

# Predictors of a successful outcome for infants with short bowel syndrome: a 30-year single-institution experience

Tatsuru Kaji<sup>1</sup> · Kazuhiko Nakame<sup>1</sup> · Seiro Machigashira<sup>1</sup> · Takafumi Kawano<sup>1</sup> · Ryuta Masuya<sup>1</sup> · Waka Yamada<sup>1</sup> · Koji Yamada<sup>1</sup> · Shun Onishi<sup>1</sup> · Tomoe Moriguchi<sup>1</sup> · Koshiro Sugita<sup>1</sup> · Motoi Mukai<sup>1</sup> · Satoshi Ieiri<sup>1</sup>

Received: 5 December 2016 / Accepted: 20 March 2017 / Published online: 22 April 2017  
© Springer Japan 2017

## Abstract

**Purpose** Short-bowel syndrome (SBS) is associated with high morbidity and mortality. We conducted this study to establish the predictors of survival and weaning off parenteral nutrition (PN).

**Methods** We reviewed the medical records of 16 SBS infants treated at our institution within a 30-year period. SBS was defined as a residual small-bowel length (RSBL) of <75 cm. Loss of the ileocecal valve (ICV), cholestasis (D-Bil >2.0 mg/dl), enterostomy, and RSBL were all evaluated. Kaplan–Meier analysis was used to analyze the predictors.

**Results** The mean RSBL was  $34.9 \pm 22.9$  cm. Six patients died (37.5%) and nine patients were weaned off PN (56.3%). Significant differences were observed in cholestasis ( $p < 0.03$ ), enterostomy ( $p < 0.01$ ), an absolute RSBL of <30 cm ( $p < 0.04$ ), and a percentage of expected RSBL of <10% ( $p < 0.04$ ) as survival predictors. Significant differences were also observed for cholestasis ( $p < 0.01$ ), loss of the ICV ( $p < 0.04$ ), an absolute RSBL of <20 cm ( $p < 0.01$ ), and a percentage of expected RSBL of <10% ( $p < 0.03$ ) as predictors of weaning off PN.

**Conclusion** These predictors may help us select the optimal treatments for pediatric patients with SBS.

**Keywords** Short-bowel syndrome · Cholestasis · Parenteral nutrition · Pediatric

## Introduction

In infants, the condition known as “short bowel syndrome” (SBS) occurs with the loss of a large section of small bowel as a result of surgical removal or a congenital defect. SBS in infants is most commonly caused by necrotizing enterocolitis (NEC), intestinal atresia, or midgut volvulus [1]. Since pediatric patients with SBS need long-term nutritional support following massive bowel resection, quality of life is poor and morbidity is high [2]. A recent study from the Pediatric Intestinal Failure Consortium reported a mortality rate of 27% over 5 years [3].

Previous studies have evaluated the risk factors contributing to the high morbidity and mortality associated with SBS, including the residual small-bowel length (RSBL), a septic infection called “catheter-related blood stream infection” (CRBSI), loss of the ileocecal valve (ICV), and cholestasis, which often develops into intestinal-failure associated liver disease (IFALD) [4–7]. However, advances have been made in the medical and surgical management of SBS over the last few decades. Several innovative therapeutic modalities have been established surgically, including autologous gastrointestinal reconstruction, such as serial transverse enteroplasty (STEP) [8] and Bianchi’s longitudinal intestinal lengthening (LILT) [9]; and also in central venous catheter (CVC) management, including ethanol lock therapy (ELT) for CRBSI [10], and fish oil-based lipid emulsion for cholestasis [11].

The aim of this study is to evaluate the predictors of successful outcomes for infants with SBS to identify the optimal treatment and management of this challenging disease entity.

✉ Satoshi Ieiri  
sieiri@m.kufm.kagoshima-u.ac.jp

<sup>1</sup> Department of Pediatric Surgery, Research Field in Medicine and Health Sciences, Medical and Dental Sciences Area, Research and Education Assembly, Kagoshima University, 8-35-1, Sakuragaoka, Kagoshima 890-8520, Japan

## Methods

### Study design

This clinical study was performed in accordance with the ethical guidelines of clinical research from the Japanese Ministry of Health, Labor, and Welfare, and approved by the Research Ethics Committee of Kagoshima University Hospital (registration number: 27-119). We reviewed the medical records of 16 pediatric SBS patients treated at our institution over the past 30 years.

