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Elements of successful intestinal rehabilitation

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Abstract

Purpose: The optimal therapy for intestinal failure (IF) is unknown. The results of a systematic, protocol-driven management strategy by a multidisciplinary team are described.

Methods: *Intestinal failure* was defined as bowel length of less than 40 cm or parenteral nutrition (PN) for more than 42 days. A multidisciplinary team and protocol to prevent PN-associated liver disease (PNALD) were instituted in 2006. Data were gathered prospectively with consent and ethics board approval.

Results: From 1998 to 2006, 33 patients were treated (historical cohort) with an overall survival of 72%. Rotating prophylactic antibiotics for bacterial overgrowth were given to 27% of patients; 6% had lipid-sparing PN, and none received fish oil–based lipids. Median time to intestinal rehabilitation was 7 ± 3.1 months, and 27% of patients who developed PNALD died. From 2006 to 2009, 31 patients were treated. Seventy-seven percent received PAB; 60%, lipid-sparing PN; and 47%, parenteral fish oil emulsion. Eighty-seven percent weaned from PN at 3.9 ± 3.8 months, and no patients developed PNALD with 100% survival. Novel lipid therapies were associated with changes in essential fatty acid profile and one case of clinical essential fatty acid deficiency.

Conclusion: The institution of a multidisciplinary team and a protocol-driven strategy to prevent PNALD improves survival in IF. Further studies are recommended.

The care of infants and children after massive resection of the small intestine or repair of gastroschisis is a challenging problem in pediatric surgery. These patients typically require prolonged support of parenteral nutrition (PN) because of poor motility and absorptive function of the remnant bowel. In this study, we followed the consensus definition of the Canadian Association of Pediatric Surgeons for *intestinal failure* (IF): remnant small intestine length of less than 40 cm (at term) or PN support for more than 42 days after intestinal resection or repair of gastroschisis [1-3]. The frequency of IF is increasing because of a combination of a rising incidence of gastroschisis worldwide and improved survival in premature infants, resulting in an increased incidence of necrotizing enterocolitis (NEC) [4-7]. The emergence of specialized team-based programs has led to improved therapeutic accuracy and consistency of clinical care. Nutritional support in a manner that minimizes the potential for the PN-associated hepatotoxicity is the cornerstone of initial therapy, followed by a careful introduction of enteral feeds to stimulate gut adaptation. Although there is still no treatment to augment the process of up-regulation of nutrient transport by the residual bowel, the improved ability to provide general supportive care for these infants has led to an apparent recent increase in survival [1,8-10].

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Despite these improvements, this patient population is still prone to PN-associated liver disease (PNALD), which is the primary problem leading to death. These patients continue to have a high proportion of septic episodes from both catheter-associated sepsis and translocation of enteric organisms as well. The relationship between sepsis and development of liver disease is now well established [1,11,12]. The care of these infants at our institution has come to revolve around a protocol that has evolved from a long-standing interest in the treatment of patients with IF [1]. Since 2006, the Children's Hospital Intestinal Rehabilitation Program (CHIRP) has implemented consistent feeding protocols or adjunctive strategies in all patients. This report describes the impact of this approach before (1998-2006) and after (2006-2009) the implementation of CHIRP on clinical outcomes. Since our last report, an additional 9 patients have been cared for, with a correspondingly greater understanding of the outcomes, particularly related to the biochemical effects of therapy with a fish oil–based parenteral lipid emulsion (Omegaven; Fresenius, Bad Homburg, Germany, via special access, Health Canada) [1]. We present a descriptive cohort study comparing a contemporary population of infants with IF with historical controls.

