such as ITx and autologous gastrointestinal reconstruction appear promising.

## AUTHORSHIP

*Guarantor of the article:* M. Dibb.

*Author contributions:* MD performed a literature search, analysed the data and wrote the article. VT performed the literature search and wrote sections of the article. AT, JS and SL reviewed and adapted the manuscript. All authors approved the final version of the manuscript.

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