ORIGINAL ARTICLE

Improved outcome of referrals for intestinal transplantation in the UK

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Aim: To describe the outcome of children with intestinal failure referred to Birmingham Children's Hospital (BCH) for consideration of intestinal transplantation (ITx), to determine factors for an adverse outcome and to analyse the impact of post-1998 strategies on survival.

Subjects and methods: A retrospective analysis was performed of children referred for ITx assessment from January 1989 to December 2003. Children were assessed by a multidisciplinary team and categorised into: (a) stable on parenteral nutrition; (b) unsuitable for transplantation (Tx); and (c) recommended for Tx. To analyse the impact of the post-1998 strategies on survival, a comparison was made between the two eras (pre-1998 and post-1998).

Results: 152 children with chronic intestinal failure were identified (63M:89F, median age 10 months (range 1–170)). After assessment, 69 children were considered stable on parenteral nutrition (5-year survival 95%); 28 children were unsuitable for Tx (5-year survival 4%); and 55 children were recommended for Tx (5-year survival 35%, which includes 14 children who died waiting for size-matched organs). Twenty three ITx and nine isolated liver transplants (iLTx) were performed. In a multivariate analysis, the following factors in combination had an adverse effect on survival: the presence of a primary mucosal disorder ($p=0.007$, OR ratio 3.16, 95% CI 1.37 to 7.31); absence of involvement of a nutritional care team at the referring hospital ($p=0.001$, OR ratio 2.55, 95% CI 1.44 to 4.52); and a serum bilirubin>100 μmol/l ($p=0.001$, OR ratio 3.70, 95% CI 1.84 to 7.47). Earlier referral (median serum bilirubin 78 μmol/l in the post-1998 era compared with 237 μmol/l in the pre-1998 era, $p=0.001$) may be a contributory factor to improved survival. The strategies of combined en bloc reduced liver/small bowel transplantation and iLTx resulted in fewer deaths on the waiting list in the post-1998 era (2 deaths in post-1998 era *v* 12 deaths in pre-1998 era). The overall 3-year survival in the post-1998 era (69%) has improved compared with the pre-1998 era (31%; $p<0.001$)

Conclusion: The changing characteristics at the time of referral, including earlier referral and innovative surgical strategies have resulted in improved long-term survival of children referred for ITx.

Intestinal failure is defined as a condition in which intestinal nutrient absorption is inadequate to sustain life and to support growth without intravenous nutritional supplementation.[1] The prevalence has increased from 2–3 per million to 5–6 per million of the population, as a result of improved survival in the newborn period.[2] There are three main causes of long-term intestinal failure: (1) short bowel syndrome (SBS), usually occurring after extensive neonatal surgical resection for necrotising enterocolitis, small bowel atresia and gastroschisis; (2) motility disorders, for example Hirschprung's disease, pseudo-obstruction; and (3) primary mucosal disorders, for example microvillous inclusion disease, tufting enteropathy.

From the 1970s successful developments in parenteral nutrition and in central venous catheter placement made it possible to maintain children with intestinal failure in a satisfactory nutritional state for many years.[3 4] However, the long-term use of parenteral nutrition is associated with life-threatening complications: liver disease, recurrent septicaemia, and thromboses resulting in difficult venous access.[4] Intestinal transplantation has evolved from an innovative procedure in the late 1980s to a technically feasible option in the late 1990s[5] and around 1300 intestinal transplants have now been performed worldwide.[6] Moreover, non-transplant surgery (for example, bowel lengthening or plication procedures) may be a treatment option in selected patients.[7] In patients with SBS who develop severe liver disease, isolated liver transplantation may be an option if there is a realistic likelihood of eventual successful intestinal adaptation and recovery from intestinal failure.[8] Thus, there are various possible treatment options for children with intestinal failure and choosing the best strategy for individual cases poses a major clinical challenge.

Children who have developed complications associated with intestinal failure in the UK have been referred to the intestinal transplant program at Birmingham Children's Hospital (BCH) since 1989, and the first intestinal transplant was performed in 1993. This centre was officially designated as the sole UK centre for paediatric small bowel transplantation in 1997. An earlier analysis of our experience between 1989 and 1997 indicated a poor survival rate (31%). At that time many referred patients were already seriously ill and many died awaiting transplantation (69%). For this reason, several new treatment strategies were implemented in 1998: combined reduced en bloc liver and small bowel transplantation; isolated liver transplantation for selected patients for short bowel syndrome; and non-transplant surgery for selected patients of short bowel syndrome with dilated dysmotile loops of bowel. The aim of this study was to describe the outcome of children with intestinal failure referred to our centre, to determine risk factors for adverse outcome and analyse the impact of the new strategies implemented since 1998 onwards.

