Infantile Short Bowel Syndrome: short and long term evaluation

Kortedarmsyndroom bij kinderen: korte- en langetermijnevaluatie

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The more you learn, the more you realize how little you know.

CONTENTS

Chapter 1

General introduction

Short bowel syndrome (SBS) is a condition characterized by increased intestinal transit time. As this is associated with diarrhea and malabsorption of nutrients, it may lead to deficiencies of micronutrients and growth retardation. In most cases malabsorption is due to the shortened bowel length resulting in less absorptive and digestive surface, which means that fewer digestive enzymes and transport proteins are available.[1] In early childhood, SBS is often the result of massive resection of the small intestine necessitated by volvulus, congenital malformations such as intestinal atresia and gastroschisis, or acquired conditions such as necrotizing enterocolitis.[1-4] Less frequently, it may be caused by a non-functional bowel, as in the case of, for example, microvillus inclusion disease, long segment Hirschsprung disease, or chronic intestinal pseudo-obstruction syndrome.[5] Then it is referred to as functional SBS.[2]

The clinical manifestation of the disease depends on various factors, such as the residual length of the jejunum and ileum, the presence of an enterostomy, the presence (or absence) of the ileocecal valve (ICV), the remaining functional length of the colon, underlying pathology, and possible complications.

TEXTBOX: CASE 1

Girl, born in February 2003 at gestational age of 24.9 weeks with a birth weight of 740 grams, developed NEC with perforation of the bowel 1½ month after birth. During the first surgical intervention the total necrotic jejunum and left colon were resected, which resulted in a residual ileal length of 26 cm (18% remaining small bowel length corrected for age), with the ICV and right hemicolon remaining. After the initial resection and clip and drop procedure, a second intervention was performed two days later, creating an anastomosis between the residual small bowel and right colon and constructing a transverse colostomy. Five days later an anastomotic leak was suspected, but not found at third laparatomy.

For the first three weeks after the initial surgical intervention, the girl received only total parenteral nutrition. She then developed a Gram negative sepsis, which was successfully treated with antibiotics; the central venous catheter could be left in place. Eighteen days after the first surgical intervention, minimal enteral feeding (MEF) with semielemental nutrition was started and stopped after a few days, because of increasing gastric secretions. One month after the first surgical intervention, MEF was restarted and continued for two weeks. After that the volume of semielemental nutrition could be increased slowly. Three months after the first surgical intervention she received 35% of her energy intake enterally and her body weight was 2.6 kg. The duration of her initial admission was 7½ months. At the age of 1 year (not corrected) she received 75% of her energy intake enterally and her body weight was 5.8 kg.

Clinical definition and incidence of SBS

Numerous definitions for SBS have been proposed, but regrettably there is no consensus in the literature on a generally applicable clinical definition. Basically, authors disagree on whether it should solely refer to remaining bowel length or to duration of postoperative parenteral nutrition, or perhaps to a combination of both criteria.

In the Netherlands, a committee charged with attaining consensus on the definition of SBS was formed in 2004. Its members were representatives of the section of Gastroenterology of the Dutch Pediatric Association and the Dutch Society of Pediatric Surgery, and dieticians of academic medical centers. The definition they agreed upon is based on consensus with regard to literature and empirical data. The committee defined SBS as;

- > 70% resection of the small bowel,[4,6] and/or
- parenteral nutrition needed for longer than 42 days after bowel resection,[7-10] and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a prematurely born child (gestational age 27 - 36 weeks), < 75 cm for term born neonates and < 100 cm for children older than 12 months.[11]

The incidence of infantile SBS in the Netherlands is not known – partly due to the pre-existing variations in definition – but clinical experience suggests it is relatively low. In Canada the incidence is estimated at 24.5 per 100,000 live births, the mortality rate at 2 per 100,000 per year.[12] In the United Kingdom the incidence is estimated at 2 to 3 per million per year, half of them being children.[13] Extrapolating these incidence rates to the Netherlands this would mean 45 per 184,000 live births per year or 24 children per million inhabitants per year.

Pathophysiology

The jejunal mucosa has long villi, a large absorptive surface and contains high concentrations of digestive enzymes, such as amylase, lipases and trypsin and transport carrier proteins. In the jejunum macronutrients are rapidly mixed and digested, followed by carrier-mediated transport of monosaccharides, amino acids and dipeptides. Water-soluble vitamins, iron, calcium and magnesium are absorbed in the proximal part of the jejunum. Fat is absorbed in the entire jejunum.[14,15]

The ileal mucosa is characterized by shorter villi and tighter junctions between the epithelial cells. The nutrient absorptive capacity of the ileum is smaller than the jejunum. Bile salts, vitamin B12, fat-soluble vitamins and electrolytes are absorbed here. Active electrolyte transport of sodium chloride occurs mainly in the ileum and

colon, allowing the reabsorption of large amounts of fluids. The ileum also produces enteric peptides, such as enteroglucagon and peptide YY, which affect bowel motility.[14,15]

Shortly after bowel resection the remaining part of the bowel attempts to increase its fluid and nutrient absorption.[16] This process of adaptation includes muscular hypertrophy (increased bowel diameter and wall thickness) and mucosal hyperplasia.[5] Enteral nutrition plays an important part in the adaptation process: the intraluminal nutrients are known to have a stimulating effect on the epithelial cells and the production of trophic hormones. Thereby intraluminal nutrients also increase pancreatic and biliary secretion.[2,16,17] The adaptation process is more pronounced in the ileum than in the jejunum. The jejunum is not able to take over specific functions of the ileum, such as absorption of vitamin B12 and bile salts. The ileum, however, can develop the same absorptive capacity as the jejunum.

TEXTBOX: CASE 2

Boy born with a gastroschisis in March 2003 at a gestational age of 36 weeks and 5 days with a birth weight of 2600 grams. Directly after birth he underwent surgical intervention and the gastroschisis was covered with a silastic bag. Subsequently the contents were gradually reduced into the abdominal cavity. Two weeks after the initial surgical intervention, the abdomen was partially closed. He received total parenteral nutrition from the first surgical intervention onward and developed PN-related cholestasis after 10 days. Lipid emulsion was stopped and restarted in very low doses after 10 days. Due to impaired gastrointestinal motility oral and enteral nutrition were not possible.

Minimal enteral feeding with breast milk was started 27 days after the first surgical intervention and stopped after 4 hours, due to increasing gastric secretions and vomiting. Two weeks later a small-bowel radiological evaluation revealed non-rotation of the small bowel and gave rise to suspicion of small bowel atresia. One month after the X-ray, he developed a Gram positive sepsis, and anal blood loss and gastric hypersecretion intensified dramatically. Ten days after treatment of the sepsis, a surgical intervention was performed and the jejunal atresia was resected, with correction of the complete non-rotation of the small bowel.

One week after the third surgical intervention, MEF with polymeric formula was started successfully.

Three months after his first surgical intervention the boy received 10% of his energy intake enterally and his body weight was 5.6 kg. The duration of the initial admission was 4 months. At the age of 1 year (not corrected) he reached full enteral autonomy and his body weight was 10 kg.

This adaptation phase will last 1 - 2 years, during which nutrient absorption of the bowel is inadequate.[5] During that period, parenteral nutrition (PN) is indispensable. Oral and/or enteral feeding may be introduced in the course of time, and patients can eventually be weaned off PN. Still it remains unclear whether this process of intestinal rehabilitation is evoked by enhanced bowel adaptation, the nature of the intestinal substrate or simply results from optimized, comprehensive care for these patients in general.[16]

Co-morbidity and mortality

Concomitant morbidities in patients with SBS are usually central catheter related; examples are sepsis and PN-associated cholestasis.[18]

Survival rates of patients with SBS have much improved over the years, and ranged from 53% to 94% in the past decade.[7,8,10,19,20] Major predictors of mortality in pediatric SBS are PN-associated cholestasis and age-adjusted remaining small bowel length. Moreover, age-adjusted small bowel length and the presence of the ileocecal valve (ICV) are major predictors of weaning from PN.[21]

Literature

Most reports on infantile short bowel syndrome in the literature are case-reports, case-series, retrospective descriptive studies or expert reviews.

TEXTBOX: CASE 3

Boy, born at full term in May 2003 was presented six weeks after birth with suspicion of mesenterial cysts. First exploratory surgical intervention showed a lymphocele, malrotation and volvulus of the small bowel. The lymphocele with adjoining bowel was resected, leaving 105 cm of small bowel of dubious vitality. At the second and third laparatomies within 72 hours the vitality of the bowel was inspected, whereby most of the small bowel was found to be necrotic and was resected. This resulted in a residual small bowel length of 10 cm (3% remaining small bowel length) of jejunum ended as an jejunostomy. The distal ileum with ICV and complete colon were sutured intra-abdominally. A central venous catheter was inserted and he received total parenteral nutrition. One week after the last surgical intervention he developed a sepsis, which was treated successfully with antibiotics. Minimal enteral feedings were started 3 weeks after the third surgical intervention with polymeric formula. A month after the third surgical intervention, a fourth surgical intervention was performed and the proximal jejenum was anastomized end-to-end to the ileum 2 cm proximal to the ICV. Five days after the last surgical intervention, MEF was restarted with semielemental nutrition. Three months after the first surgical intervention he received 45% of his energy intake enterally and his body weight was 6.7 kg. The duration of the first admission was 3 months. At the age of 1 year he received 47% of his energy intake enterally and his body weight was 9.5 kg.

The focus is on various topics: surgical treatment (STEP, Bianchi and transplantation), clinical management, PN-associated liver disease, outcomes in terms of predictors for mortality and morbidity, and effects of nutrients and adaptation. Most studies are retrospective, single-centre studies in small numbers of patients. Literature on the clinical management of SBS consists mainly of reviews, which are predominantly based on expert opinions, as properly designed randomized controlled trials are very difficult to perform. Therefore, it appears that clinical management is mostly based on "trial and error", because human data and randomized trials are lacking due to the small numbers of patients presenting annually in pediatric surgical centres. To our knowledge, studies on dietary management of SBS are scarce. Moreover, information on the long-term impact of infantile SBS on growth, physical development and quality of life is lacking. A few reports advocated the possible benefits of interdisciplinary teams on management of SBS, but fail to provide data on (financial) resource consumption.

Rationale of studies discussed in this thesis

In 2003 pediatricians in the Erasmus MC-Sophia Children's hospital were confronted with three highly complex cases of infantile SBS within a short time-span. See Textboxes. All three patients were initially completely dependent on PN and for a long time had difficulty in tolerating enteral feedings. Being dependent on PN, they had to remain in hospital. One had a functional SBS (case 2), whereas the two others had anatomical short and extreme short bowel, respectively.

In the history of our hospital this was the first time we observed children surviving with these extreme short bowels. Case-reports in the literature had meanwhile demonstrated a greater likelihood of survival for these patients, while experience with small bowel transplantation was mounting. It was thus expected that these three children would survive and remain PN-dependent for a prolonged period of time. We started to wonder, therefore, whether it would be feasible to discharge them with home parenteral nutrition. At that time however, our hospital did not have the infrastructure to support home treatment.

Questions were raised on the treatment and prognoses of these children. What is the optimal clinical management, especially feeding regimen, for these children? What surgical interventions are available to enhance bowel function? Does home parenteral nutrition have merits in terms of lower costs and does it reduce the risk of sepsis? It is against this background that an interdisciplinary team was formed to manage these children and to facilitate discharge home and to streamline procedures. Moreover, a national database registry was set up that would enable to study these patients prospectively.

The overall aim of the work presented in this thesis is to evaluate the acute and long-term consequences of infantile short bowel syndrome. In this thesis the following questions were addressed:

1. What is the prevalence of infantile SBS in our hospital and what was their first year outcome? (**chapter 2**)
2. How can we assure optimal growth and nutritional status in the acute phase of the disease? (**chapter 3**)
3. What is the optimal type of feeding and feeding regimen for these children? (**chapter 4**)
4. What are the long-term effects of infantile SBS, regarding both physical development and quality of life? (**chapters 5 and 6**)
5. What are the costs of treatment of SBS? (**chapter 7**)

THESIS OUTLINE AND AIMS

In **chapter 2** the results are discussed of a retrospective single-centre study on nutritional correlates and growth during the first year of infantile short bowel syndrome. In addition, differences in outcome between decade 1980 - 1990 and decade 1990 - 2000 were studied.

In **chapter 3** we describe the feasibility of regular nutritional assessment by means of anthropometric measurements as standard of care in a relevant subgroup of ICU patients, i.e. those with major congenital anomalies affecting the gastro-intestinal tract, including patients with infantile short bowel syndrome.

A review is presented in **chapter 4** describing the published literature on different feeding strategies in infantile short bowel syndrome, resulting in a number of recommendations based on the levels of evidence of studies according to the SIGN criteria if appropriate and on expert opinion otherwise.

The aim of the cross sectional study presented in **chapter 5** is to evaluate the long-term effects of infantile short bowel syndrome on growth, nutritional status, bone health, defecation pattern and food intake.

The aim of the cross sectional study presented in **chapter 6** is to evaluate the long-term effects on health related quality of life, using PedsQl^{TM} and SF-36 questionnaires in children and young adults with a history of infantile short bowel syndrome.

In **chapter 7** we describe in detail a prospective case series of patients managed by the interdisciplinary short bowel team, with a focus on resource consumption, combined with nutrition and growth.

The general discussion of this thesis is presented in **chapter 8,** in which we try to find an answer to the question: what is the optimal management of infantile short bowel syndrome? Furthermore we present our recommendations for future, relevant research.

The results of the studies are summarized in **chapter 9**.

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Chapter 2

Growth and nutritional aspects of infantile short bowel syndrome for the past 2 decades

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Abstract

Purpose

The aim of this retrospective study is to describe characteristics of the first year of infantile short bowel syndrome (SBS), with regard to nutritional correlates and growth. Differences in outcome between decade 1980 (1980 to 1990) and decade 1990 (1990 to 2000) were studied.

Methods

Children with infantile SBS, who had been admitted in their first year of life between January 1975 and January 2002, were included. Patient characteristics, duration of parenteral nutrition (PN), type of enteral nutrition, and every quarterly term weight and height for age were collected. Data of decade 1980 and decade 1990 were compared, using appropriate statistical analysis.

Results

Twenty-eight patients were identified for decade 1980 vs 62 patients in decade 1990. Length of stay was significantly shorter in decade 1990 (116 vs 182 days; $p = 0.018$). Residual bowel length was not significantly longer in the latter decade (74 cm vs 60 cm; not significant [ns]). Mean weight for age (SD score [SDS]) in the first year of SBS in decade 1980 was significantly lower than in decade 1990 (0.9 SDS; $p = 0.035$).

Conclusions

Improved care of patients with SBS and the slightly longer residual bowel length (ns) in decade 1990 resulted in shorter length of stay, shorter duration of PN, and significantly higher SDS for weight for age compared with decade 1980.

INTRODUCTION

Short bowel syndrome (SBS) is a condition characterized by fast intestinal transit, which leads to diarrhea and malabsorption of nutrients. Often the result of massive resection of the small intestine,[1-3] it nevertheless has also been associated with a nonfunctional bowel. Affected children will need nutritional intervention to prevent growth retardation. The exact clinical manifestation of the disease depends on the residual lengths of jejunum and ileum, the presence of an enterostomy, the presence (or absence) of the ileocecal valve (ICV), the remaining functional length of the colon, persisting bowel disease, and possible complications.[1] The most frequent underlying diagnoses of SBS in neonates are necrotizing enterocolitis (NEC), volvulus, and congenital malformations such as intestinal atresia and gastroschisis.[1,4] Necrotizing enterocolitis is especially seen in prematurely born infants. Shortly after bowel resection, the remaining part of the bowel attempts to increase its fluid and nutrient absorption.[5] This adaptation phase will last 1 to 2 years, during which absorption of the bowel is inadequate.[6] Then, parenteral nutrition (PN) is indispensable. Oral or enteral feeding may be introduced in the course of time, and patients can be weaned of PN. Still, it remains unclear whether this process of intestinal rehabilitation is evoked by enhanced bowel adaptation or simply results from optimized, comprehensive care of these patients in general.[5]

The incidence of SBS in the Netherlands has not yet been studied. In Canada, the incidence is estimated at 24.5 per 100,000 live births, the mortality rate at 2 per 100,000 per year.[7] In the United Kingdom, the incidence is estimated at 2 to 3 per million per year, half of them being children.[8] The most common concomitant morbidities in patients with SBS are central catheter related such as sepsis and PN-related cholestasis.[4]

An accurate estimation of the incidence, mortality, and morbidity rates of SBS is hampered by the variations in the definition of SBS between individual studies.[7] Therefore, in 2004, a Dutch national committee, consisting of pediatric gastroenterologists and pediatric surgeons, was formed to reach consensus on the definition of SBS and to draw up a nationwide treatment protocol for children with SBS.[9] Short bowel syndrome was defined as more than 70% of the bowel resected and/or the need for PN for more than 42 days.

A number of case series of neonatal SBS have been published, mainly focusing on underlying diagnoses, remaining bowel length, duration of PN, and incidences of sepsis.[10-16] Group size varied between 8 and 257, time frames varied between 2 and 18 years, and follow-up periods varied between 3 months and 11 years. However, to our knowledge, no previous study has described growth and nutrition in the first year, nor compared outcomes in subsequent time frames or decades.

The aim of this retrospective single-center study is to describe characteristics of the first year of infantile SBS, with regard to nutritional correlates and growth. In addition, differences in outcome between decade 1980 (1980 to 1990) and decade 1990 (1990 to 2000) were studied.

METHODS

Study population

All children with infantile (≤ 1 year of age) SBS who in their first year of life had been admitted to the Department of Pediatric Surgery in Erasmus MC-Sophia (Rotterdam, the Netherlands) between January 1975 and January 2002 were included. This tertiary care children's hospital serves a referral area of 4 million inhabitants and 35,000 births per year and runs the only pediatric surgical service (including intensive care unit) in the South- Western part of the Netherlands.

Definition of SBS

The above definition by the Dutch national committee on SBS was applied to the present study population. According to this consensus, SBS is defined as follows:

- > 70% resection of the small bowel, and/or
- parenteral nutrition needed for longer than 42 days after bowel resection, and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a premature, less than 75 cm for a term neonate, and less than 100 cm for a 12-month-old child.[9]

Data collection

To identify children with SBS, the hospital's medical databases and charts were searched using the following keywords: short bowel syndrome, total parenteral feeding, ileal and/or jejunal resection, bowel failure (not specified), and the following diseases in case of small bowel resection: NEC, malrotation, midgut volvulus, congenital diaphragmatic hernia, omphalocele, gastroschisis, small bowel atresia, apple peel ileal atresia, inflammatory bowel diseases, Hirschsprung disease, and perforated colon. Data described below were collected for the first year after diagnosis of SBS.

Patient characteristics

Relevant medical information for the first year after diagnosis of SBS was extracted retrospectively from the medical charts, and length of stay (LOS), PN duration, and if applicable, date of death were derived from data for the entire follow-up (> 1 year) until October 2007.

Demographics such as sex, underlying diagnosis, and if applicable, date and cause of death were collected as well. Other characteristics, such as gestational age, birth weight, ethnicity, dates of admission, and discharge, were included. Complications in the first year of SBS were collected as well. These included central venous catheter (CVC)-related sepsis (subdivided into Gram-positive, Gram-negative bacteria, or fungi), PN-related cholestasis, and number of CVC (re)placements as a consequence of occlusion, thrombosis, or sepsis.

Bowel characteristics

Date of primary surgery (leading to SBS) was recorded, and surgical reports were searched for length of the remaining bowel, measured distally to the ligament of Treitz, postoperative presence of the ICV, location and number of enterostomies, and number of subsequent operations (excluding CVC placements).

Percentage of remaining bowel length was calculated from predicted bowel length for gestational age.[17]

Nutrition

Dates of start and end of PN, minimal enteral feeding (MEF), and enteral nutrition (EN) were collected for the first year of SBS. Minimal enteral feeding was defined as 25 kcal/kg or less per day feeding, and its start was defined as the first day after the date of primary surgery leading to SBS. Type of nutrition was classified as polymeric, breast milk, and semielemental. Numbers of interruptions of EN, necessitated by inadequate passage through the bowel and/or gastric acid hypersecretion, were counted.

Growth

Weight (kilogram) and height (centimeter) measurements of every quarterly term in the first year of SBS were collected. After a patient's discharge from the hospital, these measurements had continued during outpatient visits. Proportions of patients still admitted to the hospital during quarterly measurements were calculated. Values were compared to national standards and expressed in SD scores (SDS), depending on sex and age and corrected for prematurity and race (Growth Analyser version 3, Dutch Growth Foundation, Rotterdam, the Netherlands).

Statistical analysis

Group size was not based on a formal power analysis. The incidence of SBS in the Netherlands is unknown but from clinical experience is judged to be relatively low. We therefore aimed at including all patients with SBS admitted between 1975 and 2002. The collected data from medical charts (date of birth, admission, surgery, enterostomy, PN, start MEF, start EN, discharge, and death) were entered into a statistical software package (SPSS version 14, SPSS in Surrey, United Kingdom). A date subtraction function

generated ages at admission, primary surgery, LOS, and duration of PN, of enterostomy, start of MEF, and EN after surgery. Frequencies of patient characteristics and bowel and nutritional variables were expressed as median (minimum-maximum). Number of deaths per diagnosis was calculated and statistically compared using a χ^2 analysis.

We created 2 time groups as follows to study possible effects of changes in medical care for these patients: "decade 1980" (patients diagnosed with infantile SBS between 1980 and 1989) vs "decade 1990" (patients diagnosed with infantile SBS between 1990 and 1999). Differences in characteristics between these groups were analyzed using χ^2 analysis or the Mann-Whitney *U* test, if applicable. For the analysis on bowel variables, the decade groups were subdivided into survivors and deceased patients. Differences between these subgroups and between the decade groups were analyzed using χ^2 analysis or the Mann-Whitney *U* test, if applicable. Analyses concerning nutrition and growth were performed for survivors only because nutrition and growth data of the deceased were limited. Kaplan-Meier curve was used to present duration of PN for the 2 decade groups.

Longitudinal analysis of growth data was performed using repeated measurement analysis of variance (Proc Mixed, SAS, Cary, NC). The analysis included comparison of mean values, so as to allow for missing data. The level of significance was set at 0.05.

RESULTS

Patient characteristics

In the period between 1975 and 2002, a total of 110 patients with infantile SBS had been admitted to Erasmus MC-Sophia. Demographics of these patients are shown in Table 1. Twelve patients had co-occurring congenital anomalies unrelated to the digestive tract – syndromes of Wolf-Hirschorn, Allagile, Goldenhar and Down, perinatal asphyxia, situs inversus abdominalis, hypoplastic heart, sacrum malformation, G6PD deficiency, and esophageal atresia. Five of them died.

Figure 1 shows numbers of deaths and survivors per underlying diagnosis of the total group. χ^2 analysis showed no significant differences for numbers of deaths ($p = 0.085$).

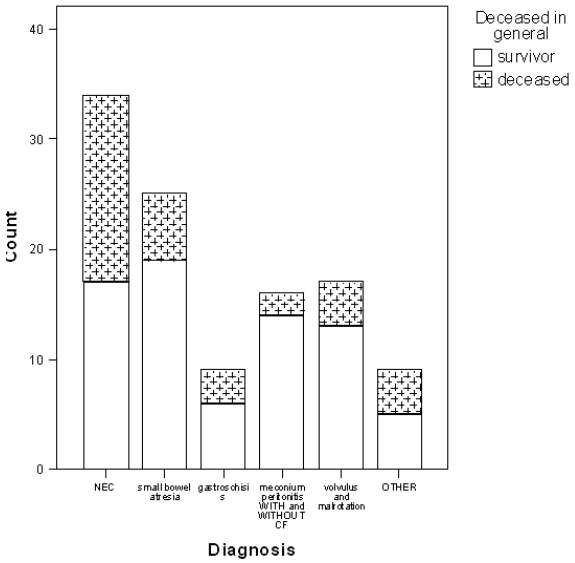
Further analysis was limited to decades 1980 and 1990. Therefore, 7 patients before decade 1980 and 13 patients after decade 1990 were excluded, leaving 90 patients.

Table 1 Demographics all patients (1975 - 2002)

Demographics	All patients n = 110 (100%)	Survivors n = 74 (100%)	Deceased patients n = 36 (100%)
Underlying first diagnosis SBS			
NEC	34 (31%)	17 (23%)	17 (47%)
Small bowel atresia	25 (23%)	19 (26%)	6 (17%)
Gastroschisis	9 (8%)	6 (8%)	3 (8%)
Meconium peritonitis no CF/CF	16 (14.5%)	14 (19%)	2 (6%)
Volvulus and/or malrotation	17 (15.5%)	13 (17%)	4 (11%)
Other	9 (8%)	5 (7%)	4 (11%)
Other anomalies unrelated to digestive tract (yes/no)	12 (10.9%) / 98 (89.1%)	7 (9%) / 67 (91%)	5 (14%) / 31 (86%)
Sex (M/F)	58 (53%) / 52 (47%)	37 (50%) / 37 (50%)	21(58%) / 15 (42%)
Survival rate: first year	77 (70%)		3 (8%)
Overall survival rate	74 (67%)		
Causes of death			
Complete necrotic bowel			16 (44.4%)
Sepsis			9 (25%)
Other			11 (30.6%)

SBS = Short bowel syndrome, NEC = Necrotising enterocolitis, CF = Cystic fibrosis, M = male, F = female.

Figure 1 Number of deaths per diagnosis, 1975 to 2002



Twenty-eight patients had been admitted in decade 1980 vs 62 in decade 1990. Between these decades, no significant differences in frequencies of underlying diagnoses, sex, survival rate, number of prematures and age at onset of SBS were observed (data shown in Table 2). The case fatality rate in decade 1980 was 36% vs 31% in decade 1990.

Table 2 Characteristics decades 1980 and 1990

	Decade 1980 n = 28	**Decade 1990 n = 62**
Underlying diagnosis resulting in SBS		
NEC	8 (29%)	17 (27%)
Small bowel atresia	7 (25%)	14 (23%)
Gastroschisis	3 (11%)	4 (7%)
Meconium peritonitis no CF/CF	3 (11%)	12 (19%)
Volvulus and/or malrotation	6 (21%)	9 (15%)
Other	1 (3%)	6 (10%)
Sex (M/F)	15 (54%) / 13 (46%)	33 (53%) / 29 (47%)
Survival rate first year	20 (71%)	44 (71%)
Survival rate overall	18 (64%)	43 (69%)
Causes of death		
Complete necrotic bowel	3 (30%)	8 (42%)
Sepsis	5 (50%)	4 (21%
End-stage liver disease	-	2 (11%)
Withdrawal of treatment	-	4 (21%)
Other	2 (20%)	1 (5%)
Number of prematures	17 (61%)	41 (66%)
Gestational age (wk)	34.9 (26.1 - 40)	35.7 (25.6 - 42)
Birth weight (g)	2000 (950 - 3590)	2367 (610 - 4200)
Birth weight (SDS)	-0.9 (-3.3 - 1.8)	-0.3 (-3.7 - 3.5)
LOS survivors (d)*	182 (43 - 552)*	116 (10 - 485)*
LOS deceased (d)	80 (1 - 983)	12 (0 - 394)
No. of hospital admittances in first year of SBS	0 (0 - 3)	0 (0 - 7)
Age initial date SBS (date surgery leading to SBS) (d)	3 (0 - 152)	3 (0 - 270)

** significant difference in LOS between decade1980 and decade 1990; p = 0.018. SBS = Short bowel syndrome, NEC = Necrotising enterocolitis, CF = Cystic fibrosis*
The causes of withdrawal of treatment in decade 1990 were diseases considered not compatible with life (total aganglionosis of the bowel and siblings with multiple atresia and immunodeficient bowel).

Length of stay in decade 1990, however, was significantly shorter (116 days) than in decade 1980 (182 days, $p = 0.018$).

Bowel characteristics

In each decade, median residual bowel length of the survivors was significantly longer than that of the deceased patients ($p < 0.05$). Bowel length was not different, however, between the survivors of both decades (60 cm vs 74 cm). To account for the effect of gestational age on bowel length, residual bowel length was also expressed as percentage of the original bowel length. These percentages were also not different between survivors in both decades (26% vs 29% remaining bowel length in decade 1980 and 1990, respectively). The ICV had been resected in 22% vs 14% of the survivors in decade 1980 and 1990, respectively, and in 50% and 78% of the deceased in both decades. This difference was significant between survivors and deceased in decade 1990 ($p < 0.05$). The number of patients (survivors and deceased) that acquired PN-related cholestasis increased from 40% in decade 1980 to 50% in decade 1990. In decade 1980, deceased patients had had significantly more PN-related cholestasis than survivors ($p = 0.035$). This phenomenon was not observed for decade 1990. All postoperative outcomes of SBS are presented in Table 3.

Nutrition

The median duration of PN in decade 1990 (90 days) was shorter than that in decade 1980 (134) but not significant ($p = 0.13$; Figure 2).

Figure 2 Duration of parenteral nutrition (days) in first year of infantile SBS

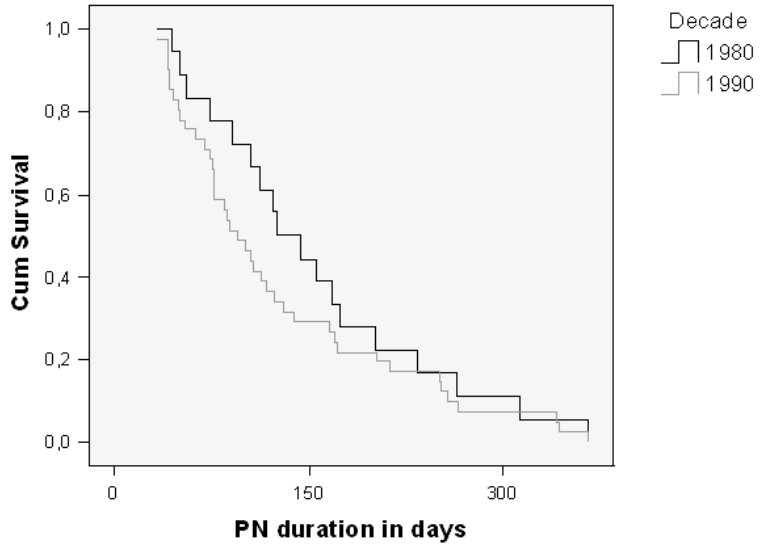


Table 3 Bowel characteristics

Bowel	**Decade 1980**		**Decade 1990**	
	Survivors (n = 18) mean% valid = 83%	**Deceased (n = 10)** mean% valid = 65%	**Survivors (n = 43)** mean% valid = 88%	**Deceased (n = 19)** mean% valid = 61%
Length residual small bowel (cm)	60 (35 - 85)*	35 (21 - 45)*	74 (30 - 120)**	35.5 (0 - 86)**
% SB remaining	26% (11 - 37)	14% (10 - 21)	29% (9.9 - 46)**	14% (0 - 40)**
Presence ICV (yes/no)	14 (78%) / 4 (22%)	3 (50%) / 3 (50%)	37 (86%) / 6 (14%)**	2 (22%) / 17 (78%)**
Enterostoma	12 (67%)	6 (60%)	35 (81%)	8 (42%)
Jejunostoma	5 (28%)	1 (10%)	17 (40%)	4 (21%)
Ileostoma	7 (39%)	5 (50%)	18 (41%)	4 (21%)
Duration of enterostoma (d)	77 (25 - 808)	125 (4 - 1403)	61 (22 - 643)	42 (3 - 122)
No. of operations (ex-central lines)	3 (1-7)	2 (1 - 5)	3 (1 - 7)**	2 (0 - 3)**
No. of sepses	2.5 (0 - 6)	1 (0 - 6)	1 (0 - 7)	0 (0 - 6)
Septic events/month PN	0.44 (0 - 0.87)	0.14 (0 - 0.5)	0.36 (0 - 1.14)	0 (0 - 0.87)
Gram positive (%)	16 (46%)	10 (91%)	31 (48%)	8 (42%)
Gram negative (%)	18 (51%)	0	29 (45%)	11 (58%)
Fungal (%)	1 (3%)	1 (9%)	5 (7%)	0
PN related cholestases	4 (27%) *	4 (80%)*	18 (46%)	5 (71%)

** Significant difference between survivors and deceased of decade 1980; $p < 0.05$*
*** Significant difference between survivors and deceased of decade 1990; $p < 0.05$*
mean% valid = mean percentage of number of patients measured.

