

# Short Bowel Syndrome: How Short is Too Short?

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## KEYWORDS

- Short bowel syndrome • Intestinal failure • Prognosis
- Enteral feeding • Neonate

Intestinal failure is characterized by the inability to maintain energy, fluid, electrolyte, or micronutrient balance and can result from surgical resection, obstruction, dysmotility, congenital defect, or disease-associated loss of absorption.<sup>1</sup> The most common condition resulting in intestinal failure is short bowel syndrome (SBS), which occurs after massive resection of small bowel.<sup>2,3</sup> In infants, necrotizing enterocolitis and intestinal anomalies are most frequently responsible for SBS. The intestinal anomalies responsible for SBS include intestinal atresias, gastroschisis, and volvulus.

Any definition of SBS must include two important concepts: a shortened length of intestine and a need for parenteral nutrition (PN). The Canadian Association of Pediatric Surgeons defines SBS as the need for PN greater than 42 days after bowel resection or a residual small bowel length of less than 25% expected for gestational age.<sup>4</sup> This definition leads us to the question that is the subject of this article, which is addressed in the next section.

Wessel and Kocoshis<sup>5</sup> make an important distinction between intestinal failure and SBS. The implied difference between the two entities is that SBS is associated with significant loss of absorptive surface area, whereas intestinal failure is a lack of satisfactory absorption despite an apparently adequate intestinal surface area.<sup>5</sup> So, patients who have SBS may have intestinal failure, whereas patients who have intestinal failure may not have SBS. This article focuses only on SBS with associated intestinal failure and attempts to elucidate the prognostic factors that ultimately predict successful weaning from PN.

Intestinal adaptation is defined as the ability to maintain normal growth and fluid and electrolyte balance without the need for PN support. It is a compensatory response that follows an abrupt decrease in mucosal surface area after an extensive small bowel resection and includes a variety of anatomic and physiologic changes that increase the gut's digestive and absorptive capacity. It begins shortly after intestinal resection and is complete within 36 to 48 months.<sup>6,7</sup>

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### HOW SHORT IS TOO SHORT?

Neonates, especially premature neonates, are at a distinct advantage with regard to intestinal adaptation. The small bowel length beyond 35 weeks of gestation is double that of an infant between 19 and 27 weeks of gestation,<sup>8</sup> suggesting that the residual intestine may have greater potential for increase in length in a preterm infant than in a full-term baby.<sup>9,10</sup> Median small bowel length increases from 114.8 cm between 19 and 27 weeks of gestation through 172.1 cm between 27 and 35 weeks of gestation to a length of 248.0 cm in neonates greater than 35 weeks of gestation.<sup>8</sup> At 1 year of age, small bowel length is approximately 380 cm.<sup>11</sup>

Intestinal resections can be divided into three categories based on the residual length of the small intestine along the antimesenteric border. Resections can be short (residual small intestine: 100–150 cm), large (residual small intestine: 40–100 cm), or massive (residual small intestine: <40 cm).<sup>7</sup> From a prognostic perspective, however, this approach is simplistic; we also need to consider the gestational age of the patient at the time of surgery, the portion of bowel resected, and the functional integrity of the remaining small intestine.<sup>7</sup>

All our knowledge about prognostic factors that determine survival and weaning from PN comes from retrospective studies. One early study suggested that the presence of 15 cm of small bowel with an ileocecal valve (ICV) or 40 cm of small bowel in the absence of an ICV was associated with survival.<sup>12</sup> These data have been partially improved on by several studies published in the past decade (**Table 1**). The newer data, too, should be interpreted carefully because all these studies included patients over several years; the shortest study studied patients over a 12-year span, whereas the longest studied patients over 27 years. Two studies have shown that infants born in more recent years have better outcomes than infants born earlier.<sup>13,14</sup>