1. Methods

1.1. Data collection

All patients having intestinal operation at the Alberta Children's Hospital and identified as having IF (<40 cm of residual small intestinal length or a requirement for PN support for >42 days after operation) were included. Patients who died of unrelated medical conditions (ie, cardiac disease or bronchopulmonary dysplasia) or early infection or progressive NEC were excluded. *Parenteral nutrition–associated liver disease* was defined as the persistence of direct bilirubin greater than 100 μmol/L for more than 2 months. The primary outcome examined was mortality. The secondary outcomes included time to intestinal autonomy, development of PNALD, weight gain, changes in liver biochemical indices, and essential fatty acid (EFA) profiles for patients on Omegaven (Fresenius). For the 1998-to-2006 cohort, patients from 1998 to 2000 were identified by reviewing the PN formulation records. Demographic, biochemistry, and feeding data were collected retrospectively, and outcomes, prospectively. The remainder of the first cohort (2000-2006) and all patients from the 2006-to-2009 cohort were followed up prospectively. Data were analyzed using the Prism statistical software (Prism, La Jolla, Calif) using standard parametric and nonparametric techniques. Continuous baseline characteristics of infants in the contemporary and historical cohorts were compared using Student *t* test. Baseline and treatment proportions were compared using Fisher exact test. A time-to-event (Kaplan-Meier) analysis was used to compare mortality rates, the time until intestinal autonomy, and the development of PNALD.

1.2. Protocol

During 1998 to 2006, patients were cared for primarily by the attending surgeons without protocols. In 2006, a standardized care protocol was instituted for the nutritional management of all gastroschisis and neonatal intestinal surgical patients by the CHIRP team. Parenteral nutrition support was initially provided with a relative lipid-sparing protocol with total energy based on conventional guidelines for weight and gestational age [13-15]. Effort was made to keep the parenteral fat from Intralipid (Fresenius Kabi, Toronto, Ontario) at less than 2 g/kg per day when possible, with even further reductions in the face of cholestasis if growth and essential fat requirements were not compromised. Continuous gastric enteral feeds were instituted when appropriate, using either breast milk (BM) or an elemental formula (Neocate; Nutricia NA, St Laurent, Quebec, Canada). Feeds were advanced by 10 to 20 mL/kg per day, monitoring tolerance by stoma/stool outputs (<40 mL/kg per day). Once feeds exceeded 5 to 10 mL/h during day time, 2 to 3 oral feeds were introduced to prevent the development of oral aversion. Bolus feedings were initiated once a target volume for continuous feeding was reached. Parenteral nutrition was tapered according to the weight gain, and cycling PN was instituted when feasible. Rotating antibiotics were used in cases of dysmotility with suspected small bowel bacterial overgrowth (SBBO) and in patients with an extremely short bowel (<40 cm). Antibiotics were administered enterally as gentamicin (2.5 mg/kg, BID) followed by a 1-week "rest" then a second week of metronidazole (10 mg/kg, BID) administration. When a patient experienced recurrent episodes of sepsis and severe dysmotility, enteral antibiotics were continued without interruption.

Promotility agents were used in cases of severe dysmotility. Typically, metoclopramide (10 mg/kg per dose, PO, QID) or erythromycin (10 mg/kg per dose, TID) was administered in successive therapeutic trials. In patients with marked dysmotility, an upper gastrointestinal series was obtained to assess for anatomic and functional dilation of the small intestine. With worsening symptoms, a repeat upper gastrointestinal series was obtained at approximately 6-month intervals to reassess for adaptation-driven dilation of the small intestine, which decreases peristaltic efficiency, promoting stasis and SBBO. In cases of progressive intestinal dilation and clinical deterioration, the serial transverse enteroplasty (STEP) procedure was performed in select patients [16-18]. If cholestasis occurred (direct bilirubin >30 μmol/L), then the lipid support (Intralipid; Fresenius Kabi) was reduced to 1 g/kg per day with a corresponding increase in glucose infusion rate and enteral fat, if possible, to maintain total energy. If bilirubin

continued to rise (>50 μmol/L), then Omegaven was instituted. Some high-risk patients were started directly on Omegaven without a phase of lipid reduction because of rapidly rising bilirubin. Omegaven was prescribed at 1 g/kg per day and adjusted as PN requirements decreased. After Diamond et al [19] demonstrated the effectiveness of using Intralipid-Omegaven in a 1:1-1-2 mix, the protocol evolved to use Omegaven as monotherapy until direct bilirubin normalizes and then to use a 1:1 mix of Intralipid and Omegaven. Serum EFA was routinely monitored.