Abbreviations: BCH, Birmingham Children's Hospital; IFALD, intestinal failure associated liver disease; SBS, short bowel syndrome.

Table 1 Characteristics of 152 children referred for intestinal transplantation

Clinical status	Stable on parenteral nutrition (n = 69)	Unsuitable for transplant (n = 28)	Recommended for transplant (n = 55)
Short bowel syndrome*	43	21	38
Median age (years)*	0.6	0.8	0.7
Range	0.04–13	0.1–1.7	0.1–14.7
Nutritional care team	27 (63%)	7 (33%)	23 (61%)
Motility disorders*	16	4	11
Median age (years)*	6.4	0.8	0.8
Range	0.6–13.9	0.3–3.5	0.3–6.8
Nutritional care team	8 (50%)	1 (25%)	6 (55%)
Mucosal disorders*	10	3	6
Median age (years)*	1.1	3.1	1.4
Range	0.04–9.4	0.3–3.8	0.8–10.9
Nutritional care team	8 (80%)	3 (100%)	6 (100%)

*No significant ($p<0.05$) differences in group medians by Kruskal–Wallis test.

SUBJECTS AND METHODS

One hundred and fifty two children (63 male and 89 female) from all parts of the UK and Republic of Ireland referred to BCH for small bowel transplantation between 1989 and December 2003 were included in the study (table 1). The data were obtained by retrospective review of medical records between 1989–96 and were recorded prospectively from 1997–2003. The following clinical variables were recorded: underlying diagnoses; age at referral; serum bilirubin at referral, history of previous management by a nutritional care team (comprising paediatric gastroenterologist, paediatric surgeon, paediatric dietitian, nutritional care nurses and parenteral nutrition pharmacist). These variables were related to the decision to offer liver ± small bowel transplantation and overall survival. The decision to offer transplantation was based on an estimate of the 12-month survival, with and without transplantation. Patients were assessed by a multidisciplinary team established with members from the departments of paediatric gastroenterology, hepatology, surgery, dietetics, pathology, radiology, pharmacy, specialist nurses, play specialists and social workers. Following assessment, patients were discussed at a multidisciplinary team meeting and placed in one of three categories:

(1) stable on total parenteral nutrition (non-progressive liver disease; at least two suitable veins for future central venous catheter placement)

(2) unsuitable for transplantation (for example, multi-organ dysfunction, serious neurological disease)

(3) recommended for transplantation (based on internationally accepted criteria[9]).

Patients were considered suitable for transplantation only if the diagnosis of irreversible intestinal failure was established, life-threatening complications of parenteral nutrition could not be resolved medically and transplantation was expected to produce a worthwhile improvement in quality of life.[9] The choice of transplant type depended on the severity of liver damage and the prognosis for intestinal function. Children with fibrosis on liver biopsy and impaired venous access were considered for isolated small bowel transplant, whereas children with evidence of cirrhosis on liver biopsy were considered as candidates for liver and small bowel transplantation. In children with SBS and end stage liver disease, isolated liver transplant was performed if at least 50% of estimated daily requirements enterally had been tolerated and at least 30 cm residual small bowel remained intact in the presence of the ileo-caecal valve and colon. Non-transplant intestinal surgery was also considered if all of the following four criteria were met: (1) estimated residual length of small bowel was at least 30 cm; and (2) dilated loops of small bowel; and (3) sustained failure to induce bowel adaptation by medical or dietetic means; and (4) absence of significant portal hypertension.

The following endpoints were recorded: survival; duration of survival; timing and success of liver ± small bowel transplantation; success in discontinuing parenteral nutrition.

Survival was compared for the pre- and post-1998 periods. Non-parametric methods (Fisher's exact test, Kruskal–Wallis test) were used for group comparisons and the Kaplan–Meier method with the log rank test and Cox proportional hazards regression used for comparison of survival times.

Table 2 Number of children according to prognostic groups in pre- and post-1998 eras

	Pre-98 era (n = 48) (%)	Post-98 era (n = 104) (%)
Stable on parenteral nutrition	11 (22)	58 (55)
Unsuitable for transplantation	18 (38)	10 (10)
Recommended for transplantation	19 (40)	36 (35)

RESULTS

Clinical characteristics and outcome of the three prognostic groups

The characteristics and the underlying diagnoses are shown in table 1. Indications for referral were "intestinal failure associated liver disease" (IFALD) (n = 100), impaired venous access (n = 28), recurrent life-threatening line infections (n = 5), evaluation of intestinal failure (n = 18) and quality of life (n = 1).