The data collected included gestational age, age at SBS surgery, etiology of SBS, RSBL, loss of the ICV, enterostomy, and the highest serum direct bilirubin level. Cholestasis was defined as a serum direct bilirubin level of  $>2.0$  mg/dl. These factors were examined as predictors of the outcome of pediatric SBS [5, 6]. Furthermore, we evaluated the RSBL in two ways: the absolute RSBL was measured at the initial operation related to SBS and, after measuring the patient's body length at surgery, we calculated the expected normal small-bowel length using the formula reported by Struijs et al. [12]. The percentage of expected RSBL was then calculated as follows: absolute RSBL/expected normal small-bowel length  $\times 100$ .

### Nutritional management strategy

Enteral feeding was started immediately after the infant's general conditions had stabilized. Patients were administered 3–5 ml of an elemental diet (Elental P; Ajinomoto Pharma Co, Ltd, Tokyo, Japan) eight times per day from 1984 to 2001. Breast milk was administered preferentially from 2002. If the amount of breast milk was not sufficient for daily requirements, an elemental diet was adopted. If a patient's appetite did not increase, gastrostomy was performed for enteral tube feeding. We increased the feeding volume and decreased the amount of PN gradually, while monitoring stool and urine volume. At 10 months of age, to prepare the patient for weaning, food such as rice gruel was given, and we gradually changed the breast milk or elemental diet to a low-residue diet (LRD). Prebiotics like soluble fiber and probiotics, as well as antidiarrheal agents, were administered at the beginning of feeding, and glutamine (0.3 g/kg/day) was administered after the age of 3 months. The PN protocol consists of an infusion of glucose electrolyte maintenance solution (7.5% glucose), gradually increasing the percentage of glucose and amino acids. Mixed PN fluid, composed of high concentration glucose fluid (Rihabix-K2™; Youshindo Co, Ltd, Toyama, Japan), amino acid fluid (Preamin-P™; Fuso Co, Ltd, Osaka, Japan), multivitamins, and microelements

(15% glucose, 1.5% amino acids) and Intralipos™ (Otsuka Pharmaceutical Factory, Inc., Naruto, Japan), was administered. The total maximum calories and fat were 100 kcal/kg/day and 1.5 g/kg/day, respectively, from 1984 to 2001. The total calories and fat were then reduced to 80 kcal/kg/day and 1.0 g/kg/day, respectively, from 2002 to prevent IFALD. We established the nutrition support team in 2005, which comprised nurses, dietitians, pharmacologists, speech therapists, and doctors (physician, surgeon, pediatric surgeon).

### Inclusion criteria

About 15,000 babies were born in our prefecture during the observation period. Most babies who required surgical intervention were referred to our institution, with a total of 655 babies (about 20 babies per year) treated. Infants were eligible for inclusion in this study if they had a clinical diagnosis of SBS, defined as an absolute RSBL of  $<75$  cm, either following surgical resection or because of a congenital defect, at the initial operation, and at least 3 months of PN dependence.

### Statistical analysis

A Kaplan–Meier analysis was used to estimate the predictors of survival and weaning off PN. For the survival analysis, the time variable was defined as the period from the onset of SBS until the time of the last follow-up for which survival was known (right-censored cases) or until death. For the analysis of weaning off PN, the time variable was defined as the time from the onset of SBS until the time of weaning off PN, or the last follow-up when the dependence on PN was known (right-censored cases). The log-rank test was used to analyze significance. Statistical analysis was completed using the Ekuseru-Toukei 2012 software program (Social Survey Research Information Co., Ltd., Tokyo). *P* values of  $<0.05$  were considered to indicate a significant difference.