2. Results

The demographics of the 2 populations are reported in Table 1. Both cohorts were primarily infants with a similar distribution of birth weight, gestational age, and primary diagnosis. The more recent cohort had a significantly longer residual small bowel length, both in absolute terms and as a percentage of bowel length expected for the given gestational age [17,20] (Table 1). In the more recent era, each of the specific treatment outlined in the algorithm was used significantly more frequently (Table 2). In the case of Omegaven and STEP procedures, the intervention was not available in the previous cohort. The most important outcome was overall survival, which was significantly increased in the modern cohort (Table 3, Fig. 1). There was also a significant decrease in the incidence of PNALD; none of the patients in the recent cohort developed severe cholestasis (direct bilirubin >100 μmol/L for >2 months), whereas 28% of patients treated during 1998 to 2006 developed severe cholestasis and died. This difference was not caused by an increase in patients adapting and weaning off PN; there was no change in the average time to intestinal adaptation in both study periods (Table 3, Fig. 2). In the recent cohort, 14 patients were started on Omegaven because of elevated bilirubin (>30 μmol/L) that did not respond to other cholestatic strategies.

Of these, 7 patients were maintained on Omegaven for more than 60 days; their nutritional intake of fat is presented in Table 4A; serum fatty acid profile, in Table 4B; and weight and biochemical end points, in Table 4C. Because of variations in the time on PN before instituting Omegaven and variability in the individual patient's course, the data are presented as the average at each time point, starting with the commencement of Omegaven therapy. Importantly, although all patients were maintained with parenteral fat at 1 g/kg per day while receiving most of their nutrition from PN, once enteral tolerance improved, the total load of fat gradually increased to an average of 7 g/kg per day by 2 months after PN was discontinued (Table 4A). In the initial experience with Omegaven, other forms of intravenous lipid were not used. In one patient with severe SBS on long-term Omegaven support, clinical signs of EFA deficiency began to develop after 4 months; she was noted to have an elevated triene-tetraene ratio of 0.25. She was dependent on PN for more than 60% of energy and was very sensitive to any increase in enteral feeds. The skin rash disappeared within a few weeks after she was switched back to Intralipid (1–g/kg

Table 1 Patient demographics

Parameter	1998-2006	2006-2009	*P*
No.	33	31	
Birth weight (g)	2480 ± 600	1980 ± 910	NS
Gestational age (wk)	33.7 ± 3.4	32.9 ± 4.8	NS
Gestational age at initial surgery (wk)	35 ± 12	35.6 ± 6.6	NS
Residual small bowel length (cm)	59 ± 33	95 ± 46	<.02
Residual small bowel length (% predicted)	62 ± 33	71 ± 30	<.02
Ileocecal valve resected	7/33	10/31	NS
Colon resected	11/33	6/31	NS
Diagnosis			
Gsc	10	9	NS
Atresia/atresia + Gsc	7/4	5/4	NS
NEC	10	9	NS
Others	5	4	NS

Data are presented as mean ± SD, ordinal data comparisons by Student *t* test and diagnosis frequency by Fisher exact test.
Gsc indicates gastroschisis; NS, not significant.

Table 2 Treatments used by era

Parameter	1998-2006	2006-2009	*P*
Rotating antibiotics	5/33	22/31	.01
Lipid reduction strategy	2/33	18/31	.04
Fish oil–based lipids	0/33	14/31	.001
STEP procedure	0/33	4/31	.03

Data are presented as subjects receiving intervention/total subjects in the group.
P values are from Fisher exact test.