Table 4 Nutrition of survivors

Nutrition	**Decade 1980 n = 18**	**Decade 1990 n = 43**	***p***
Duration PN (d) (n = 18/41)	134 (44 - 447)	90 (34 - 2345)	ns
No. of central catheters used in 1 y (n=16/42)	2 (0 - 6)	2 (1 - 8)	ns
Start MEF (n = 13/42)	18 (6 - 74)	9 (3 - 48)	0.072
Start enteral nutrition (n = 13/41)	22 (7 - 62)	24 (4 - 110)	ns
Type EN (n = 17/42			ns
Breast milk	0	5 (12%)	
Semielemental	15 (88%)	30 (71%)	
Polymeric	2 (12%)	7 (17%)	
No. of interruptions EN (n = 14/42)	3.5 (1 - 8)*	3 (1 - 7)*	0.032

*ns indicates not significant, * p = 0.032; significant difference in number of interruptions of EN between survivors 1980s and 1990s.*

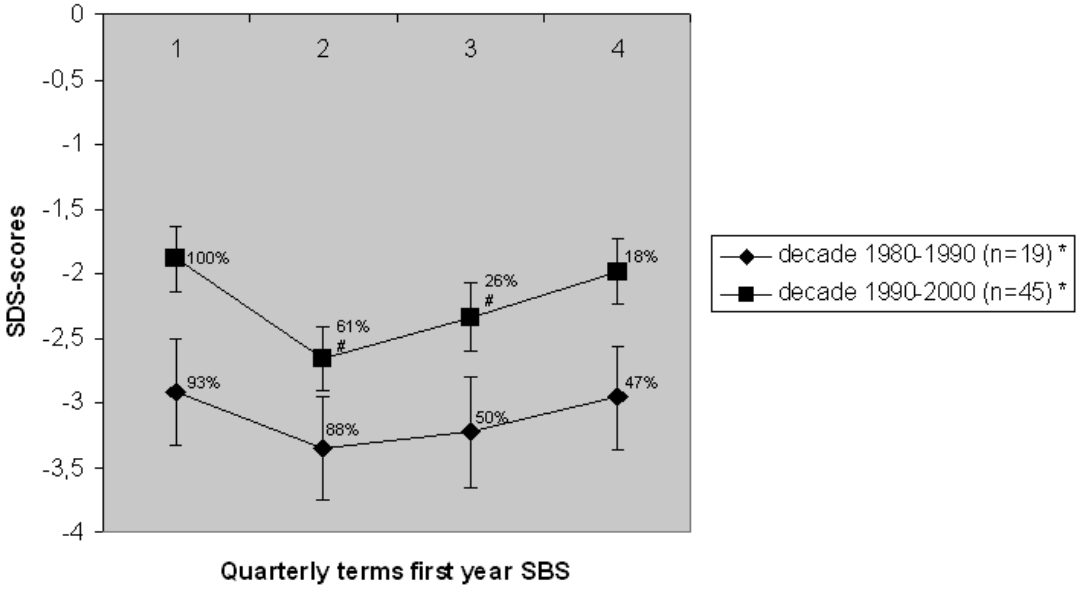
In decade 1980, MEF was started 18 days (range, 6 - 74 days) after primary surgery; in decade 1990, after 9 days (range, 3 - 48 days) (p = 0.072).

Of the patients, 88% had been fed semielemental nutrition in decade 1980, 12% polymeric feeding, and none had been fed breast milk. In decade 1990, 71% of the patients had been fed semielemental nutrition, 17% polymeric feeding, and 12% breast milk (Table 4; not significant [ns]). The frequency of interruptions of enteral feeding in decade 1980 was significantly higher than that in decade 1990 (p = 0.032).

Growth

Generally, mean weight for age (WFA)-SDS in the first year of SBS in decade 1980 was significantly lower than in decade 1990 (0.9 SDS; p = 0.035). This difference did not depend on quarterly term measurement (Figure 3). Furthermore, in decade 1990, mean WFA during terms 2 (-2.7 SDS) and 3 (-2.3 SDS) was significantly lower than that during term 1 (-1.9 SDS; $p < 0.05$). In decade 1980, no differences were found between quarterly terms. Height for age was not significantly different between children of decade 1980 and decade 1990, nor significant increases or decreases observed during the 4 quarterly terms within both groups (data not shown).

Figure 3 SD scores weight for age in first year of infantile SBS.



*Percentages of patients admitted to the hospital during moment of measurement. * indicates significant difference in curve between decade 1980 and decade 1990 (p = 0.035); # SDS in terms 2 and 3 differ significantly from SDS in term 1 in decade 1990 (p < 0.05).*

DISCUSSION

This retrospective study of infantile SBS for 2 decades showed that LOS and duration of PN decreased for the last decade. Although growth was difficult to maintain in the first year of infantile SBS in both decades, overall weight for age was higher in decade 1990. To our knowledge, this is the first study with a relatively high number of patients who compares outcome over time and focuses on growth and types of nutrition.

We realize that patients might have been missed as not all medical records for the years 1975 up to and including 1985 had been digitized yet. This would explain the lower number of patients found in decade 1980.

Because this study is retrospective, data collection is based on the accuracy of documentation of others, which might have resulted in missing data. Taking this into account as well as the heterogeneity and statistically small numbers of the study groups, we have not calculated correlations between variables.
Because most previous studies are retrospective, the present results can be compared to those outcomes, albeit hampered by differences in the definitions of SBS.[7]
The distribution of the underlying diagnoses found in our study compares well with that

reported in the literature.[1,7,11] The case fatality rate was lowest for meconium peritonitis with/or without cystic fibrosis (13%) and highest for NEC (50%), although not significantly different. Patients with NEC as underlying cause for infantile SBS are most vulnerable to complications because of prematurity and its intrinsic sequelae, immature gastrointestinal system, and diminished immunologic response.[18] The overall mortality rate of our study (33%) is in line with mortality rates reported in previous single-center studies.[7,10,11,13,14,19,20]

Comparison of remaining bowel length with previous research is difficult. No more than 2 single-center case series studies[16,21] describe the method of measurement of residual bowel length, thus limiting comparability. In addition, some previous studies have not corrected for gestational age.[12] We have demonstrated that the survivors' median residual bowel length was significantly longer than that of the deceased patients in both decades separately, suggesting that shorter residual bowel length carries greater risk of death. This might be because of the underlying diagnosis and/or complications such as sepsis. Residual bowel length in decade 1990 was longer than that in 1980, although not significantly. It would seem, therefore, that treatment has shifted to sparing the bowel as much as possible.

In both decades, the ICV had been resected in significantly more deceased patients than in survivors, indicating that the presence of ICV might be important to survive. Resection of the ICV may cause bacterial overgrowth and inflammation of the mucosa[15] and has been associated with longer duration of PN.[21,22] Apart from risk of sepsis, long-term use of PN also increases the risk of PN-related cholestasis and therefore contributes to a higher mortality. As resection of the ICV results in a larger percentage of bowel resected, it might thus have increased mortality indirectly.

Common morbidities in patients with infantile SBS are CVC related such as sepsis and PN-related cholestasis.[4] Previously reported sepsis frequencies per month PN varied between 0.12 and 0.85.[12,16] The frequencies found in the present study (0.44 and 0.36 in consecutive decades) fall within this range. In both decades, almost 50% of all sepsis consisted of either Gram-negative or Gram-positive bacteria. Sondheimer et al.[16] found more Gram-negative bacteria (57%) sepsis, whereas Wales et al.[12] found far higher frequencies of Gram-positive bacteria (80%). This discrepancy might be because of different CVC handling protocols, indications of CVC removal, and the use of different types of antibiotics. Of the patients, 40% in decade 1980 vs 50% in decade 1990 had had PN-related cholestasis. Others have reported higher frequencies, that is, 67%[12] and 62.5%.[16] Earlier research of our study group showed that only 16% of 94 neonates and infants (< 1 year old) who required PN for more than 14 days developed PN-related cholestasis.[23] This condition is probably associated with multiple risk factors including

prematurity, immature hepatic function, lack of enteral feeding, sepsis, and various toxicities or deficiencies in PN.[24] Differences between the studied populations with regard to these risk factors might underlie these differences in frequencies of PN-related cholestasis.

The median duration of PN decreased from 134 days in decade 1980 to 90 days in decade 1990. Even shorter durations have been reported, that is, 84 to 86 days,[12,19] but also longer durations, that is 245 to 4358 days.[11,13,15] Several studies show an inverse relationship between residual bowel length and duration of PN.[11,15,21,22,25] In the present study, the shorter duration of PN in decade 1990 might be partially explained by longer median bowel length but also by improved composition of PN and medical care. An overview of SBS case series are presented in Appendix.

Clinicians these days generally agree that enteral nutrition should be administered as soon as possible after bowel resection–and preferably slowly and in small volumes–so as to promote adaptation.[3,6,26,27] In line with this notion, we found that enteral nutrition in decade 1990 was started earlier after primary surgery than in decade 1980 (9 vs 18 days; not significant).

A systematic review showed that MEF in high-risk neonates decreased the time to reach full enteral feeding and reduced length of hospital stay.[28] Semielemental type of nutrition was the main choice in decades 1980 and 1990; evidence on the possible advantage of breast milk, which shortens PN duration (13), was not yet available.

Our study group earlier has pointed at children's delayed growth during the first year after bowel resection.[29,30] To our knowledge, the present study is the first to present longitudinal growth data in the first year of SBS. All patients in both decades had low mean SDS compared to the healthy normal population. The high proportion of premature infants, that is, 61% in decade 1980 and 66% in decade 1990, might partially explain these lower SDS. After correction for gestational age, the WFA-SDS remained subnormal, which is in line with previous reports of growth retardation in preterm infants.[31-33] In addition, we compared ill children to the reference values of a healthy normal population. The combined effects of prematurity and illness may lead to lower WFA-SDS. As SBS is most severe in the first 6 months, it can be hypothesized that the energy requirements are the highest and energy fulfillments are the lowest, whereas the bowel is still in a malabsorptive state. Indeed, our study showed a significant decline of weight SDS in the second and third quarterly terms in decade 1990 ($p < 0.05$), but not in decade 1980, probably because of the lower number of patients. Most of the patients in our study were hospitalized in the first 2 quarterly terms. Hulst et al.[34] have shown that long LOS is associated with lower WFA-SDS. The following factors might

have resulted in a higher WFA-SDS curve in decade 1990; improved nutritional strategies (both PN and EN), better medical and surgical care, shorter LOS, and shorter duration of PN.

Weight only does not determine growth. Height for age is equally important. Height for age was not significantly different between decade 1980 (n = 12) and decade 1990 (n = 20), nor were significant increases or decreases observed during the 4 terms within the groups. Data on height were lacking for relatively large proportions of the study groups, so statistics may be unreliable. We can only speculate why height measurements were not performed or recorded.

In conclusion, better care of SBS patients and the slightly longer residual bowel length (not significant) in decade 1990 resulted in shorter LOS, shorter duration of PN, and a significantly higher WFA-SDS as compared with SBS patients in decade 1980.
This is the first study comparing care of SBS between 2 consecutive decades, showing that the WFA-SDS declined significantly in the first 2 quarterly terms. Our results show that there is still room for improvement in the care of children with SBS, notably with regard to stimulating early nutritional intake.

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APPENDIX

Table Sample of SBS case series

Author	N	Duration	Location	Definition	Mortality	SB length (cm) median (min - max)	Duration PN (d) median (min - max)	Sepsis/month PN
Olieman (2007)	90	1980 - 2000	Nl	PN > 42 d or 30% SB	33%	60 (35 - 85)/74 (30 - 120)	134 (44 - 447)/90 (34 - 2345)	0.44/0.36
Goulet (2005)[1]	87	1975 - 1991	France	-	10.3%	34/35/57 (mean)	143.1/47.4/16.1 mo (mean)	
Wales (2005)[2]	40	1997 - 1998	Canada	PN > 42d or 25% SB	37.5%	72.9 (mean)	86 (55 - 138)	0.5
Quiros-Tejeira (2004)[3]	78	1975 - 2000	US	SB < 76 cm and PN > 42 d	27%			
Andorsky (2001)[4]	30	1986 - 1998	US	PN > 90 d	30%	83 (± 67) (mean)	606 (101 - 3287)	
Bueno (1999)[5]	257	1990 - 1998	US	iTX evaluation	47%	21 (± 1.5) (mean)	31.2 (± 2.7) mo	6 (0 - 42)
Sondheimer (1998)[6]	42	1986 - 1997	US	PN > 42 d		88/51.7/68.9 (mean)		0.31/0.36/0.12
Kaufman (1997)[7]	49	1976 - 1994	US	PN > 42 d	6%	31 (± 30)/81 (± 65)	17 (± 14) mo (mean)	
Beath (1996)[8]	74	1988 - 1992	UK	PN > 21 d			46.5 (21 - 216)/30.5 (21 - 136)	0.85 (0 - 4)/0.33 (0 - 2)
Teitelbaum (1996)[9]	25	1985 - 1995	US	30% SB	32%	41 (± 25) mean		
Liefaard (1995)[10]	8	1991 - 1993	Nl	< 50% SB		34SB%		
Georgeson and Breaux (1992)[11]	52	1978 - 1990	US	PN > 42 d	17%	49.8 (± 22.2)/46.9 (± 19.3)	25.1 (± 25.9)/11.4 (± 8.7) mo (mean)	
Galea (1992)[12]	64	1978 - 1988	UK	-	22%		84/546/63/189	
De Agustin (1999)[13]	8	1995 - 1997	Spain	25% SB	40%			
Affourtit (1989)[14]	74	1975 - 1985	Nl	< 50% SB	20%			

N indicates number of patients; SB, Small bowel; iTX: intestinal transplantation.

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Chapter 3

Nutritional assessment as standard of care on a pediatric intensive care unit; Does it work?

Joanne F. Olieman, Annelies Bos, Dick Tibboel, Corine Penning

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e-SPEN, the European e-journal of Clinical Nutrition and Metabolism (2008) 3;e203-e207.

Abstract

Background and aims

Critically ill children are at risk of developing malnutrition when receiving intensive care, especially those with digestive tract problems. This study aimed to evaluate the feasibility of nutritional assessment by means of anthropometric measurements to monitor children with major congenital anomalies of the digestive tract.

Methods

Children with congenital anomalies of the digestive tract, receiving intensive care for more than 3 days, were scheduled for weekly nutritional assessment by two anthropometrists (available for 0.4 fte). Numbers of actual measurements per patient and success rate of the individual anthropometric measurement techniques were evaluated. Reasons for missed measurements were evaluated in a separate population.

Results

Of the 89 children included, 54 (61%) underwent nutritional assessment. No more than 8 (15%) had been assessed at the proposed frequency. Follow-up was possible for 34/54 children (2 or more measurements). All applied separate nutritional assessment techniques had a success rate of 100%. Feasibility of the nutritional assessment protocol was negatively influenced by longer hospital admission. Twenty six percent of the missed assessments were due to unavailability of the anthropometrists, and 8% to children's bad condition.

Conclusions

Regular nutritional assessment in the current setting was not feasible. Adequate monitoring of nutritional status in critically ill children calls for weekly assessment. An adequate infrastructure, which guarantees structural availability of trained personnel, is the cornerstone in this setting.

INTRODUCTION

Critically ill children receiving intensive care are at risk of developing malnutrition. Major causes of malnutrition are increased metabolic demands and underfeeding due to either underprescription or interruption of feeding.[1-3] Typically, critically ill children below two years of age are more prone to develop malnutrition than older children.[4] Children with high risk of developing malnutrition are those with major congenital anomalies that directly or indirectly affect the gastro-intestinal tract and require intensive care and surgical intervention shortly after birth, such as congenital diaphragmatic hernia, anal atresia or abdominal wall defects.

During admission, regular nutritional assessment is therefore necessary to identify malnourished patients or those who are at risk, and to establish the degree of malnutrition. Moreover, it is also necessary to evaluate the adequateness of nutritional support.[5] Regrettably, regular nutritional assessment in hospitalized critically ill children is not yet common practice.

Previous studies have shown that 15 - 20% of children admitted to pediatric intensive care units were acutely or chronically malnourished.[4,6-8] On top of that, a study by our group has showed that 24% of critically ill children were already malnourished upon admission; at discharge, proportions of malnourished neonates (either preterm or term) had increased to 26% and 48%, respectively.[9] Factors associated with malnutrition were duration of hospital admission and a history of associated anomalies.[9,10]

Previously, our research group has recommended standardized nutritional assessment for all children upon and during admission at the intensive care unit (ICU), to minimize the risk of developing malnutrition and to identify children at risk.[9] However, the feasibility of this recommendation in critically ill children has never been studied systematically and prospectively.

The aim of the present study was to evaluate the feasibility of regular nutritional assessment by means of anthropometric measurements as standard of care in a relevant subgroup of ICU patients, those with major congenital anomalies affecting the gastro-intestinal tract.

MATERIALS AND METHODS

Study 1: Feasibility of protocol

Study 1 was performed from July 2004 until February 2006. Children of all ages with so-called index diagnoses (oesophageal atresia, congenital diaphragmatic hernia,

abdominal defects such as gastroschisis and omphalocele, small bowel atresia, anorectal malformation and Hirschsprung disease) admitted for more than three days to the pediatric surgical intensive care unit (ICU) of the Erasmus MC-Sophia Children's Hospital, were included. This tertiary care children's hospital serves a referral area of 4 million inhabitants and 44,000 births per year, and runs the only pediatric surgical intensive care unit in the South-Western part of the Netherlands. Children treated with Extra Corporeal Membrane Oxygenation (ECMO) during admission were excluded, since anthropometric measures might not be reliable or not feasible in ECMO-treated children due to edema.[9]

According to the previously proposed protocol,[9] nutritional assessment was planned in weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 of admission, if applicable.

In critically ill children height and weight alone may not accurately reflect their nutritional state since body composition might vary.[11-13] Therefore, additional methods for body composition measurement were applied. Nutritional assessment consisted of anthropometric measurements of weight, recumbent height, head circumference (HC), mid upper arm circumference (MUAC), calf circumference (CC), skinfold thickness of biceps (BSF) and triceps (TSF) and Bio-electrical Impedance Assessment (BIA). Body weight (kg) was measured in a standardized way on a calibrated scale (Digital baby scale, Kubota, Japan) to the nearest 0.01 kg, after removing the child's diaper and clothes. Recumbent height (cm) was determined by measuring crown-heel length to the nearest 0.1 cm using a flexible tape measure with a fixed headboard, in the supine child. Head circumference (HC; cm) was measured as described previously.[14] BSF and TSF (mm) were measured midway between the acromion and olecranon, using a Harpenden skinfold calliper (John Bull, England) to the nearest 0.1 mm (mean of three separate readings).[14] MUAC (on the midway of the acromion and olecranon) and CC (at the maximum of the calf) were measured with a flexible tape measure to the nearest 0.1 cm. BIA-values were determined with the single-frequency Bio-impedance Analyser STA (Akern SRL, Florence, Italy), which uses the tetrapolar technique. This involves placement of two electrodes (one detecting and one active, BIAmed® electrodes, Zwaag, the Netherlands) on the dorsal side of the left hand and likewise on the foot.[15] The active electrode gives a constant electrical current of 800 microampere at a constant frequency of 50 kHz. From the resulting Rz (resistance) and Xc (reactance) values, fat-free mass was calculated using the cross-validated equations of Horlick et al.[16]

Two well-trained anthropometrists, who were available for this study for 0.4 full time equivalent (fte), performed the measurements. Intra- and inter-observer rates,

obtained prior to the study, showed good reproducibility of the measurements with variation coefficients of < 2% for MUAC and CC and < 8% for BSF en TSF.

Measurement date, admission week and measurement outcomes were recorded in case record forms. Patient characteristics (diagnosis, sex, gestational age, birth weight, age at admittance, and length of stay (LOS)) were recorded. SD scores for birth weight were calculated according to Usher and McLean.[17]

After the study period, missed children with index diagnoses that had been admitted to the ICU during the study period were identified using the hospital's patient management data system (PDMS).

Study 2: Reasons missing values

After finishing study 1, it became apparent that many measurements had been missed. In order to evaluate the reasons for these missing recordings, we performed a second study from June 2006 until February 2007, fully along the lines of study 1 and we additionally recorded reasons for missing measurements.

As the protocols were performed as standard of care, the Institutional Review Board (IRB) waived approval. All parents were routinely informed about the Nutritional Assessment policy during their children's stay in hospital.

Analysis and Statistics

Group size for both studies was not based on a formal power analysis. The incidence rates of congenital anomalies of the gastrointestinal tract in European countries range from 1 in 10.000 for gastroschisis to 1 in 3000 for congenital diaphragmatic hernia (CDH).[18,19] Since this patient group is relatively small, size of the study group was based on availability of patients.

We evaluated three components of feasibility: proportion of patients assessed, frequency of successful measurements according to protocol, and reasons for missing measurements. The statistical package for social sciences (version 12.0, SPSS, Chicago, IL) was used for statistical analysis.

In study 1, patients with index diagnoses were subdivided into three groups based on actual frequency of nutritional assessment: none at all performed (group C; no NA), all measurements according to the protocol (group A; full protocol), and some of the proposed measurements according to the protocol, but not all (group B; partial protocol). The proportion of measurements according to the protocol (%) was related to LOS.

In children of group B (partial protocol), multivariate linear regression analysis was used to determine the influence of the above-mentioned patient characteristics on the actual percentage of measurements. Frequency of missing recordings in the first week was calculated. The number of patients who underwent two or more recordings was calculated. The influence of patient characteristics on feasibility of the protocol (all children of study population) was calculated using a multiple generalized estimating equations analysis (GEE), with compound symmetry as the working correlation matrix and using the logit link function. Completion of nutritional assessment (yes/no) at the separate time points of the protocol was used as outcome variable and type of index diagnosis, age at admittance, survival, LOS and the influence of time (repeated measurements) as variables. For the GEE analysis SAS (Cary, NC) version 8.02 was used. Frequencies of successfully measured items (weight, recumbent height, HC, MUAC, CC, BSF, TSF and BIA) were calculated for children of groups A (full protocol) and B (partial protocol) together.

In study 2, frequencies of reasons for missing recordings and frequencies of nutritional assessment recordings were calculated. The proportion of measurements according to protocol was related to LOS. Characteristics of patients in the two separate studies were compared using chi-square (χ^2) analysis or Mann-Whitney *U* test. The level of significance was set at 0.05.

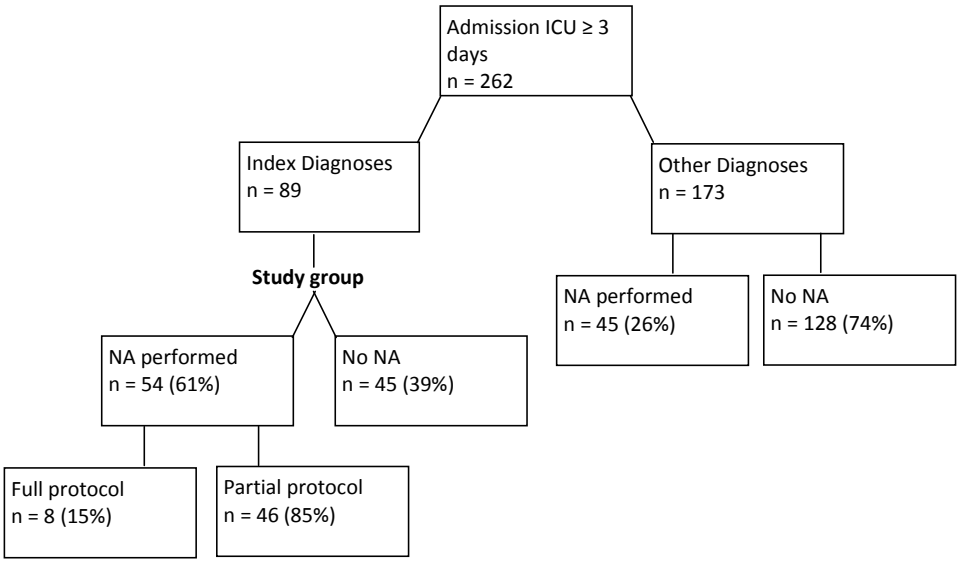
RESULTS

Study 1: feasibility

Over the study period, a total number of 262 patients had been admitted to the ICU for more than 3 days (Figure 1). Eighty-nine of these patients had so-called index diagnosis: 54 of them (61%) had undergone nutritional assessment recordings. Forty-five of the 173 other patients (26%) had also undergone nutritional assessment.

Characteristics of patients with index diagnoses (study group) are shown in Table 1, subdivided by frequency of nutritional assessment. Thirty-nine percent had not undergone any nutritional assessment (group C: no NA), nine percent had undergone nutritional assessment according to the proposed frequency (group A: full protocol), and 52% had had some of the scheduled measurements according to the protocol (group B: partial protocol). Due to the relatively small numbers of children, no statistical comparisons were made between the groups. The number of successful NA recordings in the study group at the time points of the protocol is visualized in Figure 2.

Figure 1 Flow chart study 1



Nutritional assessment (NA) measurements in children who had been admitted to the ICU for 3 days or longer, subdivided by children with or without index diagnoses. Children with index diagnoses either had had no NA recordings, all recordings according to the protocol (full protocol) or some of the scheduled recordings (partial protocol).

Forty-six patients of group B (partial protocol) underwent several, but not all, scheduled assessments according to the protocol. Thirty-two of these (70%) had had no NA recording in the first week of admission, hampering the interpretation of the follow-up measurements. The median percentage of actual recordings in this group, related to LOS, was 48% (range 18% - 75%).

No association could be shown between the percentage of actual measurements in group B and patient characteristics such as diagnosis, age, survival or LOS. In group B, 29 patients (63%) had undergone two or more nutritional assessment recordings, allowing follow-up.

Results of the multiple GEE analyses are shown in Table 2. The time factor was a significant (p = 0.006) predictor of completion of the scheduled measurements at the subsequent time points, indicating that the chance of completing the measurement at a given time point was significantly higher in children with shorter hospital admission versus those with longer hospital admission. Length of stay reached near significance (p = 0.056), indicating that the chance of completing the measurement increased with length of stay, although not significantly. For all performed measurements, the median percentage of successful items measured was 100% (range 0% - 100%, data not shown) for all items (weight, recumbent height, HC, MUAC, CC, BSF, TSF and BIA).

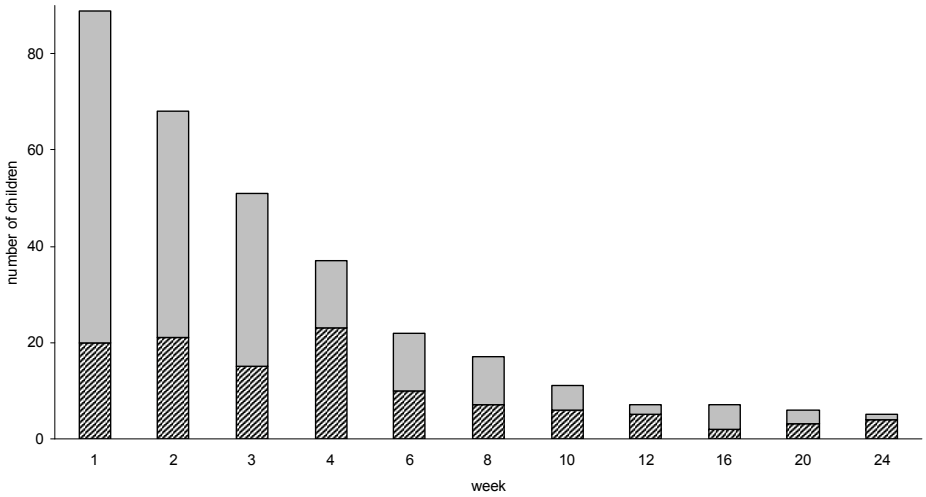
Table 1 Patient characteristics

Characteristics	**Total** n (%)	**Group A (full protocol)** n (%)	**Group B (partial protocol)** n (%)	**Group C (no NA)** n (%)
Index diagnoses	89 (100%)	8 (9%)	46 (52%)	35 (39%)
Congenital diaphragmatica hernia	11 (12.4%)	0 (0%)	7 (15.2%)	13 (28.9%)
Oesophageal atresia	34 (38.2%)	2 (25%)	19 (41.3%)	13 (28.9%)
Hirschsprung disease	9 (10.1%)	2 (25%)	2 (4.3%)	5 (11.1%)
Anal atresia	6 (6.7%)	1 (12.5%)	2 (4.3%)	4 (8.9%)
Abdominal wall defect	18 (20.2%)	1 (12.5%)	10 (21.7%)	7 (15.6%)
Bowel atresia	11 (12.4%)	2 (25%)	6 (13.0%)	3 (6.6%)
Gender (M/F)	46 (52%) / 43 (48%)	4 (50%) / 4 (50%)	27 (59%) / 19 (41%)	15 (43%) / 20 (57%)
Survival rate	82 (92%)	8 (100%)	40 (87%)	34 (97%)
Number of neonates (< 28 days*)	62 (70%)	4 (50%)	39 (85%)	19 (54%)
	Median (min - max)	Median (min - max)	Median (min - max)	Median (min - max)
Age at admittance (days)*	1 (0 - 1203)	43 (0 - 1203)	1 (0 - 379)	4 (0 - 895)
Gestational age (days)	262 (201 - 297)	268 (240 - 296)	257 (201 - 297)	269.5 (236 - 290)
Birth weight (grams)	2400 (1130 - 4350)	1920 (1460 - 4350)	2338 (1130 - 4200)	2630 (1475 - 4185)
Birth weight (SDS)[#]	-1.02 (-3.18 - 2.30)	-1.36 (-3.08 - 2.30)	-0.98 (-2.84 - 2.04)	-0.88 (-3.18 - 1.90)
LOS (days)	20 (3 - 499)	14.5 (4 - 17)	37 (15 - 499)	10 (3 - 54)

NA = nutritional assessment, Total: all admitted patients with so-called Index diagnoses, Group A (full protocol): patients with Index diagnosis and all scheduled recordings performed, Group B (partial protocol): patients with Index diagnoses and a fraction of the scheduled recordings performed, Group C (no NA): patients with Index diagnosis but no NA performed, LOS = Length of stay

** age not corrected for prematurity, [#] according to Usher and McLean (J Pediatr; 1969).*[17]

Figure 2 Successful nutritional assessment recordings per week



Children from the study group that had undergone successful nutritional assessment recordings (striped bars) per time point of the protocol, versus those who had not (grey bars).

Study 2: missing values

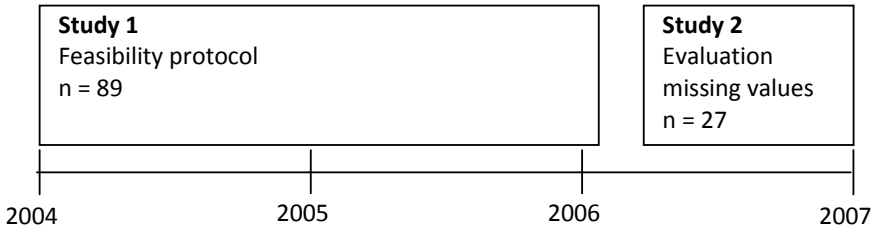
Twenty-seven patients with index diagnoses were enrolled in the second study (Figure 3). Patient characteristics are shown in Table 3. Compared to study 1, children in study 2 significantly more often (p = 0.021) had anal atresia. Other characteristics were not different. Six patients (22%) had not undergone any nutritional assessment; 21 (78%) had undergone some of the scheduled NA recordings, but not all. Related to LOS, 48% of the 93 planned measurements had actually been performed.

Summarizing, 24 assessments (26%) had been missed due to absence of both anthropometrists, 12 (13%) had been missed due to random events associated with ICU admission and 7 (8%) had been missed due to severe illness or instability of the patient (Table 4).