## Results

### Demographics

Table 1 summarizes the characteristics of the 16 infants with SBS identified in this study. There were six male and ten female infants with a mean gestational age of  $36.7 \pm 2.3$  weeks (range 30–40 weeks), a mean birth weight of  $2592 \pm 497$  g (1602–3482 g), and a mean age at first surgery of  $13.2 \pm 19.4$  days (0–61 days). SBS was diagnosed within the first 6 weeks of life in all but one

**Table 1** Demographics of the 16 infants with short-bowel syndrome

Sex	Male 6, female 10
Gestational age	36.7 ± 2.3 weeks (30–40 weeks)
Birth weight	2592 ± 497 g (1602–3482 g)
Age at fist surgery	13.2 ± 19.4 days (0–61 days)
Residual small bowel length (RSBL)	
Absolute RSBL <sup>a</sup>	34.9 ± 22.9 cm (6.5–73 cm)
Percentage of expected RSBL <sup>b</sup>	22.0 ± 14.6% (3.2–47.9%)
Etiology of SBS	
Midgut volvulus	6 (37.5%)
Intestinal atresia	4 (25.0%)
Necrotizing enterocolitis	3 (18.7%)
Miscellaneous	3 (18.7%)

Mean ± SD, values inside the bracket present range

<sup>a</sup> Absolute RSBL was measured at the initial operation related to SBS

<sup>b</sup> Percentage of expected RSBL was calculated based on the criteria described in Struijs's report [12] as follows, absolute RSBL/expected normal small bowel length × 100

**Table 2** Outcomes

Cholestasis (direct bilirubin >2.0 mg/dl)	5 (31.3%)
Weaning off PN	9 (56.3%)
Prognosis	
Alive	10 (62.5%)
Dead	6 (37.5%)
Cause of death	
CRBSI	3
IFALD	2
Hypokalemia	1

PN parenteral nutrition, CRBSI catheter-related blood stream infection, IFALD intestinal-failure associated liver disease

infant. One infant underwent surgery at 61 days of age, for idiopathic intestinal torsion without malrotation. The mean absolute RSBL was 34.9 ± 22.9 cm (6.5–73 cm) and the mean percentage of the expected RSBL was 22.0 ± 14.6% (3.2–47.9%). The causes of SBS were midgut volvulus ( $n = 6$ , 37.5%), intestinal atresia ( $n = 4$ , 25.0%), NEC ( $n = 3$ , 18.7%), and other causes ( $n = 3$ ; 18.7%); namely, idiopathic intestinal torsion ( $n = 1$ ), meconium peritonitis ( $n = 1$ ), and congenital short small bowel associated with cloacal exstrophy ( $n = 1$ ). The mean follow-up period was 91.8 ± 83.4 months (163 days to 19.6 years).

## Outcomes

Cholestasis developed in five infants (31.3%) and nine were weaned off PN (56.3%; Table 2). Two patients still depend

on PN. One infant underwent STEP and one underwent living-related small-bowel transplantation. Six patients (37.5%) died: three of CRBSI, two of IFALD, and one of hypokalemia. IFALD caused the direct bilirubin level in one male infant to rise to 10.0 mg/dl at 6 month of age, so he underwent living-related SBT from his mother. Although the transplanted small bowel survived, the infant died without improvement of jaundice 2 weeks after surgery. The patient who died of hypokalemia had been weaned off PN support at 2.6 years of age, but suffered viral enterocolitis at 7 years of age, with ensuing daily massive watery stool leading to hypokalemia and fatal cardiac arrest.

## Predictors of survival and weaning off PN

There were significant differences in cholestasis ( $p < 0.03$ ), enterostomy ( $p < 0.01$ ), an absolute RSBL of <30 cm ( $p < 0.04$ ), and percentage of expected RSBL of <10% ( $p < 0.04$ ) as predictors of survival (Table 3). There were significant differences in cholestasis ( $p < 0.01$ ), absence of the ICV ( $p < 0.04$ ), an absolute RSBL of <20 cm ( $p < 0.01$ ), and percentage of expected RSBL of <10% ( $p < 0.03$ ) as predictors of weaning off PN (Table 3). Figure 1 shows a significantly higher survival rate associated with an absolute RSBL of ≥10% than with an absolute RSBL of <10% ( $p = 0.04$ , Fig. 1). Figure 2 shows that the percentage of PN dependence was significantly lower if the expected RSBL was ≥10% than if the expected RSBL was <10% ( $p = 0.03$ , Fig. 2). Figure 3 illustrates the association among the percentage of expected RSBL, the period of PN dependence, and prognosis, at our institution. Three of the six patients with a percentage of expected RSBL of <10% died, two have been dependent on PN for over 3 years, and only one has survived without PN dependence. Figure 3 demonstrates that prognosis and PN dependence were strongly associated with a percentage of expected RSBL of 10%.