Table 3 Patient outcomes by era

Parameter	1998-2006	2006-2009	*P*
Survival	24/33	31/31	.01
Enteral adaptation	24/33	26/31	NS
Median time to intestinal autonomy (mo) [a]	7.0 ± 3.1	3.9 ± 3.8	NS
Time to death/follow-up if not adapted (mo)	14.6 ± 3.2	13.8 ± 1.5	NS
Total time of follow-up (mo)	82 ± 16	17 ± 10	.01

Data are presented as mean ± SD, comparison by Fischer exact test.
[a] Time to enteral adaptation of infants who did adapt. In the 1998-to-2006 cohort, patients who died were entered as nonadapted at time of death as were the 5 patients in the 2006-to-2009 cohort that have not yet adapted as of August 30, 2009.

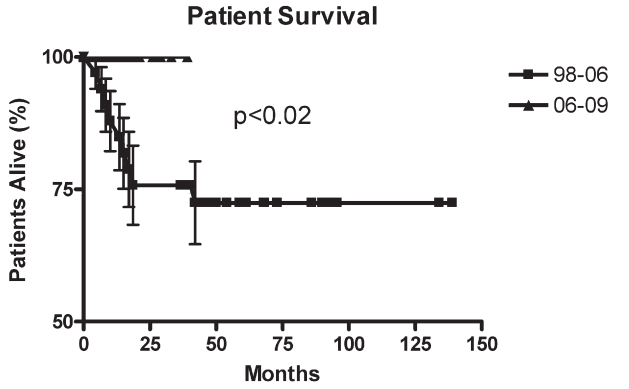

Fig. 1 Survival in the 2 cohorts. Patients were censored at the time of last follow-up if alive or registered as an event at the time of death (*$P < .02$ by Kaplan-Meier analysis).

per day dosage). The resulting EFA profiles are outlined in Table 4B. It is notable that although the ω-3 EFA, eicosapentaenoic acid, and docosahexaenoic acid are elevated, the "proinflammatory" fatty acids, such as arachidonic acid, had a diminished trend after 3 to 6 months of Omegaven therapy. Despite this, all other patients maintained normal triene-tetraene ratio and Mead acid level, suggesting an acceptable fatty acid profile (data not shown). The hematologic and biochemical profiles of the patients during this same period showed the expected improvement in bilirubin and alanine aminotransferase but without adverse effects on platelets, bleeding parameters, or triglycerides and a good growth profile (z scores for weight) (Table 4C). Finally, we performed the STEP procedure on 4 patients; 1 patient has had the procedure repeated 3 times, and a second patient, twice; both are still PN dependent. These patients showed a modest increase in the tolerance of enteral nutrients.

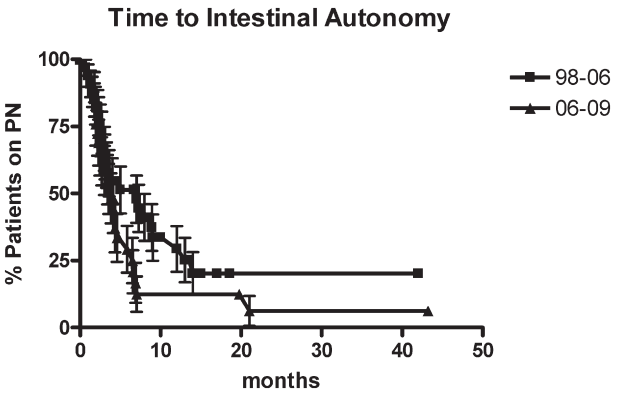

Fig. 2 Time to intestinal autonomy. The patients were followed up and censored at the achieved intestinal autonomy. Patients who died without achieving autonomy were recorded as unadapted at that time point. There were no significant differences in the time to intestinal autonomy between the 2 cohorts by Kaplan-Meier analysis.