Children with serum bilirubin >100 μmol/l at the time of assessment had a 40% risk of death by one year and 60% risk of death by two years from the time of assessment (fig 1).

The categorisation of children according to the prognostic groups in the pre- and post-1998 eras is outlined in table 2.

Stable on parenteral nutrition (n = 69)

Of the 69 children considered to be stable on parenteral nutrition, 43 children had SBS as the underlying diagnosis. Improved tolerance to enteral feeds was achieved by: (1) modification of feed composition (n = 4), (2) continuous enteral tube feeding (n = 7), (3) alteration and/or introduction of anti-motility agents (n = 5). Eventually, 22 children achieved a much reduced level of dependence on parenteral nutrition, while 11 of the 43 with SBS were able to discontinue parenteral nutrition completely, thus showing that they did not in fact have intestinal failure.

Five children initially considered to be stable on parenteral nutrition subsequently deteriorated and were included in the transplant group for final analysis.

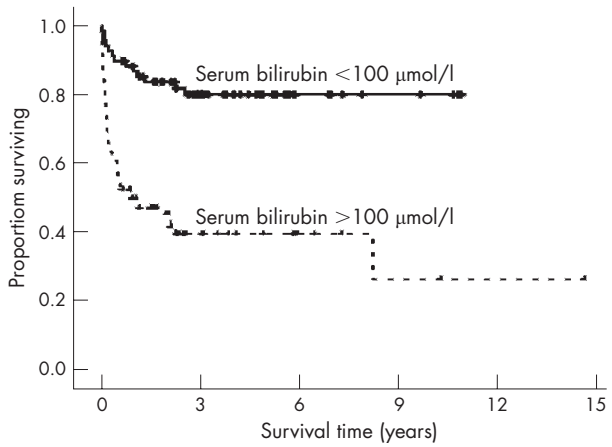

Figure 1 Survival of children referred for intestinal transplantation depending on the bilirubin at the time of assessment.

Unsuitable for transplantation (n = 28)

Twenty three (82%) of the 28 patients considered unsuitable for transplantation had SBS. Of these, 24 children had end-stage IFALD at the time of referral with a median bilirubin of 280 μmol/l (range 105–760 μmol/l), two children were too small, one child had severe neurological handicap and one child was subsequently transplanted following successful cardiac intervention. Eighteen of the 48 children (37%) assessed in the pre-1998 era were unsuitable for transplantation compared with 10 of the 104 children (9%) assessed in the post-1998 era ($p = 0.001$), which reflects on the improvement in referral patterns over a period of time.

Recommended for transplant (n = 55)

Fourteen children died on the waiting list and seven families declined transplantation. Of the remaining 34 children, 23 underwent intestinal transplantation, nine children had isolated liver transplantation for SBS and IFALD, one child improved while awaiting transplant and was suspended, and one child was lost to follow-up. Most of the children who were recommended for intestinal transplantation (n = 23) had SBS and IFALD (n = 14). Of the 23 children who underwent intestinal transplantation, four died in the hospital before discharge (median time to death 37 days, range 7–41 days), 19 children were discharged from the hospital. Ten children died on follow-up (median time to death 446.5 days, range 184–2408 days) and nine are currently alive, have been weaned off parenteral nutrition and are thriving.

The outcome and survival of the prognostic groups is shown in figures 2, 3, 4 and 5.

Nutritional care team

Eighty nine children (58%) had been managed by a multidisciplinary nutritional care team at a regional centre. Children managed by a nutritional care team (n = 89) were referred with less advanced liver disease (median bilirubin 86 μmol/l) than those who had not been managed by an nutritional care team (median bilirubin 200 μmol/l, $p = 0.03$). The survival of patients referred from a nutritional care team (3-year survival 64%) was significantly better (log rank test $p = 0.02$) than the survival of children not managed by a nutritional care team (3-year survival 50%). The proportion of children referred to us who had been managed by a nutritional care team increased from 50% in 1996 to 64% in 2003.