### FACTORS PREDICTING MORTALITY

In a large population-based study, the overall incidence of SBS was 22.1 per 1000 neonatal intensive care unit (NICU) admissions and 24.5 per 100,000 live births, with a much greater incidence in premature infants.<sup>15</sup> The SBS case fatality rate was 37.5%.<sup>15</sup> In the retrospective studies detailed in this article, mortality has ranged from 10.3% to 27.5%. In general, studies have found increased mortality with decreased small bowel length (<15 cm<sup>16</sup> or <10% of a given infant's length for gestational age<sup>17</sup>) and with persistent cholestasis (defined as a direct bilirubin measurement  $\geq 2$  mg/dL<sup>16</sup> or  $\geq 2.5$  mg/dL<sup>17</sup>).

### ANATOMIC PREDICTORS OF ADAPTATION

All the newer retrospective studies have found that small bowel length is an important prognostic factor.<sup>6,7,14,16,17</sup> Two studies identified children with residual small bowel length greater than 15 cm<sup>16</sup> and greater than 40 cm<sup>7</sup> as more likely to be weaned off PN. Spencer and colleagues<sup>17</sup> found that small bowel length  $\geq 10\%$  of expected length for gestational age was a significant predictor of adaptation.

Absolute residual length measurements should no longer be used as a predictor of adaptation. Infants who have SBS today span a much wider gestational age range than their counterparts in the late 1970s (three of the “newer” studies date back to patients from that era). If one were to prognosticate purely on the basis of residual small bowel length, the most accurate method of prediction would be to use the percentage of small bowel length for gestational age. These data also suggest that surgeons should report the remaining length of small bowel accurately. If surgeons report

Table 1

Factors predicting successful weaning from total parenteral nutrition that have been identified by five retrospective studies

	Sondheimer and colleagues <sup>6</sup>	Andorsky and colleagues <sup>14</sup>	Quiros-Tejeira and colleagues <sup>16</sup>	Goulet and colleagues <sup>7</sup>	Spencer and colleagues <sup>17</sup>
No. children	44	30	78	87	80
Study period	1985–1996	1985–1998	1975–2000	1975–1991	1977–2003
<b>Surgical factors</b>					
Small bowel length	Yes	Yes	>15 cm	>40 cm	≥ 10% of expected length for gestational age
Presence of ICV	No	No	Yes	Yes	Yes
Intact colon	—	No	Yes	—	—
<50% of colon resected	—	No	Yes	—	—
Primary anastomosis	—	No	Yes	—	—
More recent year of surgery	—	Yes	—	No	—
<b>Enteral intake</b>					
Percentage of daily kilocalories through the enteral route at 6 weeks	—	Yes	—	—	—
Percentage of daily kilocalories through the enteral route at 12 and 24 weeks	Yes	—	—	—	—
<b>Potentially modifiable factors</b>					
Intake of breast milk	—	Yes	—	—	—
Intake of amino acid-based formula	—	Yes	—	—	—

Data from Refs. <sup>6,7,14,16,17</sup>

only the resected length, the estimated residual small bowel length can be calculated from the known small bowel length for the child's gestational age.<sup>8</sup>

Although the length of the resected specimen is important, it is also important to know the portion of small bowel that was resected (ie, jejunum versus ileum) because the area of small bowel that is resected also influences the degree of adaptation that is possible. The ileum has a much greater capacity for adaptation than the more proximal portions of the bowel.<sup>18</sup> In addition to intrinsic differences between these two small bowel segments, chyme moves less rapidly through the ileum than through the jejunum because of less vigorous motility. This increases the opportunity for nutrient absorption during adaptation.<sup>19</sup> Also, ileal resection causes the rate of gastric emptying to hasten as a result of the loss of the ileogastric reflex that normally slows it down, diminishing the opportunity for nutrient absorption.<sup>20</sup>