## Discussion

Pediatric SBS is associated with high morbidity and mortality and selecting the best treatments for these infants is difficult. Evaluating the predictors of a good outcome is crucial to establish the optimal treatment strategies for SBS; thus, we evaluated the key predictors of survival and weaning off PN at our institution over the past 30 years. The current study identified cholestasis, enterostomy, an absolute RSBL of <30 cm, and a percentage of expected RSBL of <10% as predictors of survival; and cholestasis, loss of the ICV, an absolute RSBL of <20 cm, and a percentage of expected RSBL of <10% as predictors of weaning off PN.

**Table 3** Analyses of the predictors of survival and weaning off parenteral nutrition

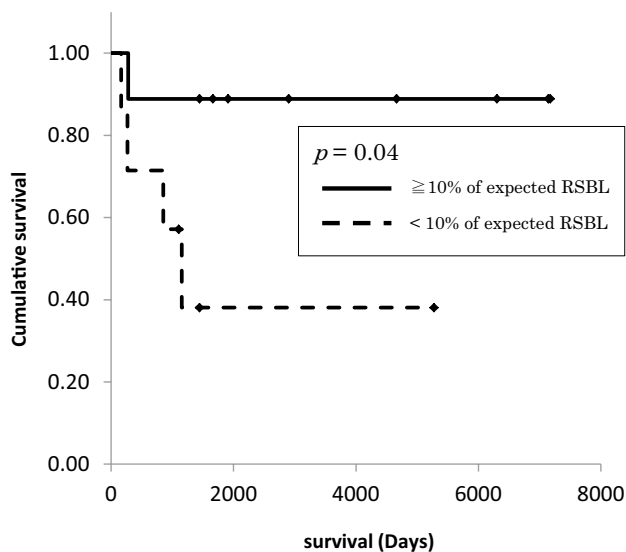
Predictors	Survival				Weaning off PN			
	Group	<i>n</i>	Death	<i>p</i>	Group	<i>n</i>	Off PN	<i>p</i>
Weaning off PN	(+)	9	1	<b>&lt;0.01</b>	–	–	–	–
	(–)	7	5					
Cholestasis	(–)	10	2	<b>0.03</b>	(–)	10	8	<b>&lt;0.01</b>
	(+)	6	4		(+)	6	1	
Ileocecal valve	(+)	13	4	0.10	(+)	13	9	<b>0.04</b>
	(–)	3	2		(–)	3	0	
Enterostomy	(–)	14	4	<b>0.01</b>	(–)	14	9	0.17
	(+)	2	2		(+)	2	0	
Absolute RSBL <sup>a</sup>	≥30 cm	8	1	<b>0.04</b>	≥20 cm	9	8	<b>0.01</b>
	<30 cm	8	5		<20 cm	7	1	
Percentage of expected RSBL <sup>b</sup>	≥10%	9	1	<b>0.04</b>	≥10%	9	8	<b>0.03</b>
	<10%	7	4		<10%	7	1	

RSBL residual small bowel length

*p* values shown in bold mean statistically significant differences

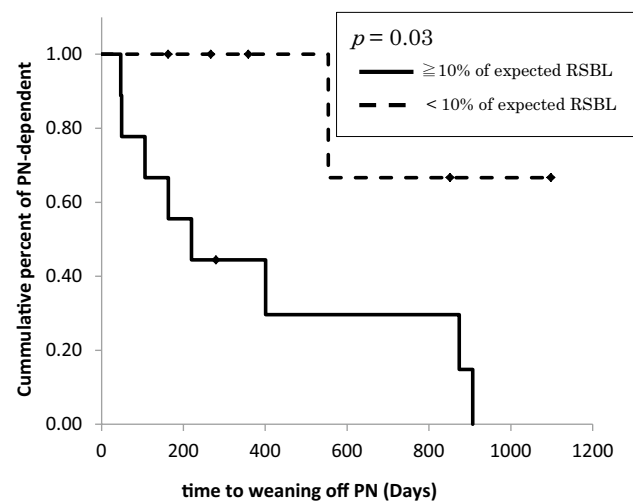
<sup>a</sup> Absolute RSBL was measured at the initial operation related to SBS