3. Discussion

The recent cohort showed a clear improvement in outcomes, with a significant increase in survival and a dramatic reduction in the incidence of PNALD as compared with a previous cohort of patients or those described by other recent series [3,21-23]. Although many of the traditional management methods such as stimulating adaptation with enteral feeds, treatment/prophylaxis of SBBO, and promotility agents have been used for years, a systematic and consistent application of these therapies has been lacking. Novel therapies such as the use of Omegaven and STEP procedure show hepatoprotective functions [19] and apparent improvements in enteral tolerance, respectively [17,24]. In our study, the implementation of multidisciplinary care team and the multifactorial treatment protocol demonstrated that the use of a consistent paradigm, which incorporates traditional and novel therapies, can have an impact on patient outcomes and provides a framework within which to plan future studies.

The use of a true multidisciplinary team in caring for this population has been well established [8,25]. It provides an internal "institutional" memory for the care of these children, a mechanism for dealing with the complicated care pathways requiring safe PN, and a support system for families and the staff. The primary obstacle to further developing such teams is lack of adequate resources; however, as the cost of care of these patients becomes better understood, an economic argument for centralized teams with a mandate for improving support for the care of the child with home PN can be better made [22]. Interestingly, the justification for using BM preferentially, or an elemental formula such as Neocate, is supported by the observation that there was no significant cow's milk protein allergy noted in the recent cohort. This has been a common problem in the past, often requiring cessation of specific enteric formula and a "working back" with BM or elemental diet [26]. The benefit of cautiously advancing feeds is seen in the steady progress in the enteral feeding tolerance (Fig. 2). Moreover, we have not had any deaths or major episodes of recurrent NEC in the recent cohort, whereas at least 1 death in the previous cohort was caused by NEC in a child with gastroschisis [27]. The use of antibiotics for SBBO prophylaxis and treatment did not result in any episodes of sepsis with multiresistant organisms in the recent cohort, further suggesting no ill effects. However, the specific effects on the enteric flora and on the systemic inflammatory response are the subject of ongoing study.

The use of lipid minimization and ω-3 fish oil–based lipid preparations in improving liver function in infants with PNALD is the subject of a number of ongoing prospective trials (SMOF Trial, Toronto, Ontario, clinical trial no. NCT00793195 and the Omegaven Trial, Boston, Mass, NCT00512629). Our observations add to the evidence that these are effective measures and result in a reliable improvement in liver function (Table 4B and C). Another

Table 4A Fat intake of patients on Omegaven for 60 days or more

Value: months on Omegaven	0 (pretreatment)	1	3	6	9	12	18	Poststopping PN + 2 mo
No.	7	7	7	2	2	2	2	5
Days on PN	107 ± 66	138 ± 71	208 ± 81	300 ± 100	390 ± 100	480 ± 100	660 ± 100	52 ± 8 (days off PN)
Omegaven intake (g/kg per day)	0	1.2 ± 0.5	1.0 ± 0.2	1.1 ± 0.3	0.7 ± 0.3	0.5 ± 0.7	0.5	0
Intralipid intake (g/kg per day)	2.1 ± 0.3	0.4 ± 0.7	0.3 ± 0.5	0.4 ± .05	1.0 ± .03	0.8 ± 0.3	0.8 ± 0.3	0
Enteral fat (g/kg per day)	0.7 ± 0.3	0.8 ± 1.1	0.9 ± 1.6	1.0 ± 0.7	1.4 ± 0.5	2.8 ± 0.5	2.9 ± 1.6	7.1 ± 1.3
Total fat (g/kg per day)	2.8 ± 1.1	2.7 ± 1.7	2.2 ± 1.2	2.1 ± 1.0	3.2 ± 0.3	4.8 ± 1.4	4.8 ± 1.6	7.1 ± 1.3

