Necrotizing Enterocolitis and Central Line Associated Blood Stream Infection Are Predictors of Growth Outcomes in Infants with Short Bowel Syndrome

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Objectives To describe the natural history of growth patterns and nutritional support in a cohort of infants with short bowel syndrome (SBS), and to characterize risk factors for suboptimal growth.

Study design A retrospective chart review of 51 infants with SBS followed by our intestinal rehabilitation program. Weight and length data were converted to age, sex, and gestational age-standardized weight-for-age *z*-scores (WAZ) and length-for-age *z*-scores (LAZ).

Results Median (IQR) age at enrollment was 8.3 (0.9-14.6) weeks, and follow-up duration was 10 (8-13) months, including both inpatient and outpatient visits. Both WAZ and LAZ followed a U-shaped curve, with median for newborns (WAZ = −0.28; LAZ = −0.41), a nadir at age 6 months (−2.38 and −2.18), and near recovery by age 1 year (−0.72 and −0.76). Using multivariable regression analysis, diagnosis of necrotizing enterocolitis was independently associated with significant decrements of WAZ (−0.76 ± 0.32; P = .02) and LAZ (−1.24 ± 0.32; P = .0001). ≥2 central line–associated bloodstream infections was also independently associated with decreases in WAZ (−0.95 ± 0.33; P = .004) and LAZ (−0.86 ± 0.32; P = .007).

Conclusion In a cohort of infants with SBS, we observed a unique pattern of somatic growth, with concomitant deceleration of both WAZ and LAZ and near recovery by 1 year. Inflammatory conditions (necrotizing enterocolitis and central line–associated bloodstream infections) represent potentially modifiable risk factors for suboptimal somatic growth. *(J Pediatr 2015;167:35-40)*.

See editorial, p 6 and related article, p 29

Short bowel syndrome (SBS) is a condition in which a significant small intestine deficit leads to malnutrition, dehydration, and electrolyte depletion.[1] Parenteral nutrition (PN) is the mainstay of treatment for this condition when nutritional requirements cannot be met by enteral feeds.[2] Over time, intestinal adaptation allows for greater absorption, weaning of PN, and advancement of enteral feeding.[3] The most common etiologies in infants are necrotizing enterocolitis (NEC), intestinal atresia, midgut volvulus, and gastroschisis.[4,5]

The prognosis for patients with SBS depends on the underlying disease, residual small bowel length, presence of an ileocecal valve, presence of colon, and associated complications.[2] The goals of nutritional therapy are to optimize linear growth and lean mass accrual, as well as to achieve appropriate developmental milestones. Studies addressing what constitutes adequate nutrition in patients with SBS are limited, and anecdotal evidence suggests that some children require very high amounts of parenteral and/or enteral energy intake to attain normal growth rates.

Infants with SBS are particularly vulnerable to poor somatic growth. During infancy, energy requirements for growth are at a postnatal high, even in healthy individuals. SBS is associated with metabolic stress, as demonstrated by variabilities in resting energy expenditure,[6] intestinal malabsorption, and comorbidities of prematurity, all of which can significantly compromise growth. With advances in management, the weight-for-age *z*-scores (WAZ) in children with SBS have improved slightly but remain abnormally low.[7] At age 18-22 months, 74% of very low birth weight preterm infants with surgical SBS were reported to have weight, length, or head circumference below the 10th percentile.[8] In older children, weaning of PN has been shown to negatively impact WAZ.[9] Whether a

CLABSI	Central line–associated bloodstream infection
LAZ	Length-for-age *z*-score
NEC	Necrotizing enterocolitis
PN	Parenteral nutrition
PNALD	Parenteral nutrition–associated liver disease
SBS	Short bowel syndrome
WAZ	Weight-for-age *z*-score

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similar pattern is seen in infants is unknown, even though this is the period during which the majority of patients are weaned from PN.[3] The aims of this retrospective study were to describe growth patterns in infants with SBS, as well as to characterize risk factors for suboptimal growth.

Methods

Following Institutional Review Board approval, we carried out a retrospective medical record review of patients followed between January 2003 and December 2008 at Boston Children's Hospital's Center for Advanced Intestinal Rehabilitation, a multidisciplinary program involving intestinal failure specialists in pediatric gastroenterology, surgery, nutrition, nursing, pharmacy, and social work.[10] Included were children aged 0-6 months at initial hospitalization who had a diagnosis of SBS (ie, a malabsorptive state resulting from congenital or acquired gastrointestinal disease leading to dependence on PN for at least 90 days) and who required PN for at least 30 days during the initial hospitalization. We excluded subjects with fewer than 30 days of inpatient nutritional intake data available for review.