<sup>b</sup> Percentage of expected RSBL was calculated based on the criteria described in Struijs's report [12] as follows, absolute RSBL/expected normal small bowel length, × 100



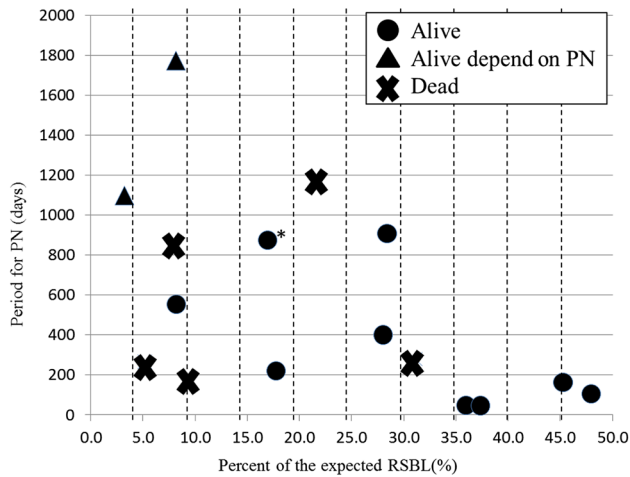
**Fig. 1** Kaplan–Meier survival plots according to the percentage of expected residual small-bowel length and survival. Patients were stratified based on a percentage of expected RSBL of <10%. RSBL residual small bowel length

Previous studies have found cholestasis to be a significant predictor of survival [5, 6, 13]. In our study, cholestasis was shown to be a key predictor of both survival and weaning off PN. Long-term PN was more closely associated with the onset of cholestasis in pediatric SBS patients than in adult SBS patients [14]. The cause of the onset of cholestasis in SBS patients, especially those requiring long-term PN has been investigated. The components of lipids



**Fig. 2** Kaplan–Meier survival plots according to the percentage of expected residual small-bowel length and parenteral nutrition dependence. Patients were stratified based on a percentage of expected RSBL of <10%. PN parenteral nutrition, RSBL residual small bowel length

have been studied and omega-6 fatty acids, which are included in soy-bean based fat emulsion, have been found to be associated with cholestasis. Recent studies show that a fish oil-based emulsion attenuates the development of cholestasis and IFALD [11, 15, 16]. However, fish oil-based fat emulsion, such as Omegaven<sup>TM</sup>, has been approved for humans in only a limited area and is not recommended as monotherapy by the manufacturer. A new fat emulsion containing soybean oil, medium-chain triglycerides, olive



**Fig. 3** Association among the percentage of expected residual small bowel length, period of parenteral nutrition dependence and prognosis. Prognosis and PN dependence were strongly associated with a percentage of expected RSBL of 10%. PN parenteral nutrition, RSBL residual small bowel length. Asterisk indicates that this patient was weaned off PN after 874 days, but died of hypokalemia derived from viral enterocolitis-associated diarrhea at the age of 7 years

oil, and fish oil has been developed recently and clinically shown to decrease the serum bilirubin level [17]. This new treatment modality is expected to reduce the risk of cholestasis from PN, which would improve the prognosis of SBS patients.

More than 40 years ago, Wilmore reported that all patients with a RSBL of <40 cm and absence of the ICV died [4]. PN has resulted in great progress, with recent reports stating that absence of the ICV was associated only with weaning off PN [6, 18], as in this study. The ICV is associated with intestinal transit, nutrient absorption, and bacterial overgrowth [19]. The ileum has a greater adaptability after bowel resection than the more proximal intestinal segments [20]. In this study, we identified the residual ileal length in 11 patients. All five patients with less than 2 cm of residual ileum were unable to be weaned off PN. Moreover, glucagon-like peptide-2 (GLP-2), which induces augmentation of the intestinal mucosal height and intestinal length, while being associated with intestinal adaptation following bowel resection [21, 22], is secreted by the distal ileum. Thus, the ICV is considered to play a pivotal role in weaning off PN.