Table 2 Outcome of multiple generalized estimating equations analysis (NA completed at separate time points)

Variable	**Chi-square** (χ^2)	***p*-value**
Time	7.58	0.006
Index diagnosis	1.90	0.862
Age upon admission	0.76	0.383
Survival	0.76	0.382
Length of stay	3.66	0.056

Figure 3 Time frame studies 1 and 2



Time frame indicating the periods in which studies 1 and 2 have been performed.

Table 3 Patient characteristics of studies 1 and 2

Characteristics	**Study 1** n (%) feasibility protocol	**Study 2** n (%) reasons missing values
Index diagnoses	89 (100%)	27 (100%)
Congenital diaphragmatica hernia	11 (12.4%)	5 (18.5%)
Oesophageal atresia	34 (38.2%)	6 (22.2%)
Hirschprung disease	9 (10.1%)	2 (7.4%)
*Anal atresia**	6 (6.7%)*	6 (22.2%)*
Abdominal defect	18 (20.2%)	4 (14.8%)
Bowel atresia	11 (12.4%)	4(14.8%)
Gender (M/F)	46 (52%) / 43 (48%)	14 (52%) / 13 (48%)
Survival rate	82 (92%)	27 (100%)
Number of neonates (< 28 days[#])	62 (70%)	21 (78%)
		Median (min - max)
Age at admittance (days)	1 (0 - 1203)	0 (0 - 365)
LOS (days)	20 (3 - 499)	23 (2 - 112)

** Significant difference in number of patients with anal atresia (p = 0.021)*
[#] age not corrected for prematurity

DISCUSSION

This study has demonstrated that in the present setting, weekly nutritional assessment in children with congenital anomalies of the intestinal tract was not feasible, since in only 15% of the studied 89 children all measurements had been performed according to the proposed frequency. Feasibility was negatively influenced by length of hospital stay, and a major reason for missed measurements was unavailability of the anthropometrists.

Table 4 Study 2: causes of missed measurements

Reasons	**Observed frequency** n (% of total)
Total number of planned measurements	93 (100%)
Successful measurements	45 (48%)
Missed measurements by category:	
A Patient too instable or ill	7 (8%)
B Patient away for examination	3 (3%)
Parental visit	2 (2%)
Patient discharged from ICU	6 (7%)
Patient being nursed	1 (1%)
C No anthropometrist available	24 (26%)
D Measurement failed	0 (0%)
E Index-diagnosis not recognized in time	5 (5%)
Total of missed measurements:	48 (52%)

Feasibility categories: A = disease-related, B = random events during admission, C = lack of personnel, D = feasibility of measurement techniques, E = eligible patients had been overlooked by either the anthropometrists or the attending physicians.

In general, accurate nutritional assessment in children is complex, because of linear growth, changes in energy requirements, varying body composition and (acute) disease.[11] Measurement of body composition provides more detailed information about nutritional status than measurements of height and weight alone, because the body compartments are indicative of nutritional stores.[20] Besides, measurement of weight alone is not reliable as consequence of possible weight shift by third spacing of fluids.[21] In this study we have chosen to use multiple assessment techniques in order to describe the nutritional status as accurate as possible in critically ill children.

A previous study by our research group has demonstrated that while longitudinal reliable assessment of nutritional status, using non-invasive methods (i.e. weight, height, skinfolds) at an ICU is feasible, feasibility decreased for children with more severe illness and higher age upon admission.[12] These findings were reason to recommend implementation of standardized nutritional assessment in order to promote individualization of patient care.[12]

The present study has demonstrated that the feasibility of implementation of this protocol in its current form is merely limited by absence of personnel. This absence is to be explained by the fact that two anthropometrists were available for no more than

0.4 full time equivalent on working days (14 hours per week). In addition, the GEE analysis demonstrated that longer length of stay negatively influences completion of the measurements, which is probably also due to lack of availability of personnel: as hospital stay increases, the protocol requires more measurements and the chances of missing a measurement increase as well. In addition Hulst et al. also reported that feasibility of nutritional assessment was lower during the earlier stages of admission.[12] In our first study, 32 measurements (70%) had not been performed during the first week of admission. This might have been due to acute disease, since patients are in the acute phase upon ICU admission. Study 2 also revealed that 8% of missed measurements were due to illness or instability, while 13% was due to random events associated with hospital admission, such as parental visit or the patient being nursed. Thus, insufficient feasibility cannot be explained by lack of staff only. The near significant increase of feasibility during admission might be explained by increasing health status while children are admitted longer, but this assumption could not be confirmed by the results of the present study.

Reasons for missing values were investigated in the second study only. As background characteristics of patients in both studies did not differ significantly, apart from distribution of diagnoses, we assume that extrapolation to study 1 is allowed. Indeed, proportions of actual recordings did not differ between the cohorts (48% in both groups).

Previous studies on feasibility of nutritional assessment techniques in the critically ill are limited and most pertain to adults. Studies assessing the nutritional status of critically ill children predominantly used weight and height, measured upon admission only.[6,22] Leite et al. performed measurements in critically ill children upon admission, using weight, height and tricipital skinfold measurements and reassessed these measurements at the final follow up in 48% of the initial measurements.[23] Neither of these studies specified numbers of children in whom measurements could not be performed. In our study, when measurements were indeed performed, almost all elements (i.e. weight, height, etc.) could be correctly obtained. This implicates that it is feasible to perform different nutritional assessment techniques in critically ill children.

A decrease in growth rate during infancy is one of the earliest indicators of malnutrition. Therefore a single anthropometric measurement in an individual is not sufficient to monitor growth and/or nutritional status.[13] Another consideration is the error of measurement of a single measurement, and in case of anthropometric equations the prediction error.[13] Therefore, nutritional assessment should be repeated regularly, so as to be able to monitor changes in nutritional status, diagnoses or conditions that might put the child at nutritional risk.[24] In our study, two or more

assessments were performed in 63% of the patients in group B, thus allowing individual follow-up. However measurements were performed at different moments of time per patient, therefore group analysis was not possible.

In summary, in order to improve the frequency of weekly monitoring of nutritional status in critically ill children during ICU hospital stay, trained staff should be structurally available.

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Chapter 4

Enteral nutrition in infants with short bowel syndrome; Current evidence and recommendations for the clinician

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Provisionally accepted, J Am Diet Assoc.

Abstract

The enteral feeding regimen in children with short bowel syndrome is under debate. The purpose of this article is to present an overview of literature data on feeding strategies in children with short bowel syndrome. A structured literature search (up till 1 January 2008) was performed to identify human studies in children directly addressing nutrition (or specified nutrients) in relation to short bowel syndrome. Eight relevant studies were graded by seven experts according to the Scottish Intercollegiate Guidelines Network (SIGN) criteria. This grading system is based on the applied study design and methodological quality of individual studies. Recommendations were made based on the outcome according to SIGN if appropriate and on expert opinion otherwise. Most important recommendations are:

- enteral nutrition should be initiated as soon as possible after bowel resection to promote intestinal adaptation.
- enteral nutrition should be administered in a continuous fashion.
- breast milk or standard polymeric formula (depending on the age) is recommended as preferred type of nutrition.
- bottle-feeding (small volume) should be started in neonates as soon as possible to stimulate the suck and swallow reflexes. Solid food can be introduced at the age of 4-6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behavior.

Conclusion

High-quality research on the preferred types of enteral and oral nutrition in children with short bowel syndrome is scarce. Multi-center prospective studies on the effects of polymeric enteral nutrition on bowel adaptation, fecal production, linear growth and outcome are required to find the optimal feeding regimen in children with short bowel syndrome.

INTRODUCTION

Short bowel syndrome (SBS) is defined as a state of malabsorption secondary to either congenital shortening or massive small bowel resection, which impairs the capacity to maintain an adequate nutritional status and hence may lead to deficiencies of micronutrients and growth retardation.[1,2] The malabsorption is due to the shortened bowel length, which is associated with less absorptive and digestive surface and thus fewer digestive enzymes and transport proteins.[3] In childhood, SBS may result from massive resection of the small intestine necessitated by volvulus, congenital malformations such as intestinal atresia and gastroschisis, or necrotizing enterocolitis.[3-6] The current incidence of SBS in the United States is unknown.[7] In Canada, however, the incidence is estimated at 24.5 per 100,000 live births, the mortality rate at 2 per 100,000 per year.[8]

The clinical manifestation of the disease is determined by the residual length of the jejunum and ileum, the presence of an enterostomy, the presence (or absence) of the ileocecal valve, the remaining functional length of the colon, underlying pathology and possible complications. These factors affect the bowel adaptation process and therefore functionality of the gastrointestinal tract, which in turn effects feeding options. Therefore, recommendations for the type and duration of parenteral and enteral nutrition are variable, with the child's age as an additional key factor. After surgery, initiation of parenteral nutrition is inevitable in order to meet the energy requirements. Some patients will require supplemental parenteral nutrition for a limited period, whereas others remain dependent on parenteral support and ultimately require bowel transplantation.[1,9]

The enteral feeding regimen in children with SBS is under debate. Subjects of debate are mode of administration (continuous or portions), time of introduction, composition (polymeric or semi elemental or elemental), time of introduction and composition of oral feeding, and the supplementation of fibers. Most data on enteral nutrition in children with short bowel syndrome are derived from outcomes of retrospective observational studies and/or case reports.[4]

Systematic research on the onset, type and dose of enteral nutrition in children with short bowel syndrome is scarce. The purpose of this article is to present a structured overview of literature data on feeding strategies in children with short bowel syndrome, including levels of evidence of the individual studies according to the Scottish Intercollegiate Guidelines Network (SIGN). Clinical recommendations are given based on the current literature if possible and on expert opinion otherwise.

METHODS

A structured literature search was performed in Medline, CINAHL and Cochrane databases from 1966 up to and including 2007 with specific search terms (Figure 1). In addition, a hand-search was done for relevant references in the retrieved publications. The goal was to identify all human studies (in clinical setting) in children directly addressing nutrition (or specified nutrients) in relation to SBS. The following key questions were formulated:

1. At what time should enteral nutrition be initiated?
2. How should enteral nutrition be administered?
3. What type of enteral nutrition should be used?
4. At what time should oral nutrition be introduced, and what kind?
5. Should there be a focus on specific macronutrients in the diet?

Literature studies addressing these questions were graded according to the SIGN criteria.[10] This grading system is based on study design and methodological quality of individual studies (Table 1). Seven experts in the field individually determined the levels of evidence of literature on the guidance of a SIGN-checklist. Six experts have vast clinical experience with regard to the patient population and nutritional research in general, and all 7 experts have thorough scientific schooling and experience.

Figure 1 Search terms used in Medline, CINAHL and Cochrane databases from 1966 up to and including 2007

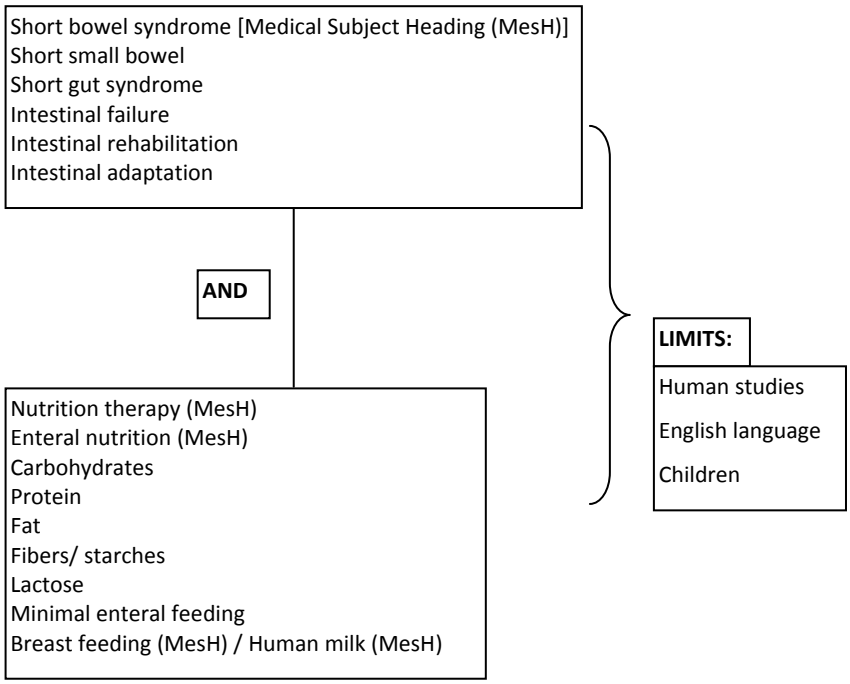

Table 1 Grading according to Scottish Intercollegiate Guidelines Network (SIGN) criteria[10]

Levels of evidence	Requirements
1++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs or RCTs with high risk of bias.
2++	High quality systematic reviews of case-control or cohort studies *or* high quality case-control or cohort studies with very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies eg case reports, case series
4	Expert opinion and/or clinical experience of respected authorities

Each expert individually performed a structured evaluation of the methodological quality of the eligible articles using design-specific checklists provided with the SIGN guidelines.[10] Next, levels of evidence of the separate studies were established in consensus. For each key question, clinical recommendations were made based on the present literature if allowed by the level of evidence (level 1 and 2) or based on clinical experience if this level was insufficient. The first draft of this review was prepared and discussed by all experts.

Definitions

Enteral nutrition is defined as a method of supplying nutrients to the gastrointestinal tract. It refers to breast milk, formulas for premature infants and for infants, pediatric oral feeding and pediatric enteral tube feeding. It can be administered orally, via nasogastric tube, gastrostomy or jejunostomy. Administration can be continuously or in portions. Continuous administration requires the use of an enteral infusion pump. The hourly dose is calculated as the total amount of nutrition required to meet the daily energy requirement divided by the total amount of hours available. The amount per portion is determined by dividing the total amount of nutrition per day by the number of portions used. Minimal enteral feeding is defined as 12 ml/kg/day or < 25 kcal/kg/day during 5 to 10 days in infants.[11] Standard enteral nutrition is a polymeric formula, consisting of mixtures of polypeptides (whole proteins), vegetable oil and carbohydrates (mostly dextro-maltose) and additional vitamins and minerals. Oligomeric (semielemental) or monomeric (elemental) formulas are available as well.

Oligomeric formulas consist of hydrolyzed proteins (oligopeptides and free amino acids), a mixture of vegetable oil (LCTs; long chain triglycerides) and medium chain triglycerides (MCTs) and dextromaltose as source of carbohydrates. The composition of a monomeric formula is similar to that of an oligomeric formula, but its protein source consists of amino acids only.

Due to the expected paucity of eligible studies, the same literature search was repeated for adults with short bowel syndrome. Results of that search are given in the Appendix.

RESULTS

A total number of 8 pediatric studies were identified. Two studies covered the timing of initiation of enteral nutrition.[11,12] Three studies covered type of nutrition.[13-15] One study covered method of administration.[16] No studies were found on oral nutrition. Two studies focused on specific nutrients in relation to SBS.[17,18] An overview is presented in Table 2.

1 At what time should enteral nutrition be initiated?

It is generally accepted that enteral nutrition should be administered as soon as possible after bowel resection, so as to promote intestinal adaptation. A clinical controlled trial (level 1-) demonstrated that, newborns tolerated small volumes of breast milk well, 12 hours after abdominal surgery. The first stool and toleration of full oral feeding occurred earlier and hospital stay was shorter, compared to controls who received oral feeding after resolution of postoperative ileus.[12] The literature agrees on starting enteral nutrition slowly and in small volumes. A systematic review of randomized controlled trials in neonates showed that minimal enteral feeding was associated with less time needed to reach full enteral feeding and with shorter hospital stay (level 1+).[11] Characteristics of the control groups in these trials seemed to be comparable. None described gut function, however, so we cannot exclude that the neonates in the MEF group perhaps had more functional gut, which might have led to better outcomes.

The literature provides no information on the desired time frame for stepping up enteral feeding in children with SBS. A few experts[4,19] recommended gradual increase if the child appeared to tolerate this (level 4). Others advised to adjust volume increases to fecal production and pH and fecal sugar reduction[20,21] (level 4). Vanderhoof et al. suggested that 1 ml/h/day steps can be sufficient to improve tolerance of enteral nutrition (level 4).[20]

Table 2 Summary table of studies on nutrition and short bowel syndrome in children

Question	Type of evidence	Country of origin	Level of evidence	Results
At what time is enteral nutrition initiated?	Systematic review[11]		1+	MEF decreases time to full enteral feeds and hospital stay
	Clinical controlled trial (n = 56)[12]	Turkey	1-	Early postoperative small volume breast milk is well tolerated after abdominal surgery in newborns
Way of administration?	Case series (n = 11)[16]	USA	3	Continuous enteral infusion promotes nutrient retention and weight gain
Type of enteral nutrition?	Randomized controlled trial (n = 10)[14]	Poland	1+	No difference in absorption between polymeric and oligomeric formulas
	Case series (n = 30)[13]	USA	3	Use of breast milk showed high negative correlation with PN duration
	Case series (n = 4)[15]	Australia	3	Oligomeric formulas improve feeding tolerance
Time and kind of oral nutrition?	None			
Focus on specific nutrients?	Case study (n = 1)[17]	UK	3	Pectin prolongs transit time and enhances nitrogen absorption
	Case study (n = 1)[18]	USA	3	Adding green beans and guar gum to diet improves feeding intolerance

Abreviations: MEF: minimal enteral feeding; PN: parenteral nutrition.

Evidence-based recommendations

Enteral nutrition should be initiated as soon as possible (i.e. a few days after bowel resection) to promote intestinal adaptation. This supposition is supported by level 1 literature studies.

Recommendations based on clinical experience

We recommend to gradually increase volumes (e.g. twice a week) by small amounts (e.g. 1 ml/h), so that the bowel is given enough time to adapt to larger volumes. Tolerance of new volumes can be assessed by a) vomiting (> 3 times a day/ > 20% of their daily enteral intake is extensive and indicates non-tolerance) and b) quantity and consistency of stool, pH and sugar reduction of stool. Feeding might be stepped up when quantities and consistency of stool are acceptable, indicating that the child is able to maintain hydration status.

2 How should enteral nutrition be administered?

Various experts recommend continuous administration of enteral nutrition (level 4).[19-22] This is thought to enhance enteral absorption by maximizing saturation of the carrier proteins, thereby increasing intestinal function. According to Vanderhoof and Young, it enhances bowel adaptation, because small quantities of nutrients are delivered over an extended period of time, which enables the nutrients to function as luminal factors. Continuous administration of enteral nutrition also avoids osmotic diarrhea, which can occur with bolus delivery of nutrients.[20] Parker et al. reported that continuous enteral infusion promoted nutrient retention and weight gain in 9 infants with protracted diarrhea and 2 infants with SBS (level 3).[16]

Although unconfirmed, continuous administration has been suggested to prevent osmotic diarrhea that might occur with portion administration.[20] Still, even though the latter resembles the physiologic situation, Goulet et al. found that this is less well tolerated than continuous feeding (level 4).[19]

Evidence-based recommendations

No level 1 and 2 evidence studies are available in the literature.

Recommendations based on clinical experience

Supported by a level 3 study in the literature, we recommend continuous drip when enteral nutrition is started.

3 What type of enteral nutrition should be used?

Breast milk contains high amounts of nucleotides, IgA and leucocytes, which are thought to support the neonate's immune system.[23,24] Breast milk also contains glutamine and growth factors, such as growth hormone and epidermal growth factor

(EGF), which possibly promote bowel adaptation.[4,9] Andorsky et al. showed in a retrospective case series of 30 neonates that the use of breast milk was associated with a shorter duration of parenteral nutrition (PN) (level 3).[13] Mean duration of PN was 290 days in patients receiving breast milk versus 720 days in non-breast-fed patients.[13]

As a consequence of increased bowel permeability due to bowel adaptation, children with SBS are at risk of developing food allergies.[25,26] Goulet et al. recommend oligomeric formulas when breast milk is not available, or when children are intolerant to breast milk, since these formulas are well tolerated (level 4).[19] A few experts advised to use polymeric formula as from the age of 1 or 2 years, respectively, because allergic reactions mostly do not occur after that age (level 4).[4,27] A randomized controlled trial found no difference in absorption between polymeric and oligomeric formulas (level 1+).[14] A small case series, however, found that a monomeric formula improved feeding tolerance (level 3).[15]

The literature described shows a preference for the administration of breast milk in neonates. Otherwise, there is less unanimity on choice of formula. A few studies demonstrated no difference in absorption between polymeric and oligomeric formulas, whereas others found improvement of absorption with oligomeric formulas.

Evidence-based recommendations

There is no difference in absorption between polymeric and oligomeric formulas (level 1+).

Recommendations based on clinical experience

Based on clinical experience we recommend the use of breast milk. This is supported by a level 3 study in the literature. If breast milk is not available, we recommend either a premature infant formula or standard infant formula.

For prematurely born infants with birth weight below 3500 gram, a premature infant formula is recommended. This has higher protein and energy content and thus stimulates weight and height gain. It would seem best to start with a standard polymeric formula in older children; when this is not tolerated, an oligomeric formula should be used.

4 At what time oral nutrition should be introduced, and what kind?

There are no systematic studies available on the timing of introduction and type of oral nutrition in children with SBS. However, a consensus guideline has been published on the importance of starting bottle feeding (small volumes) as soon as possible to stimulate the suck and swallow reflex.[19,20] Solid food can be introduced at the age of 4-

6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behavior (level 4).[4,19-21] The type of solid food depends on age, type of bowel resection, remaining functional length of the bowel and the child's general health. Clinical experience shows that infants and young children will best tolerate high-fat and high-protein meals (level 4).[4,21]

Evidence-based recommendations
No level 1 and 2 evidence studies in the literature are available.

Recommendations based on clinical experience
Based on clinical experience we recommend to start bottle feeding as soon as possible. Oral feeding can be used in alternation with continuous enteral feeding therapy. For example, continuous feeding might be stopped for one hour, and replaced by a one hour dose per bottle. Furthermore, it is important to introduce solid food at the age of 4-6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behavior. It is essential to start solid food at low volumes, because larger volumes might cause diarrhea.

5 Should there be a focus on specific macronutrients in the diet?

Two case studies focused on specific nutrients in children with SBS. One described longer transit time and higher nitrogen absorption when pectin was added to the diet of a 3-year-old boy with SBS (level 3).[17] The other reported a positive effect of adding green beans and guar gum on enteral feeding tolerance in an infant with SBS (level 3).[18]

Evidence-based recommendations
No level 1 and 2 evidence studies in the literature are available.

Recommendations based on clinical experience
In line with the above-mentioned level 3 study we recommend to use dietary fibers at the developmentally appropriate age (starting from age 4 - 6 months).

SUMMARY AND CONCLUSIONS

The route of administration and composition of the diet of children with SBS are best determined on the basis of the underlying disease, location and length of the remaining bowel, presence of the colon, and the child's age. Children with SBS have normal energy requirements. However, due to poor bowel function shortly after resection, they inevitably need parenteral nutrition at first. Gradually, as the remaining bowel adapts, the amount of enterally administered nutrients can be increased. In our

experience, parenteral nutrition will often be needed for a considerable time along with enteral nutrition in order to maintain normal growth.

Enteral nutrition should be initiated as soon as possible (i.e. a few days after bowel resection) to promote intestinal adaptation. This supposition is supported in the literature by level 1 studies.[11,12] Based on clinical experience the best way to increase the volume of enteral nutrition is by twice-weekly adjustments. When higher amounts of enteral nutrition are well tolerated (i.e. no vomiting, no increased volume of diarrhea), the amount of parenteral nutrition can be reduced accordingly. Noteworthily, not all calories of the enteral nutrition are absorbed; therefore parenteral nutrition should not be decreased iso-calorically. It can be recommended to administer enteral nutrition in a continuous fashion. This recommendation is supported by a level 3 study.[16] When half of the energy requirements are provided by enteral nutrition, intermittent administration of enteral nutrition can be started. At a later stage, administration can be in portions during the day and continuously over the night. Gastric feeding is the most physiologic method of administration, but in case of vomiting and/or gastric retention, enteral nutrition can be administered by duodenal or jejunal enterostomy.

Concerning type of enteral feeding, breast milk or standard polymeric formula (depending on the age) is recommended (level 1 and 3 studies).[13,14] When polymeric nutrition is not tolerated, it may be replaced with an oligomeric or monomeric formula. Small volumes of bottle-feeding should be started as soon as possible to stimulate the neonate's suck and swallow reflexes. Solid foods can be introduced at the age of 4 - 6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behavior. When the colon is present, soluble fibers and starches can be added to the diet. Still, it is important to monitor fecal output.

Little systematic research is available on aspects of enteral and oral nutrition in children with SBS. Such studies are difficult to perform, since the incidence of the disorder is low and its manifestation may vary in every patient. Consequently, dietary management is highly variable. Moreover, comparison of existing studies is hampered by differences in definitions of SBS.[8] Multi-center prospective studies on the effects of polymeric enteral nutrition on bowel adaptation, fecal production, linear growth and outcome are required to find the optimal nutritional regimen in children with SBS. At the time of writing, it is not possible to solely base the desired nutritional regimen of children with SBS on evidence obtained from previous scientific studies. Studies focusing on effectiveness of different feeding options in this relatively small patient population are rather scarce and most have relatively low methodological quality. Thus, future

research is needed to provide evidence-based findings that may guide clinicians in the management of these patients.

Suggestions for future research

In general, consensus should be reached on the definition of SBS, so as to reduce heterogeneity of the patient groups. Multi-center studies using the same definition of SBS are needed to increase the sample size.

1. At what time should enteral nutrition be initiated?
   Further randomized controlled trials are needed to confirm the advantages of early (i.e. 1 - 2 days post surgery) (minimal) enteral feeding.
2. How should enteral nutrition be administered?
   Further randomized controlled trials are needed to confirm the advantages of continuous administration mode versus bolus feeding.
3. What type of enteral nutrition should be used?
   Randomized controlled trials are needed to investigate the role of breast milk on bowel adaptation. Moreover, randomized controlled trials are needed to confirm the advantages of breast milk over formula feeding, with enteral tolerance and time to enteral autonomy as endpoints.
4. At what time should oral nutrition be introduced, and what kind?
   Randomized controlled trials are needed to investigate what kind of solid food is best tolerated; for example fresh fruit with peel or vegetables or porridge (of rice cereals) or meat.
5. Should there be a focus on specific macronutrients in the diet?
   Randomized controlled trials are needed to investigate the effect of soluble fibers on enteral feeding tolerance and to investigate the potential benefits of MCTs (improved fat absorption) in SBS patients with an intact colon.
   Finally, randomized controlled trials are needed to study effectiveness of lactose-free formula vs. standard formula.

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APPENDIX – RESULTS IN ADULTS

The literature search described in the manuscript was repeated for studies in adults. Studies on glutamine and/or growth hormone and diet were excluded, as in those studies the effect of diet was not the main objective.

Ten relevant studies were identified. One study covered the initiation of enteral nutrition.[1] Two studies covered the type of nutrition.[2,3] No studies were found on method of administration Seven studies focused on specific nutrients in relation to SBS.[4-11] Main characteristics and outcomes of these studies and their levels of evidence are presented in table A1.

1 At what time should enteral nutrition be initiated?

Case series in adults with SBS showed that enteral autonomy can be attained as early as 36 days (mean) after surgery (level 3).[1]

2 How should enteral nutrition be administered?

In the above-mentioned case series continuous enteral nutrition was started early (mean of 14 days after surgery), and parenteral nutrition was stopped after a mean of 36 days (level 3).[1]

3 What type of enteral nutrition should be used?

Contradictive findings concerning the type of nutrition were also found in adult studies. A clinical controlled trial in 7 adults with a high jejunostomy revealed no difference in absorption between polymeric and oligomeric formulas (level 1-).[2] A small randomized controlled trial in adults with high jejunostomy demonstrated, however, that nitrogen absorption improved with an oligopeptide diet (level 1+).[3]

4 At what time should oral nutrition be introduced, and what kind?

No studies were found on this subject.

5 Should there be a focus on specific macronutrients in the diet?

Seven studies focused on specific nutrients.

A randomized controlled study demonstrated that a diet containing high concentrations of MCTs in patients with a jejuno- or ileostomy can cause osmotic diarrhea as a result of rapid hydrolysis of MCTs (level 1-).[6] In contrast, MCTs improved fat absorption in patients with an intact colon.[6]

Carbohydrate modules consist mostly of the polysaccharide dextromaltose. A high load of carbohydrates (mainly mono-/disaccharides) might cause diarrhea (level 4).[12]

Vanderhoof et al. claimed that restriction of the overall enteral carbohydrate load is beneficial in reducing the osmotic load and decreasing substrate for bacterial overgrowth.[12]. We did not find other studies to support this theory. A clinical controlled trial showed that neither a high fat diet nor a high carbohydrate diet were beneficial to the overall absorption (level 1+).[4] Another study demonstrated that a high fat diet did not influence the volume of jejunostomy output compared to a high carbohydrate diet (level 1-).[7]

Lactose-intolerance might occur in patients with proximal jejunum resection. Still, a cross-over study in adults with SBS demonstrated similar tolerance of a lactose-free diet and a diet containing 20 grams lactose a day (level 2+).[8] A comparable study in adults with SBS showed that lactose in the form of yogurt was better absorbed than lactose in the form of milk (level 2+).[9]

Soluble non-starch polysaccharides and some other starches (i.e. in bananas and potatoes) are generally not absorbed by the small bowel. They pass undigested into the colon where colonic bacteria ferment them into short chain fatty acids (SCFAs), which are an important source of energy.[13] They are estimated to account for 5 - 10% of the total energy requirements (level 4).[14] SCFAs may stimulate sodium and water absorption and therefore decrease fecal output (level 4).[11,15] In a descriptive case series, Royall et al. showed that adults with SBS and intact colon malabsorbed approximately 48% of the 50 gram ingested carbohydrates, which were fermented in the colon (level 3).[10] A case series in adults with SBS found that patients with intact colon on a high carbohydrate diet showed significantly less fecal loss of energy than those on a diet high in fat (level 3); no difference in fecal energy loss was observed in patients without a colon.[11] Carbohydrate malabsorption may be reason to restrict mono-/disaccharide intake.

The studies above showed that soluble fibers and starches could be added to the diet when the colon is present and that a diet containing MCTs might improve fat absorption. Still, it is important to monitor fecal output. In general, a lactose-free diet is not necessary.

Table A1 Studies on nutrition in adults with short bowel syndrome

Question	Type of study	Country of origin	Level of evidence (SIGN criteria)[16]	Results
At what time should enteral nutrition be initiated?	Case-series (n = 62)[1]	France	3	Early enteral autonomy can be attained when continuous enteral nutrition started early
Way of administration?	No results			
Type of enteral nutrition?	Randomized controlled trial (n = 7)[2]	UK	1-	No difference in absorption between polymeric and oligomeric formulas
	Randomized controlled trial (n = 6)[3]	France	1+	Oligomeric formulas improve feeding tolerance
Time and kind of oral nutrition?	No results			
Focus on specific nutrients?	Randomized controlled trial (n = 19)[6]	Denmark	1-	Only patients with colon gain from MCT diet
	Randomized controlled trial (n = 5)[7]	Denmark	1-	High fat diet does not influence the jejunostomy output compared to a high carbohydrate diet
	Clinical controlled trial (n = 8)[4]	Canada	1+	Neither a high fat diet nor a high carbohydrate diet were beneficial to the overall absorption
	Cohort (n = 14)[8]	France	2+	No difference in tolerance between lactose free diet and lactose containing diet
	Cohort (n = 17)[9]	Switzerland/ France	2+	Patients without colon absorbed lactose in form of yoghurt better than in form of milk
	Case series (n = 14)[11]	Denmark	3	High carbohydrate diet reduces fecal loss of energy in patients with colon compared to high fat diet
	Case series (n = 12)[10]	Canada	3	Patients with a colon malabsorbed 48% of 50 g carbohydrate which was fermented in the colon

Levels of evidence according to the SIGN criteria.[16]

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Chapter 5

Long-term impact of infantile short bowel syndrome on nutritional status and growth

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Submitted.

Abstract

Objective
Evaluation of long-term consequences of infantile short bowel syndrome (SBS).

Summary background data
Short-term bowel adaptation has been documented, but data on long-term effects are scarce.

Methods
Cross-sectional assessment (2005 - 2007) of growth, nutritional status, defecation pattern and health status in individuals with a history of infantile SBS, born between 1975 and 2002. Data are compared with reference values of healthy controls and presented as mean (SD) or median [minimum-maximum].