Because the ileum is contiguous with the ICV, which, in turn, is contiguous with the colon, these three elements have to be considered together. The ICV slows the transit time of intestinal contents and prevents reflux of colonic contents and bacteria into the ileum. Resection of the ICV can cause bacterial reflux into the small bowel. The ensuing bacterial overgrowth can deconjugate bile salts, reduce bile salt absorption, and impair gut function.<sup>5</sup> An intact colon or remnant of colon may contribute to adaptation after small bowel loss.<sup>21,22</sup> In colonic resections, the usual colonic functions of water, electrolyte, and short-chain fatty acid (SCFA) absorption and slowing of intestinal transit are lost.<sup>23</sup> Thus, colonic resection may also diminish adaptation.

Most studies have identified preservation of the ICV as a favorable indicator of long-term adaptation. Whether this actually reflects the ICV itself or the terminal ileum that is contiguous with it is unclear. Spencer and colleagues<sup>17</sup> found it difficult to separate the influence of ICV resection from colonic resection and decided to use only ICV resection in their analysis. Quiros-Tejeira and colleagues<sup>16</sup> were able to show that apart from patients with a preserved ICV, patients with an intact colon or with at least greater than 50% of colon length remaining were more likely to adapt. However, these researchers also showed that primary anastomosis rather than an ostomy or ostomies was associated with a greater degree of adaptation.<sup>16</sup> The benefits of maintaining intestinal continuity can be physiologically explained by the fact that all portions of the gut are exposed to enteral nutrients and biliary and pancreatic secretions, leading to a greater degree of adaptation.

Apart from the length of bowel remaining after a resection, the condition, area, and motility of the bowel may affect the ability of the infant or child to tolerate enteral feedings. These factors can be indirectly assessed by the enteral tolerance to breast milk or formula at specific intervals after the initial resection. Sondheimer and colleagues<sup>6</sup> assessed the percent of daily energy intake through the enteral route at 12 weeks after surgery. In infants obtaining 75% of their calories enterally by 12 weeks, the likelihood of weaning off PN is 90%, whereas those tolerating 50% of their calories enterally have only a 75% likelihood of being weaned off PN. In children who tolerate only 25% enterally, the likelihood of weaning is only 50%.<sup>6</sup> These investigators also extended their observations to 24 weeks after surgery, whereas Andorsky and colleagues<sup>14</sup> confirmed that this is generally true even 6 weeks after the initial surgery.

Most of the anatomic predictors are not modifiable, with the possible exception of restoring intestinal continuity at the time of intestinal surgery. Only one of these studies<sup>14</sup> has shown that use of breast milk and amino acid-based formulas is associated with a shorter duration of PN. The effect of these and other nutrients is discussed further in the section on nutritional modifiers of adaptation.

From a clinical perspective, these data lead us to the following conclusions. We should use the percentage of residual small bowel length for gestational age as the prime anatomic predictor of adaptation—the greater the percentage, the better is the likelihood of adaptation. Other anatomic factors should then be added into the prognostic mix: presence of the ICV, presence of an intact colon or most of the colon, and presence of an ostomy. Because these infants usually spend at least 3 to 6 weeks in the NICU after surgery, the percentage of enteral calories tolerated by these infants at specific time intervals can be used to refine the prognosis.

### NUTRITIONAL MODIFIERS OF ADAPTATION

In rodent models, sole use of PN without enteral feeding causes small bowel atrophy.<sup>24</sup> The use of enteral feeding contributes greatly to intestinal adaptation. After massive small bowel resection, only limited adaptation can occur in the absence of enteral nutrition.<sup>24</sup> In protracted diarrhea of infancy, the combination of PN and enteral nutrition is superior to PN alone in stimulating intestinal regeneration of disaccharidases.<sup>25</sup> The same is considered to be true of intestinal adaptation in SBS.