Data collected included demographic factors (date of birth, sex, race/ethnicity, ZIP code), medical/surgical history (gestational age, birth weight, diagnoses leading to SBS, intraoperatively measured residual small bowel length, presence of ileocecal valve), laboratory studies (international normalized ratio, direct bilirubin, total bilirubin, alanine aminotransferase, albumin, and serum citrulline). Anthropometric data (weight and length) and nutritional intake (enteral and PN intake) were collected weekly on the same day of the week. When measurements were not available on the assigned day, the measurement obtained closest to that day within the same week was chosen. A digital scale accurate to 1 gram was used to measure weight, and a length board accurate to 0.1 cm was used to measure length.

Each central line–associated bloodstream infection (CLABSI) was recorded (date of positive cultures and organisms) and classified according to Centers for Disease Control and Prevention definitions.[11] Clinical data were collected from inpatient and outpatient encounters up to age 1 year. An encounter was defined as a visit for which nutrition intake and anthropometric data were available. Data recorded included the type, concentration, and volume of parenteral dextrose, amino acids, and lipids received, as well as the type, concentration, and volume of enteral feeds. Patients were considered PN-independent after 2 or more consecutive weeks without PN. PN duration was calculated as the difference between the last PN date recorded (or the end of the study) and the entry date, accounting for any gaps in PN administration.

Dieticians used recommended dietary allowances to devise energy intake recommendations, and titrated PN and enteral nutrition prescriptions for appropriate weight gain and clinical events. Enteral nutrition was advanced as tolerated according to our standard feeding algorithm.[12] Enteral feeds with breast milk were preferred, if available; otherwise, amino acid-based formulas were used. Feeds were typically advanced in increments of 10 mL/kg/day, with close monitoring of ostomy/stool output.[12,13]

WAZ and length-for-age *z*-score (LAZ) were calculated using World Health Organization 2000 growth charts.[14] For infants with gestation-corrected postnatal age <0, WAZ was calculated according to available published data.[15] The percentage of enteral energy intake was calculated as the amount of dietary energy intake derived by enteral routes divided by the total energy intake multiplied by 100. Patients weaned from PN were assigned a parenteral energy intake of 0. Cholestasis was defined as the occurrence of serum direct bilirubin >2.0 mg/dL on 2 separate measurements obtained at least 1 week apart. Coagulopathy was defined as at least 1 occurrence of an international normalized ratio >1.5.

WAZ, LAZ, and weight-for-length raw data were reviewed. Points 6 *z*-scores higher or lower than the median were excluded, as suggested by the World Health Organization macro,[16] as were points increasing or decreasing from baseline by more or less than 2 *z*-scores within a 30-day window, because these likely resulted from measurement error. Categorical data were summarized with frequency counts and percentages, and continuous data were summarized as median (IQR) unless specified otherwise. A generalized estimating equation, using an empirical sandwich estimator,[17] was used to investigate the independent associations of demographic data, underlying etiology of SBS, gastrointestinal anatomic features, and nutritional and medical factors with WAZ and LAZ over the first year of life. The relationship of outcomes both WAZ and LAZ with age was curvilinear, and thus was modeled as the square of age (measured in weeks since birth). In subsequent regression analyses of associations between predictors and growth outcomes (WAZ or LAZ), the strong nonlinear age effect was always adjusted. CLABSI was dichotomized to reflect a location shift between 0-1 and 2-7 CLABSIs observed in scatterplots.

Univariable correlates of growth (adjusted for nonlinear age) were investigated, and those significant at $P < .10$ were considered collectively in a multivariable model. Backwards elimination was then used to obtain a final multivariable model. All tests of significance were 2-sided, and comparisons at $P < .05$ were considered statistically significant. Statistical analysis and graphical presentation of the data were conducted with SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

Fifty-one infants (27 males; median age at enrollment, 8.3 [0.9-14.6] weeks) with SBS were studied over 10 (8-13) months (**Table I**). Thirty-nine subjects (85%) had low, very low, or extremely low weight at birth. Among the 22 subjects aged 0-1 month at the first study week, only 1 (5%) was receiving any enteral nutrition. Baseline anthropometric measurements were within normal ranges. The median intraoperative residual bowel length was 57 (30-77) cm, and 18 subjects (40%) had a resected ileocecal valve.