Results
Forty patients (16 male and 24 female; mean age 14.8 ± 6.8 years) had received parenteral nutrition during a median of 110 [43 - 2345] days, following small bowel resection. Children 's mean SD-scores for weight for height and target height were normal, mean SD-score for height for age was -0.9 ± 1.3. Adults' median BMI was 19.9 [17 - 26] kg/m^2, mean SD-score for height for age was -1.0 [-2.5 - 1.5]. Height in general was significantly shorter than target height, and 53% of children and 78% of adults were below target height range. Most subjects had normal body fat percentage. SD-scores for total body bone mineral density were generally normal. Children's SD-scores for bone mineral content were -1.0 (1.1). Mean energy intake was 91% of the estimated average requirements. Subjects' frequencies of defecation and bowel complaints were significantly higher than in healthy controls.

Conclusions
Infantile SBS results in shorter stature and low bone mineral content, but normal weight for height and body fat percentages.

INTRODUCTION

Short bowel syndrome (SBS) is a condition characterized by an increased intestinal transit time, leading to diarrhea and malabsorption of nutrients and potentially growth retardation. The most frequent underlying diagnoses in neonates are necrotizing enterocolitis (NEC), volvulus, intestinal atresia and gastroschisis.[1,2]

Bowel adaptation starts shortly after bowel resection and may last 1 - 2 years, during which nutrient absorption is relatively inadequate.[3]

Improved care has led to increased survival rates of infants with SBS, but little information is available on the long-term impact of infantile SBS on growth and physical development. Short stature has been reported,[4] as well as delayed onset of puberty.[5] The latter, however, is generally associated with chronic malabsorption, and with growth delay and the pubertal growth spurt.[6] Chronic illness with malabsorption also has a negative effect on bone maturation as documented in children with inflammatory bowel disease.[7,8]

The aim of this cross-sectional study was to evaluate the long-term effects of infantile SBS on growth, nutritional status, defecation pattern and dietary intake.

METHODS

Population

Children with SBS were identified from the hospital's medical databases and charts as reported elsewhere.[9] All surviving children or adults with infantile (≤ 1 year of age) SBS treated in their first year of life in the Erasmus MC-Sophia Children's Hospital between January 1975 and January 2003 were asked to participate. Patients with psychomotor retardation due to additional anomalies were excluded, because most measurements cannot reliably be performed.

Definition of Short bowel syndrome

The definition of SBS used in this study was that the one formulated by the Dutch committee on intestinal failure:

- > 70% resection of the small bowel,[2,10] and/or
- parenteral nutrition needed for longer than 42 days after bowel resection,[11-14] and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a premature (gestational age 27 - 36 weeks) and < 75 cm for a term neonate.[15,16]

Subjects and parents received written information on the study design, and written informed consent from the parents for subjects younger than 18 years and separately from subjects older than 12 years of age were obtained. The study protocol was approved by the Erasmus MC Ethical Review Board.

Study design

In this single-centre, cross-sectional study all diagnostic measurements concerning subject's growth, nutritional and dietary status were performed during a single outpatient visit in the period from November 2005 until August 2007. Measurements were performed by a dietician (nutritional assessment, dietary intake), physician (general health examination) or nuclear laboratory technician (DEXA-scan).

Clinical characteristics during the first year of life

Demographics such as date of birth, sex, underlying diagnosis leading to SBS, gestational age and birth weight were collected retrospectively. Surgical reports were searched for presence of the ileocecal valve (ICV) and the remaining small bowel length, measured distally to the ligament of Treitz. Percentage of remaining small bowel length was calculated from predicted bowel length for gestational age.[15] Number of operations in the first year of SBS was counted. The number of central venous catheter (CVC) (re)placements as a consequence of occlusion, thrombosis or sepsis was also recorded. Length of stay (LOS) and parenteral nutrition (PN) duration were derived from data for the entire follow-up period (> 1 year) until October 2007.

Dates of start and end of minimal enteral feeding (MEF)[9,17] and enteral nutrition (EN) were collected. Type of nutrition was classified as breast milk, polymeric or semielemental. Numbers of interruptions of EN, necessitated by inadequate passage through the gastrointestinal tract, were counted.

Detailed information on growth and nutrition in these patients' first year of life has been published elsewhere.[9]

Measurements

Subjects were asked not to eat or drink within two hours before measurement and to refrain from strenuous exercise on this day.

Height and weight

Body weight was recorded to the nearest 0.1 kilogram (kg) using an electrical scale (Seca Alpha 770, Hamburg, Germany). Height was measured to the nearest 0.1 centimetres (cm) using a stadiometer (Stanley Mabo, London UK). The parent's height was measured in the outpatient clinic if possible or by their general practitioners. The

subject's Target Height (TH) was calculated as [(fathers height + mothers height ± 13) / 2] + 4.5 centimetres. Target height range (THR) was defined as TH-SDS ± 1.3 SDS. In adults the Body Mass Index (BMI) was calculated using weight (kg)/height (m)^2.

Skinfolds

Skinfold thickness in the biceps, triceps, subscapular and supra-iliac region was measured three times[18] to the nearest 0.1 millimetres (mm) with a Harpenden calliper (John Bull, England) on the non-dominant side of the body, and the mean value was calculated. Body fat percentage was calculated from the sum of four skinfold measurements in children[19] and in adults[20] using group-specific equations. Skinfold measurement is a cost-effective and non-invasive nutritional assessment method with reasonable accuracy.[21]

Dual-Energy X-ray absorptiometry (DEXA)

Total body DEXA was performed using a Lunar-Prodigy (GE Healthcare, Wisconsin, USA) scanner in order to determine bone mineral density (BMD, g/cm^2) of the lumbar spine (ls) and total body (tb). Total body DEXA also measured bone mineral content (BMC, grams) and lean body mass (LBM, grams), with percentage body fat (%BF) given for total tissue mass. Many studies found DEXA to be a good reference method for nutritional assessment, due to its high correspondence with outcome of isotope dilution techniques.[21-23]

Children's values of BMDls, BMDtb, BMC, LBM and %BF (measured with DEXA) were compared to Dutch reference data, depending on age and sex[24] and expressed in standard deviation scores (SDS). Adult values of BMDls and BMDtb were compared to reference values delivered by the manufacturer and expressed in SDS.

Furthermore measurements of skinfolds were compared to measurements of DEXA in children to examine the inter-relationship.

Dietary intake

Prior to the outpatient visit, subjects were asked to record quantities of foods and beverages consumed during one weekend day and two weekdays. During the outpatient visit, a trained dietician cross-checked the records and asked the subjects to specify entries if necessary and add missing items or amounts. The dietary intakes were compared to the recommended daily allowances (RDA) for children and adults and when appropriate, to estimated average requirements (EAI), depending on age and sex.[25,26]

Defecation pattern

The defecation pattern was determined by a self-developed questionnaire based on the symptom checklist of Poley et al.[27] It comprised stool frequency, subjects' self-estimated quantity of stool, the Bristol stool form scale[28] and applicable symptoms from the Rome II criteria,[29] such as bowel cramps, flatulence and bloating. Since control data were not available, the questionnaire was additionally filled out by age- and gender matched healthy controls, recruited through schools and the university in Rotterdam.

Current Health Status and Tanner stages

General medical, neurological and pubertal development[30] was examined by a physician. For patients in puberty, delay in puberty was determined by comparing Tanner stage and age with reference data of Dutch children.[31] Blood pressure (expressed in mmHg) and heart rate (bpm) were measured once by Dinamap Procare (GE Healthcare, Waukesha, Wisconsin, USA). Values were compared to reference data.[32]

Statistical analysis

Group size was not based on a formal power analysis. The incidence of SBS in the Netherlands is unknown, but from clinical experience is judged to be relatively low. We therefore aimed at including all patients with SBS admitted to our hospital between 1975 and 2003. Descriptive statistics (frequencies, mean, median, SD and minimum and maximum) were calculated. The patients were stratified in two age groups: 5 - 18 years (children) and over 18-year-olds (adults); and differentiated by sex.

Kruskal-Wallis tests and chi-square tests served to identify differences between the study group and all eligible patients. Cystic fibrosis (CF) itself might be associated with impaired growth; therefore data for the whole study group were compared by appropriate tests to data for a subgroup excluding patients with CF.

Values of weight, height, TH and skinfolds were compared to national standards[33-36] and expressed in standard deviation scores (SDS), depending on sex, age and race (Growth Analyser version 3, Dutch Growth Foundation, Rotterdam, the Netherlands).

Bland & Altman plots were used to assess the agreement between outcomes of skinfold measurements and DEXA.[37] One-sample *t*-tests were performed to compare the mean SDS values to normal values. Means were compared using paired *t*-tests. When data were not normally distributed, median values were compared using the Wilcoxon-Rank test or chi-square test. The level of significance was set at 0.05.

RESULTS

Of the 72 eligible subjects, 32 did not participate in the study because either they did not give informed consent (n = 15) or could not be located (n = 17) (Figure 1). Kruskal-Wallis tests and chi-square tests identified no differences in underlying diagnoses, sex, age, percentages of premature birth or length of remaining bowel between the groups "included", "no informed consent" and "not located" (data not shown).

Thus, forty subjects (16 males and 24 females) with mean age 14.8 ± 6.8 years participated in the study. Underlying diagnoses were normally distributed and are shown in Table 1. Other diagnoses were long-segment Hirschsprung disease (n = 1) and ischemic small bowel of unknown origin (n = 1). Parenteral nutrition (PN) had been given for a median period of 110 (43 - 2345) days and all subjects were weaned off PN by time of measurement. The clinical characteristics representing the first year of life are presented in Table 1.

Growth

Weight and height are presented in Table 2. Mean age of the children (12 m, 19 f) was 11.8 ± 4.2 years. Their mean weight for age and height for age were significantly lower than reference values (p = 0.005 and p = 0.001 respectively). Mean weight for height and mean Target Height were normal. Mean Height for age was significantly (p = 0.000) lower than Target Height. Fifty-three percent were below their target height range.

Due to the small number of adults the results are presented in median [minimum-maximum]. Median age of the adults (4m, 5f) was 24.9 (21.8 - 29.7) years. Median BMI and weight for height were normal. Median height for age was significantly lower than Target Height (Z = -2.68, p = 0.008). Seventy-eight percent were below their target height range.

Figure 1 Flow chart

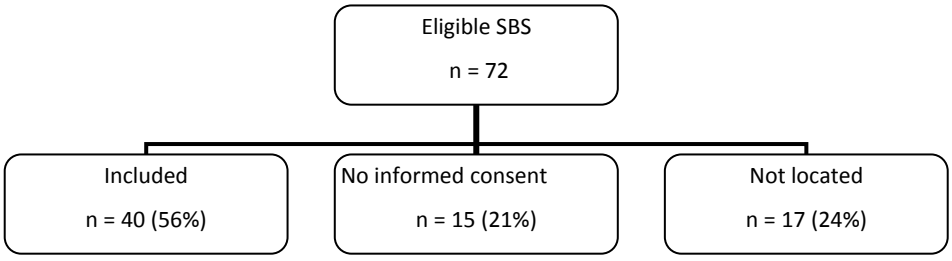

Table 1 Clinical characteristics first year of life

	n = 40 (100%)
Underlying 1st diagnosis SBS	
Small bowel atresia	14 (35%)
NEC	8 (20%)
Volvulus and/or malrotation	6 (15%)
Meconium peritonitis with CF	4 (10%)
Gastroschisis[1]	3 (7.5%)
Meconium peritonitis no CF	3 (7.5%)
Other	2 (5%)
Sex M / F	16 (40%) / 24 (60%)
Number of prematures (GA ≤ 36 wks)	23 (58%)
Gestational age (weeks) Mean (sd)	35.3 (4.2)
Birth weight (grams) Mean (sd)	2270 (898)
Birth weight (SDS) Mean (sd)	-0.7 (1.5)
LOS first admission (days) Median (min-max)	137 (13 - 552)
Number of hospital admittances in first year of SBS median (range)	1 (0 - 8)
Age initial date SBS (date surgery leading to SBS) (days)	3 (0-270)
Length residual small bowel (cm) Mean (sd) n = 28	70.8 (23.5)
% SB remaining Mean (sd)	26.5% (8%)
Presence ICV (yes/ no)	33 (83%) / 7 (17%)
Number of operations (ex central lines)	3 (1 - 7)
Duration PN (days)	110 (43 - 2345)
Number of central catheters used in 1 year	2 (0 - 8)
Start MEF (days)	11 (3 - 74)
Start enteral nutrition (days)	26 (6 - 110)
Type EN	
Breast milk	4 (10%)
Semielemental	28 (72%)
Polymeric	7 (18%)
Number of interruptions EN	3 (0 - 8)

[1] *one patient lost more bowel at the age of 11 years as result of strangulation and underwent a Bianchi procedure at the age of 12 years and was measured at 16 years.*
NEC: necrotizing enterocolitis, CF; Cystic Fibrosis, M; male, F; female, GA; gestational age, SDS; standard deviation score, LOS; Length of stay, SBS; short bowel syndrome, SB; short bowel, ICV; ileocecal valve, PN; Parenteral nutrition, MEF; minimal enteral feeding, EN; enteral nutrition.

Body composition

For children, the mean of the sum of 4 skinfolds was -0.9 ± 1.0 SDS. Their mean BMC (-1.0 ± 1.1 SDS) and mean LBM (-1.2 ± 1.0 SDS) were significantly lower than reference values (p = 0.000). Only the mean BMD of the lumbar spine (-0.47 ± 1.2 SDS) was significantly lower than reference values (p = 0.036).

In adults BMDls and BMDtb did not differ significantly from reference values. SD-scores of BMC, LBM and %BF of adults could not be calculated for lack of appropriate reference values. Table 3 reports the bone composition of all patients as measured by DEXA.

Table 2 Weight and height

	Children n = 31 mean (sd)	**Adults** n = 9 median [min - max]
Age (years)	11.8 (4.2)	24.9 [21.8 - 29.7]
Gender (F/M)	19 (61%) / 12 (39%)	5 (56%)/4 (44%)
Weight for age (sds)	-0.7 † (1.2)	
BMI		19.9 [17 - 26]
Weight for height (sds)	0.1 (1.0)	-0.5 [-2.1 - 1.5]
Height for age (sds)*	-0.9§ (1.3)	-1.0 [-2.5 - 2.0]
Target Height (sds)*	0.3 (1.1)	0.5 [-0.8 - 2.3]

*BMI; body mass index, * significant difference between Height and Target Height (p = 0.000) in children and p = 0.008 in adults, † significantly lower than reference value (p = 0.005), § significant lower than reference value (p = 0.001).*

Table 3 Bone composition measured by DEXA

	Children n = 31 mean (sd)	**Adults** n = 9 median [min-max]
BMDtb (sds)	-0.04 (1.4)	-0.1 [-1.0 - 1.8]
BMDls (sds)	-0.47 (1.2)#	0.0 [-1.5 - 2.5]
%BF (sds)	0.36 (0.73)	
LBM (sds)	-1.21 (1.2)#	
BMC (sds)	-1.0 (1.1)#	

 # significantly lower than reference values p < 0.05
BMDtb; Bone mineral density total body, BMDls; Bone mineral density lumbal spine, BF; body fat, LBM; lean body mass, BMC; bone mineral content.

Body fat percentages calculated from DEXA and skinfold measurements are shown in Table 4. Three of the 4 adult males and 5 of the 11 male children had body fat percentages below 10%, indicating malnutrition. All females but one had normal (15 - 25%BF) body fat percentages.

The limits of agreement of %BF for the 2 methods in children are shown in Figure 2. Skinfolds underestimated %BF with 4.1% (CI 1.97 - 6.23). Paired sample *t*- tests showed significant differences in means between %BF measured by skinfolds and %BF measured by DEXA ($p = 0.001$).

Table 4 Body composition

	Sum of 4 skin folds		DEXA	
Body fat (%)				
children				
male (n = 11)	11.8 (2.5)	[8.9-17.3]	12.6 (6.1)	[7.0-30.0]
female (n = 17)	15.5 (2.6)	[11.9-21.6]	23.0 (7.7)	[12.4-40.2]
adults				
male (n = 4)	4.2	[3.3-16.1]	7.7	[5.7-36.1]
female (n = 5)	20.7	[16.6-23.0]	26.0	[24.5-34.5]

Mean (sd) [min - max] in children and Median [min - max] in adults.

Dietary intake

Dietary intakes are shown in Table 5. Mean energy intake was 2107 ± 581 kcal, which is 91±28% of the estimated average requirements (EAR). Seventeen subjects (45%) had a caloric intake more than 10% below EAR; six (17%) had a caloric intake more than 10% above EAR. Four subjects (10%) were using enteral supplements (i.e. tube feeding). Nineteen (50%) had a dietary calcium intake more than 10% below RDA.

Defecation pattern

The results of the questionnaire are presented in Table 6. Stool frequency for all subjects (median 2 [0.3 - 7] per day) was significantly higher than that in the healthy population (median 1 [0.3 - 5]; $p = 0.000$). Thirty-five percent reported abnormal stool form (type 1, 6 and 7 of Bristol stool form scale) versus 2% of the healthy population. Subjects self-estimated stool quantity was significantly ($p = 0.014$) higher than that for the normal population and they also reported significantly more complaints such as bowel cramps, bloating and flatulence ($p < 0.05$).

Figure 2 Bland-Altman plot %BF skinfolds and DEXA

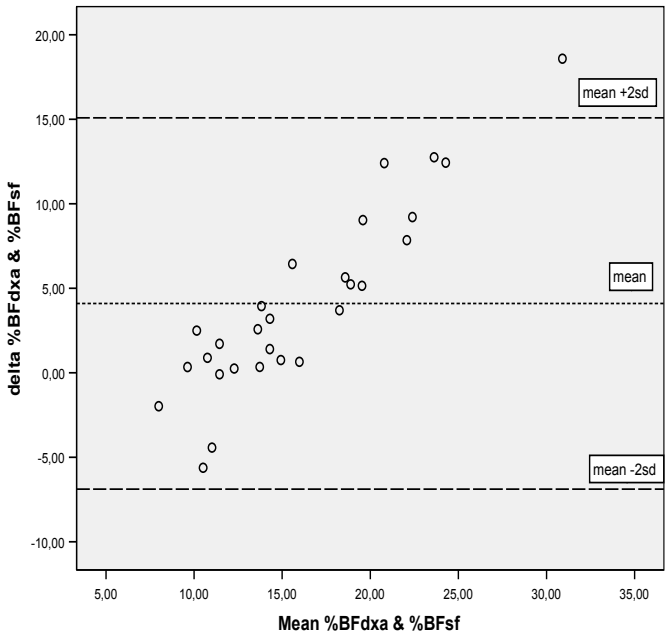

Table 5 Dietary intake

Dietary Assement	**Total group** n = 38	**Children** n = 29 mean (sd)	**Adults** n = 9 median [min - max]
Energy (kcal)	2107 ± 581 [1058 -3654]	2113 (258)	1805 [1210 - 3566]
Energy (%EAR)	91 ± 28 [42 - 160]	95 (26)	65 [49 - 146]
Protein (g/day)	73 ± 20 [44 - 126]	72 (19)	68 [44 - 123]
Protein (%RDA)	193 ± 76 [71 - 339]	212 (76)	128 [71 - 202]
Fat (en%)	34 ± 5 [23 - 45]	35 (5)	31 [26 - 41]
Fat (%RDA)	85 ± 13 [59 - 112]	87 (13)	79 [66 - 103]
Carbohydrate (en%)	51 ± 7 [34 - 65]	51 (6)	50 [34 - 60]
Carbohydrate (%RDA)	124 ± 18 [85 - 162]	124 (16)	124 [85 - 151]
Calcium (%AI)	Median 91 [34 - 221]	Median 98 [53 - 221]	80 [34 - 142]
Vitamin D (%AI)	Median 96 [28 - 1340]	Median 92 [28 - 1340]	116 [40 - 160]

EAR: estimated average requirements, RDA: recommended daily allowance, AI: adequate intake.

Table 6 Defecation pattern

	Subjects (n = 40) Mean age 14.8 ± 6.8 years 16m/24f %	**Healthy controls** (n = 322) Mean age 12.9 ± 5.1years 135m/187f %	**p-value**
Bristol stool form scale			0.000
Type 1	0	1%	
Type 2	8%	4%	
Type 3	37%	63%	
Type 4	15%	28%	
Type 5	5%	3%	
Type 6	32%	1%	
Type 7	3%	0	
Aspect stool			0.000
Normal	63%	95%	
Contains mucus	15%	0	
Contains blood	0	1%	
Contains undigested material	15%	2%	
Different	7%	2%	
Quantity stool per movement			0.014
< 50 grams	10%	17%	
100 - 200 grams	73%	79%	
> 500 grams	17%	4%	
Bowel cramps			0.000
Never	3%	17%	
Sometimes	45%	63%	
Often	35%	16%	
Always	18%	4%	
Flatulence			0.041
Never	7%	21%	
Sometimes	53%	52%	
Often	33%	20%	
Always	7%	8%	
Bloating			0.000
Never	28%	58%	
Sometimes	59%	35%	
Often	10%	6%	
Always	3%	1%	

Current health status and Tanner stages

Most children had Tanner stages corresponding with their age.

One girl was in early puberty (age 9 years, Tanner stage 2) and two girls had delayed puberty (15 and 17 years old and both in Tanner stage 3). Most subjects had normal heart rates and blood pressure (data not shown). Standard neurological examination by the physician revealed no neurological problems.

Measurement results for the whole group did not differ from those for the subpopulation excluding subjects with CF (data not shown). Subjects with CF were in the same range as those with other underlying diagnoses.

DISCUSSION

Increasing concern about morbidity following infantile bowel resection has resulted in intestinal rehabilitation programs in different institutions.[38-43] Multidisciplinary data on long-term outcomes in patients with infantile SBS are still scarce, however. The present study was conducted to add to the knowledge on nutritional status and growth parameters after infantile SBS. More than half of the children and three quarters of adults had not reached their target height range. Weight in general was normal for height and most subjects had normal percentages of body fat. Lean body mass and bone mineral content evaluated by DEXA were significantly below reference values.

Recently we reported that the SD-scores for weight for age in these subjects' first year of life were subnormal and had even declined significantly in the second and third quarterly terms.[9] From the results of the present study it can be concluded that weight for age seems to revert to normal on the long run. SD-scores for height for age had also improved over the years, but still were significantly below reference values and target height. In contrast, Goulet et al. reported that the final height in 57 children after 16 years follow-up generally was not different from their target height.[44] As a possible explanation, Goulet et al. used Tanner's formula (1970) for calculation of target height, which typically yields heights 4.5 cm shorter than those resulting from the calculation method we used (Dutch growth study 1997). Some other studies also found short stature (defined as < 50th percentile of height for age) in 60% to 90% of children with SBS after weaning from PN.[45-47] In contrast, several studies reported normal growth for most subjects.[48-50] The conflicting data seem to arise from differences in reference populations, definitions of short stature, and moments of measurement.

The children in the present study showed reduced bone mineralization only in the lumbar spine, which seems to suggest that only the trabecular bone, which is predominant in the lumbar spine, was affected.[51] In contrast to children, the BMD of

the lumbar spine for the adults was normal. Leonberg et al. also found subnormal BMC values, i.e. in 4 out of 9 children with SBS.[50] These values were established by single-photon absorptiometry in the forearm using other reference values[52] than we used. Dellert et al. did not find subnormal BMC after adjusting the values for weight and height, but did when adjusting for age.[53] It is not easy to compare results, as these researchers used another type of DEXA (Hologic) and studied two age, sex and race matched controls per subject. Moreover, these controls were significantly heavier and taller than the children with SBS[53] – a finding most likely explained by either malabsorption or prolonged inadequate dietary intake in the subjects.[54] The differences in BMC when control subjects and patients with SBS were matched for age is an indication for some sort of nutrient deficiency.[54] This is also seen in patients with inflammatory bowel disease.[7] Differences in BMC may reflect differences in either bone size or bone density.[55] Ahmed et al. suggested that children with IBD often have small bones for age as result of growth retardation.[55] When they interpreted DEXA data adjusted for bone size, bone mass was generally found to be adequate.[55] It seems therefore that low BMC values in our study can partially be explained by the subjects' short stature with its inherent small bones.

Haderslev et al. found that PN-independent adults (mean age 50.6 years) who had undergone bowel resection a mean 11 years ago had lower weight and mainly lower %BF compared to reference values.[56] This holds true for only 9 (22%) of the subjects in the present study. Most of the children and female adults had normal weight for height and %BF. Two other studies also found normal weight for height and %BF.[49,50]

The present study showed wide limits of agreement between outcomes of DEXA and skinfold thickness measurements, which indicates that these methods are not interchangeable. This finding is consistent with prior studies.[57-60] Skinfold thickness measurements are based upon two assumptions. First, the thickness of subcutaneous adipose tissue reflects a constant proportion of total body fat; secondly, the sites selected for measurement represent the average thickness of subcutaneous adipose tissue.[61] Moreover body composition measured by skinfold thickness is based on a two-compartment model; fat free mass and fat mass. DEXA is based on a three-compartment model; bone mineral content, lean body mass and fat mass. The predictive equations used to calculate the body composition in this study were developed and validated in healthy individuals, which might explain the wide levels of agreement. We have to realize that the degree to which subcutaneous adipose tissue reflects total body fat mass may change with age, sex, race and disease.[59,62,63] It would seem, therefore, that DEXA is to be preferred.

The subjects' mean reported dietary intake was lower than their average estimated intake. Dietary intake is difficult to measure and it is easily under or overrated.[64] Protein intake was high compared to RDA, but similar when compared to a Dutch food consumption survey.[65] Moreover 50% of the patients had a dietary calcium intake 10% below the RDA. These results might be skewed, because oral supplementation of calcium supplements (i.e. calcium carbonate) was not taken into account. Assuming that the dietary records truly reflected dietary intake over the previous years, the lower dietary intake might explain the subjects' shorter stature and lower values of BMC.

Several studies showed that the Bristol stool scale form is correlated with whole gut transit time and can be used to monitor change in intestinal function.[28,66-69]
The subjects in the present study reported higher frequency of stools than that reported by healthy aged-matched controls, and 35% had abnormal stools, which might indicate malabsorption and can partly explain lower BMC values. Moreover, they appeared to have significantly more often complaints such as bowel cramps, bloating and flatulence. The questionnaire was designed to ask what their normal bowel habits were and we realize that this does not describe the bowel habits and changes over time. It does reveal, however, that SBS is associated with intestinal bowel dysfunction on the longer term.

The present study has limitations in its cross-sectional design, which causes age-differences, in the absence of a functional test to determine the actual absorptive function of the bowel, and in the absence of a hand x-ray to determine bone age. Moreover, subjects were identified from medical records and eligible patients could have been missed. Finally, the group is heterogeneous with respect to underlying diagnosis and remaining bowel lengths, which nevertheless is inherent to short bowel syndrome.

On the other hand, the study covered a long period, from 5 years to 30 years after infantile SBS. This enabled us to describe the natural history of SBS into adulthood. As another strength, we used a unique combination of parameters to determine a broad spectrum of long-term effects in a relatively large group of patients.

CONCLUSION

Subjects in this study had shorter stature, low BMC, but normal weight for height and percentages of body fat. This might be explained by the low energy-intake and intestinal bowel dysfunction reported. These results show that continuing follow up into adulthood is important even after subjects have reached nutritional autonomy. This way, low energy intake and intestinal bowel dysfunction might be identified early,

enabling prevention of short stature by targeted nutritional management. Measurement of body composition is an essential aspect of providing optimal nutritional management and should preferably be done by DEXA.

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Chapter 6

Impact of infantile short bowel syndrome on long-term health-related quality of life

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Submitted.

Abstract

Objective

To determine health-related quality of life (HRQoL) in children and adults with a history of infantile short bowel syndrome (SBS) compared to that of same-aged healthy controls.

Methods

Cross-sectional assessment (2005 - 2007) of health-related quality of life in individuals with a history of infantile SBS, born between 1975 and 2002, using generic HRQoL measures. Children aged 5 - 18 years and their parents filled out the PedsQI™ and adults aged 19 years and older the SF-36.

Results

Thirty-one children (19 female and 12 male; mean age 11.8 ± 4.2 years) and 9 adults (5 female and 4 male; median age 24.9 years) participated. These children and their parents reported significantly lower HRQoLs than healthy children and their parents ($p < 0.05$). These adults scored significantly lower than the healthy controls in the domains "General Health" and "Vitality" ($p < 0.05$). On the other domains the adult patients obtained relatively low scores, but differences did not reach statistical significance.

Conclusion

Individuals with a history of infantile short bowel syndrome have a lower quality of life than the healthy population. This finding suggests a need for targeted interventions to address these dimensions of impaired HRQoL.

INTRODUCTION

Short bowel syndrome (SBS) is a condition characterized by increased intestinal transit time, leading to diarrhea and malabsorption of nutrients and potentially to growth retardation. Most frequent underlying diagnoses of SBS in neonates are necrotizing enterocolitis, volvulus and congenital malformations such as intestinal atresia and gastroschisis.[1-4] The incidence of SBS in the Netherlands is not known, but clinical experience suggests it is relatively low. In Canada the incidence is estimated at 24.5 per 100,000 live births, the mortality rate 2 per 100,000 per year.[5]

Survival rates of patients with SBS have increased, and now range from 53% to 94%.[6-11] Major predictors of mortality in pediatric SBS are parenteral nutrition(PN)-associated cholestasis and age-adjusted remaining small bowel length. The latter factor is a major predictor too, of weaning from PN, and so is presence/absence of the ileocecal valve.[12] With increasing survival rates, morbidity of the survivors has become more important. Therefore, overall survival is no longer regarded as the only endpoint when considering the effectiveness of medical intervention. An equally essential endpoint is quality of life.[13] Quality of life is hard to define and even harder to assess, especially in younger children. Individuals have their own unique perspective on quality of life, which depends on present lifestyle, past experience, hopes for the future, dreams and ambition. Relevant in a medical context is the concept of health-related quality of life (HRQoL). This is generally conceptualized as a multidimensional construct encompassing physical, emotional, and social domains.[13] HRQoL measures are of potential value in comparing outcomes in clinical trials, evaluating interventions and assessing the outcomes of new treatments.[13]

Once the bowel has adapted following bowel resection, SBS turns from a mere life-threatening into a chronic disorder with symptoms such as defecation problems or abdominal complaints persisting during adolescence and early adulthood. In addition, the disease might have led to growth retardation, thus affecting bodily appearance. All this might influence (long-term) HRQoL. So far, only a few studies have described quality of life of children with SBS.[14,15] The study populations were small, however, and quality of life was assessed by taking return to regular school as outcome measure. Thus, they were more informative on aspects of functioning than on quality of life. A few other studies in adults with SBS acquired in adulthood reported lower quality of life than in healthy controls.[16-18]

Since systematic research on the long-term influence of infantile SBS on quality of life is lacking, the aim of this cross-sectional study is to compare HRQoL in children and adults with infantile SBS to that of same-aged healthy controls. In addition, it aims to

determine to what extent long-term or persistent health effects of SBS, such as growth retardation and/or abnormal stool consistency, might have influenced HRQoL.

METHODS

Population

All surviving children or adults with infantile SBS treated in their first year of life and admitted to the Erasmus MC-Sophia Children's Hospital between January 1975 and January 2003, were asked to participate. Subjects were identified as published previously.[11] Patients with psychomotor retardation due to additional anomalies were excluded, since they were considered unable to fill out questionnaires.

Definition of Short bowel syndrome

The definition of SBS used in this study is that of the Dutch committee on intestinal failure:

- > 70% resection of the small bowel,[4,19] and/or
- parenteral nutrition needed for longer than 42 days after bowel resection,[6,9,10,20] and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a premature (gestational age 27 - 36 weeks) and < 75 cm for a term neonate.[21,22]

Procedure

Older subjects and parents of children younger than 18 years received written information on the study design. Written informed consent was obtained from the parents of subjects < 18 year and separately from those older than 12 years. The study protocol was approved by the Erasmus MC ethics review board.

Study design

In this single-centre, cross-sectional study performed in the period from November 2005 until August 2007. The subjects' HRQoL was measured through validated questionnaires filled out either during or prior to a single outpatient visit.

