Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes

David J. Andorsky, BA, Dennis P. Lund, MD, Craig W. Lillehei, MD, Tom Jaksic, MD, PhD, James DiCanzio, MS, Denise S. Richardson, RN, Sharon B. Collier, RD, Clifford Lo, MD, PhD, and Christopher Duggan, MD, MPH

Objectives: To determine correlates of clinical outcomes in patients with short bowel syndrome (SBS).

Methods: Retrospective medical record review of neonates treated between 1986 and 1998 who met our criteria for SBS: dependence on parenteral nutrition (PN) for at least 90 days after surgical therapy for congenital or acquired intestinal diseases.

Results: Thirty subjects with complete data were identified; 13 (43%) had necrotizing enterocolitis, and 17 (57%) had intestinal malformations. Mean (SD) residual small bowel length was 83 (67) cm. Enteral feeding with breast milk ($r = -0.821$) or an amino acid–based formula ($r = -0.793$) was associated with a shorter duration of PN, as were longer residual small bowel length ($r = -0.475$) and percentage of calories received enterally at 6 weeks after surgery ($r = -0.527$). Shorter time without diverting ileostomy or colostomy ($r = 0.400$), enteral feeding with a protein hydrolysate formula ($r = -0.476$), and percentage of calories received enterally at 6 weeks after surgery ($r = -0.504$) were associated with a lower peak direct bilirubin concentration. Presence of an intact ileocecal valve and frequency of catheter-related infections were not significantly correlated with duration of PN. In multivariate analysis, only residual small bowel length was a significant independent predictor of duration of PN, and only less time with a diverting ostomy was an independent predictor of peak direct bilirubin concentration.

Conclusions: Although residual small bowel length remains an important predictor of duration of PN use in infants with SBS, other factors, such as use of breast milk or amino acid–based formula, may also play a role in intestinal adaptation. In addition, prompt restoration of intestinal continuity is associated with lowered risk of cholestatic liver disease. Early enteral feeding after surgery is associated both with reduced duration of PN and less cholestasis.

(J Pediatr 2001;139:27-33)
small intestine, such as necrotizing enterocolitis, gastrochisis, volvulus, or multiple intestinal atresias. Patients undergoing intestinal surgery for these conditions often must meet some or all of their nutrient requirements through parenteral nutrition.2

After resection, the residual small bowel undergoes intestinal adaptation, a process characterized by mucosal hyperplasia, villus lengthening, increased crypt depth, and bowel dilatation.3-6 If the adaptation is adequate, the bowel will be able to absorb sufficient enteral nutrition to allow normal growth, and the patient can be weaned from PN. The clinical course of patients with SBS during this time can be prolonged and largely unpredictable. Prolonged dependence on PN is associated with a number of complications, including recurrent central venous catheter sepsis, cholestatic liver disease, and inadequate bone mineralization.7 Because many of these morbidities are correlated with the duration of PN, prompt weaning of patients from parenteral support is critical for optimal outcomes. In addition, the costs of providing PN are quite substantial,9 even if the patient is discharged home.10,11

Given the risks and expense that prolonged PN entails, it would be useful to identify risk factors for prolonged dependence on PN and the development of cholestasis among patients with SBS, particularly if these factors are amenable to change in clinical care. In the present study we sought to examine clinical factors that influence the duration of dependence on PN and the development of liver disease.

**Methods**

We performed a retrospective review of the medical records of all patients born at Children’s Hospital, Boston, in 1985 or later who fit our definition of SBS. We defined SBS as dependence on PN for at least 90 days for diagnoses resulting from congenital intestinal malformations and/or intestinal resection. We restricted our study to patients who were given a diagnosis of SBS in the neonatal period (age <30 days). The primary outcome variables were duration of PN use and peak serum direct bilirubin concentration.

During the study period, the nutritional management of these patients was generally unchanged. As soon as postoperative ileus resolved, a small amount of either breast milk or protein hydrolysate formula was administered in a continuous fashion. The use of breast milk was dictated by family preference and availability of breast milk. Enteral feedings were advanced as tolerated and titrated to ostomy output or other signs of intolerance as previously described.12 PN was provided with dextrose and intravenous soybean oil. Until August 1990, the intravenous amino acid solution used for infants was Aminosyn PF (Abbott Laboratories, Chicago, Ill); after that point, Trophamine (McGaw Laboratories, Irvine, Calif) was used. The change in amino acid products has not been associated with a change in incidence of cholestasis at our institution.13 Patients were fully weaned from parenteral support when they were able to maintain adequate hydration and growth while receiving enteral feedings.