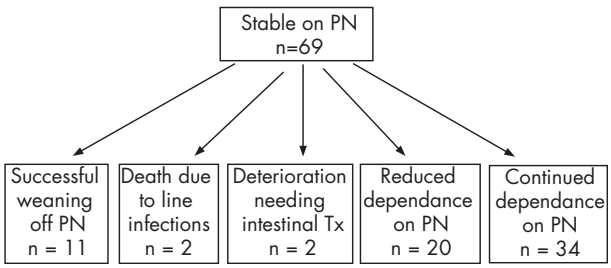

Figure 2 Outcome of children categorised as stable on parenteral nutrition after assessment for small bowel transplantation from 1989–2004.

Impact of the new strategies

Small bowel transplantation

In pre-1998 era, six intestinal transplants were performed (four size-matched liver and small bowel transplant, two isolated intestinal transplant), while 10 children died on the waiting list. In the post-1998 era, 17 intestinal transplants were performed (four isolated intestinal transplant and 13 combined en bloc reduced liver and small bowel transplant), while four children died on the waiting list.

Isolated liver transplantation

This technique was only introduced in 1998 and nine children had isolated liver transplantation carried out for children with end-stage IFALD and SBS. Seven children were weaned from parenteral nutrition onto full enteral feeds. One child is tolerating 30% of their intake enterally, and one child died of infection 18 months after liver transplant.

Non-transplant surgery

Four children underwent intestinal lengthening (n = 3) and intestinal tapering (n = 1) surgery in the post-1998 era. Two children had isolated liver transplant followed by non-transplant surgery (one child had intestinal tapering and one child had intestinal lengthening) subsequent to the transplant and have been weaned from parenteral nutrition. Of the other two children with intestinal lengthening procedures, one has discontinued parenteral nutrition and the other is being weaned from parenteral nutrition.

Survival and Cox regression multifactor analysis

In univariate analysis, the survival of children with primary mucosal disorders (52.6%) was not significantly different from that of children with SBS (56.8%) or primary motility disorders (70.9%) (log rank test $p = 0.4$). The overall survival curve (fig 6) of children has significantly improved from a 3-year survival of 31% (pre-1998) to a 3-year survival of 68% (post-1998) (log rank test $p = 0.001$).

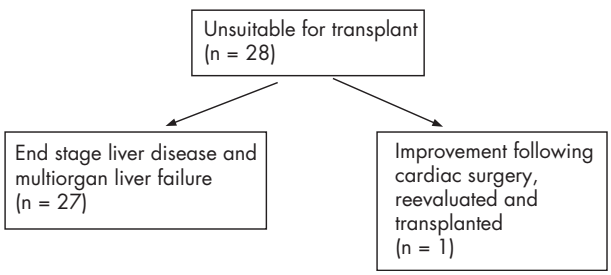

Figure 3 Outcome of children categorised as unsuitable for transplant after assessment for small bowel transplantation from 1989–2004.

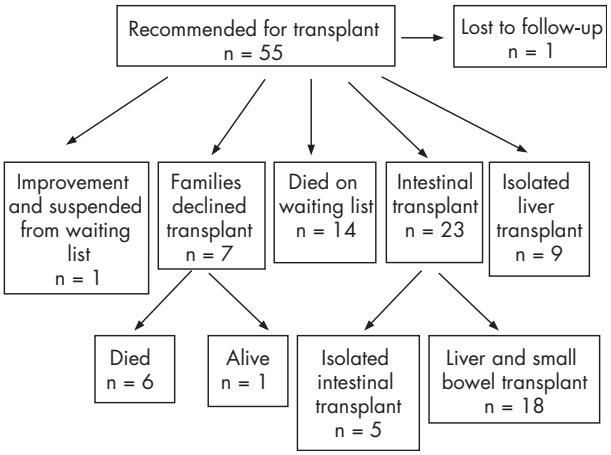

Figure 4 Outcome of children categorised as recommended for transplant after assessment for small bowel transplantation from 1989–2004.

In a multivariate Cox proportional hazards regression analysis of survival time, using diagnostic group together with the potential explanatory factors (sex, age at evaluation, nutritional care team, bilirubin at assessment) it emerged that the presence of a primary mucosal disorder ($p = 0.007$, OR 3.16, 95% CI 1.37 to 7.31), lack of involvement of nutritional care team at referring hospital ($p = 0.001$, OR 2.55, 95% CI 1.44 to 4.52) and serum bilirubin>100 μmol/l ($p = <0.001$, OR 3.70, 95% CI 1.84 to 7.47) at assessment were factors jointly having an adverse impact on survival (table 3).