Demographics

Demographics such as date of birth, sex, and disease leading to SBS were collected. Duration of parenteral nutrition (PN) was derived from data of the entire follow-up (> 1 year) until October 2007. We also collected data on present stool consistency and growth in length. Subjects' height was measured to the nearest 0.1 centimetres (cm) using a stadiometer (Stanley Mabo, London UK) during a single outpatient visit. The parent's height was measured in the outpatient clinic if possible or otherwise by their general practitioners. A subject's Target Height (TH) was calculated as [(father's height

+ mother's height ± 13) / 2] + 4.5 centimetres. Target height range (THR) was defined as Standard Deviation Score of TH ± 1.3 (SDS). SD-scores of height for age < -1.3 of SD-score TH were considered to be below THR. The stool form was determined by a questionnaire using the Bristol stool form scale,[23] whereby stool consistencies 1, 6 or 7 were considered abnormal.

A general questionnaire was used to obtain general data, such as socioeconomic status (SES), which was based on parents' occupation and education. SES was assessed using a nine-point scale, with 1 - 3 corresponding with low SES, 4 and 5 with middle SES and 6 to 9 with high SES.[24] Studies on chronic diseases have indicated that HRQoL is influenced by age, sex and SES, with disadvantaged groups typically reporting lower HRQoL.[25-29] Studies in healthy populations also indicate that SES is inversely associated with children's HRQoL.[30-33]

Instruments

Children differ from adults in their understanding of health, causes of illness and their beliefs about how medications work.[34] In addition, children's views about quality of life change with age. Therefore, it will not be sufficient to rate the child's quality of life only by a parent's vision (proxy rating). Thus we used a multi-informant approach by obtaining the views of the children themselves, next to surveying the parents as proxy raters of their child's HRQoL. We used generic HRQoL instruments, which have special merit in situations where comparisons across disease groups or between ill and healthy groups are required.[34]

Pediatric Quality of Life inventory (PedsQL™) questionnaire

The Pediatric Quality of Life inventory (PedsQL™) 4.0[35-37] is one of the more thoroughly developed generic measures currently available.[13] It encompasses the core health dimensions formulated by the World Health Organisation (WHO), is well validated and has proven useful for measuring quality of life of children suffering from different diseases.[35-37] Its completion time is relatively short and parallel versions for child and parent informants and for different age groups are available, allowing comparison between results of different informants and children of different ages.[38]

The Dutch version of PedsQL™ generic core scale has recently been validated.[39] We used both the self-report and the parent-proxy report for age groups 5 - 7 years, 8 - 12 years, and 13 - 18 years. The separate versions contain parallel items, differing in developmentally appropriate languages, or first or third person tense. During the single outpatient visit parents and subjects were asked to fill in the questionnaires independently.

The PedsQL™ consists of 23 items scored on a five-point "Likert" scale ranging from "never-a-problem" to "almost-always-a-problem" (corresponding scores 100, 75, 50, 25, or 0). The PedsQL™ asks how much of a problem each item had been during the past month. The answer categories of the self-report version for children aged 5 - 7 years are simplified into a three-point scale (100, 50, or 0). Generally, a higher PedsQL™ score corresponds with better quality of life.

Four subscales can be computed: Physical (8 items), Emotional (5 items), Social (5 items) and school functioning (5 items). Moreover a psychosocial health summary score (15 items; comprising the emotional, social and school functioning subscales) and a total score (all 23 items) can be calculated. Individual scale scores are computed as the sum of the item scores divided by the number of items answered.

Since Dutch reference data were available only from a small population,[39] the PedsQL™ questionnaire was additionally filled out by age- and sex-matched healthy controls and their parents, who were recruited through primary and secondary public schools in Rotterdam. Written information to the parents had been distributed through the schools. First the parents completed questionnaires at home and returned them to school by a specific date. Those children, whose parents had returned completed questionnaires, were then asked to complete questionnaires in class, after having been given verbal and written information. A researcher was available for questions and directly assisted the 5 to 7-year-olds. In addition to PedsQl™, all families completed a questionnaire concerning demographic information, such as age, sex, SES and the child's health status. Children with chronic health problems were excluded from the healthy control sample.

Short Form 36 (SF-36) questionnaire

Subjects aged 19 years and older completed the Short Form 36 (SF-36) prior to or during a single outpatient visit. The SF-36 is an internationally well-known, psychometric sound instrument,[40-42] is suitable for self-administration, is cognitively simple and takes only 5 - 10 minutes to complete.

The SF-36 consists of 36 items organized into 8 domains: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. One item asks the responder to rate his or her health compared to one year ago. This item is not included in one of the 8 domains.

All raw scale scores were linearly converted to a 0 to 100 scale, with higher scores indicating better quality of life. Scores were compared to those of same-aged healthy controls from a Dutch population study.[43]

Statistical analysis

Group size was not based on a formal power analysis. The incidence of SBS in the Netherlands is unknown, but from clinical experience is judged to be relatively low. We therefore aimed at including all consecutive survivors of a cohort of patients with infantile SBS treated between 1975 and 2003. In order to enhance statistical power, we aimed to include at least four healthy controls for each single subject.

Kruskal-Wallis tests and chi-square tests were used to identify general differences between the study group and eligible subjects that did not participate.

Subjects were stratified in two age groups: 5 - 18 years (children) and 19 years or older (adults). Descriptive statistics (frequencies, mean, median, SD and minimum and maximum) were calculated.

Analyses subgroup children

Differences between subjects and controls regarding the distribution of supposed effects of SES, age and sex were calculated using Mann-Whitney or chi-square analyses. Spearman rank correlations served to explore associations between SES and age versus scale scores of PedsQL™ within each separate group. Differences in effect of sex on scale scores of PedsQL™ were calculated using independent sample *t*-tests. Differences in scores between subjects and controls were analyzed using independent sample *t*-tests. Further analysis of covariance (ANCOVA), taking into account age, sex and SES, was used to compare outcomes of subjects with those of controls. In case of a significant interaction between these predictors and groups, the magnitude of this effect-modification was further investigated.

Some of the infantile SBS patients had also been diagnosed with cystic fibrosis (CF), a condition that might be associated with lower HRQoL; therefore we also compared scores of SBS patients with CF to those of SBS patients without CF using appropriate tests.

The relationship between self and proxy-report was assessed using Spearman Rank correlations. In subjects, Mann-Whitney tests were performed to determine relationships of PedsQl™ total score with stool form (abnormal vs. normal) and THR (below range vs. within range).

Analyses subgroup adults

Differences between adult subjects' scores and SF-36 reference data were analyzed using independent sample *t*-tests.

The level of significance was set at $p < 0.05$.

RESULTS

Patients

Of the seventy-two eligible patients with SBS, 17 could not be located (Figure 1). Forty of the remaining 55 gave informed consent and completed the questionnaires (response rate of 73%). Kruskal-Wallis tests and chi-square tests identified no differences in underlying diagnosis, sex, age at start of cross-sectional study, percentages of premature birth or length of remaining bowel between the groups "included", "no informed consent" and "not located" (data not shown).

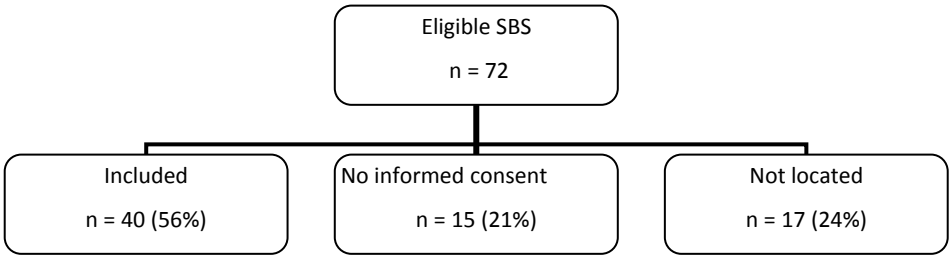
Underlying diagnoses for the 40 subjects (16 males and 24 females) included necrotizing enterocolitis (n = 8), small bowel atresia (n = 14), volvulus and/or malrotation (n = 6), gastroschisis (n = 3), meconium peritonitis without cystic fibrosis (n = 3), meconium peritonitis with cystic fibrosis (n = 4), long-segment Hirschsprung disease (n = 1), and ischemic small bowel of unknown origin (n = 1).

All were now off parenteral nutrition, for periods ranging from several months to years. Median dependency of PN had been 110 (43 - 2345) days. Fifty-three percent of the children were below THR and 35% reported abnormal stool forms (data not shown).

Healthy controls PedsQL

Six hundred questionnaires were distributed through schools, of which 277 questionnaires were returned (response rate 46%). Two of these questionnaires were excluded because the children concerned reported chronic health conditions.

Figure 1 Flow chart



PedsQL™

Of the 40 subjects, 31 were children (mean age 11.3 ± 4.1 years, 19 girls and 12 boys). As PedsQL scores of the four children with CF did not differ from those of the other 27, these four were not excluded from the study group.

PedsQL scores of subjects and controls are shown in Table 1.

Table 1 PedsQl scores 5 - 18 years

		Subjects (n=31)	**Controls (n=275)**	**p-value**
Age (years) mean (± SD)		11.3 (± 4.1)	11.2 (± 3.2)	0.90
Sex M:F		12 (39%): 19 (61%)	117 (42%): 158 (58%)	0.68
SES				0.01
Low		6 (19%)	35 (13%)	
Middle		17 (55%)	92 (34%)	
High		8 (26%)	147 (54%)	
Child self-report	**Items (n)**	Mean (± SD)	Mean (± SD)	
Total score	23	75.6 (± 14.9)	82.1 (± 12.5)	0.01[ab]
Physical functioning	8	81.3 (± 13.0)	86.7 (± 12.3)	0.02[ab]
Psychosocial health	15	72.6 (± 17.3)	79.6 (± 13.9)	0.01[ab]
Emotional functioning	5	69.4 (± 20.3)	74.4 (± 18.5)	0.16 ns
Social functioning	5	79.7 (± 19.6)	85.8 (± 15.7)	0.10 ns
School functioning	5	68.7 (± 23.4)	78.8 (± 14.9)	0.03 [ab]
Parent proxy-report				
Total score	23	74.9 (± 15.9)	86.0 (± 10.9)	0.00[c]
Physical functioning	8	79.8 (± 21.6)	92.2 (± 11.1)	0.00[c]
Psychosocial health	15	72.3 (± 15.8)	82.6 (± 12.6)	0.00[cd]
Emotional functioning	5	71.0 (± 15.6)	78.6 (± 16.0)	0.01
Social functioning	5	74.9 (± 20.9)	87.4 (± 15.0)	0.00[cd]
School functioning	5	70.8 (± 19.8)	81.9 (± 14.3)	0.01[cd]

[a] age was a significant (p < 0.01 for interaction) effect modifier on these scales: older controls had higher scores than younger controls, and there was no relation with age in the subjects group.
[b] Healthy controls had significantly (p ≤ 0.02) higher scores than subjects from the age of 11 years onward (ANCOVA).
[c] SES was a significant effect modifier (p ≤ 0.001 for interaction). Significant differences were only found in middle class SES, with highest scores for controls (ANCOVA).
[d] Age was a significant effect-modifier (p ≤ 0.05 for interaction). Differences in scores were only found in middle class SES, and differences increased between the groups with the increasing age. Parents of older patients in middle class SES had significantly decreased (p ≤ 0.001) scores than parents of younger patients, whereby parents of older controls in middle class SES showed higher scores (ns) than parents of younger controls.

For subjects, 84% of parent-proxy reports were filled out by the mothers, versus 92% in the control population (ns). Distribution of age and sex did not differ significantly between subjects and controls, but the former predominantly were of middle class SES versus predominantly high class SES for controls ($p = 0.01$).

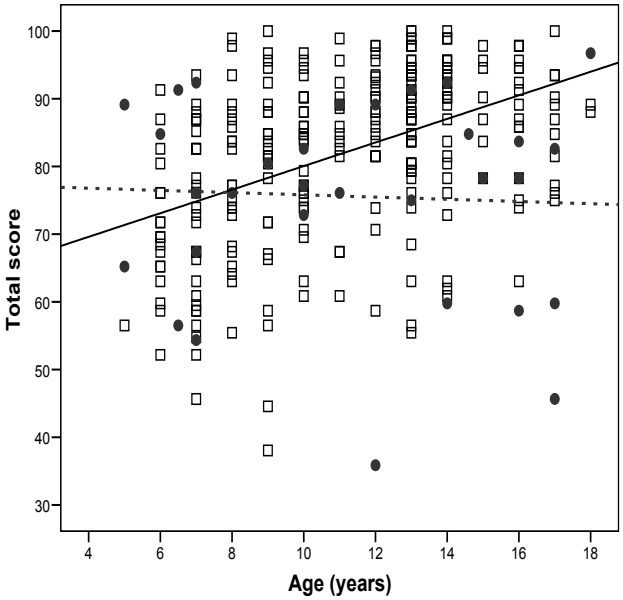
The subjects themselves scored significantly lower than controls on the total score, psychosocial health summary score and on the physical functioning and school functioning subscales ($p < 0.05$), but not on emotional and social functioning ($p = 0.16$ and $p = 0.10$, respectively). Further ANCOVA analyses showed that only age was a significant effect modifier ($p \leq 0.01$ for interaction). Older controls had higher total scores than younger controls, whereas there was no relation with age for subjects. Further analysis showed that controls had significantly ($p \leq 0.02$) higher total scores than subjects from the age of 11 years and onward (Figure 2). Similar effects were observed on the physical functioning and school functioning subscales and on the psychosocial health summary score (data not shown).

Parent-proxy scores for subjects were significantly lower than those for controls on all scales ($p < 0.01$) (Table 1). ANCOVA analyses showed that SES was a significant effect modifier ($p \leq 0.001$ for interaction) for group differences on all scales except emotional functioning. Further analyses showed that differences between groups on total and physical scales were only found in subjects with middle class SES, whereby controls with middle class SES had higher scores than subjects with middle class SES.

Moreover, next to SES also age was a significant effect-modifier ($p \leq 0.05$ for interaction) for group differences on the psychosocial health summary score and the social and school functioning subscales. Group differences in scores of psychosocial health were only found in middle class SES, and the differences increased with increasing age (Figure 3). Parents of older subjects with middle class SES had significantly lower ($p \leq 0.001$) psychosocial scores than parents of younger subjects, whereas parents of older controls in middle class SES showed higher scores than parents of younger controls ($r_s = 0.2$ for scores versus age; $p = 0.08$). Similar results were found for scores on subscales social and school functioning (data not shown).

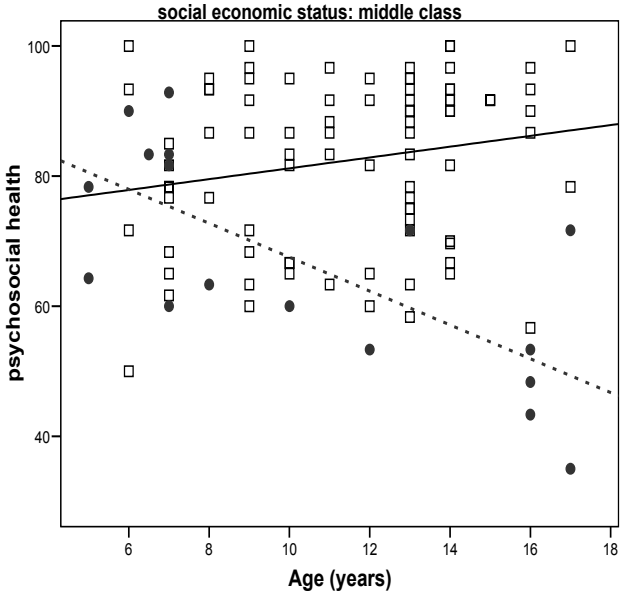
Table 2 shows the correlation between outcomes of the children's self-report and parent-proxy report. Both for subjects and healthy controls, moderate positive correlations were observed between both types of reports on total score and subscales. Median [min - max] total PedsQL scores did not differ significantly between subjects with normal (77.7 [35.9 - 96.7]) versus abnormal stool consistency (78.3 [45.7 - 91.3]) or between subjects within THR (77.7 [54.4 - 92.4]) versus those below THR (77.7 [35.8 - 96.7]).

Figure 2 Scatter plot of total PedsQl scores versus age with regression lines



□ _____ *controls*
● -------- *subjects*

Figure 3 Scatterplot of psychosocial health in parent-proxy report versus age in middle class SES with regression lines



□ _____ *controls*
● -------- *subjects*

Table 2 Correlation between scores of child self-report and parent-proxy report

Scale	Subjects (r_s)	Healthy controls (r_s)
Total score	0.50**	0.43*
Physical functioning	0.47**	0.35*
Psychosocial health	0.41**	0.43*
Emotional functioning	0.45**	0.38*
Social functioning	0.37**	0.39*
School functioning	0.43**	0.47*

** $p < 0.01$*
*** $p < 0.05$*

SF-36

Nine of the subjects in the study were adults (median age 24.9 [21.8 - 29.7] years, 5 females and 4 males). As shown in Table 3, they scored significantly lower than the controls in the domains "General Health" and "Vitality" ($p < 0.05$). In the domain of social functioning they showed a non-significant trend toward poorer functioning than controls ($p = 0.09$). Moreover, subjects scored relatively lower in all other domains (between 6 and 12 points on the 0-100 scale), but none of these differences did reach statistical significance.

Most adult subjects (56%) reported stable health, while 22% reported better health and 22% reported worse health than one year previously. Mean item score of health change was 7 points (0-100 scale) below the mean item score of controls and was not significantly different.

Table 3 SF-36 in adults > 18 years

Domains	Subjects n = 9	controls n = 356	Difference (95% CI)	*p*-value
Physical functioning	83.9 (± 14.3)	90.3 (± 16.7)	-6.4 (-17.5 to 4.6)	0.25
Physical role	72.2 (± 44.1)	83.8 (± 31.2)	-11.6 (-32.6 to 9.4)	0.28
Bodily pain	77.3 (± 20.4)	85.5 (± 22.8)	-8.2 (-23.3 to 7.0)	0.29
General health	60.6 (± 15.9)	77.3 (± 20.0	-16.8 (-30.1 to -3.5)	0.01
Vitality	54.3 (± 17.0)	69.1 (± 18.8)	-14.9 (-27.4 to -2.4)	0.02
Social functioning	77.8 (± 32.9)	88.7 (± 18.4)	-11.0 (-23.5 to 1.6)	0.09
Emotional role	74.1 (± 40.1)	84.6 (± 31.5)	-10.5 (-31.7 to 10.6)	0.33
Mental health	68.9 (± 15.7)	76.8 (± 18.7)	-7.9 (-20.3 to 4.6)	0.21

Data shown are mean (± sd). Abbreviation: CI, confidence interval.

DISCUSSION

Over the years, survival rates of patients with infantile SBS have improved considerably. Simultaneously, the quality of survival has emerged as a fundamental focus of pediatric chronic disease management.[44] The aim of this cross-sectional study was to compare the long-term HRQoL in surviving children and adults with infantile SBS to that of healthy controls. Children with a history of infantile SBS reported a significantly lower HRQoL than healthy children, and so did the parents for their children. General health and vitality of adults with a history of infantile SBS health status were significantly below those of healthy controls.

This is the first study that reports on long-term quality of life outcomes in a considerable number of children, adolescents and adults with infantile SBS. Nevertheless, it has some limitations that may hamper interpretation of some results. For one, we did a single assessment of HRQoL in a cross-sectional sample, whereas HRQoL is more likely to be dynamic and may fluctuate over time. Furthermore, subgroup sizes tended to be rather small, with inherent lower statistical power. To overcome this problem, we included a large number of healthy controls. Finally, the patient group – by nature – is heterogeneous with respect to underlying diagnosis and remaining bowel lengths, which might have influenced outcomes. Notwithstanding these limitations, the strength of our study is that it covered a long period, from 5 to 30 years after infantile SBS, and thus includes outcomes into adulthood. Moreover, we used HRQoL instruments with adequate psychometric properties and we achieved an acceptable response rate.

The finding that children with infantile SBS show lower HRQoL is consistent with studies in other patient groups with chronic diseases. Patients with irritable bowel disease had significantly lower HRQoL than healthy children,[45,46] and Varni et al. reported progressively more impaired self-reported overall HRQoL in children with diabetes, gastrointestinal conditions, cardiac conditions, asthma, obesity, end stage renal disease, psychiatric disorders, cancer, rheumatologic conditions and cerebral palsy when compared with healthy children.[47] These studies did not investigate the effects of age, sex and SES between groups (chronic conditions vs. healthy). However, in line with the present findings, these studies also observed effects of age on scores within the groups.

Studies on long-term HRQoL in children and adolescents with SBS are scarce. A few described a "generally satisfying" quality of life in children with SBS largely on the basis of attending a regular school, which seems an all too narrow interpretation of quality of life.[14,15]

Gottrand et al. showed that quality of life in patients (median age of 4 years) dependent on PN (median duration of 2 years) was not different from that of healthy children.[48] Moreover, quality of life of parents of HPN-dependent children was low.[48] Median age of these children was lower than that of our patients. In our younger patients we found similar results. HRQoL was measured with another type of questionnaire, however, which might influence comparisons.

Two reports in the literature showed that patients with neonatal SBS who were weaned off PN had relatively normal mental and motor development.[49,50] We did not investigate mental and motor development, but taking the present scores of physical and school functioning as indicators for mental and motor development leads to the tentative conclusion that mental and motor development is probably slightly delayed.

PedsQL™

Children and adolescents with infantile SBS were found to have a significantly lower HRQoL than their healthy peers, both when self-reported and rated by their parents. On only two self-report subscales the differences did not reach statistical significance; this might be due to the relatively small group sizes.

Differences in scores between subjects and controls started at age of 11 years and onward. This is the age when adolescence starts, a stressful stage with marked biological, social and psychosocial changes. Adolescents are seeking their own identity, are becoming sexual mature and, with ongoing cognitive development, gain the capacity of formative thinking. Adolescents become more aware of their body and its functioning. They are focused more on peers than on parents and therefore are vulnerable to feelings of insecurity and vulnerability.[51] Having experienced a chronic disorder with permanent scars may increase these feelings. This might explain why adolescent patients had lower scores than healthy control adolescents.

Middle class SES and age were significant effect modifiers on parent-proxy scores of subjects. These effect modifiers make it somewhat difficult to interpret the results. Age was a significant effect-modifier on psychosocial health, social and school functioning. Parents of older subjects with middle class SES reported significantly lower HRQoL regarding their children than did parents of younger subjects, whereas a non-significant inverse trend was seen in controls. Thus, also according parent-proxy reports differences between the groups increased with increasing age. Parents may have been alert to lower experienced HRQoL of their children, as reported in the self-reports. In addition, for parents of children with a chronic disorder, adolescence of their children may be a difficult and critical period. Parents may be struggling with letting go, enhancing the child's autonomy (especially regarding health behaviors).[52] Clinical

experience learns that parents may be concerned about the (future) health of their children and its possible impact on educational attainments, professional career and future family life. Thus, parent ratings of HRQoL might be biased by these concerns. This might explain the lower parent-ratings in the psychosocial health, social and school domains (for middle class SES subjects). Moreover, parent-ratings may be influenced by their own feelings and additional life stresses.[53]

In healthy controls a higher SES seemed to increase the parent-proxy HRQoL scores, but not significantly. In standardized HRQoL instruments, test items should be interpreted similarly across age, sex, language, SES, and race/ethnicity subpopulations, irrespective of mode of administration and health status categories.[54] A study of Limbers et al. showed that children across SES groups interpreted items on the PedsQL™ in a similar manner, indicating that differences across SES groups are more likely to be real differences in self-perceived HRQoL, rather than differences in interpretation of the PedsQL™ items as function of SES.[54] Thus, the observed differences are not likely to be influenced by SES and are more likely real differences in HRQoL between patients and controls. However, one should keep in mind that the number of patients in each class of SES was low, which compromised statistical interpretation.

Moderate correlations were found between self-reports and parent-proxy reports of the children's HRQoL. Parents' views about their child's HRQoL may be influenced by their own concerns about the child's illness,[13] which might explain the moderate correlation. Although self-report is considered the standard for measuring perceived HRQoL, it is the parent's perception of their child's HRQoL that influences health care utilization.[55]

SF-36

In this study, we used so-called generic HRQoL measures. This allows for a comparison between our patients with SBS and the general population or other patient groups, providing an indication of the relative impact of the disease. SF-36 scores revealed that the adult patients fared less well than the general population, especially regarding 'general health' and 'vitality', while differences in 'social functioning' nearly reached significance. This is in line with findings of two studies from a Swedish center.[17,18] Of note here is that the subjects with SBS in the study by Carlsson and co-workers had lower scores than our subjects on all but one domains of the SF-36.[17] However, the adults in these two studies had acquired SBS in adulthood and therefore might not be comparable to our group. Their lower scores might be due to having known a healthy state before acquiring disease, which might be a reason for lower scores than our patients, they have had SBS for as long as they can remember.

The subjects with SBS in the present study have a poorer HRQoL than adults born with congenital anorectal malformations,[56,57] congenital diaphragmatic hernia,[56,58] esophageal atresia,[59] Hirschsprung disease,[57] omphalocele,[60] or gastroschisis.[60] Notwithstanding the fact that all these studies used the SF 36 questionnaire as well, these comparisons should be interpreted with some caution, as group sizes and ages and sex of the subjects differ.

In summary, our study demonstrated that children, adolescents and young adults with a history of infantile SBS have impaired HRQoL in terms of physical and psychosocial functioning. We did not find a relationship between HRQoL and possible explanatory variables such as abnormal stool consistency and height below THR. It might be hypothesized that abnormal stool consistency is associated with higher frequency of bowel movements and abdominal complaints, which could influence the HRQoL negatively. Moreover short stature might influence appearance and self-esteem negatively. However, in line with our results, other studies showed that patients with short stature had normal HRQoL.[61,62] The reason that we did not find any relation between HRQoL and these explanatory variables might be due to the low number of patients. Furthermore, this study was designed to investigate whether HRQoL was lower than healthy controls, rather than explore possible contributing factors. Therefore further studies are needed to investigate variables that contribute to lower HRQoL. Recently we have demonstrated that medical care of SBS has improved over the years in terms of shorter duration of hospital stay and longer remaining bowel length.[11] This might explain why the HRQoL of younger children with infantile SBS is better than that of older patients with SBS. Due to the small numbers of patients some caution is necessary in interpretation and generalizations.

CONCLUSION

Overall, patients with a history of infantile short bowel syndrome have a lower quality of life than the healthy population. Targeted interventions are required to address these dimensions of impaired HRQoL.

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Chapter 7

Interdisciplinary management of infantile short bowel syndrome; resource consumption, growth and nutrition

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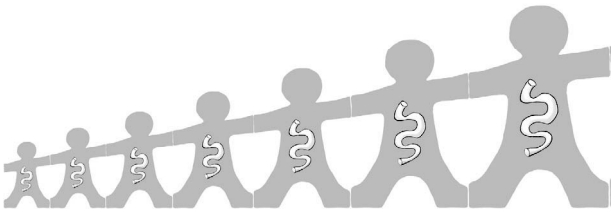


Abstract

Objective

The aim of this study is to prospectively evaluate a case series of children treated by an interdisciplinary short bowel team, with a focus on resource consumption.

Methods

Data were collected for ten children with infantile short bowel syndrome (≤ 1 year of age) born between January 2002 and January 2007 and treated by our interdisciplinary team between August 2003 and December 31, 2007. Data included demographic and medical data of the first admission and data on resource consumption, growth and type of nutrition for the total follow-up period.

Results

Seven of the 10 patients were discharged with home parenteral nutrition. Total follow up varied between 9 months and 5.5 years (median 1.5 years). Six patients could be weaned off parenteral nutrition and 5 patients off enteral tube feeding, resulting in full oral intake. Seven patients had normal growth. Median duration of initial hospital admission was 174 days, and average costs of initial admission amounted to 166,045 euros. Total admission days varied from 84 to 478 days with a median of 409 days. Average total costs were 269,700 euro reaching to maximum of 455,400 euros. These costs mainly comprised hospital admissions (82%).

Conclusions

Treatment of short bowel syndrome requires considerable resource consumption, especially when patients depend on parenteral nutrition. As the costs mainly comprise those of hospital admissions, early home parenteral nutrition could contribute to costs reduction. Interdisciplinary teams have the potential to facilitate home parenteral nutrition and thus reduce health care costs, while at the same time benefiting patients' health.

INTRODUCTION

Short bowel syndrome (SBS) is a condition characterized by increased intestinal transit, and thus malabsorption of nutrients and eventually growth retardation. It is often the result of massive resection of the small intestine,[1-4] but has also been associated with dysfunction of a large segment of bowel. The most frequent underlying diagnoses in neonates are necrotizing enterocolitis, volvulus and congenital anomalies such as intestinal atresia and gastroschisis.[1,4,5] Intestinal adaptation after resection of the small bowel, with gradually increasing fluid and nutrient absorption, may last several years during which absorption is inadequate.[6,7] During this period parenteral nutrition (PN) is indispensable. Enteral tube feeding or oral feeding may be introduced in the course of time, after which patients can be weaned off PN.

Survival rates of patients with SBS have much improved over the years, and ranged from 53% to 94% in the past decade.[8-13] Major predictors of mortality in pediatric SBS are PN-associated cholestasis and age-adjusted small bowel length. Moreover, age-adjusted small bowel length and the presence of the ileocecal valve (ICV) are major predictors of weaning from PN.[14] The better survival rates can be attributed to improving care and advancing technology. For example, PN is no longer exclusively given in the hospital, but is gradually giving way to home parenteral nutrition (HPN). Furthermore, patients with SBS are typically treated by several individual professionals, who will see the patients in their own outpatient clinics. However, there is much to say for introducing some type of integrated care that facilitates early discharge home and streamlines redundant procedures, bearing in mind that treatment for SBS can be very costly.[15] Indeed, several reports in the literature emphasize the importance of an integrated, interdisciplinary approach for optimal long-term management of SBS.[4,16,17]

The aim of this study is to prospectively evaluate a case series of patients treated by an interdisciplinary short bowel team, particularly resource consumption, together with information on nutrition and growth.

METHODS

This is a longitudinal observational evaluation of a case series.

Setting

The Erasmus MC-Sophia Children's hospital is a tertiary academic facility equipped with all major pediatric and surgical specialities. It runs the only pediatric surgical service (including ICU) in the South-Western part of the Netherlands. The referral area has 4 million inhabitants with 44,000 infants born annually.

Following on the recommendations in the literature,[4,16,17] an interdisciplinary SBS team was formed in August 2003. Consisting of a pediatrician, a pediatric surgeon, a pediatric gastroenterologist and a dietician, the team is responsible for the clinical assessment and management of children with SBS. Other specialists are available for consultation; such as a neonatologist, a pediatric intensive care physician, a pharmacist, a nurse specialized in caring for enterostomies, and a social worker.

Patients

This case series includes ten children with infantile SBS (i.e. SBS resulting from intestinal problems ≤ 1 year of age) born between January 2002 and January 2007, and treated by the interdisciplinary SBS team between August 2003 and December 31, 2007. They were either PN-dependent or could not be easily weaned off PN. We adhered to the definition by the Dutch committee on SBS, which includes representatives of the section of Gastroenterology of the Dutch Pediatric Association and the Dutch Society of Pediatric Surgery, and dieticians of academic medical centers. The definition is based on consensus on literature and empirical data. The committee defined SBS as;

- > 70% resection of the small bowel,[1,18] and/or
- parenteral nutrition needed for longer than 42 days after bowel resection,[8,11,12,19] and/or
- residual small bowel length distal to the ligament of Treitz less than 50 cm for a premature (gestational age 27 - 36 weeks), < 75 cm for term born neonates and < 100 cm for children aged > 12 months.[20]

Patient characteristics and outcome measures first hospital admission

Demographic and medical data including sex, gestational age, birth weight and underlying diagnosis were collected. Date of primary surgery (leading to SBS) was recorded as well as residual small bowel length, measured distal to the ligament of Treitz, and post-operative presence of the ileocecal valve (ICV). Complications such as sepsis episodes, PN-related cholestasis and central venous catheter (CVC) (re)placements as a consequence of occlusion, thrombosis or sepsis were recorded. Cholestasis is defined as serum conjugated bilirubin level ≥ 2.5 mg/dl (≥ 43 µmol/l).[14] Furthermore, discharge home with HPN was recorded.