important observation in the present study is the effects of Omegaven on systemic fatty acid profile (Table 4B). This is an area of intense interest because of concern about the EFA status of the developing infant. Although serum fatty acid levels are a proxy for the more physiologically relevant lipid profiles from cell membranes, there is a striking paucity of any data in this realm from patients on Omegaven therapy [28,29]. We found that there is a slight reduction in the ostensibly proinflammatory ω-6 fatty acids and an increase in the "antiinflammatory" fatty acids during the early phase of Omegaven therapy (Table 4B). All of these values normalized without obvious explanations as treatment continued. One case of EFA deficiency may be relevant; the subsequent use of a combination of an Intralipid and Omegaven protocol for those children on prolonged PN has resulted in a reassuring serum fatty acid profile, no evidence of any clinical deficiencies, and no deterioration in liver function (Table 4B and C). Further study of these parameters is clearly needed. Other studies have shown that the use of Omegaven and Intralipid in a 1:1 ratio reverses cholestasis, although the time to normalization may be longer than demonstrated with sole Omegaven therapy [19,24]. Furthermore, the long-term relationship between normalization of bilirubin and progression of hepatic fibrosis in this setting is not known; fibrosis may worsen despite biochemical improvement [30].

Our results were not from a shortened time to intestinal adaptation; the average time to discontinuation of PN was

Table 4B Serum fatty acid levels of patients on Omegaven for 60 days or more

Value: months on Omegaven	0 (pretreatment)	1	3	6	9	12	18	Poststopping PN + 2 mo
No.	7	7	4	2	2	2	2	5
Days on PN	107 ± 66	138 ± 71	208 ± 81	300 ± 100	390 ± 100	480 ± 100	660 ± 100	52 ± 8 (days off PN)
Linoleic acid 18:2φ-6 (1600-3500)	2200 ± 1100	1700 ± 640	1490 ± 300	740 ± 850	1005 ± 280	1730 ± 215	2208 ± 650	2416 ± 480
Arachidonic acid 20:4φ-6 (350-1030)	520 ± 220	550 ± 230	420 ± 70	470 ± 110	320 ± 110	170 ± 170	350 ± 90	270 ± 40
Docosapentaenoic acid 22:5φ-6 (10-50)	30 ± 17	47 ± 18	36 ± 18	45 ± 11	34 ± 12	30 ± 20	14 ± 8	16 ± 15
α-Linolenic acid 18:3φ-3 (20-120)	120 ± 80	100 ± 50	40 ± 20	44 ± 8	36 ± 10	50 ± 35	110 ± 60	110 ± 70
Eicosapentaenoic acid 20:5φ:3 (8-90)	380 ± 380	1320 ± 980	790 ± 480	1280 ± 310	770 ± 80	340 ± 30	560 ± 380	180 ± 120
Docosahexaenoic acid 22:6φ-3 (30-160)	700 ± 630	1870 ± 1000	950 ± 540	1500 ± 360	1010 ± 300	662 ± 320	670 ± 160	445 ± 230
Triene-tetraene ratio (0.013-0.05)	0.04 ± .03	.03 ± .002	.02 ± .002	.022 ± .008	.028 ± .01	.08 ± .09	0.013 ± .001	.05 ± 0.04
Total fatty acids (4.4-14.3)	9.7 ± 1.8	12.1 ± 4.3	8.0 ± 1.5	9.6 ± 1.1	6.8 ± 1.7	6.8 ± 1.6	7.7 ± 1.1	8.3 ± 0.5

Values are outside "normal" pediatric reference range (Mayo Medical Laboratories).
Data are presented as mean ± SD. All fatty acid values are in μmol/L, except ratio.

Table 4C Biochemical and weight values of patients on Omegaven for 60 days or more