Medical records from 1985 to 1998 were reviewed. Subjects were identified by 3 methods: (1) International Classification of Diseases, Ninth Revision code of 579.5 (post-surgical malabsorption, commonly used to code for SBS); (2) review of the list of patients receiving PN at home who were followed up by the Clinical Nutrition Service at The Children’s Hospital, Boston; and (3) survey of attending surgeons, gastroenterologists, and nutrition physicians at The Children’s Hospital. A total of 40 patients were preliminarily identified. Of these, 10 were excluded because their medical records were incomplete. Most of these had only been seen briefly for a second opinion.

Data were abstracted from the charts of the 30 qualifying patients. Demographic information, gestational age, birth weight, birth length, and initial diagnosis resulting in SBS were recorded. Residual small bowel length was recorded from the operative note. In cases in which residual bowel had not been measured at the time of surgery (n = 11), we estimated residual small bowel length based on published data correlating total small intestinal length with gestational age.14 Using these estimates for total small intestinal length, we subtracted the resected length according to the pathology report, yielding an estimate for residual small bowel length. For each intestinal surgery, we recorded whether the ileocecal valve was still intact and whether intestinal continuity was preserved. All central venous catheter placements and all episodes of positive blood cultures were recorded.

Nutritional intake data were recorded from nursing flowsheets every 2 weeks for the first year of PN dependence and every 2 months after the first year. We recorded the concentration and volume of parenteral dextrose, amino acids, and lipids received; the type, concentration, and volume of oral and tube feeds received; and the patient’s weight. We calculated daily energy, protein, and fat intake (per kilogram) and the daily percentage of energy intake from enteral nutrition. The date on which PN was begun was recorded from the flowsheets, and the date on which the patient was weaned from PN was recorded from either flowsheets or outpatient visit notes. Patients were considered to be PN-independent if they did not resume PN for at least 12 months.

The z-scores for anthropometric data were calculated by using the EpiInfo 6 software package.15 Laboratory data (total and direct bilirubin, albumin, triglyceride, aspartate aminotransferase, and alanine aminotransferase
levels) were recorded at the same intervals as nutritional data.

Data were analyzed with the Statistical Package for Social Sciences (SPSS for Windows, version 10.0; SPSS Inc, Chicago, Ill). Categorical data were compared by using \( \chi^2 \) analysis or the Fisher exact test. Discrete and continuous data were analyzed with the Mann-Whitney \( U \) test. Univariate and multiple regression analyses were performed to relate the duration of PN and peak direct bilirubin concentration with selected clinical variables. To investigate the relationship between the clinical variables and the probability of successful weaning, we performed multiple stepwise logistic regression. \( P \) values < .05 were considered significant.

RESULTS

Thirteen (43%) of the patients had necrotizing enterocolitis, and 17 (57%) had congenital gastrointestinal malformations (Table I). Median residual small bowel length was 61 cm. The ileocecal valve was preserved in 57% of the patients. The shortest duration of PN use was 101 days, the longest was 3287 days, and the median was 245 days.

Of the 30 patients in the study, 20 (67%) were weaned from PN; 9 of the 10 PN-dependent patients died while receiving PN. The causes of death were progressive liver failure in 6 subjects, sepsis in 2, and cardiac arrest in one. One patient received a combined small bowel–liver transplant that enabled her to discontinue PN, so she was considered, for the purposes of the study, to not have been weaned from PN. The duration of PN among those patients who were weaned from PN was not statistically different from those whose death or transplantation led to the discontinuation of PN (mean (SD) days of PN: 553 (376) vs 629 (831), \( P = .73 \)). Other factors that were not different among the patients who died versus the survivors included mean residual small bowel length, gestational age, birth weight, diagnosis of necrotizing enterocolitis, and race (data not shown).

Table I. Characteristics of 30 infants with SBS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>14</td>
</tr>
<tr>
<td>Gestational age (wk) [mean (SD)]</td>
<td>32.8 (5)</td>
</tr>
<tr>
<td>Birth weight (g) [mean (SD)]*</td>
<td>2017 (984)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>15 (43%)</td>
</tr>
<tr>
<td>Intestinal atresias</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Malrotation/volvolus</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Residual small bowel length (cm) [mean (SD)]*</td>
<td>85 (67)</td>
</tr>
<tr>
<td>Presence of ileocecal valve</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Duration of PN (d) [mean (range)]</td>
<td>606 (101-3287)</td>
</tr>
<tr>
<td>Peak direct bilirubin concentration (mg/dL) [mean (SD)]*</td>
<td>9.0 (7.4)</td>
</tr>
</tbody>
</table>

*\( n = 29 \).