Follow-up

The total follow-up period was defined as the time (in years) elapsed after discharge from the first hospital admission until either the date of study closure (December 31, 2007) or the date of last evaluation (applicable to patients not followed by the SBS team anymore at study closure). Duration of follow-up by the SBS team was defined as the time (in years) elapsed after the patient's first treatment by the interdisciplinary SBS team until either the date of study closure (December 31, 2007) or the date of last evaluation. Age at

start of treatment by the SBS team was recorded, as well as number and main reason for hospital re-admissions, sepsis episodes and CVCs after the first admission.

Weight (kg) and height (cm) were recorded every 3 months in the first year of SBS and every 6 months thereafter. Body weight (kg) was uniformly measured on a calibrated scale (Digital baby scale, Kubota, Japan) to the nearest 0.01 kg, after having removed the child's diaper and clothes. Recumbent height (cm) was measured to the nearest 0.1 cm using a rigid length board with a moveable foot piece. The parents' height was measured in the outpatient clinic or by the general practitioner. Target Height (TH) was calculated as [(fathers height + mothers height ± 13) / 2] + 4.5 centimetres. Target height range (THR) was defined as TH-SDS ± 1.3 sds. Values were compared to national standards[21] and expressed in standard deviation scores (sds), depending on sex and age and corrected for prematurity (until the age of 2 years) and race (Growth Analyser version 3, Dutch Growth Foundation, Rotterdam, the Netherlands).

Nutrition

Dates on which minimal enteral feeding (MEF) and enteral nutrition started or stopped were recorded. MEF was defined as ≤ 25 kcal/kg/day feeding and its start was defined as the first day after the date of primary surgery leading to SBS. Clinical practice shows that MEF is initiated with a volume as low as 6 ml/day. Enteral nutrition is a way to provide food through a tube to the gastrointestinal tract, and is further referred to as enteral tube nutrition (ETN). Type of nutrition was classified as polymeric, breast milk, or semielemental. Interruption of ETN, necessitated by inadequate passage through the intestinal tract, was recorded. Furthermore duration of PN was recorded, distinguished into PN during admission and HPN.

Resource consumption and costs

The resource consumption and direct medical costs related to the treatment of SBS were evaluated. Length of stay (LOS; in days) was determined, regarding both the initial admission and all readmissions, broken down for length of stay in intensive care units and medium care/high care units. In addition, prior hospital stays in referring clinics preceding the initial admission to our hospital were included. All surgical interventions related to the diagnosis of SBS were recorded. Mean PN and ETN intakes were calculated. Finally, outpatient visits to the SBS team and previous visits to individual specialists were regarded.

Following established methods,[22] we proceeded to calculate real economic costs. There are basically two approaches i.e. "top down" and "bottom up". The former allocates total hospital costs down to the level of a unit (e.g., a nursing ward or operating room), resulting in average costs per patient. The latter measures the resource items specific

to individual patients.[23-25] In this study, a combination of these two methods was adopted. The cost price of a hospitalization day was largely calculated using the top down method and, therefore, mainly referred to all patients of the pediatric surgery department. The integral cost price included personnel costs, costs of materials and medications, and overhead costs (eg, housing, utilities, cleaning, management, etc.). The cost prices of surgical interventions (combination of top down and bottom up) consisted of both fixed costs per surgical intervention (e.g., costs for materials, sterilization, and the recovery room) and variable costs depending on the duration of the intervention (e.g., costs for equipment, operating room assistants, anesthesia nurses, surgeons, and anesthetists). Costs of parenteral and enteral nutrition were calculated separately. Finally, cost prices of the initial visit to the outpatient clinic and revisits were calculated from personnel costs, costs of material, and indirect costs (top-down method), as well as from costs of medical specialists, a nurse, and a dietician (bottom-up method). All costs were calculated for the year 2006 and reported in Euro (€).

Data Analysis

Due to the descriptive character of this study, no statistical analyses were performed other than reporting frequencies expressed as median and ranges unless stated otherwise.

RESULTS

Patient characteristics and outcomes of the first hospital admission

The underlying diagnoses for the ten patients with infantile SBS reported here are shown in Table 1. Patient 7 had a completely necrotic small bowel with only the duodenum and 10 cm of colon in situ. Patients 8 and 10 underwent a Bianchi procedure a few weeks after the diagnosis of SBS, in which the remaining small bowel was doubled in length. Seven patients were discharged with HPN. Patient 10 was still in the hospital at the end of the study period. Two patients (1 and 9) did not have an anatomical SBS, but received PN > 42 days. All characteristics of the first admission are shown in Table 1.

Follow-up

The total follow-up period varied between 9 months and 5.5 years (median 1.5 years). Three patients were lost to follow-up. Two of them (patients 2 and 4) recovered very well and were discharged from treatment by the SBS team; patient 7 entered the waiting list for combined liver and small bowel transplantation and further care was transferred to Belgium. Four patients were discharged home before the SBS team was established and had previously been seen several times by individual specialists. All follow-up data are shown in Table 2.

Table 1 Patient characteristics and characteristics of the first admission

Pt	Sex	GA (wks)	BW (sds)	Age SBS (days)	Diagnosis	Bowel length (cm)	ICV	Surgical interventions (n)[c]	LOS in days (IC/HC, MC)	HPN	Sepsis/month PN (n)	CVCs (n)	PN related Cholestasis
1	M	39.3	-0.4	3	M.Hirschsprung[b]	100	No	5	137 (22/115)	Yes	0.22	2	Yes
2	F	38.3	0.7	3	Volvulus	32	Yes	9[d]	182 (155/27)	Yes	0.87	7	Yes
3	F	34	3.0[a]	4	Meconium peritonitis	30	Yes	6	218 (218/0)	No	0.8	6	Yes
4	F	33.3	2.5	15	NEC	86	No	5	229 (91/138)	Yes	0.28	2	Yes
5	F	24.9	-1.1	46	NEC	26	Yes	5	223 (147/76)	Yes	0.27	3	Yes
6	M	40		47	Volvulus	10	Yes	5	92 (92/0)	Yes	0	2	No
7	M	37.4	-1.4	2	Gastroschisis	0	No	3	165 (28/137)	Yes	0	1	Yes
8	M	35.1	2.0	1	SIA	21	No	5	136 (45/91)	Yes	0.45	4	Yes
9	F	34.6	0	1	Volvulus	58	Yes	2	84 (17/67)	No	0.40	1	No
10	M	35.3	0.3	3	SIA	8	Yes	7[d]	> 350 (19/331)[e]	n.a.	0.26	4	Yes

Abbreviations: BW, birth weight; SDS, standard deviation score; SBS, short bowel syndrome; CVC, central venous catheter; EN, enteral feeding; F, female; GA, gestational age; HC/MC, high care/medium care; HPN, home parenteral nutrition; IC, intensive care; ICV, ileocecal valve; LOS, length of hospital stay; M, male; PN, parenteral nutrition; NEC, necrotizing enterocolitis; SIA, small intestinal atresia.

[a] *sds BW is skewed, because patient was born with fetal hydrops.*

[b] *Long segment Hirschsprung's disease.*

[c] *Including insertion and/or removal central venous catheters.*

[d] *One of these interventions was performed in another hospital prior to admission to our hospital and thus had to be omitted from the cost calculations.*

[e] *Patient was still admitted on December 31, 2007.*

Table 2 Results follow-up

Patient	Year of diagnosis*	Total follow-up (years)	Length of follow-up by SBS team (years)	Age at start treatment by SBS team (years)	Hospital re-admissions (n)	Main indication readmission	Total LOS in days (IC/HC, MC)	Surgical interventions (n)†	Sepsis/ month PN (n)	CVCs (n)	Previous outpatient visits (n)	Outpatient visits SBS team (n)
1	2002	5.48	4.18	1.54	37	Sepsis	272 (7/265)	27	0.30	18	22	31
2	2002	1.26	0.17	1.75	1	Sepsis	14 (14/0)	0	2	0	15	2
3	2002	4.64	2.72	0.93	2	PEG insertion	6 (0/6)	1	0	0	1	6
4	2002	0.77	0.35	1.05	2	Sepsis/pneumonia	10 (0/10)	0	0.36	0	11	4
5	2003	4.29	4.14	0.63	9	Sepsis	128 (1/127)	3	0.24	2	0	26
6	2003	4.26	4.22	0.39	52	Diarrhea/sepsis	> 386 (6/380)‡	22	0.28	14	0	53
7	2005	1.49	1.45	0.49	11	Sepsis/cholangitis	74 (2/72)	8	0.17	5	0	10
8	2006	1.18	1.05	0.38	2	Sepsis/pneumonia	11 (0/11)	0	0.27	0	0	12
9	2006	1.17	0.88	0.28	0	-	0	0	0	0	0	4
10‡	2007	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

Abbreviations: SBS, short bowel syndrome; CVC, central venous catheter; IC, intensive care; HC/MC, high care/medium care; LOS, length of hospital stay; PN, parenteral nutrition; PEG, Percutaneous endoscopic gastrostomy; n.a., not applicable.

** For all patients, this is also the year of birth.*

† Including inserting and/or removing central venous catheters.

‡ Patient was still admitted on December 31, 2007.

Figures 1 and 2 show the growth charts of all patients. All grew according to their growth line, except patient 6, whose height declined from -1 SD to -2 SD. This patient had only 10 cm remaining small bowel and is still dependent on HPN. Still, patients 3, 5 and 6 heights remained below the limits of the THR. Patients 3 and 5 were both born prematurely. Patient 5 with gestational age of 24 weeks has always been under THR even after correction. And patient 3 dropped below THR after the correction for gestational age stopped.

Nutrition

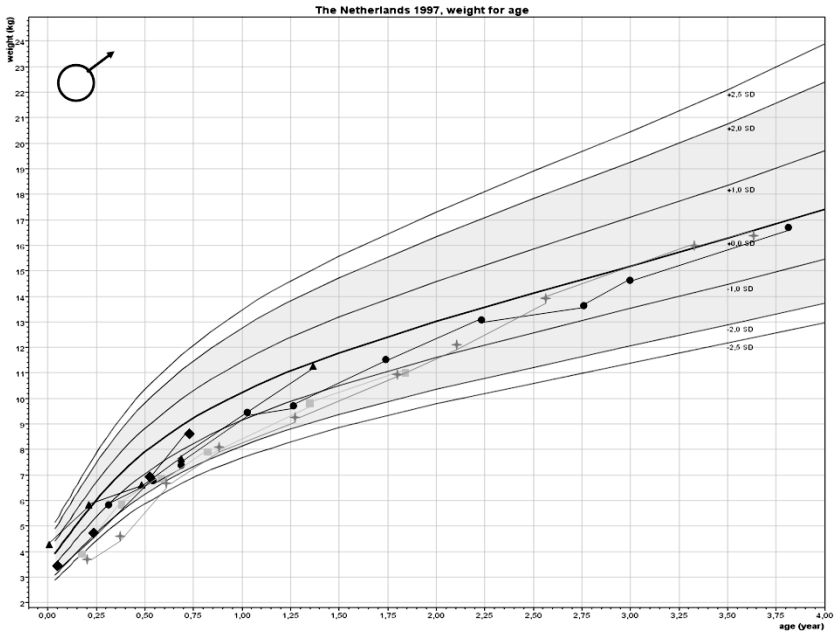
MEF was started as early as two days and as late as 83 days after the initial operation. Table 3 provides details of PN and ETN intakes. Most patients started MEF with either breast milk or semielemental nutrition. Six patients could be weaned off PN after 77 - 477 days (median 218 days) and five patients could be weaned off ETN after 86 - 429 days (median 359 days). Patient 3 is still ETN-dependent as a result of oral food aversion. To sustain their optimal growth, patients 1 and 6 still need ETN to obtain as many calories as possible enterally.

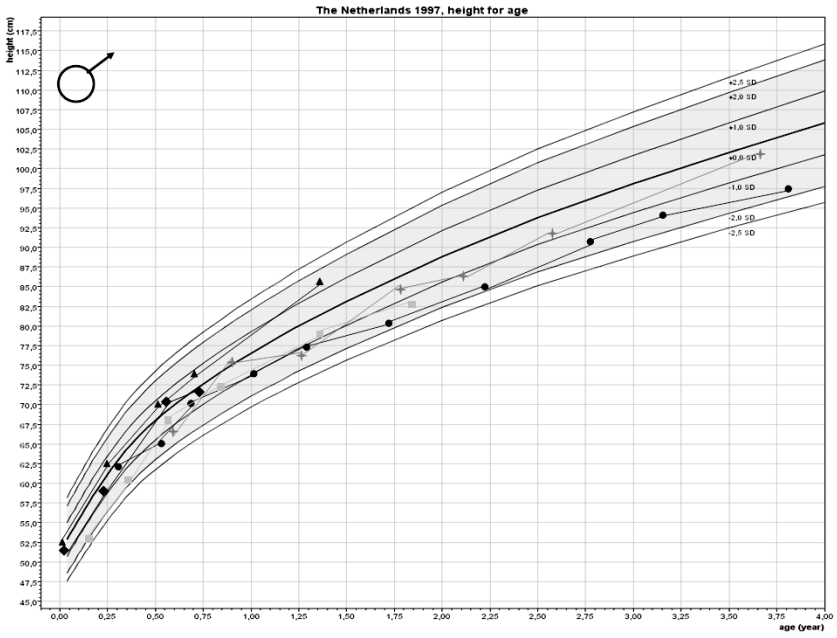
Resource consumption and costs

As shown in Table 1, initial length of stay (LOS) varied between 84 days and 350 days. Median LOS was 174 days (mean 182 days): 83 ICU days, 98 HC/MC days. A median of five surgical interventions (range 2 - 9) was performed during initial admission. The median number of re-admissions was 2 (range 0 to 52; 0 - 386 hospital days) (Table 2). The outlying value for patient 1 was mostly due to recurrent central line sepsis, that for patient 6 to diarrhea and sepsis. Overall, sepsis was the main reason for readmission. The number of outpatient visits was strongly related to duration of follow-up by the SBS team: the three patients who had been followed for more than 4 years were seen 26, 31, and 53 times, respectively, and had been admitted for a median of 409 days (total of all admissions). Median LOS for all ten patients was 239 days (range 84 to 478 days).

Table 4 lists the cost prices. Multiplying these prices by the respective volumes gave total costs of hospital admissions, surgical interventions, nutrition, and outpatient visits for each patient (Table 5). The average cost of the first hospital admission is € 166,045 (for hospital days only). Total costs (first admission and follow up) reached a maximum of € 455,400 for patient 6 (average € 269,700; median, € 250,500). On average, the total costs mainly comprise costs of hospital admissions (82%), followed by nutrition (12%), surgical interventions (5%), and outpatient visits (1%). Obviously, the costs are related to duration of follow-up. Therefore, we plotted the cumulative costs against the patient's ages (Figure 3). The average costs at the age of 3 years are € 321,000 (median, € 327,000).

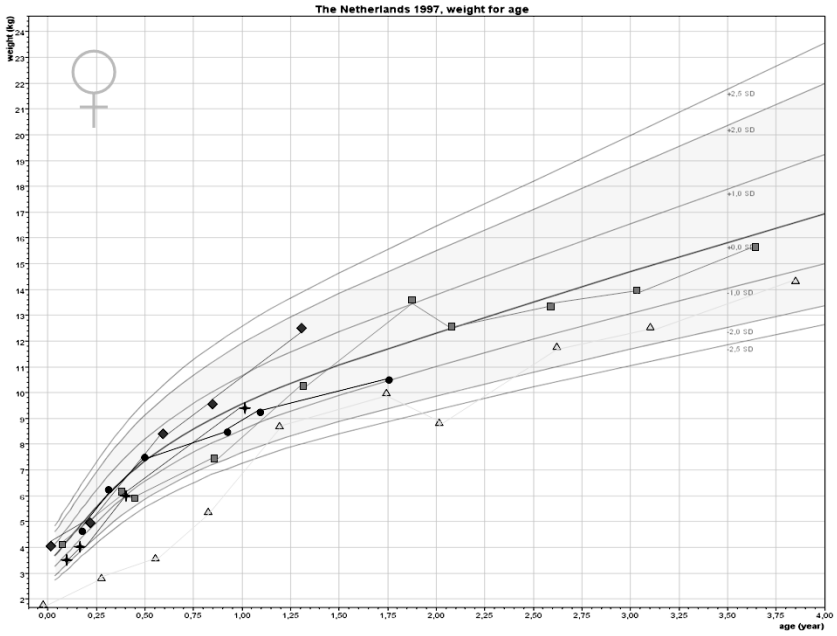
Figure 1 Growth charts males

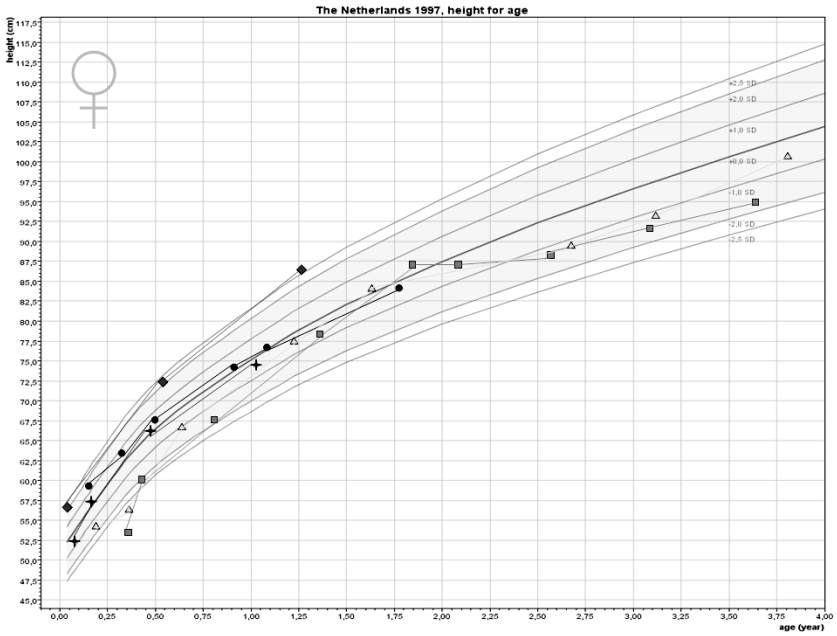




✦ *Patient 1*
● *Patient 6*
■ *Patient 7*
▲ *Patient 8*
◆ *Patient 10.*

Figure 2 Growth charts female





- *Patient 2*
- *Patient 3*
- *Patient 4*
- *Patient 5*
- *Patient 9.*

Table 3 Nutrition

					Total Nutrition					
	Enteral Nutrition during first admission				Parenteral Nutrition			Enteral Nutrition		
Patient	Start MEF (days)	Start ETN (days)	Type of Nutrition	Interruptions[†] (n)	Mean Intake[‡] (ml/day)	Duration (days)	HPN (days)	Mean Intake[‡] (ml/day)	Duration (days)	Mean Type ETN
1	3	6	Polymeric	3	559 ml	> 1,985[*]	> 1,682[*]	649	> 2,131[*]	50% semielemental / 50% polymeric
2	6	10	Semielemental	3	285 ml	190	1	699	359	semielemental
3	6	27	Semielemental	7	285 ml	189	-	848	> 1,879[*]	35% semielemental / 65% polymeric
4	13	23	Breast milk	6	290 ml	300	77	537	345	semielemental
5	18	49	Semielemental	1	206 ml	477	162	398	429	semielemental
6	24	51	Semielemental	1	413 ml	> 1,508[*]	> 1,036[*]	455	> 1,595[*]	70% semielemental / 30% polymeric
7	-	-	-	-	920 ml	> 706[**]	> 465[**]	-	-	-
8	2	64	Breast milk	4	412 ml	247	106	297	425	polymeric
9	3	6	Breast milk	0	273 ml	77	-	301	86	polymeric
10	83	162	Breast milk	5	740 ml	> 347[*]	n.a.	102	> 185[*]	11% semielemental/ 89% polymeric

Abbreviations: MEF, minimal enteral feeding; ETN, Enteral Tube Nutrition; HPN, home parenteral nutrition.
** Patient was still on total parenteral/enteral nutrition at December 31, 2007, ** Patient was still on HPN when lost to follow-up.*
[†] Number of interruptions in enteral feeding, [‡] Mean intake/day for the total period they received PN and or ETN.

Table 4 Costs of units pertaining to the direct medical costs of treating patients with SBS

Hospital days	
Intensive care	€ 1,359
Medium care/high care	€ 538
Surgical interventions*	
Bowel	€ 1,772
Inserting and/or removing a CVC	€ 939
Other (e.g., endoscopies, biopsies)	€ 821
Nutrition	
Parenteral nutrition (per day)	€ 37 - € 73†
Enteral tube nutrition (per day)	€ 0.19 - € 14†
Outpatient visits	
SBS team	
First visit	€ 175
Revisit	€ 162
Regular visit	
First visit	€ 60
Revisit	€ 48

* *Not all surgical interventions performed on the patients can be enumerated here. To give an impression of the costs, interventions were organized into three categories, of which the table gives the average prices.*
† *Depending on the quantity and type of nutrition.*

DISCUSSION

So far, the interdisciplinary SBS team in our department followed 10 children with infantile short bowel syndrome. To our knowledge this is the first study describing resource consumption. Management of these children makes a substantial claim on health care resources, with an average total cost of € 269,700. The costs mainly comprised hospital admissions (82%). Seven patients had normal growth. Six patients could be weaned off PN, and five could be weaned off ETN, resulting in full oral intake.

The literature contains several studies on interdisciplinary SBS teams.[26-31] The picture emerging from these studies is that such teams have great merits and that early referral is important for successful management.[4,26,30,31] A study by Modi et al., using a historical comparison group, indeed indicated that a multidisciplinary SBS program, coordinating both inpatient and outpatient management, was associated with a higher survival rate.[29] Diamond et al. used a similar methodology, but their study did not confirm these findings: an SBS program did not show better overall survival and nutritional outcomes.

Table 5 Costs of hospital admissions, surgery, nutrition, and outpatient visits

Patient	Hospital admissions			Surgical interventions	Nutrition	Outpatient visits	Total costs
	First admission	Readmissions	Total				
1	€ 91,900	€ 151,700	€ 243,600	€ 37,000	€ 117,000	€ 6,100	€ 403,700
2	€ 225,700	€ 19,400	€ 245,100	€ 7,500	€ 10,300	€ 1,100	€ 264,000
3	€ 295,700	€ 3,400	€ 299,100	€ 9,700	€ 34,000	€ 1,000	€ 343,800
4	€ 197,800	€ 5,600	€ 203,300	€ 7,700	€ 14,000	€ 1,200	€ 226,200
5	€ 240,600	€ 69,800	€ 310,400	€ 9,900	€ 20,000	€ 4,200	€ 344,500
6	€ 124,600	€ 212,700	€ 337,300	€ 26,600	€ 82,900	€ 8,600	€ 455,400
7	€ 111,600	€ 41,400	€ 153,000	€ 11,100	€ 46,900	€ 1,600	€ 212,600
8	€ 109,600	€ 5,700	€ 115,200	€ 11,500	€ 14,500	€ 2,000	€ 143,200
9	€ 58,700	-	€ 58,700	€ 4,000	€ 3,100	€ 700	€ 66,500
10	€ 204,100	n.a.	€ 204,100	€ 7,500	€ 25,300	n.a.	€ 237,000

Figures are rounded to the nearest € 100.
Abbreviation: n.a., not applicable.

Still, mortality from liver failure had decreased, and fewer septic periods were noted.[28] Torres et al. showed that under the management of an interdisciplinary team, liver function and nutritional parameters had improved even in patients with < 40 cm intestinal length or < 10% of normal bowel length; they could be weaned off PN while maintaining growth.[31] In addition, interdisciplinary SBS teams may deliver other more intangible benefits to the patients and their parents, such as integration of expert management, better continuity of care and improved communication with and satisfaction of parents.[27,30] None of the above mentioned studies described the costs of such teams nor costs of treatment.

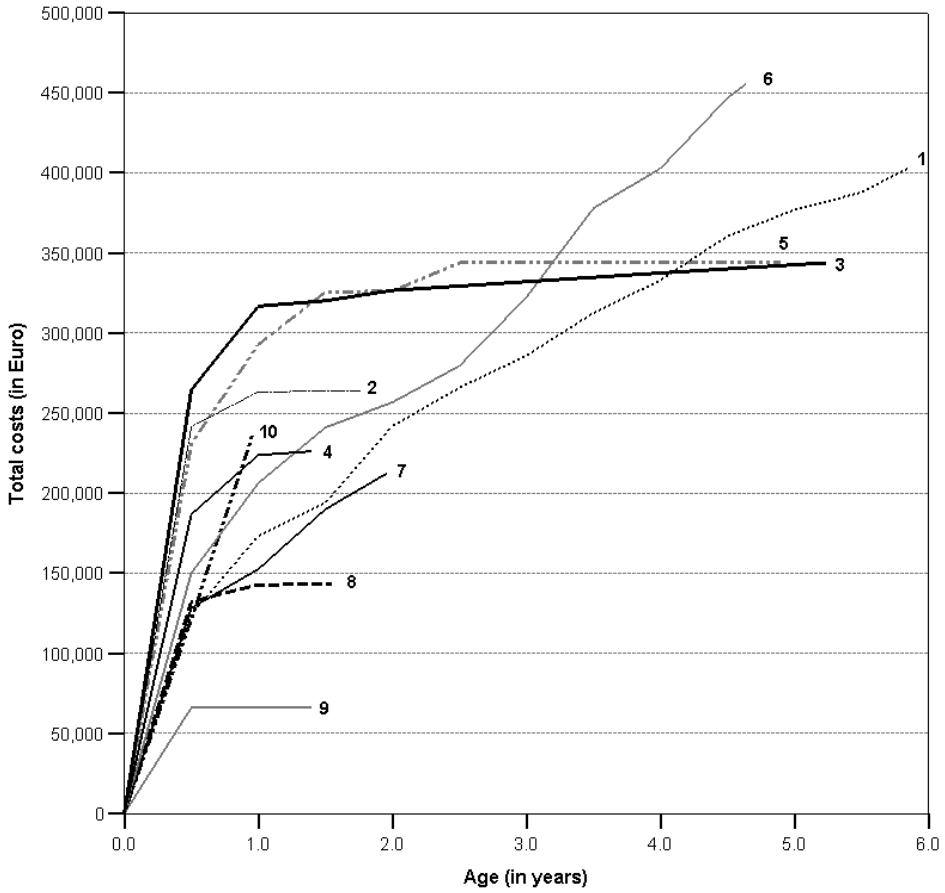
The scarce studies into resource consumption and costs of SBS treatment, have mostly been limited to the initial hospitalization and are somewhat outdated. For example, in the 1989 study of Caniano and co-workers, the average cost of the initial hospitalization was $ 315,000 -equivalent to € 389,000 in 2006-, with an average stay of 450 days in 10 patients.[15] Recently, Longworth et al. showed that the average costs of 24 stable SBS patients (not requiring transplantation) were £ 159,000 based on 1998/1999 prices equivalent to € 266,000 in 2006- over 30 months with a mean hospital stay of 50 (± 74sd) days.[32] To compare costing studies from different countries is a perilous exercise, because of differences in the range of health care facilities available, in incentives to health care professionals and institutions, and in absolute and relative prices of health care resources.[33,34] Still, the findings by Longworth seem roughly in line with the costs calculated in our study (average total costs of € 321,000 at the age of 3 years). It seems that the costs in our study (initial hospitalization costs of € 166,045, for hospital days only) are clearly lower than the costs reported by Caniano et al. This may be explained by the 2.5 times longer initial hospitalization in the patient group described by Caniano.

A growing interest in evidence-based and cost-effective medicine has emerged.[35,36] Society increasingly demands to provide insight into whether the effects of treatment are large enough to justify its costs. The present study calculated considerable direct medical costs of treatment for SBS. From the perspective of a decision maker faced with scarcity of resources, the question is whether the outcomes in terms of length and quality of survival are worth these high costs. Mental and motor development and health-related quality of life of patients with SBS as described in the literature are generally satisfying.[37-39] The design of our study did not provide for an evaluation of the (cost-) effectiveness of the interdisciplinary SBS team. Such evaluations, using a controlled design, are not easy to achieve, because it is difficult to create a genuinely comparable control group. Nevertheless, we feel that the interdisciplinary team has important merits, in terms of efficiency and quality of care. The SBS team was launched with the explicit aim of facilitating patients' transition from inpatient PN to HPN and

therefore reduction of costs can be expected. As early as 1993, Schalamon and co-workers had calculated that the annual cost for PN in hospital is approximately $ 205,000 compared to $ 90,000 for HPN.[40] Other authors also showed that HPN is about 50 - 75% percent more "economical" than in-patient hospital care.[41-43]

It can be concluded from Figure 3 that the costs for most patients seem to reach a plateau within a couple of years, probably reflecting completion of intestinal adaptation and thus less need for PN. Costs for two patients (1 and 6) steadily increased, however, as they could not be weaned from PN with concomitant complications.

Figure 3 Total cumulative costs per patient by age during follow-up



There are some points to bear in mind when interpreting the costing results of our study. First, the number of patients was rather small. Second, we did not calculate costs of laboratory tests, diagnostic radiology, intercollegial consultations and medications of outpatients. It is plausible however that these costs make up only a minor proportion of the total costs, and that this omission therefore did not bias the results. Third, we adopted a combination of top down and bottom up calculations, which is common practice. Applying bottom up techniques for all cost items would have resulted in more precise calculations, but is very labor intensive and is unlikely to have substantial effects on the overall outcomes of the calculations. Despite these reservations, we have confidence in the results, as we applied established methods, for example calculating real economic costs and not relying on charges, which do not provide a true representation of the real costs incurred.

Previously we have shown shorter LOS, shorter duration of PN and significantly higher SD-scores for weight for age for SBS patients in the years 1990 - 1999 as compared with the preceding decade.[13] We concluded that there was still room for improvement, notably with regard to stimulating early nutritional intake.[13] Comparison cannot be extended however, to present case series, as these 10 patients have much shorter bowel lengths than the ones in decade 1990 (Median 28 cm [0 - 100 cm (range)] versus 74 cm [30 - 120 cm (range)]).

For none of the patients, SD-scores on weight for age declined in the first year of life. All patients but one grew according to their growth curve. This is consistent with a study performed by Torres et al.[31] Our observation that three out of the ten children grew below their target height range is more in line with other studies reporting higher percentages of growth failure.[27,30,44] Two of the three patients with impaired growth had been born prematurely. Few studies showed that premature children even after catch-up growth will have suboptimal growth attainment.[45-47] Two patients needed no longer be followed after 2 - 4 outpatient visits. Bowel adaptation occurred under the management of the SBS-team and they grew properly on oral nutrition without the support of PN nor ETN.

Minimal enteral feeding was started as early as 2 days to as late as 83 days after surgery. Early MEF seemed to shorten PN dependency, except for the patient diagnosed with long segment Hirschsprung disease. A sicker bowel is likely to be associated with later start of MEF. Duration of ETN lasted between 86 to over 2131 days. Duration of ETN did not differ between five patients who received polymeric nutrition (of whom four breast milk) and the four who received semielemental nutrition. Likewise Ksiazyk et al. did not find any difference in absorption between polymeric and semielemental nutrition.[48] Moreover, Koehler et al. also did not find an

association between the type of formula used and successful weaning from ETN.[27] These studies are in line with our previous findings on protein absorption in preterm neonates after bowel resection.[49] We demonstrated that protein absorption capacity of the small intestine is intact and that the findings do not support the use of semielemental formula to improve the amino acid uptake.[49] Since semielemental formula is much more expensive than polymeric formula, the latter would therefore be the preferred formula. Nevertheless, we studied a small and heterogeneous group of patients with different bowel lengths and underlying diagnoses.

In conclusion, treatment of infantile SBS requires considerable resource consumption, especially when patients depend on PN. As the costs mainly comprise hospital admissions, early HPN could contribute to cost reduction. Systematic nutritional strategies are essential to wean SBS patients off PN as soon as possible and thus prevent, delay or reverse complications such as PN-induced liver disease. The ultimate goal is to optimize intestinal adaptation while preserving adequate growth and development. Interdisciplinary teams have the potential to facilitate early HPN, and to optimize growth by tailor made treatment. Thus, they may be instrumental in reducing health care costs, while at the same time benefiting patients' health and quality of life of both patients and parents.