DISCUSSION

This report demonstrates the improved outcome in children referred for ITx and the main factors are: early referral to a specialised centre, implementation of a range of treatment options and the presence of nutritional care team in the management of children with SBS before referral. Earlier referral has not resulted in a rise in the proportion of patients undergoing ITx, but it has allowed us to identify clearly those patients with a good long-term prognosis (table 2). Surgical strategies such as isolated liver transplantation and combined en bloc reduced liver and bowel transplantation have resulted in fewer children being classed as unsuitable for transplantation and dying on the waiting list. The exact reasons for the effect of the nutritional care team on improved outcome are probably the same as documented in the literature, but are difficult to determine in our cohort due to the confounding variables—for example, different case mix, different complications rate and possibly different rate of progression of liver disease, etc.[10 11]

There have been few case series of similar size describing the outcome of children with intestinal failure. Koehler *et al* reported on a comparable group of 103 children with intestinal failure assessed in the intestinal care centre at Pittsburgh from 1996 onwards.[12] Guarino *et al* reported on a collaborative network of centres involved in the management of 109 children with intestinal failure in Italy, since 1997.[13] The mode of assessment and the diagnostic categories of the subgroup of children reported by the two groups are similar to the multidisciplinary assessment and the diagnostic categories in our group.

In our study, 69 children were stable on parenteral nutrition and had a 5-year survival rate of 96%, which compares well with the figures reported from the Italian collaborative national network (94%) and a national figure of 89% surveyed by the British Artificial Nutrition Survey.[13 14] It is important to recognise those who will remain on parenteral nutrition indefinitely, as this subgroup of children have a lifetime risk

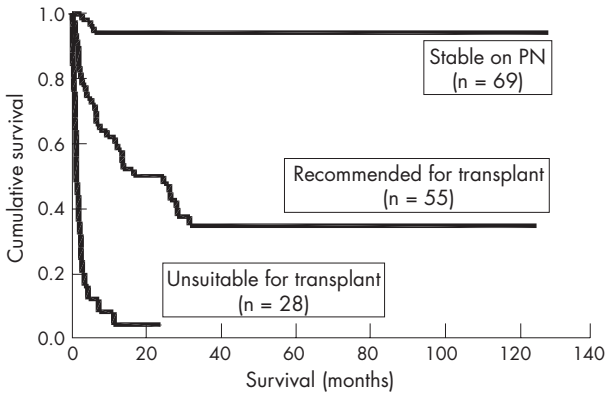

Figure 5 Survival of 152 children with complications of intestinal failure according to the prognostic groups after assessment for small bowel transplantation.

of dying of complications of parenteral nutrition.[15] In this cohort of children, three who were initially stable on parenteral nutrition deteriorated and underwent isolated liver transplantation and another two underwent combined liver and bowel transplant. Eleven children with SBS were weaned from parenteral nutrition and it is thus crucial to identify these children who would benefit from conservative management of intestinal failure. This particular subgroup of children with SBS were managed according to specific protocols to promote intestinal adaptation.[16]

Children recommended for transplantation had a high mortality while on the waiting list due to a shortage of size-matched donor organs and the tendency of children with end-stage IFALD to deteriorate rapidly.[17 18] Reduction of size of the liver and bowel from adult donors to fit into the small abdominal cavity of children has extended the range of possible donors, and led to a decrease in the waiting list mortality from 57% (pre-1998) to 8% (post-1998).[19] The outcome of children undergoing small bowel transplant has been described elsewhere and a manuscript detailing the latest results is in preparation.[20]

Some infants with intestinal failure due to SBS have a native bowel capable of adaptation, but unfortunately develop rapidly progressive liver disease. It is this group who may benefit from isolated liver transplantation.[8] In this study, 8/9 children with isolated liver transplant have been weaned from parenteral nutrition and are on full enteral nutrition. In this study discontinuation of parenteral nutrition was possible in two

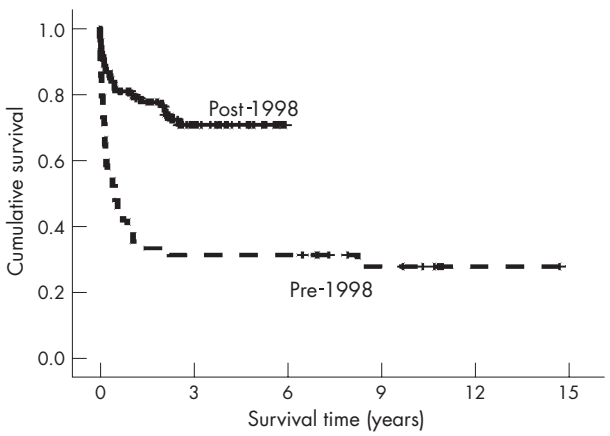

Figure 6 Survival of children referred for intestinal transplantation according to the era of assessment.