Enterostomy was associated with survival, but as only two patients with enterostomy were dependent on PN in this study, we speculate that there was no significant difference in this predictor for weaning off PN. Enterostomy prevents the enterohepatic circulation of bile acids, which can cause both cholestasis with subsequent IFALD. In fact, one of our two patients with enterostomy died of IFALD at 5 months of age. Thus, we recommend that enterostomy be

created if the patients' condition is severely compromised, although it should be closed as soon as possible once the general condition has stabilized.

Based on the findings of a Kaplan–Meier analysis, the prognosis of survival was related to PN dependence. Since weaning off PN dependence resulted in the improvement of survival prognosis, an absolute RSBL of 20 cm or percent of expected RSBL of 10% is considered a crucial predictor. Thus, preserving as much of the small intestine as possible during surgery is very important for these patients. As shown in Fig. 3, three of our patients with an expected RSBL of <10% died (two of IFALD and one of CRBSI). The total calories and fat emulsion delivered were 100 kcal/kg/day and 1.5 g/kg/day, respectively, until 2001, when ELT against CRBSI had not yet been developed. From 2002 onward, we decreased the total calories and fat emulsion, and since 2009, have used ELT to treat CRBSI. The two surviving patients who are dependent on PN were treated from 2010 and may benefit from the modification of our nutritional strategy and new therapy.

In 2009, Fitzgibbons et al. reported that serum citrulline levels were very useful as a predictive marker of weaning off PN for pediatric SBS patients [23]. Since serum citrulline levels were measured in only the five most recent patients in this study, we did not evaluate this marker as a predictor. The serum levels of citrulline in three patients who could not be weaned from PN were <12  $\mu\text{mol/l}$ . One patient's citrulline level was 18.0  $\mu\text{mol/l}$  and her oral intake was good, although because her stool volume was high, she required more fluid supplementation than PN support. The citrulline level of the other patient dependent on PN was <10  $\mu\text{mol/l}$ , which increased to 14.6  $\mu\text{mol/l}$  when he was weaned off PN at 3 years of age.

Several limitations associated with the present study warrant mention. First, this was a single-center study and since we do not have special therapeutic centers for SBS in Japan like North America or Europe, the number of SBS patients was limited to a single institution. Second, previous studies have reported that the frequency of sepsis is associated with the prognosis. In the present study, the cause of infection was unknown in the patients from more than 20 years ago. Therefore, it was difficult to evaluate the precise number of cases of septic infection. However, the management of CVC is a crucial point in the treatment of SBS patients. Recently, therapeutic ELT has been reported to prevent the removal of CVC caused by CRBSI. At our institution, monthly prophylactic ELT is considered a safe and effective modality for reducing the replacement of CVC from CRBSI [10].

In conclusion, we evaluated the predictors associated with survival and weaning off PN support based on our institutional experience of treating pediatric SBS patients. We found that cholestasis and RSBL were predictors of

mortality, whereas RSBL and absence of the ICV were predictors of weaning off PN. These data will allow us to better predict the outcomes of pediatric SBS patients, which will help in selecting the optimal treatment and management of this challenging disease entity.

**Acknowledgements** This study was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS, No. 25462777, No. 16K10094, No. 16K10095, No. 16K10434, No. 16K10466.). This study was supported by the Institute of Laboratory Animal Sciences, Kagoshima University (Frontier Science Research Center). We thank Mr. Brian Quinn for comments and help with the manuscript.