Value: months on Omegaven	0 (pretreatment)	1	3	6	9	12	18	Poststopping PN + 2 mo
No.	7	7	7	2	2	2	2	5
Days on PN	107 ± 66	138 ± 71	208 ± 81	300 ± 100	390 ± 100	480 ± 100	660 ± 100	52 ± 8 (days off PN)
Bilirubin (direct) (0-7 μmol/L)	66 ± 18	80 ± 23	7 ± 7	2 ± 1.5	3 ± 0.7	2 ± 1	2 ± 1	6 ± 2
Alanine aminotransferase (1-35 U/L)	115 ± 53	320 ± 130	95 ± 70	60 ± 50	100 ± 40	130 ± 110	70 ± 12	45 ± 25
Triglycerides (0.40-1.3 μmol/L)	1.6 ± 0.2	2.2 ± 0.9	1.2 ± 0.6	0.9 ± 0.3	0.7 ± 0.2	0.5 ± 0.1	1.6 ± 0.4	1.1 ± 0.3
PT/INR (0.9-1.1 s)	1.3 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± .0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0
Platelets (150-400 × 10^9/L)	320 ± 95	360 ± 140	355 ± 140	240 ± 50	240 ± 25	250 ± 30	240 ± 30	275 ± 85
Weight (*z* score)	−1.3 ± 0.9	−0.9 ± 0.7	−1.1 ± 1.6	0.6 ± 1.5	−0.7 ± 0.7	−1.4 ± 0.3	−0.7 ± 0.4	0.4 ± 1.2

not significantly different between the cohorts (Table 3, Fig. 2). However, the long-term preservation of liver function may improve the ability of the residual intestine to adapt. In the initial cohort of patients, very few infants were able to be weaned from PN after the development of significant PNALD and portal hypertension; these patients experienced increased episodes of catheter- and gut-related sepsis and decreased enteral feed tolerance. In the recent cohort, we observed stable liver function and improvement in their gradual tolerance of enteral feeds. The role of the STEP procedure in the care of the child with IF also continues to evolve. Participation in the multiinstitutional registry of all centers will maximize our understanding of the indications and benefits of this procedure. The tendency of some patients who could not achieve intestinal autonomy was to develop dilated, "overadapted" segments of proximal small bowel even after the STEP procedure. In our experience, 2 patients showed improved peristalsis for a period of time before redilating and remaining on PN. The redilation before STEP remains an unsolved problem in this population, but it may be a bridging effort for some patients. It is not yet known whether patients with SBS vs gastroschisis respond differently to this procedure.

This study is limited by the use of historical controls and the corresponding changes in management that have occurred over time. The increase in residual small intestinal length in the recent cohort may reflect a trend toward less aggressive surgeries with any type of neonatal intestinal resection. The difference in follow-up between the 2 cohorts may also be confounding; however, no patients in the initial cohort developed liver failure after more than 3 years of PN, which is the time of follow-up of the 2 longest-treated patients in the modern cohort. Furthermore, of the 5 patients still on PN at the time of the submission of this report, 3 are now on full enteral feeds. Thus, it is unlikely that we will see a significant drop of outcomes in the recently treated cohort. Based on these results, we suggest that the treatment paradigm described herein is an appropriate therapeutic strategy for the care of infants with IF. Further evaluations of the components used in this protocol, along with novel specific therapies to more directly stimulate intestinal adaptation, are suggested.

References

[1] Sigalet D, Boctor D, Robertson M, et al. Improved outcomes in paediatric intestinal failure with aggressive prevention of liver disease. Eur J Pediatr Surg 2009;19:348-53.

[2] Sigalet DL. Short bowel syndrome in infants and children: an overview. Semin Pediatr Surg 2001;10(2):49-55.

[3] Wales PW, de Silva N, Kim J, et al. Neonatal short bowel syndrome: population-based estimates of incidence and mortality rates. J Pediatr Surg 2004;39(5):690-5.

[4] Alvarez SM, Burd RS. Increasing prevalence of gastroschisis repairs in the United States: 1996-2003. J Pediatr Surg 2007;42(6):943-6.

[5] Molik KA, Gingalewski CA, West KW, et al. Gastroschisis: a plea for risk categorization. J Pediatr Surg 2001;36(1):51-5.

[6] Skarsgard ED, Claydon J, Bouchard S, et al. Canadian Pediatric Surgical Network: a population-based pediatric surgery network and database for analyzing surgical birth defects. The first 100 cases of gastroschisis. J Pediatr Surg 2008;43(1):30-4.

[7] Uauy RD, Fanaroff AA, Korones SB, et al. Necrotizing enterocolitis in very low birth weight infants: biodemographic and clinical correlates. National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 1991;119(4):630-8.