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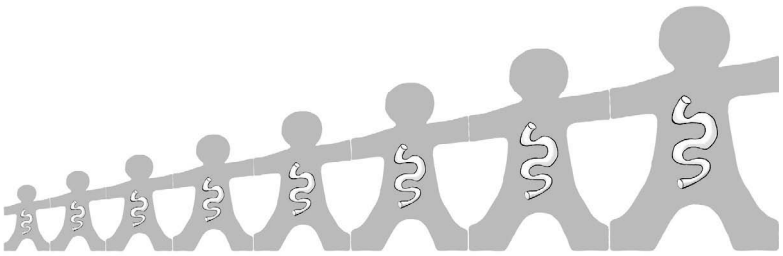
Chapter 8

General discussion



INTRODUCTION

Short bowel syndrome (SBS) is defined as a state of malabsorption secondary to either congenital intestinal shortening or massive small bowel resection, which impairs the capacity to maintain an adequate nutritional status.[1,2] Some of the underlying diseases, such as gastroschisis and intestinal atresia, not only affect residual bowel length, but may also influence its residual function and adaptation potential.[3] Successful bowel adaptation refers to the capacity of structural and physiological alterations of the bowel that allow children with SBS to grow healthily while receiving oral and/or enteral nutrition. There is a range of factors that may predict whether adaptation will be successful. These include: age, underlying diagnosis leading to SBS, length and section of small and/or large bowel resected, presence or absence of the ileocecal valve and/or colon, intrinsic adaptive potential of remaining bowel, health of other organs involved in digestion and absorption, and the presence or absence of bacterial overgrowth of the small intestine.[4] Furthermore, the long-term outcome is determined by the rate at which enteral feedings can be provided postoperatively while the child is on parenteral nutrition (PN), and by the type of enteral feedings.[4]

Infantile short bowel syndrome has significant morbidity and is potentially lethal – especially when intestinal loss is extensive.[5] A multitude of complications may occur secondary to long-term hospitalization and prolonged PN, such as central line related complications, multiple systemic infections, PN-associated liver disease (PNALD), and failure to thrive.[6] Major predictors of mortality in pediatric SBS are PN-associated cholestasis and shorter age-adjusted remaining small bowel length.[7] On the other hand, intestinal continuity and preservation of the colon are predictors of survival.[6,8]

PNALD is one of the most common and severe morbidities in children with infantile SBS. It is associated with a mortality rate approaching 100% within 1 year of diagnosis when children cannot be weaned off PN or will not receive a liver/small bowel transplant.[6] One study demonstrated a 25% prevalence of PNALD in 36 patients with chronic intestinal failure, of whom 43% had SBS.[9] A review estimated that generally 30-60% of children develop hepatic dysfunction while receiving long-term PN.[10] Risk factors for developing PNALD include prolonged PN, prematurity, frequent surgical procedures, lack of enteral intake and thus disruption of the enterohepatic cycle, intestinal stasis with subsequent bacterial overgrowth, early and/or recurrent catheter related sepsis.[1,4,11]

Survival rates of neonatal SBS patients have considerably improved over the years, reaching 70 to 90%.[6,8,12-14] This progress is mainly due to improved composition of PN, improved protocols for handling central venous catheters (CVC), interdisciplinary patient management and better outcomes of small bowel transplantation. Still,

reported mortality rates vary from 6 to 47%[6,8,12-18] and have not declined over the years. This discrepancy might be explained by different definitions of SBS used, differences in measured / documented bowel lengths and differences in durations of PN-dependency.

In light of this improved survival, the acute and long-term consequences of infantile SBS with respect to nutrition, nutritional status and growth, and health-related quality of life have been underreported so far. Exploring these aspects was therefore the overall aim of the work presented in this thesis.

Retrospective outcomes in the first year of infantile short bowel syndrome

Advances in knowledge of the outcome and potential complications in children with SBS, for whom only few data were available, should lead to plan the therapeutic options that guarantee progress toward optimal intestinal autonomy. Moreover, assessing the factors that predict the development of definitive dependence on PN is of equal importance.[19] It was against this background that we have first addressed the question: What is the incidence of infantile SBS in our hospital and what was their first year outcome? From the study reported in chapter 2 it appeared that from 1990 - 2002 the Erasmus MC-Sophia Children's hospital admitted 75 new patients with infantile SBS, which roughly comes down to 6 new patients a year. For our referral area of 4 million inhabitants and 44,000 births per year, this would implicate an incidence rate of roughly 14 new patients per 100,000 births.

In the same vein, preliminary results of the national registry of short bowel syndrome estimated an incidence in the Netherlands of 14.2 per 100,000 births in May 2006 - May 2007 (Personal communication National Short bowel syndrome registry).

The study reported in chapter 2 also revealed that length of hospital stay (LOS) and duration of PN had decreased over the last decade. Furthermore, the length of the residual bowel in decade 1990 tended to be longer than that in decade 1980, which might explain the shorter LOS and the shorter duration of PN. This is in line with the study of Spencer et al, in which residual small bowel length was found to be a major predictor for weaning from PN.[7]

Moreover we showed that SD-scores of weight for age (corrected for gestational age) in the first year were significantly higher in children admitted in decade 1990, albeit still subnormal. The high proportion of premature infants (almost two thirds) might partially explain the subnormal SD-scores. Cole et al. found growth deficits in premature patients with SBS to be more severe than in premature patients without SBS after a follow-up of 18 - 22 months, indicating the impact of SBS. Possible reasons were not

identified, but it can be assumed that patients were not receiving adequate nutrition from their current mode of feeding (eg, enteral feeds may have been given at targeted rates, but nutrients might have been lost via the stool).[20] Subnormal growth might lead to malnutrition on the long term and even delay further growth and development.[21]

Given these outcomes (chapter 2) there is still room for improvement in the care of children with SBS, notably with regard to nutritional status and support. Improvement could be reached by having an interdisciplinary team manage these children. An important player in such a team is a pediatric dietician with special knowledge and interest in this subject. Given the low incidence of this condition and the variable functional capacity of the remaining bowel, excellent collaboration between pediatric surgeons, dieticians and pediatric gastroenterologists is an important step in improving care for this vulnerable patient group (see further below).

Measuring nutritional status

As we have shown in chapter 2, improvement in the acute care of children with infantile SBS is needed, notably with regard to nutritional status and growth. Decrease in growth rate during infancy is one of the earliest indicators of malnutrition. This is a condition that might lead to poor wound healing, higher risks of infections due to poor immune defence, reduced gastrointestinal function, longer dependency on mechanical ventilation, and longer hospital stay.[22] It might also jeopardize future growth and development.[21] So it would seem very important to identify those children with pre-existing poor nutritional status and those at risk for developing malnutrition during admission.[23] In general, accurate nutritional assessment in children is complex, in view of their linear growth, changes in energy requirements, varying body composition and (acute) disease.[24] Measurements of weight and height alone are not sufficient in critically ill children. Determining body composition provides more detailed information of nutritional status because body compartments are indicative of nutritional stores.[25] The more so because a possible weight shift by third spacing of fluids could lead to weight overestimation.[26]

Earlier we demonstrated that longitudinal reliable assessment of nutritional status using non-invasive methods (i.e. weight, height, skinfolds) in critically ill children at an intensive care unit (ICU) is feasible, feasibility decreased for children with more severe illness and higher age upon admission.[23] These findings were reason to recommend implementation of standardized nutritional assessment.[23] In chapter 3 we studied how implementation had proceeded. Weekly nutritional assessment in a group of children at high risk of developing malnutrition, namely those with congenital anomalies of the intestinal tract (including SBS patients), proved not feasible in the present setting. In no more than 15% of these 89 children all measurements had been performed according

to the proposed frequency. Feasibility was negatively influenced by length of hospital stay, and a major reason for missed measurements was unavailability of the anthropometrists. In order to improve the frequency of weekly monitoring of nutritional status in critically ill children during ICU hospital stay, trained staff should be structurally available. Summarizing, during admission infantile SBS patients showed impaired growth (chapter 2) and structural measurement of nutritional status in critically ill children (which includes SBS patients in the first few months) was hampered by lack of trained personnel (chapter 3).

Both findings justify the institution of a nutritional support team that provides the necessary infrastructure for reliable nutritional assessment measurements. The nutritional support team should collect and store measurement data, evaluate and interpret the nutritional status on a weekly basis, and if necessary provide information on adequate nutritional support. Moreover, it could be of major importance in educating all caring personnel on nutritional assessment, and reduce possible inter-observer variability.[27] Furthermore such a team, consisting of physicians, nurses and dieticians, should construct clinical guidelines and perform longitudinal research on nutritional status and nutritional support, during admission and long-term follow up, in relevant groups of children at risk of developing malnutrition.

Nutrition and SBS

The previous chapters have underlined the importance of measuring nutritional status in the acute phase of SBS. Malnutrition should be avoided by optimizing individual nutritional support. This observation raised the question: what is the optimal nutritional support in children with SBS? Systematic research on the type and onset of enteral and oral nutrition in children with short bowel syndrome is scarce. Such studies are difficult to perform in a methodologically sound way. The incidence of the disorder is assumed to be low and the underlying etiology, remaining bowel length and thus its manifestation may vary in every patient. Thus, dietary management will be highly variable. In clinical practice, the route of administration and composition of the diet of children with SBS are best determined on the basis of the underlying disease, location and length of the remaining bowel, presence of the colon, and the child's age. The enteral feeding regimen in children with SBS is under debate. Subjects of discussion are its mode of administration (continuously or portions), its time of introduction, its composition (polymeric or semielemental or elemental), introduction of oral feeding (time and composition) and the supplementation of fibers.

The goals of nutritional support in patients with SBS are twofold – providing safe, adequate supplemental nutrients to preserve lean body mass and function, and if possible, supporting and accelerating the body's own adaptive mechanisms.[28]

Therefore, different approaches are needed, especially in the first acute phase of SBS. For example, when aiming at providing as many calories as possible, we might choose a type of enteral nutrition that differs from that aiming at promoting bowel adaptation. In a review of the literature (chapter 4) we have presented the current state of the research in children with SBS and gave evidence-based recommendations where possible (according to the Scottish Intercollegiate Guidelines Network criteria (SIGN).[29] In the absence of evidence, clinical recommendation based on expert opinion was integrated in this chapter. Evidenced-based recommendations were: Enteral nutrition should be initiated as soon as possible (i.e. a few days after bowel resection) to promote intestinal adaptation. This supposition is supported in the literature by level 1 studies.[30,31] There is no difference in absorption between polymeric and oligomeric formulas (level 1+),[32] therefore polymeric nutrition is recommended as first choice of enteral feeding. Multiple experts recommended breast milk as first choice of enteral feeding,[33-37] but this recommendation is not evidenced-based. Breast milk will be discussed in a next section.

Several clinical recommendations were based on level 3 evidence or even based on expert opinion (level 4); Administer enteral nutrition in a continuous fashion as this promotes nutrient absorption (level 3).[38] Gradually (eg. twice a week) increase volumes with small amounts (eg. 1 ml/h), so that the bowel has enough time to adapt to increasing volumes. Small volumes of bottle-feeding should be started as soon as possible to stimulate the neonate's suck and swallow reflexes. Solid foods can be introduced at the age of 4 - 6 months (if necessary corrected for gestational age) to stimulate oral motor activity and to avoid feeding aversion behaviour. When the colon is present, soluble fibers and starches can be added to the diet in order to prolong transit time.

As shown in chapter 4, it is not possible at the time of writing, to solely base the nutritional regimen of children with SBS on evidence obtained from previous scientific studies. Studies focusing on effectiveness of different feeding options in this relatively small patient population are rather scarce and most have relatively low methodological quality. Thus, future research is needed to provide evidence-based findings that may guide clinicians in the management of these patients. As the incidence rate of SBS is low, it is important to perform multi-center studies to increase the number of patients and thereby improve statistical power. In order to perform multi-center studies a prerequisite is consensus on the definition of SBS.

Nutrition and bowel adaptation

It is generally accepted that enteral nutrition enhances bowel adaptation. The mechanism by which enteral nutrients stimulate adaptation is complex and can be broken down into three major categories:

1. by stimulation of mucosal hyperplasia by direct contact with epithelial cells,
2. stimulation of trophic gastrointestinal hormone secretion, and
3. stimulation of the production of trophic pancreatobiliary secretions.[36,39]

Suggested luminal factors are presented in Textbox 1.[36,39,40] After neonatal small intestinal resection it may take over five years before adaptation is complete. The composition of the diet should be considered in an effort to balance gastrointestinal tolerance with specific nutrients in a complex form that may further stimulate the adaptive process.[40]

It is strongly recommended to find ways in which adaptation can be facilitated, for example by adding novel substrates to enteral feeds.

TEXTBOX 1: LUMINAL FACTORS IN BOWEL ADAPTATION

Nutrients

- *Long chain triglycerides (LCT)*
- *Proteins*
- *Glutamine*
- *Dietary fiber*

Hormones

- *Enteroglucagon*
- *Growth hormone*
- *Glucagons-like peptide 2*
- *Cholecystokinin*
- *Gastrin*
- *Neurotensin*
- *Glucagons-like peptide YY*

Growth factors

- *Epidermal growth factor (EGF)*
- *Insulin like growth factor I (IGF-I)*

Prostaglandines

Polyamines

Glutamine

A potential candidate, glutamine is known to serve as a metabolic substrate for the small intestine. Four major findings supports its candidacy:

1. Glutamine is an essential fuel for the enterocyte and for immune cells and cannot be substituted by other amino acids,
2. during periods of stress, a state of relative glutamine deficiency exists, as evidenced in plasma glutamine levels,
3. supplementation of exogenous glutamine delivers essential fuel to tissues in need,
4. the small intestinal mucosa becomes atrophic when the gut is deprived of glutamine, as in the case during total parenteral feeding.[41]

Parenteral glutamine supplementation in animals following massive intestinal resection enhanced mucosal hyperplasia.[42,43] One study found that increasing glutamine content of feeds to 25% of total amino acids produced, enhanced jejunal and ileal hyperplasia, even on a hypocaloric feed, and improved overall weight gain.[44] Several other animal studies could not demonstrate a stimulatory effect of glutamine enriched enteral nutrition on adaptation.[45-47] At present, studies in humans are very limited. Glutamine supplementation of parenteral nutrition in newborns and infants after major digestive surgery did not decrease sepsis rate.[48] Neither did enteral glutamine supplementation affect the sepsis rate in 314 very low birth weight (VLBW) infants.[49] Others showed that enteral glutamine supplementation in VLBW infants decreased the sepsis rate but did not improve feeding tolerance.[50] In six studies in adults with SBS, glutamine was administered orally and/or intravenously for 28 - 56 days, which did not result in significant changes in the surrogate parameters tested in four studies.[51-54] The two other studies showed a significant increase in lean body mass.[55,56] In conclusion, even though the animal studies were encouraging, so far neither enteral nor parenteral supplementation of glutamine has proven to enhance bowel adaptation.

Dietary fiber

Another luminal nutrient potentially enhancing bowel adaptation is dietary fiber. Fiber can be subdivided into soluble and insoluble forms. Insoluble forms (e.g. cellulose found in cereals) bind to water and cause bulking and softening of the stool and decrease whole gut transit time. Soluble fiber (e.g. pectin, guar gum found in fruits and vegetables) slow gastric emptying and overall gut transit time, resulting in a mild anti-diarrheal effect.[57,58] Bacterial fermentation of soluble fiber in the colon produces short chain fatty acids (SCFAs), which are an important source of energy:[59] SCFAs account for 5 - 10% of the total energy requirements.[60] Animal studies have shown that pectin enhanced bowel adaptation.[61,62] There are no human studies on the effect of pectin on bowel adaptation. As described in chapter 4, only one case study reported that pectin

supplementation in one patient caused a prolonged transit time and higher nitrogen absorption.[63]

Breast milk

The health benefits of breast milk have been amply documented; its use is associated with significantly decreased risks of infection, allergy, respiratory diseases, diabetes and otitis media.[64] Exclusively breastfed children have reduced risk of infectious diseases such as diarrhea and respiratory infections.[65] It has been postulated that breast milk, which contains glutamine and growth factors (e.g. growth hormone and epidermal growth factor), might also enhance bowel adaptation.[36,37] A few cohort studies have demonstrated that breast milk contains high amounts of nucleotides, immunoglobulin A and leucocytes, which support the immune system of the neonate.[66,67] As described in chapter 4, one study found that breastfed infants with SBS were weaned off PN earlier than non-breastfed SBS infants.[34] Human studies on the effect of breast milk on bowel adaptation are lacking. However, some studies have suggested that breast milk decreases the risk of necrotizing enterocolitis (NEC) in newborns.[68-71] One third of all NEC patients require surgical intervention, and a quarter of those patients develop SBS.[72] As shown in chapter 3, thirty percent of all SBS patients had NEC as the underlying diagnosis. Therefore it might even be hypothesized that breast milk might prevents NEC to some extent and thus lowers the incidence of SBS.

Donor breast milk is an alternative form of milk when the mother's own milk is not available or is in short supply.[71] The use of donor breast milk varies across the world.[71] Donor milk is pasteurized (heated to 62.5 ^{o}C for 30 minutes) and then frozen. This process inactivates HIV, cytomegalovirus and other viruses, but also affects the nutritional and immunological properties of breast milk.[73] These properties of breast milk might be important for bowel adaptation. Although a few studies have shown that donor breast milk also decreases the risk of developing NEC compared to formula feeding,[70,71] it is unknown whether donor breast milk also has the potential to enhance bowel adaptation.

Strong evidence continues to demonstrate that breast milk is the optimal source of nutrition for infants. It is associated with lower rates of infections diseases during infancy and therefore also recommended as the first choice of enteral feeding in SBS patients (chapter 4).

Randomized controlled trials are needed to investigate the role of (donor) breast milk on bowel adaptation. Other randomized controlled trials should confirm the advantages of (donor) breast milk over formula feeding, with enteral tolerance and time to enteral autonomy as primary endpoints.

Long-term outcomes of infantile SBS after 5 years or more

In the light of improved survival, patient evaluation should not only focus on outcome of growth, nutritional status and potential adequate nutritional support over the first year. It is equally important to determine the long-term impact of infantile SBS so that parents can be informed of their child's future perspectives. To this end different types of outcome measures should be included, such as nutritional status, body composition, symptoms, general health, and health-related quality of life (HRQoL). Therefore a cross-sectional study, in which SBS patients ranging in age from 5 to 30 years participated, was set up to obtain information on general health, disease impact, growth and nutritional status during different phases of life.

In chapter 5 we have demonstrated that these subjects had shorter stature and lower bone mineral content than healthy controls. Strikingly, they had normal weight for height and percentages of body fat. Shorter stature might have resulted from chronic malnutrition. All patients who participated in the cross-sectional study were also in the retrospective study (chapter 2), which allows us to make a rough comparison between the first year and the follow-up measurement. Even when SD scores for weight for age in the first year of life were subnormal, over time they reached almost normal values. It seems that growth impairment in the first year was worse (lower SD score) than after 5 years or more, but patients have not shown full catch-up growth. During the cross-sectional study, SBS patients reported low energy intake as well as intestinal bowel dysfunction, which might explain the growth impairment if both should have been present for a prolonged period. Linear growth in childhood is regulated by circulating growth hormone (GH) and insulin-like growth factors (IGFs) among other things.[74] However, prolonged malnutrition triggers adaptive mechanisms geared towards conserving energy, diverting substrates away from growth and reproduction to serve as alternative source of energy for critical homeostasis.[74] One consequence is relative GH resistance, reflected by normal or high spontaneous and stimulated GH serum and low IGFs levels.[75] There is potential for catch-up growth if the underlying growth inhibiting condition can be suppressed or modified. Catch-up growth is seen as accelerated linear growth and normalization of height towards parental target height.[74] Bone age represents skeletal maturation and is inversely related to linear growth potential, which makes delayed bone age a good predictor of catch-up growth.[76] It was expected that SBS patients also would have delayed bone maturation. Yet we could not demonstrate delayed bone maturation was, as total bone mineral density was found to be normal, unlike bone mineral content. The latter was lower, and could be explained by their smaller bones.

Future research should include determination of bone age by hand X-ray and measurement of serum GH and IGFs. Using these data we can explore the reasons for

shorter stature. The results of chapter 5 show that strict follow up into adulthood is important even after subjects have reached nutritional autonomy. Measurement of body composition is an essential aspect of providing optimal nutritional management (chapter 3 and 5) and should preferably be done by DEXA. This is a reliable instrument for body composition, including bone mineral density.

We have seen that survival of patients with infantile SBS has improved considerably. As shown in chapter 5, patients are in relatively good condition, as judged from their normal body composition and general health status. There is more to it, however, than these two aspects. To convey the full effect of a disease from the perspective of the patient, measuring HRQoL should be an integral component of long-term follow-up. HRQoL is concerned with the opportunities that a person's health status affords, the constraints that it places upon the person, and the value that a person places on his or her health status.[77] In the cross-sectional study described in chapter 6 we determined the long-term HRQoL in surviving children and adults with infantile SBS compared to healthy controls. Children with a history of infantile SBS reported a significantly lower quality of life (physical and psychosocial domains) than healthy children. The same was observed when questioning their parents. In adults with a history of infantile SBS quality of life was significantly lower than healthy controls on the domains of general health and vitality. Other domains were also relatively low, but differences did not reach statistical significance. The finding that children and adults with infantile SBS show lower HRQoL is consistent with studies in other patient groups with chronic diseases.[78-80] These findings stress the need for targeted interventions to address these dimensions of impaired HRQoL. HRQoL is dynamic and may fluctuate over time, therefore it should be routinely screened during standard interdisciplinary visits. Moreover, it is important to identify predictors of poorer HRQoL. In chapter 6 no correlation between shorter stature or abnormal stool consistency and HRQoL was found. The small sample size of patients might explain this. Identifying predictors contributing to poorer HRQoL enables the clinician to modify therapeutic approaches. This study has shown that surviving SBS and reaching nutritional autonomy (weaning from PN) with maintaining growth and good nutritional status should not be the only endpoint. An equally essential endpoint is quality of life.

Interdisciplinary team and resource consumption

Several institutions have developed intestinal rehabilitation programs in response to increasing concerns about morbidity following infantile bowel resection.[81-86] The ultimate goal of these programs is to optimize intestinal adaptation while preserving adequate growth and development. A few studies have shown that an interdisciplinary SBS program, coordinating both inpatient and outpatient management, improved patients' clinical outcome.[81,84,85] A rehabilitation program may have a surgical

component, i.e. lengthening the remaining small bowel in order to increase nutrient and fluid absorption, by either slowing the transit time or increasing the surface area.[1] Intestinal lengthening procedures take advantage of the bowel dilatation that often occurs in the foreshortened remaining small bowel.[4] One of these lengthening procedures is called serial transverse enteroplasty procedure (STEP).[87] A recent study reported that after a median follow-up of 12.6 months after STEP, enteral tolerance increased by 116% in 38 patients and that nearly half of them had been weaned off PN.[87]

Patients who cannot be weaned off PN and whose intestinal failure is considered to be permanent are considered candidates for intestinal transplantation when PN results in life-threatening complications.[4] The 1-year survival rate after intestinal transplantation has reached 80%;[88] the average survival rate 5 years after transplantation 50%.[89]

As stated earlier, PNALD is one of the most common morbidities. Early enteral feeding may slow its progression and may even reverse it once PN is discontinued and full enteral autonomy is reached.[90] Discontinuing PN is challenging in SBS patients who have not yet reached complete bowel adaptation and therefore still have poor bowel function.[91] The etiology of PNALD is unknown, but a contributing factor may be the intravenous fat emulsion, which mostly is derived of soybean fat.[92] Recently a few studies have shown that parenteral fish oil emulsion reverses PNALD.[92-94]

As reported above, SBS is a surgical and medical disorder associated with potentially life-threatening complications and long-lasting dependence on artificial nutrition. In earlier days, the management of patients with SBS was typically in the hands of several individuals, all specialists in their own discipline. Yet, to effectively meet the complex medical, psychological, and social needs of these patients and to guarantee continuity of care, it is increasingly acknowledged that treatment of SBS is best accomplished by an interdisciplinary team.[4] Such a team should include pediatric gastroenterologists and surgeons, specialized nurses, dieticians, social workers and psychologists.[82] Interdisciplinary teams are likely to be of particular value in early identification of patients at risk for long-term PN dependency, the first step toward avoiding severe complications. Close monitoring of nutritional status, steady and early introduction of enteral nutrition, and aggressive prevention, diagnosis, and treatment of infections such as catheter related sepsis and bacterial overgrowth can significantly improve the prognosis.[4]

In chapter 7 we described outcomes of the 10 children with infantile SBS followed by the interdisciplinary SBS team in our department so far. To our knowledge this was the first study describing resource consumption. Management of these children makes a

substantial claim on health care resources, with an average total cost of € 269,700 per patient. The costs were mainly comprised of hospital admissions (82%), with many of the readmissions being caused by (central catheter related) sepsis. The sepsis frequency per month PN was on average 0.3. As described in chapter 3, the retrospective patients had 0.44 and 0.36 septic events/month PN in decade 1980 and 1990 respectively. The current 10 patients seem to have lower frequencies of sepsis. This is remarkable in view of the fact that these patients have a shorter remaining small bowel and that a higher proportion lost their ileocecal valve (ICV) compared to preceding decades. Loss of ICV is associated with higher incidence of bacterial overgrowth and bacterial translocation, which might cause sepsis. In contrast to the patients of the preceding decades, the 10 patients described in chapter 7 went home with PN (HPN) and were managed by the interdisciplinary team. This led us to conclude that HPN and interdisciplinary management reduce the risk of sepsis.

Seven of the ten patients had normal growth. Six could be weaned off PN, and five could be weaned off ETN, resulting in full oral intake.

Chapter 7 concluded that treatment of infantile SBS requires a considerable amount of resources, especially when patients depend on PN. As the costs mainly comprise hospital admissions, early HPN could contribute to cost reduction. Systematic nutritional strategies are essential to wean SBS patients off PN as soon as possible and thus prevent, delay or reverse complications such as PNALD. Interdisciplinary teams have the potential to facilitate early HPN, and to optimize growth by tailor made treatment. The interdisciplinary team should be involved in the treatment immediately after the initial surgical intervention, so that continuity of care can be guaranteed. Moreover the team can educate parents in HPN as soon as possible, which enables early discharge of these patients and therefore costs reduction.

We consider such teams as instrumental in reducing health care costs and at the same time benefiting patients' health and quality of life of both patients and parents, which would result in a favorable cost-effectiveness profile. However, testing these hypotheses on the cost-effectiveness of the interdisciplinary team was outside the scope of this thesis. Further work is required in order to evaluate the cost-effectiveness of the interdisciplinary team, as well as that of the entire SBS treatment process. Generally, current knowledge on the cost-effectiveness of neonatal surgery is still incomplete.[95,96] This may put the discipline in a weaker position in decisions on the allocation of resources, because as a society we increasingly demand that treatments offer good value for money.

The findings presented here have still other implications, which relate to the organization and financing of health care. Bearing in mind the low number of patients (approximately 26 new patients per year in the Netherlands) and the treatment's complexity, it may be argued that in the Netherlands the treatment of SBS should be concentrated at a single center – which should be in cooperation with and preferably coordinated by the Dutch Association of Pediatric Surgery. After all, centralization of complex treatments in designated centers ensures a sufficient case load of patients and thereby ensures appropriate levels of expertise and experience.[97,98]

Several financial issues should be taken into consideration. To protect the financial stability of the hospital, the state's hospital financing system should recognize and support the treatment by interdisciplinary teams. To this aim, the financing system should preferably be expanded with a new diagnosis treatment combination (DBC). DBCs form the basis of the recently revised hospital financing system in the Netherlands. When an innovative intervention comes available, an interested party may apply for a new DBC. This will subsequently be subjected to a health technology assessment (for example considering effectiveness, cost-effectiveness, and necessity).[99] In this view the data presented in chapter 7 have provided an important contribution towards requirements for application for a new DBC.

METHODOLOGICAL CONSIDERATIONS

Study population

The group of patients studied in this thesis is heterogeneous with respect to the underlying diagnosis and remaining small bowel lengths, which is inherent to SBS. Therefore, clinical presentation and severity of symptoms might have varied.

Subjects for our studies (chapters 2, 5 and 6) were identified from medical records and eligible patients could have been missed. It is possible that significant differences in outcomes did not surface, because the study population was too small. Due to the small number of patients, formal power analyses were omitted for two reasons. First, previous studies that give estimates used in the power calculation are scarce. Second, if power analyses would have been based on data from other populations, it would have been difficult or even impossible to include the required number of patients in a single-center study. To increase the sample size and therefore improve statistical power future multiple-center studies are advocated, potentially within European context.

Study design

The study design in chapter 2 was retrospective, thus the data collection is based on the documentation of others, which might have resulted in missing data.

The cross-sectional design (chapters 5 and 6) resulted in a single assessment of parameters, which are likely to fluctuate over time. For example, bowel function is an individual parameter and may be different in childhood than in adolescence. Moreover, time between the onset of SBS and follow-up assessment was different between patients; therefore every patient could have been in a different phase of SBS, which might have influenced the medical and HRQol outcomes.

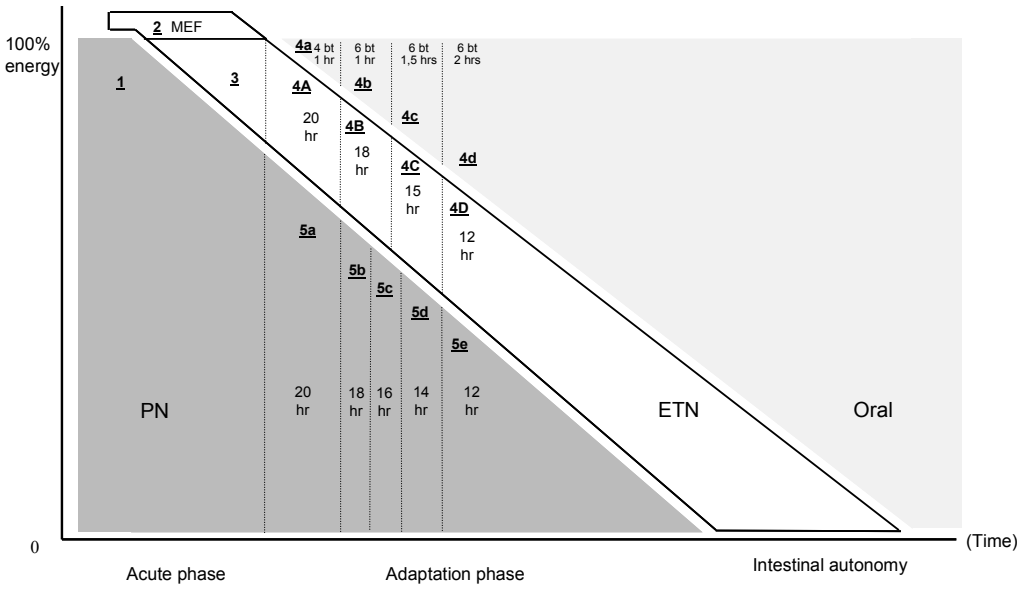
Prospective cohort studies (course of the disease and long-term outcomes) and randomized controlled trials (effectiveness of treatment) with multiple centers participating Europe-wide, funded by European grants, would be ideal to make a significant step towards increasing the knowledge of SBS.

CLINICAL IMPLICATIONS

Previously clinical management was based on "trial and error". The studies presented in this thesis have shown that there is still room for improvement of care in this vulnerable group of patients. It is important to provide continuity of care, especially in dietary management. Even though the manifestation of SBS is variable in every patient and care should be tailor made, it is important to have systematic nutritional strategies that can be adapted to the patient's specific needs. In Figure 1 and the accompanying Table 1 we propose a systematic nutritional strategy based on the findings of our research, current literature and our clinical experience. It consists of a visual time frame based on the phases of SBS.[33] It is not possible to present exact time intervals in days/months/years, because the course of the disease varies in every patient. Minimal enteral feeding is placed on top of the 100% energy intake, because it is not considered to provide energy, but rather as luminal nutrient for bowel adaptation. Oral feeding can be used at the same time as continuous enteral feeding therapy. We recommend to start bottle feeding as soon as possible. For example, stop continuous enteral feeding for one hour and give one hour dose per bottle (step 4, Table 1) to stimulate the suck and swallow reflex.