#### Compliance with ethical statement

**Conflict of interest** We declare no conflicts of interest in association with the present study.

## References

- McMellen ME, Wakeman D, Longshore SW, McDuffie LA, Warner BW. Growth factors: possible roles for clinical management of the short bowel syndrome. *Semin Pediatr Surg.* 2010;19:35–43.
- Vanderhoof JA, Young RJ. Enteral and parenteral nutrition in the care of patients with short-bowel syndrome. *Best Pract Res Clin Gastroenterol.* 2003;17:997–1015.
- Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. *J Pediatr.* 2012;161:723–8.
- Wilmore DW. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. *J Pediatr.* 1972;80:88–95.
- Spencer AU, Neaga A, West B, Safran J, Brown P, Btaiche I, et al. Pediatric short bowel syndrome: redefining predictors of success. *Ann Surg.* 2005;242:403–9.
- Demehri FR, Stephens L, Herrman E, West B, Mehringer A, Arnold MA, et al. Enteral autonomy in pediatric short bowel syndrome: predictive factors 1 year after diagnosis. *J Pediatr Surg.* 2015;50:131–5.
- Fallon EM, Mitchell PD, Nehra D, Potemkin AK, O'Loughlin AA, Gura KM, et al. Neonates with short bowel syndrome: an optimistic future for parenteral nutrition independence. *JAMA Surg.* 2014;149:663–70.
- Mercer DF, Hobson BD, Gerhardt BK, Grant WJ, Vargas LM, Langnas AN, et al. Serial transverse enteroplasty allows children with short bowel to wean from parenteral nutrition. *J Pediatr.* 2014;164:93–8.
- Bianchi A. Intestinal loop lengthening—a technique for increasing small intestinal length. *J Pediatr Surg.* 1980;15:145–51.
- Kawano T, Kaji T, Onishi S, Yamada K, Yamada W, Nakame K, et al. Efficacy of ethanol locks to reduce the incidence of catheter-related bloodstream infections for home parenteral nutrition pediatric patients: comparison of therapeutic treatment with prophylactic treatment. *Pediatr Surg Int.* 2016;32:863–7.
- Puder M, Valim C, Meisel JA, Le HD, de Meijer VE, Robinson EM, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. *Ann Surg.* 2009;250:395–402.
- Struijs MC, Diamond IR, de Silva N, Wales PW. Establishing norms for intestinal length in children. *J Pediatr Surg.* 2009;44(5):933–8.
- Kelly DA. Liver complication of pediatric parenteral nutrition—epidemiology. *Nutrition.* 1998;14:153–7.
- Ginn-Pease ME, Pantalos D, King DR. TPN-associated hyperbilirubinemia: a common problem in newborn surgical patients. *J Pediatr Surg.* 1985;20:436–9.
- Strang BJ, Reddix BA, Wolk RA. Improvement in parenteral nutrition-associated cholestasis with the use of omegaven in an infant with short bowel syndrome. *Nutr Clin Pract.* 2016;31:647–53.
- Le HD, de Meijer VE, Robinson EM, Zurakowski D, Potemkin AK, Arsenault DA, et al. Parenteral fish-oil-based lipid emulsion improves fatty acid profiles and lipids in parenteral nutrition-dependent children. *Am J Clin Nutr.* 2011;94:749–58.
- Goulet O, Antébi H, Wolf C, Talbotec C, Alcindor LG, Corriol O, et al. A new intravenous fat emulsion containing soybean oil, medium-chain triglycerides, olive oil, and fish oil: a single-center, double-blind randomized study on efficacy and safety in pediatric patients receiving home parenteral nutrition. *J Parenter Enteral Nutr.* 2010;34:485–95.
- Khan FA, Squires RH, Litman HJ, Balint J, Carter BA, Fisher JG, et al. Pediatric intestinal failure consortium. predictors of enteral autonomy in children with intestinal failure: a multicenter cohort study. *J Pediatr.* 2015;167:29–34.
- Roland BC, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE, et al. Low ileocecal valve pressure is significantly associated with small intestinal bacterial overgrowth (SIBO). *Dig Dis Sci.* 2014;59:1269–77.
- Thompson JS, Quigley EM, Adrian TE. Factors affecting outcome following proximal and distal intestinal resection in the dog: an examination of the relative roles of mucosal adaptation, motility, luminal factors, and enteric peptides. *Dig Dis Sci.* 1999;44:63–74.
- Kaji T, Tanaka H, Redstone H, Wallace LE, Holst JJ, Sigalet DL. Temporal changes in the intestinal growth promoting effects of glucagon-like peptide 2 following intestinal resection. *J Surg Res.* 2009;152:271–80.
- Muto M, Kaji T, Mukai M, Nakame K, Yoshioka T, Tanimoto A, et al. Ghrelin and glucagon-like peptide-2 increase immediately following massive small bowel resection. *Peptides.* 2013;43:160–6.
- Fitzgibbons S, Ching YA, Valim C, Zhou J, Iglesias J, Duggan C, et al. Relationship between serum citrulline levels and progression to parenteral nutrition independence in children with short bowel syndrome. *J Pediatr Surg.* 2009;44:928–32.