Table II. Significant univariate correlates with duration of PN use among 30 infants with SBS

<table>
<thead>
<tr>
<th>Variable</th>
<th>( R )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of days fed breast milk*</td>
<td>–.821</td>
<td>.023</td>
</tr>
<tr>
<td>Percentage of days fed amino acid–based formula†</td>
<td>–.793</td>
<td>.033</td>
</tr>
<tr>
<td>Percentage of kilocalories fed enterally 6 wk after surgery</td>
<td>–.527</td>
<td>.017</td>
</tr>
<tr>
<td>Residual small bowel length</td>
<td>–.475</td>
<td>.009</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>–.474</td>
<td>.04</td>
</tr>
</tbody>
</table>

*As calculated by (Number of days fed breast milk/Number of days enterally fed) \times 100.
†As calculated by (Number of days fed formula/Number of days enterally fed) \times 100.

Among those weaned from PN, mean (SD) residual bowel length was 88.6 (53) cm versus 71.7 (95) cm in those not able to be weaned (\( P = .06 \)). The year of surgery was also correlated with duration of PN, with surgery performed earlier in our 13-year cohort requiring PN for longer periods. The following variables were not significantly correlated with duration of PN: sex, gestational age, birth weight, diagnosis of necrotizing enterocolitis versus non-necrotizing enterocolitis, presence of an ileoceleal valve, use of protein hydrolysate formula, and frequency of bloodstream infections.

We then performed stepwise multivariate analysis using as candidate variables the significant univariate cor-
relates listed in Table II. We used criteria for entry into the model $P \leq .05$ and removal $P \geq .10$. Only residual small bowel remained as a significant independent predictor in the model ($R^2 = .388$, $P = .005$ for the model). Stepwise logistic regression analysis indicated that only the measured resid-

ual small bowel length was a significant independent predictor of successful weaning (odds ratio = 1.08, $P = .03$). The theoretical relationship between bowel length and the probability of weaning is shown in Fig 2.

Table III shows significant univariate correlates of peak direct bilirubin concentration: days without intestinal continuity, percentage of nutrient intake received by the enteral route 6 weeks after intestinal resection, number of Gram-positive central venous catheter infections, and percentage of enteral feeding days when protein hydrolysate formula was given. The number of Gram-negative catheter infections was not significantly correlated with peak direct bilirubin concentration, nor was length of time receiving PN or underlying diagnosis leading to SBS. In multivariate analysis of the univariate correlates of peak direct bilirubin concentration, only days without intestinal continuity remained significant ($R^2 = .690$ and $P = .005$ for the model).

**DISCUSSION**

Our study indicates that longer residual small bowel, higher percentage of calories received enterally at 6 weeks, and enteral feeding with breast milk or an amino acid–based formula are associated with shorter duration of PN. Longer residual small bowel, shorter time with a diverting ostomy, fewer Gram-positive infections, and feeding with a protein hydrolysate formula are associated with a lower peak direct bilirubin concentration.

Previous case series have identified residual small bowel length as a major factor in determining whether and when a patient with SBS can be weaned from PN.\textsuperscript{16-21} Residual small bowel length has also been correlated with survival\textsuperscript{17,22} and/or need for referral for small intestinal transplantation.\textsuperscript{23} Several studies indicate that the presence of an ileocecal valve shortens the duration
of PN use, but this has not been a universal finding. In this series we did not find a relationship between presence of an ileocecal valve and duration of PN. Other factors that have been implicated in prolonging PN dependence include the presence of cholestatic jaundice, bacterial overgrowth, and the inability to institute early enteral feeding.

Our study provides further evidence that not only the mode (enteral vs parenteral) of nutritional support but also the content (breast milk vs certain formulas) may modify outcomes in infants with SBS. Sondheimer et al, in their retrospective study of 44 infants with SBS, described the relationship between early enteral nutrition and subsequent weaning from parenteral support. They reported that a greater percentage of calories received enterally at 12 weeks’ adjusted age was correlated with weaning from PN. When we created this variable in our data set, however, many of the patients were close to the end of their course of PN, because, on average, 12 weeks’ corrected age placed them at 20 weeks’ chronological age. We therefore did not use this variable as a suitable baseline characteristic. Sondheimer et al also noted a relationship between longer residual small bowel length and earlier discontinuation of PN, similar to our findings.