Table 3 Multivariate Cox regression analysis of children referred for small bowel transplantation

	Odds ratio	95% CI	p Value
Female *v* male	1.65	0.98–2.77	0.055
Age at evaluation: >2 years *v* <2 years	0.36	0.14–0.89	0.027*
Primary mucosal disorders *v* short bowel syndrome	3.16	1.37–7.31	0.007*
Motility disorders *v* short bowel syndrome	1.28	0.57–2.92	0.54
Absence of nutritional care team	2.55	1.44–4.52	0.001*
Serum bilirubin at assessment>100 μmol/l	3.70	1.83–7.47	<0.001*

*Variables with a p value <0.05 were considered to be significantly associated with a reduction in survival.

children following isolated liver transplant only after an intestinal lengthening (n = 1) and intestinal tapering (n = 1) operation.

Non-transplant bowel surgery may be indicated in a subgroup of children with intestinal failure and SBS.[21] In our series, intestinal lengthening (n = 3) and tapering procedures (n = 1) were carried out in four children. In addition to the two described above, one was weaned from parenteral nutrition while the other remains on a combination of enteral feeding and parenteral nutrition.

The severity of the liver disease is an important factor in determining the outcome of children with complications associated with intestinal failure. Fecteau *et al* reported on the importance of early referral for successful small bowel transplantation.[22] A 1-year actuarial survivals of 40% and 30% respectively in children with serum bilirubin greater than 3 mg/dl (equivalent to approximately 50 μmol/l) or cirrhosis on histopathological examination has been reported.[23] In a previous report we found that children with a bilirubin level of >100 μmol/l in association with splenomegaly and cirrhosis rarely survived for more than six months. Most of the children considered unsuitable for transplant (27/28 deaths within 3 months) and dying on the waiting list (14/55 deaths within 6 months) had end stage liver disease and died within a few months after assessment. However in the past few years referrals have been taking place earlier, as evident from the median serum bilirubin (78 μmol/l in the post-1998 era *v* 237 μmol/l in the pre-1998 era, p = 0.001) and severity of the liver disease (55% are stable on parenteral nutrition in post-1998 era as opposed to 22% in pre-1998 era, p = 0.001; table 2). This is probably due to the significant developments in regional gastroenterology services over the last few years including nutritional care teams, close collaboration within teams, development of managed clinical networks and better formulation of total parenteral nutrition.

In the multivariate analysis, children with primary mucosal disorders had a poor outcome and the exact reason is not clear.

The limitation of this study is that it describes the outcome of children with intestinal failure over a decade of continuously improving medical and surgical management. We have tried to address the limitation by comparing the outcome in two different time eras in order to evaluate the new forms of therapy.

It is important to remember that the current strategies have been developed in the setting of intestinal transplantation achieving relatively poor long-term survival rates compared with uncomplicated home parenteral nutrition. With improved results of intestinal transplantation being reported, it is likely that our current strategies will have to be modified.[24] Progress in the management of complex intestinal failure has recently been alluded to in an article commissioned by *Archives of Disease in Childhood* which was written while this manuscript was in preparation.[25]

In conclusion, referral to our intestinal transplant unit historically used to occur at a late, even terminal, stage, but is now occurring earlier. An opportunity to offer a range of innovative surgical strategies in combination with early referral has resulted in improving outcome of children referred for ITx at our centre.

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What is already known on this topic

- New surgical and medical strategies in the management of intestinal failure have evolved in the last decade. Intestinal transplantation is now technically feasible, with improving medium-term survival in adults and children.
- Intestinal transplantation may be an option for children who develop life-threatening complications related to intestinal failure.
- The natural history of children with intestinal failure in the era of small bowel transplantation has not been documented.

What this study adds

- This study demonstrates the feasibility of intestinal transplantation in children in the UK.
- This study shows categorisation of different prognostic groups following assessment for and importance of the timing of referral for small bowel intestinal transplantation.
- This study further demonstrates the efficacy of multidisciplinary nutritional teams in regional gastroenterology centres in the management of children with intestinal failure.

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