[8] Diamond IR, de SN, Pencharz PB, et al. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. J Pediatr Surg 2007;42(5):806-11.

[9] Modi BP, Langer M, Ching YA, et al. Improved survival in a multidisciplinary short bowel syndrome program. J Pediatr Surg 2008;43(1):20-4.

[10] Torres C, Sudan D, Vanderhoof J, et al. Role of an intestinal rehabilitation program in the treatment of advanced intestinal failure. J Pediatr Gastroenterol Nutr 2007;45(2):204-12.

[11] Meehan JJ, Georgeson KE. Prevention of liver failure in parenteral nutrition–dependent children with short bowel syndrome. J Pediatr Surg 1997;32(3):473-5.

[12] Quiros-Tejeira RE, Ament ME, Reyen L, et al. Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: a 25-year experience. J Pediatr 2004;145(2):157-63.
[13] Blau J, Sridhar S, Mathieson S, et al. Effects of protein/nonprotein caloric intake on parenteral nutrition associated cholestasis in premature infants weighing 600-1000 grams. JPEN J Parenter Enteral Nutr 2007;31(6):487-90.
[14] Koehler AN, Yaworski JA, Gardner M, et al. Coordinated interdisciplinary management of pediatric intestinal failure: a 2-year review. J Pediatr Surg 2000;35(2):380-5.
[15] Goulet OJ, Revillon Y, Jan D, et al. Neonatal short bowel syndrome. J Pediatr 1991;119(1 (Pt 1)):18-23.
[16] Duggan C, Piper H, Javid PJ, et al. Growth and nutritional status in infants with short-bowel syndrome after the serial transverse enteroplasty procedure. Clin Gastroenterol Hepatol 2006;4(10): 1237-41.
[17] Modi BP, Javid PJ, Jaksic T, et al. First report of the international serial transverse enteroplasty data registry: indications, efficacy, and complications. J Am Coll Surg 2007;204(3):365-71.
[18] Javid PJ, Kim HB, Duggan CP, et al. Serial transverse enteroplasty is associated with successful short-term outcomes in infants with short bowel syndrome. J Pediatr Surg 2005;40(6):1019-23.
[19] Diamond IR, Sterescu A, Pencharz PB, et al. Changing the paradigm: Omegaven for the treatment of liver failure in pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr 2009;48(2):209-15.
[20] Struijs MC, Diamond IR, de SN, et al. Establishing norms for intestinal length in children. J Pediatr Surg 2009;44(5):933-8.
[21] Spencer AU, Neaga A, West B, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg 2005;242(3):403-9.
[22] Spencer AU, Kovacevich D, Kinney-Barnett M, et al. Pediatric short-bowel syndrome: the cost of comprehensive care. Am J Clin Nutr 2008;88(6):1552-9.
[23] Wales PW, de Silva N, Kim JH, et al. Neonatal short bowel syndrome: a cohort study. J Pediatr Surg 2005;40(5):755-62.
[24] Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil–based fat emulsion in the treatment of parenteral nutrition–associated liver disease. Pediatrics 2008;121(3):e678-86.
[25] Goulet O, Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology 2006;130(2 Suppl 1):S16-S28.
[26] Andorsky DJ, Lund DP, Lillehei CW, et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001;139(1):27-33.
[27] Snyder CL. Outcome analysis for gastroschisis. J Pediatr Surg 1999;34 (8):1253-6.
[28] Agostoni C. Role of long-chain polyunsaturated fatty acids in the first year of life. J Pediatr Gastroenterol Nutr 2010;47(Supplement): S41-4.
[29] Innes S. Omega-3 fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? J Pediatr Gastroenterol Nutr 2009;48(Supplement):S16-S24.
[30] Fitzgibbons SC, Jones BA, Hull MA, et al. The relationship between biopsy proven parenteral nutrition associated liver fibrosis and biochemical cholestasis in children with short bowel syndrome. J Pediatr Surg 2010;45:95-9.