Bines et al reported a series of 4 patients with SBS and persistent feeding intolerance. After receiving an elemental amino acid–based formula, all 4 patients discontinued PN within 15 months. In addition, histologic and functional measures of small bowel function improved concurrently. Amino acid–based formulas may improve outcomes in SBS for at least two reasons. Gastrointestinal allergy has been reported in children with SBS, so the use of an elemental formula may be beneficial. In addition, the amino acid–based formula used during the study period (Neocate, SHS Inc) contains a high percentage of long-chain fatty acids, which in animal models have been shown to stimulate mucosal adaptation better than medium-chain fatty acids. Data comparing intestinal responses to long-chain and medium-chain fats in patients with SBS have not been published.

Our study correlates the use of breast milk with shorter duration of PN in patients with SBS. Although the number of patients who received breast milk was low and a selection bias cannot be fully excluded, the strong negative correlation between duration of PN and use of breast milk was striking. There are several properties of breast milk that may be beneficial for patients with SBS. Breast milk contains high levels of IgA, nucleotides, leukocytes, and other components that bolster the neonate’s immature immune system. For instance, a recent study of very low birth weight infants demonstrated that the use of breast milk was associated with lower rates of infection and sepsis or meningitis. However, infants in our study who received breast milk had rates of central venous catheter infections similar to those of infants who did not (data not shown), so the anti-infective properties of human milk cannot easily be invoked to explain the improved outcomes of breast-fed infants. Many other components of breast milk may play a role in successful intestinal adaptation. These include long-chain fats, free amino acids including glutamine, and growth factors such as growth hormone and epidermal growth factor. Finally, the association of breast-feeding with a protective colonic flora is well-known; some have reported improvements in patients with SBS who were treated with Lactobacillus organisms.

We showed that early restoration of intestinal continuity correlates with less severe liver disease. Although the exact etiology of PN-induced cholestasis is not known, several leading pathogenic mechanisms are consistent with our observations. It has been proposed that during long periods of intestinal stasis, bacteria translocate across the epithelial barrier and release endotoxin. Endotoxin binds to CD14 receptors on hepatic macrophages inducing them to release inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor, which can cause hepatic injury. Because most intestinal bacteria reside in the colon, colonic stasis, as seen with prolonged diversion of the bowel, might predispose to cholestasis. Exposing food to the gastrointestinal tract increases expression of insulin-like growth factor 1 and other growth factors, which themselves may improve hepatic function. The timing of surgery to reestablish intestinal continuity in patients with SBS has not been agreed upon. Our results indicate that prompt establishment of intestinal continuity may ameliorate the development of PN-associated cholestasis. In addition, lack of enteral stimulation may decrease secretion of cholecystokinin, which promotes gallbladder emptying and bile flow. Our finding that a lowered proportion of nutrition

### Table III. Significant univariate correlates of peak direct bilirubin concentration among 30 infants with SBS

<table>
<thead>
<tr>
<th>Variable</th>
<th>R</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of days with diverting ostomy</td>
<td>.400</td>
<td>.055</td>
</tr>
<tr>
<td>Percentage of total kilocalories fed enterally wk after surgery</td>
<td>−.504</td>
<td>.023</td>
</tr>
<tr>
<td>Number of Gram-positive infections</td>
<td>.511</td>
<td>.006</td>
</tr>
<tr>
<td>Percentage of days fed protein hydrolysate formula</td>
<td>−.476</td>
<td>.014</td>
</tr>
</tbody>
</table>

*As calculated by (Number of days fed formula/Number of days enterally fed) × 100.
received enterally at 6 weeks after surgery is a risk factor for increased direct bilirubin levels also supports the importance of enteral feeding for these patients.

Our study has several limitations, most notably its small sample size and retrospective nature. The study covered 13 years, over which time available technologies may have changed and influenced the outcomes of our patients. We found, for example, that prognosis for these infants gradually improved over the course of the study period. Others have also reported an improvement in outcome for these children in the 1990s versus the 1980s. In addition, the amino acid–based formula given to some patients was introduced in the United States in 1995.

This study suggests that certain nutritional and other postoperative practices can reduce the duration of PN use, as well as ameliorate the development of cholestasis in neonates with SBS. Prospective, multicenter studies will be necessary to fully assess the efficacy of these and other therapies in the management of SBS. In the meantime, use of breast milk, early enteral nutrition, and prompt closure of diverting ostomies should be encouraged.

We thank Drs Glenn Furuta, Athos Bousvaros, and Moritz Ziegler for comments on earlier drafts.

REFERENCES

32. Xanthou M, Bines J, Walker WA. Human milk and intestinal host de-