It is important to increase the volume of enteral feeding not too aggressively, as an aggressive strategy will probably cause osmotic diarrhoea and/or vomiting. Therefore we advocate patience and a strategy in which the volume is slowly increased by 1 ml/hr twice a week. In addition, we recommend the use of breast milk as the preferred type of enteral feeding. Moreover, it should be considered to set up a donor milk bank to provide donor breast milk when the mother's breast milk is not available.

Figure 1 Proposed systematic nutritional strategy



The numbers in the figure correspond with the steps presented in Table 1.
Abbreviations: PN: parenteral nutrition, MEF: minimal enteral feeding, ETN: enteral tube nutrition, bt: bottle, hr: hour

Other clinical implications are:

- The severity and complexity of SBS patients require a structured long-term program of care, which should be provided by an interdisciplinary team. The ultimate goal of this team should be to optimize intestinal rehabilitation, while preserving adequate growth and development of the child. Such a team should include pediatric gastroenterologists and surgeons, specialized nurses, dieticians, social workers and psychologists. Centralization of care for these patients improves the expertise and experience and can optimize cost-effectiveness.
- Early and frequent assessment of nutritional status prevents malnutrition and enables clinicians to provide optimal nutritional support.
- Long-term follow-up in these children and their families is needed to provide them with optimal care with regard to growth, nutritional status, mental and motor development, and HRQoL.

Table 1 Proposed systematic nutritional strategy infantile SBS

Step	Description	Start	Components	Type	Starting dose	Dose increase/decrease	Conditions
1	Full PN	Directly post-op	PN	Glucose, aminoacids and lipids	Full RDA		
2	Introduction MEF	1 - 2 days post-op	PN	Glucose, aminoacids and lipids	Full RDA		
			MEF	Breast milk or polymeric	24x1 ml/hr continuously	2x a week increase with 1 ml/hr, until ED (24 ml/kg/day or 5ml/hr)	No vomiting, extensive diarrhea
3	Introduction ETN	When ≥ ED ml/hr	TPN	Glucose, aminoacids and lipids		Decrease isovolemic, with attention to calories	When increasing ETN and Oral
			ETN	Breast milk or polymeric*	24x ≥ ED ml/hr	2x a week increase with 1 ml/hr	No vomiting, extensive diarrhea
4	Introduction oral feed	As soon as possible	PN	Glucose, aminoacids and lipids		Decrease isovolemic, with attention to calories	When increasing ETN and Oral
			ETN	Breast milk or polymeric*	A) 20x D ml/hr B) 18x D ml/hr C) 15x D ml/hr D) 12x D ml/hr	2x a week increase with 1 ml/hr	Don't increase volume and frequency bottle at same time, no extensive vomiting / diarrhea,
			oral	Breast milk or polymeric*	a) 4 bottles hr dose b) 6 bottles hr dose c) 6 bottles 1.5 hr dose d) 6 bottles 2 hr dose	2x a week increase with 1 ml/hr	ETN stop on time bottle, No extensive vomiting / diarrhea
5	Cycling TPN	a) 25% cal ETN & oral b) 30% cal ETN & oral c) 35% cal ETN & oral d) 40% cal ETN & oral e) 50% cal ETN & oral	PN	Glucose, aminoacids and lipids	a) 20 hrs/day b) 18 hrs/day c) 16 hrs/day d) 14 hrs/day e) 12 hrs/day		No hypoglycemia

Abbreviations: PN: parenteral nutrition; ETN: Enteral tube nutrition; MEF: Minimal enteral feeding; ED: enteral dose D: dose
** Type of nutrition depends on age and/or availability of breast milk*

FUTURE PERSPECTIVES

The information gained from the studies presented in this thesis revealed that future research is desperately needed, especially in the area of nutrition. Considering the relatively low sample size in single-center studies, it is essential to conduct cohort studies and/or randomized controlled trials in (preferably) European multi-center studies. In order to perform multi-center studies, it is essential that consensus is reached on the definition of SBS first.

In 2005 a National Short bowel syndrome registry was set up in the Netherlands. Similar database registries exist in other countries. Combine these databases would enable us to study more patients prospectively.

Nutrition

Studies to identify optimal parenteral and enteral nutrition support regimens are necessary to prevent PNALD and impaired growth.
Moreover, studies investigating the role of different types of feedings – e.g. breast milk, polymeric and semielemental formula – in bowel adaptation are indispensable for further improvement of nutritional management of children with infantile SBS. Topics in nutrition that need to be addressed are:

- The potential advantages of early (i.e. 1 - 2 days post surgery) (minimal) enteral feeding.
- The potential advantages of continuous administration mode versus bolus feeding.
- The role of (donor) breast milk on bowel adaptation.
- The potential advantages of (donor) breast milk over formula feeding, with enteral tolerance and time to enteral autonomy as endpoints.
- What kind of solid food is best tolerated; for example fresh fruit with peel or vegetables or porridge (of rice cereals) or meat.
- The effect of soluble fibers on enteral feeding tolerance.
- The potential benefits of MCTs on fat absorption in SBS patients with an intact colon.
- The effectiveness of lactose-free formula vs. standard formula on feeding tolerance.

Nutritional status and body composition

In chapter 5 we demonstrated that patients had a shorter stature and lower BMC than healthy subjects, but normal bone mineral density, weight for height and percentages of body fat. Future research is needed to explain why bone mineral density would be normal when bone mineral content values are low.

Proposed topics of research are:

- Determination of bone age by hand X-ray and measurement of serum GH and IGFs, variables that might explain shorter stature
- Evaluation of serum vitamin and mineral status, such as vitamin B12, D, calcium and zinc.
- Nutritional support team is a key factor in collecting longitudinal data on nutrition and nutritional status. We should perform longitudinal research on nutritional status and nutritional support, during admission and long-term follow up, in relevant groups of children at risk of developing malnutrition.

Health-related quality of life

In chapter 6 we demonstrated lower HRQoL in children and adults with a history of infantile SBS. Further research is needed to identify factors that cause lower HRQoL. Furthermore, longitudinal prospective studies are needed to evaluate the HRQoL over time.

Resource consumption

In chapter 7 we hypothesized that interdisciplinary teams are instrumental in reducing health care costs. At the same time they benefit patients' health and quality of life of both patients and parents, which would result in a favorable cost-effectiveness profile. Further research is needed to evaluate the cost-effectiveness of the interdisciplinary team, as well as that of the entire SBS treatment process.

Interdisciplinary team

This thesis has clearly emphasized the importance of an interdisciplinary team managing patients with SBS. This interdisciplinary team should coordinate a prospective longitudinal study with clearly documented and statistical interpretable parameters at preset time frames. Parameters described in this thesis can serve as basis for further research.

A recent report showed that the long-term outcome of children with infantile SBS is similar to that of patients who develop SBS in adolescence, despite differences in origin of SBS and intestinal anatomy.[3] It seems therefore reasonable to also investigate adolescents with SBS prospectively. Even though it was beyond the scope of this thesis we assume that certain study parameters can be extrapolated. For example, future research on luminal nutrients, such as dietary fibers on bowel adaptation, should also be performed in adolescents with SBS.

CONCLUDING REMARKS

The results of our studies emphasize the importance of short and long term evaluation of infantile short bowel syndrome. We advocate the establishment of a nutritional support team for these acutely ill children and further improvement of the existing interdisciplinary short bowel team. These teams should perform further research as suggested above and continue to improve the management of patients with SBS, thereby contributing to essential advances in knowledge of SBS leading to improvement of clinical care.

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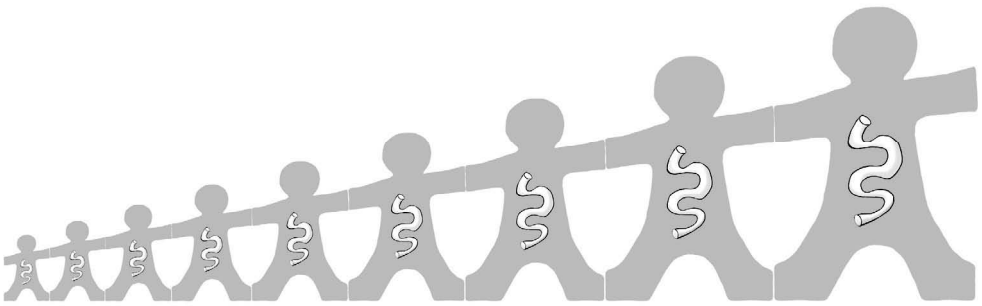
Chapter 9

Summary

Samenvatting



SUMMARY

Infantile short bowel syndrome is a condition which is characterized by malabsorption of nutrients, as a result of congenital intestinal shortening or massive small bowel resection. Survival rates have improved over the years, but morbidity remains high and clinical management of these patients is complex. The overall aim of this thesis is to describe the acute and long-term consequences of infantile short bowel syndrome.

Chapter 2 describes a retrospective single-centre study over the past two decades on the characteristics of the first year of infantile short bowel syndrome, with regard to nutritional correlates and growth. Twenty-eight patients were identified in decade 1980 versus 62 patients in decade 1990. In decade 1990, length of hospital stay was significantly shorter and the residual bowel length and duration of parenteral nutrition was respectively slightly but not significantly longer and shorter than in decade 1980. In both decades the mean SD-scores for weight for age in the first year of SBS were subnormal, whereas in decade 1980 mean scores were significantly lower than in decade 1990. However, in decade 1990 the SD-scores declined significantly in the second and third quarterly term of the first year compared to the first quarterly term. Improved care of patients with SBS in general and the slightly longer residual bowel length (ns) in decade 1990 resulted in shorter length of stay, shorter duration of parenteral nutrition and significantly higher SD-scores for weight for age compared with decade 1980. Our results show that there is still room for improvement in the care of children with SBS, notably with regard to maintaining nutritional status and to stimulating early nutritional intake.

Chapter 3 describes the feasibility of regular nutritional assessment by means of anthropometric measurements as standard of care in a relevant subgroup of ICU patients at risk of developing malnutrition, i.e. those with major congenital anomalies affecting the gastro-intestinal tract, including patients with infantile short bowel syndrome.
Of the 89 children included, 61% underwent nutritional assessment and no more than 15% had been assessed at the proposed frequency. Follow-up was possible in 63% of the children (2 or more measurements), whereas the success rate of all applied separate nutritional assessment techniques was 100%. The results of our study showed that the feasibility of the nutritional assessment protocol was negatively influenced by longer hospital admission. A major reason for missed measurements was unavailability of the anthropometrists. Other reasons were children's bad condition and random events associated with hospital admission, such as parental visit or the patient being nursed. In conclusion, regular nutritional assessment in the current setting was not feasible. Adequate monitoring of nutritional status in critically ill children calls for

weekly assessment. An adequate infrastructure which guarantees structural availability of trained personnel is the cornerstone is this setting.

Chapter 4 describes an overview of the currently available literature on feeding strategies in children with short bowel syndrome, resulting, if possible, in evidence-based recommendations (according to the Scottish Intercollegiate Guidelines Network criteria) or in the absence of evidence, in clinical recommendations based on expert opinion. In general, few studies were available on this topic and methodology was flawed in most of them. The evidenced-based recommendations were: Enteral nutrition should be initiated as soon as possible (i.e. a few days after bowel resection) to promote intestinal adaptation. And, as there is no difference in absorption between polymeric and oligomeric formulas, polymeric formula is recommended as first choice of enteral feeding. Clinical recommendations were based on level 3 evidence or even based on (our own) expert opinion (level 4): Enteral nutrition should be administered in a continuous fashion and breast milk is considered as first choice of enteral feeding. Moreover, bottle-feeding (small volume) should be started in neonates as soon as possible to stimulate the suck and swallow reflexes. Solid food can be introduced at the developmentally appropriate age to stimulate oral motor activity and to avoid feeding aversion behavior.
At the moment, it is not possible to solely base the nutritional regimen of children with SBS on evidence obtained from previous scientific studies. Since studies focusing on effectiveness of different feeding options in this relatively small patient population are virtually absent and methodological quality is relatively low in most cases, future research is needed to enable clinicians to manage these patients using evidence-based strategies.

Chapter 5 describes a cross-sectional study on the long-term effects of infantile short bowel syndrome on growth, nutritional status, bone health, defecation pattern and food intake. Forty SBS patients ranging in age from 5 to 30 years participated. The mean SD-scores for weight for height and target height were normal in 31 children, whereas the mean SD-scores for height for age were significantly lower than reference values and lower than SD-scores of target height. More than 50% of the children and 75% of the adults were below target height range. Most subjects had normal body fat percentage and the SD-scores for total body bone mineral density were generally normal. However the SD-scores for bone mineral content were significantly below references values. Mean energy intake was 91% of the estimated average daily requirements while subjects' self-reported frequencies of defecation and bowel complaints were significantly higher than in healthy controls. It was concluded that subjects in this study had shorter stature, low BMC, but normal weight for height and percentages of body fat. This might be explained by the low energy-intake and

intestinal bowel dysfunction reported. These results show that continuing follow up into adulthood is important even after subjects have reached nutritional autonomy. In that way, low energy intake and intestinal bowel dysfunction might be identified early, enabling prevention of short stature by targeted nutritional management.

Chapter 6 describes the outcomes of a cross-sectional study on the long-term effects of infantile short bowel syndrome on health related quality of life (HRQoL) compared to healthy controls. Thirty-one children (self-report) and their parents (report by proxy) and nine adults with a history of infantile short bowel syndrome participated. These children and their parents reported significantly lower HRQoL in physical and psychosocial domains than healthy children and their parents. The adults scored significantly lower than the healthy controls on the domains "General Health" and "Vitality". On the other domains the adult subjects obtained relatively low scores, but differences did not reach statistical significance.
In children with a history of infantile short bowel syndrome we did not find a relationship between HRQoL and possible explanatory variables such as abnormal stool consistency and height below target height range.
Overall, patients with a history of infantile short bowel syndrome have a lower quality of life than the healthy population. These findings stress the need for targeted interventions to address these dimensions of impaired HRQoL.

Chapter 7 describes a detailed prospective case series of 10 patients treated by the interdisciplinary short bowel team, with a focus on resource consumption, combined with nutrition and growth. Seven patients were discharged with home parenteral nutrition. Total follow up varied between 9 months and 5.5 years (median 1.5 years). Six patients could be weaned off parenteral nutrition and 5 patients off enteral tube feeding, resulting in full oral intake. Seven patients had normal growth. Median duration of initial hospital admission was 174 days, and average costs of initial admission amounted to 166,045 euros. Total admission days varied from 84 to 478 days with a median of 409 days. Average total costs were 269,700 euros reaching to maximum of 455,400 euros. As 82% of the costs were comprised of hospital admissions, early home parenteral nutrition could contribute to costs reduction. Interdisciplinary teams have the potential to facilitate early home parenteral nutrition, and to optimize growth by tailor made treatment. Thus, they may be instrumental in reducing health care costs, while at the same time benefiting patients' health and quality of life of both patients and parents.

In **Chapter 8** we discuss our findings and possible limitations of the chosen study designs and study population. Furthermore, we discuss the implications of our findings

for clinical management of patients with short bowel syndrome and suggest a systematic nutritional strategy. Finally, we make recommendations for future studies.

The main **conclusions** obtained from the studies described in this thesis are the following:

- Improvement in the care of children with SBS, notably with regard to nutritional status and to stimulating early nutritional intake is necessary.
- Adequate monitoring of nutritional status in critically ill children calls for weekly assessment. An adequate infrastructure which guarantees structural availability of trained personnel is the cornerstone is this setting.
- At the moment, it is not possible to solely base the nutritional regimen of children with SBS on evidence obtained from previous scientific studies.
- Subjects with a history of infantile short bowel syndrome had shorter stature and lower bone mineral content (BMC) than healthy controls, but strikingly, had normal weight for height and percentages of body fat.
- Subjects with a history of infantile short bowel syndrome had impaired health related quality of life.
- Treatment of short bowel syndrome requires considerable resource consumption, especially when patients depend on parenteral nutrition. Interdisciplinary teams have the potential to facilitate home parenteral nutrition and thus reduce health care costs, while at the same time benefiting patients' health.

SAMENVATTING

Het kortedarmsyndroom bij kinderen wordt gekenmerkt door een tekort aan functionele darmmassa ten gevolge van aangeboren afwijkingen of het wegnemen van een groot stuk van de darm. Dit leidt tot onvoldoende absorptie van nutriënten en groeivertraging. Meer en meer van deze patiënten overleven tegenwoordig deze aandoening. Ze hebben echter grote kans op ziekte, bovendien is medische behandeling van deze patiënten complex. Het doel van dit proefschrift is het beschrijven van effecten van het kortedarmsyndroom bij kinderen op de korte en lange duur.

Hoofdstuk 2 beschrijft een retrospectieve studie naar de verschillen bij patiënten in ons ziekenhuis in twee opeenvolgende decennia. Het ging hierbij met name over voedings-karakteristieken en groei in het eerste jaar na het ontstaan van het kortedarmsyndroom. Voor de jaren '80 van de vorige eeuw vonden we 28 patiënten tegen 62 patiënten voor het daaropvolgende decennium. In dit laatste decennium was de opnameduur in het ziekenhuis significant korter dan in het decennium 1980 - 1989. De lengte van de resterende darm was langer in het decennium 1990 - 1999, de duur van parenterale voeding was korter, maar de verschillen waren niet significant. In beide decennia lag de gemiddelde standaarddeviatie (SD-)score voor gewicht naar leeftijd, in het eerste jaar na het kortedarmsyndroom, onder de normaalwaarden. De gemiddelde SD-scores in het decennium 1980 - 1989 waren significant lager dan de SD-scores in het volgende decennium. In de jaren '90 daalden de SD-scores in het 2^{e} en 3^{e} kwartaal van het eerste levensjaar significant ten opzichte van het 1^{e} kwartaal. De significant kortere opnameduur, kortere duur van parenterale voeding en significant hogere SD-scores voor gewicht naar leeftijd, in het decennium 1990 - 1999 zijn waarschijnlijk te danken aan betere zorg en de iets grotere resterende darmlengte. De resultaten van deze studie laten echter zien dat er nog ruimte is voor verbetering in de zorg voor kinderen met het kortedarmsyndroom. Dit geldt vooral voor de voedingstoestand en het stimuleren van vroegtijdige introductie van enterale voeding.

Hoofdstuk 3 beschrijft de haalbaarheid van het wekelijks meten, volgens een anthropometrisch standaardprotocol, van de voedingstoestand van kinderen op de intensive care (IC) die een verhoogd risico hebben op ondervoeding. Dit zijn kinderen met ernstige aangeboren afwijkingen van de tractus digestivus, inclusief het kortedarmsyndroom. In de periode van juni 2004 tot februari 2006 behoorden 89 kinderen tot de risicogroep. Bij 61% van deze kinderen is inderdaad de voedingstoestand gemeten, maar slechts bij 15% hiervan is het volgens de voorgeschreven frequentie verricht. Bij de overige kinderen was bijna de helft van de geplande meetmomenten (mediaan) de voedingstoestand gemeten. Het vervolgen van de voedingstoestand was mogelijk bij 63% van de kinderen (hierbij zijn 2 of meer

metingen verricht). Mediaan waren alle afzonderlijke meetmethoden (gewicht, lengte, etc) voor 100% gemeten. Uit de resultaten van deze studie blijkt dat de haalbaarheid van het meten van de voedingstoestand volgens protocol negatief werd beïnvloed door een langere opnameduur. De belangrijkste reden voor gemiste meetmomenten was het feit dat de antropometristen dan niet beschikbaar waren. Andere redenen waren dat het kind zich in instabiele toestand bevond, dat het op dat moment werd verzorgd, of dat de ouders op bezoek waren tijdens het geplande meetmoment. De conclusie van deze studie is dat het regelmatig meten van de voedingstoestand in de huidige setting niet haalbaar is. Structurele inzet van daarvoor getraind personeel is een randvoorwaarde voor het adequaat volgen van de voedingstoestand middels wekelijkse anthropometrie bij ernstig zieke kinderen.

Hoofdstuk 4 geeft een overzicht van de beschikbare literatuur over voedingsstrategieën bij kinderen met het kortedarmsyndroom. Een aantal aanbevelingen voor de praktijk wordt gedaan zo mogelijk op basis van wetenschappelijk bewijs (evidence-based) volgens de criteria van de Scottish Intercollegiate Guidelines Network (SIGN). Als wetenschappelijk bewijs ontbreekt, worden er aanbevelingen gedaan op basis van klinische ervaring en meningen van experts. Over het algemeen is er maar weinig onderzoek gedaan naar dit onderwerp, en dit is veelal van lage methodologische kwaliteit. De belangrijkste evidence-based aanbeveling is dat het kind zo spoedig mogelijk enterale voeding dient te krijgen, het liefst een paar dagen na darmresectie, zodat de resterende darm kan adapteren. Aangezien er geen verschil in absorptie is gevonden tussen polymere voeding en oligomere voeding, wordt polymere voeding als eerste keus aanbevolen. Klinische aanbevelingen waren gebaseerd op evidence van niveau 3 en de mening van experts (niveau 4): Enterale voeding dient continu te worden toegediend en borstvoeding wordt beschouwd als eerste keus in soort voeding. Bovendien dient het kind ook zo snel mogelijk flesvoeding te krijgen, om een zuig- en slikreflex te stimuleren. Daarnaast kan vanaf 4 - 6 maanden à terme gestart worden met vaste voeding om de ontwikkeling van de mondmotoriek te bevorderen. Op deze manier wordt een mogelijke voedselaversie tegengegaan. Het is op dit moment nog niet mogelijk om een voedingsvoorschrift voor kinderen met kortedarmsyndroom op te stellen dat volledig gebaseerd is op wetenschappelijk bewijs uit gepubliceerde onderzoeken. Zoals eerder gezegd zijn er maar weinig van die studies gedaan die gericht zijn op de effectiviteit van verschillende voedingsstrategieën in deze relatief kleine patiëntenpopulatie en is de methodologische kwaliteit in de meeste gevallen onvoldoende. Daarom is het belangrijk om kwalitatief methodologisch sterk wetenschappelijk onderzoek te verrichten, zodat in de toekomst de clinicus deze patiënten volgens evidence-based strategieën kan behandelen.

Hoofdstuk 5 beschrijft een cross-sectionele studie naar effecten op de lange termijn, van het kortedarmsyndroom welke is ontstaan in het eerste levensjaar. Aandachtsgebieden waren groei, voedingstoestand, botdichtheid, ontlastingspatroon en voedselinname. Veertig voormalige patiënten die nu tussen de 5 en 30 jaar zijn, namen deel aan de studie. De gemiddelde SD-scores voor gewicht naar lengte en target-lengte, gebaseerd op de lengte van de ouders, waren normaal bij 31 kinderen. Daarentegen waren de gemiddelde SD-scores, voor lengte naar leeftijd, significant lager dan de normaalwaarden en de berekende target-lengte. Meer dan 50% van de kinderen en 75% van de volwassenen zaten onder de spreiding van hun target lengte. De meeste deelnemers aan de studie hadden een normaal percentage lichaamsvet en over het algemeen vielen de SD-scores van botdichtheid binnen de normaalwaarden. Echter, de SD-scores van het mineraalgehalte van het bot waren significant lager dan de referentiewaarden. De gemiddelde energie-inname was 91% van de gemiddelde dagelijkse behoefte. Bovendien rapporteerden de deelnemers een hogere defecatie-frequentie en hadden ze significant meer buikklachten dan gezonde personen van een controlegroep. De conclusie van deze studie was dat de voormalige patiënten een geringere lichaamslengte en een laag gehalte aan botmineralen hadden, maar dat hun gewicht naar lengte en lichaamsvetpercentage normaal was. Dit alles zou mogelijk verklaard kunnen worden door een lage energie-inname en slechtere werking van de darmen. Deze studie heeft aangetoond dat het belangrijk is om patiënten met het kortedarmsyndroom te volgen tot de volwassen leeftijd, ook al hebben ze volledige voedingsautonomie bereikt. Zodoende zouden een lage energie-inname en slechte werking van de darmen in een vroeg stadium aan het licht kunnen komen, en worden ondervangen met een doelgerichte voedingsbehandeling. Uiteindelijk kan hiermee een geringe lichaamslengte worden voorkomen.

Hoofdstuk 6 beschrijft de resultaten van een cross-sectioneel onderzoek naar de kwaliteit van leven van patiënten, die in hun eerste levensjaar kortedarmsyndroom hebben gekregen, vergeleken met die van gezonde leeftijdgenoten.
Het betreft hier dezelfde groep (leeftijd van 5 tot 30 jaar) als in het vorige hoofdstuk, dat wil zeggen 31 kinderen (en hun ouders) en 9 volwassenen. Deze kinderen en hun ouders rapporteerden een significant lagere gezondheidgerelateerde kwaliteit van leven dan gezonde kinderen en hun ouders. De volwassen deelnemers van de studie scoorden significant lager op de domeinen van "algemene gezondheid" en "vitaliteit" ten opzichte van gezonde leeftijdgenoten. De scores op andere domeinen waren ook lager, maar deze verschillen waren niet significant. Voor de patiëntengroep is er geen relatie gevonden tussen kwaliteit van leven en mogelijke verklarende factoren, zoals de consistentie van de ontlasting en een lichaamslengte die onder de spreiding van de target-lengte valt. Gezien deze bevinding van lagere kwaliteit van leven op latere leeftijd, vergeleken met de gezonde populatie, lijkt het van belang de mogelijk

verklarende factoren die een lagere kwaliteit van leven veroorzaken, verder te onderzoeken.

Hoofdstuk 7 beschrijft een prospectieve evaluatie van 10 gevallen van kortedarmsyndroom. Dit betreft kinderen die door het multidisciplinaire Darmfalenteam van het Sophia Kinderziekenhuis zijn behandeld. De aandacht ging met name uit naar de kosten van de zorg, daarnaast is de voeding en groei van deze patiënten beschreven. Ze werden poliklinisch gevolgd gedurende een periode variërend tussen 9 maanden en 5,5 jaar (mediaan 1,5 jaar). Zeven patiënten waren met parenterale voeding uit het ziekenhuis ontslagen. Zes patiënten konden uiteindelijk zonder parenterale voeding gevoed worden en 5 zelfs zonder enterale (sonde)voeding, resulterend in volledige orale voeding. Zeven patiënten vertoonden normale groei. De mediane duur van de eerste ziekenhuisopname was 174 dagen en de gemiddelde kosten daarvoor bedroegen € 166.045. De totale opnameduur varieerde tussen 84 en 478 dagen met een mediaan van 409 dagen. De kosten van behandeling bedroegen gemiddeld € 269.700, met een maximum van € 455.400. De kosten van behandeling van kinderen met kortedarmsyndroom zijn hoog, zeker bij afhankelijkheid van parenterale voeding. Aangezien 82% van de kosten toe te schrijven is aan ziekenhuisopnames, zouden kosten bespaard kunnen worden door eerder ziekenhuisontslag en dan parenterale voeding thuis. Het multidisciplinaire Darmfalenteam maakt het mogelijk om in een vroeg stadium thuis parenterale voeding te faciliteren en het bevordert de groei van de individuele patiënt door een behandeling op maat te bieden. Het multidisciplinair Darmfalenteam bevordert hiermee niet alleen de gezondheid van het kind en de kwaliteit van leven van zowel het kind als de ouders, maar verlaagt bovendien de zorgkosten.

In **Hoofdstuk 8** bediscussiëren we de resultaten van bovengenoemde studies, alsmede de mogelijke beperkingen van de gekozen studieopzet en studiepopulaties. Het hoofdstuk gaat ook in op de implicaties van de resultaten voor de klinische behandeling van patiënten met kortedarmsyndroom en doet een voorstel voor een systematische voedingsstrategie. Tenslotte volgen aanbevelingen voor toekomstige studies.
Uit de studies beschreven in dit proefschrift kunnen de volgende **conclusies** getrokken worden:

- De zorg voor kinderen met kortedarmsyndroom dient nog verbeterd te worden. De aandacht moet worden gericht op de voedingstoestand en het stimuleren van vroegtijdige introductie van enterale voeding.
- De voedingstoestand van ernstig zieke kinderen zou wekelijks gemeten moeten worden. Hierbij is structurele inzet van daarvoor getraind personeel een randvoorwaarde.

- Op dit moment is het niet mogelijk om een voedingsvoorschrift voor kinderen met kortedarmsyndroom te adviseren dat volledig gebaseerd is op wetenschappelijk bewijs uit gepubliceerde studies.
- Zij die in hun eerste levensjaar kortedarmsyndroom hebben gekregen, hebben later een geringere lichaamslengte en een laag gehalte aan botmineralen, maar het gewicht naar lengte en het lichaamsvetpercentage zijn normaal.
- Zij die in hun eerste levensjaar kortedarmsyndroom hebben gekregen, hebben later een lagere gezondheidgerelateerde kwaliteit van leven.
- De behandeling van kinderen met kortedarmsyndroom is erg duur, zeker zolang ze afhankelijk zijn van parenterale voeding. Multidisciplinaire teams kunnen parenterale voeding thuis faciliteren en daarmee de kosten van ziekenhuisopname verminderen. Tegelijkertijd draagt dit bij aan de gezondheid van de patiënt.

Appendix

Dankwoord

Curriculum vitae

PhD portfolio summary

DANKWOORD

Het voelt onwerkelijk, maar het boekje is af en nu ben ik toegekomen aan het meest gelezen onderdeel van mijn proefschrift.
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Joanne

CURRICULUM VITAE

Joanne Olieman was born on 10th of February in Utrecht, The Netherlands in 1976. She passed her secondary school exam at the Stedelijk Gymnasium in Utrecht in 1994, and she spent a year at the Université Paul Valéry- Institut Etranger in Montpellier, France learning the French language. She then started studying Health Sciences at the University of Maastricht. In 2000 she obtained her master's degree in biological health sciences. The same year she started studying Nutrition and Dietetics at the Haagse Hogeschool in The Hague and she graduated in 2002. From 2002 onwards she worked as a registered dietician in the Erasmus MC-Sophia Children's Hospital. In 2003 she joined the just founded interdisciplinary short bowel team as a pediatric dietician. In 2004 she started to work part-time as a research-dietician at the department of Pediatric Surgery of the Sophia Children's Hospital working on the research presented in this thesis (supervised by Prof. dr. D. Tibboel and Dr. C. Penning). She is living together with Patrick Heynen.

PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Name PhD student: Joanne Olieman	PhD period: 2004 - 2009
Erasmus MC Department: Pediatric Surgery	Promotor(s): Prof. dr. D. Tibboel
Research School:	Supervisor: Dr. C. Penning

	Year	Workload (Hours/ECTS)
1 PhD training		
General academic skills	-	-
Research skills		
Statistics	2007	16 hrs
In-depth courses (e.g. Research school, Medical Training)		
Course IPOKRaTES; Nutrition: Scientific basis, nutritional strategies, nutrition and disease	2004	24 hrs
Presentations		
Oral presentation abstract international symposium	2006	40 hrs
Oral presentation poster Congress Dutch Pediatric Society	2007	24 hrs
Oral presentation Growth, Dutch Dietetic Congress	2007	40 hrs
Oral presentation abstract international symposium	2008	40 hrs
International conferences		
9th International small bowel transplantation symposium	2005	8 hrs
4th international pediatric intestinal failure and rehabilitation symposium	2006	21 hrs
5th international pediatric intestinal failure and rehabilitation symposium	2008	21 hrs
Seminars and workshops		
Seminar intestinal failure Congress Dutch Pediatric Society	2004	8 hrs
2 Teaching activities		
Lecturing		
Nutrition and short bowel syndrome	2004	16 hrs
Fibers and short bowel syndrome	2005	16 hrs
Nutrition at the ICU	2006	16 hrs
Capita Selecta short bowel syndrome	2008	16 hrs
Supervising practicals and excursions	-	-
Supervising Master's theses	-	-
Other		
Supervising Bachelor's thesis	2004	40 hrs