Specific enteral nutrients stimulate epithelial cell proliferation through a complex process. These nutrients probably work through trophic paracrine hormones that are secreted in the intestinal epithelium to stimulate epithelial cell proliferation and reduce apoptosis.<sup>26</sup> Among digestible carbohydrates, it has been shown that disaccharides are more trophic to the rat small bowel than monosaccharides.<sup>27</sup> This has led to the “functional workload” hypothesis.<sup>28</sup> This hypothesis states that it is the workload induced in the epithelium—the need for digestion and absorption of nutrients within the lumen—that serves as an important trophic stimulus for adaptation.<sup>28</sup> Certain enteral nutrients may be more effective stimulants than others, probably because they confer a greater workload while being digested and absorbed or because they result in enhanced release of trophic factors. They probably orchestrate these changes through afferent sensory neurons that detect changes in the chemical contents of the gut lumen and then set off the subsequent neural, hormonal, and immune signals supporting nutrient digestion and absorption.<sup>29–31</sup> This “functional workload” premise should also apply during the consumption of a mixed diet.

Evaluation of specific macronutrients reveals that hydrolyzed protein is more trophic to the gut than intact protein.<sup>32</sup> Similarly, long-chain fats stimulate small bowel adaptation better than medium-chain fats.<sup>32</sup> Free fatty acids are more trophic than long-chain triglycerides (LCTs), protein, starch, or medium-chain triglycerides (MCTs) in enhancing intestinal adaptation.<sup>33</sup> LCTs seem to be potentially more trophic than MCTs; LCTs also stimulate biliary and pancreatic secretions, which, in turn, are also trophic factors.<sup>34</sup> Among long-chain fatty acids, eicosapentanoic and docosahexanoic acids are more effective in inducing structural changes associated with adaptation than less highly unsaturated fats.<sup>35</sup> Despite their inability to stimulate adaptation to the extent of LCTs, MCTs are considered to be beneficial in SBS for several reasons. MCTs are hydrolyzed more rapidly than LCTs by pancreatic lipase into free fatty acids and glycerol. They can also be absorbed intact into the portal circulation even in the absence of lipase and bile.<sup>36</sup> MCTs can be absorbed to a certain extent from the stomach and duodenum; the unabsorbed fraction is then absorbed in the proximal jejunum.

Biliary and pancreatic secretions can also serve as potent stimuli for small bowel adaptation. Surgical manipulations in rodents, such as transplantation of the ampulla of Vater into the distal small intestine<sup>37</sup> or diversion of pancreatic and biliary secretions into self-emptying ileal loops, induce villus hyperplasia in the ileum.<sup>38</sup>

Gut adaptation involves hormonal mediators, such as enteroglucagon, glucagon-like peptides, neurotensin, peptide YY, growth hormone, and insulin-like growth factor. A detailed review of these hormones and their role in gut adaptation is outside the scope of this article and can be found elsewhere.<sup>39–41</sup> Other factors in the intestinal lumen that potentially contribute to intestinal adaptation include polyamines (spermine and spermidine), epidermal growth factor (EGF), and trefoil peptides.<sup>18,42</sup> Glutamine, an enterocyte fuel, and SCFAs, a fuel for colonocytes produced by bacterial fermentation of dietary fiber, also play roles in intestinal adaptation.<sup>42,43</sup>

### **ENTERAL FEEDING IN SHORT BOWEL SYNDROME: WHAT TO FEED AND HOW TO FEED**

There are no prospective or randomized data to guide the choice of enteral feeds in SBS. Only one of the retrospective studies addressed this question.<sup>14</sup> In this study, breast milk feeding was shown to be an important factor in gut adaptation.<sup>14</sup> Breast milk, surprisingly, fulfills many of the needs of infants who have SBS. Its chemical complexity is a double-edged sword. Although it is a complex food that definitely increases functional overload, the presence of lactose, complex fats, and proteins can lead to feeding intolerance in infants who have SBS. From a trophic perspective, however, lactose is a disaccharide, and although breast milk lacks hydrolyzed protein, it has LCTs, glutamine,<sup>44</sup> and growth factors like growth hormone<sup>45,46</sup> and EGF.<sup>47,48</sup> As is discussed elsewhere in this article, breast milk is also less likely to provoke an allergy in the neonate.

Amino acid–based formulas were also found to be associated with a shorter duration of PN in the study by Andorsky and colleagues.<sup>14</sup> Even before this study, Bines and colleagues<sup>49</sup> reported on four patients who had SBS and feeding intolerance, who were all weaned off PN within 15 months of being started on an amino acid–based formula. Physiologic data fail to lend significant support to an amino acid–based formula in SBS. Such a formula does not increase functional workload significantly because of its elemental nature. The carbohydrates are glucose polymers, and the protein is in the form of amino acids. A factor that could favor amino acid–based formulas, however, is that the formula used in the study by Bines and colleagues<sup>49</sup> had a large proportion of LCTs. Second, allergic sensitization<sup>50</sup> and allergic colitis have been described in infants who have SBS.<sup>51,52</sup>

Although there are no clinical data to support them, semielemental formulas containing hydrolyzed protein and MCTs are used widely and are generally well tolerated.

A practical approach to infant feeding in SBS is outlined here. Breast milk becomes the feed of choice when it is available. When it is unavailable or poorly tolerated, it may be appropriate to consider a protein hydrolysate formula initially, especially in children with good anatomic prognostic factors who are likely to adapt successfully. In children with poor prognostic factors, an elemental formula may be considered initially in the absence of breast milk. In any child in whom there is persistent feeding intolerance, an amino acid–based formula must be considered.

#### ***How to Feed***

In all children who have SBS requiring PN, a continuous enteral infusion of breast milk or formula must be considered. The sole exception may be children with practically no small bowel, such as after surgery for extensive midgut volvulus. As soon as postoperative ileus resolves, feeds are administered in a continuous fashion through a nasogastric or a gastrostomy tube. Children who seem to have a poorer prognosis may benefit from early gastrostomy tube placement. Continuous feeds optimize absorption (and probably adaptation) by permitting total saturation of the transporters in the gut

24 hours a day. Enteral nutrition is usually started slowly and advanced based on stool or ostomy output and other abdominal symptoms and signs.

When there is an ostomy and an accompanying mucus fistula, the ostomy output can be infused into the mucus fistula with the aim of providing nutrients for absorption and luminal secretions, both of which should encourage adaptation of the distal bowel. A review on this topic concluded that mucus fistula refeeding is safe, improves weight gain, and potentially reduces total PN-related complications in infants who have SBS.<sup>53</sup> However, skin breakdown, bag leakage, and difficulties in performing this at home may make this difficult.<sup>54,55</sup>

#### **OTHER FACTORS THAT MAY INFLUENCE ADAPTATION**

In an effort to provide SCFAs as an energy source to an intact colon, dietary fiber in the form of pectin, a soluble fiber,<sup>56</sup> or green beans<sup>56</sup> has been used. SCFAs are meant to stimulate sodium and water absorption, and patients can be expected to have decreased stool output while receiving supplemental fiber. This approach does not always decrease stool output and may cause abdominal distention from the fermentation of fiber. In patients without a colon or with a short colon and no ICV, dietary fiber would not be expected to work and should be avoided. There are no controlled studies on the use of these materials, and more study is needed.

Children who have SBS with small bowel bacterial overgrowth are more difficult to wean off PN.<sup>57</sup> This suggests that in children who have SBS, bacterial overgrowth should be aggressively managed.

#### **SUMMARY**

SBS is the most common cause of intestinal failure in infants and is often caused by necrotizing enterocolitis and intestinal anomalies. Several anatomic factors can be used to predict patients with a poor prognosis. These prognostic factors can be used to guide various therapies and to counsel parents. The few modifiable factors, such as the use of continuous enteral feeding along with PN, should be used to optimize outcome.

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