

## REVIEW ARTICLE

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## Pediatric Intestinal Failure

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ONCE A CONDITION THAT WAS ALMOST ALWAYS FATAL,<sup>1</sup> PEDIATRIC INTES-  
tinal failure is now considered a complex but survivable syndrome that  
afflicts tens of thousands of children. Deaths due to dehydration and  
malnutrition, which claimed more than half of infants with the short-bowel syn-  
drome, were reduced with the advent of parenteral nutrition in the 1960s.<sup>2</sup> Neo-  
nates with extremely short residual bowel, who previously would have received  
palliative care, could now receive more effective nutritional therapy. However, one  
study involving 272 infants with intestinal failure who were enrolled between 2000  
and 2004 showed 58 deaths (largely from multiorgan system failure [including  
liver disease], sepsis, and hemorrhage) related to prolonged parenteral nutrition  
and 10 additional deaths from complications related to intestinal transplantation,  
for an overall mortality rate of 25%.<sup>3</sup> More recent advances have resulted in sub-  
stantially improved survival rates (>90%) for these infants (see Table S1 in the  
Supplementary Appendix, available with the full text of this article at NEJM.org),  
who are often critically ill after surgery for gastrointestinal diseases and have  
ongoing surgical, medical, and nutritional complications.

## DEFINITION, EPIDEMIOLOGY, AND CAUSES

Intestinal failure has been defined as “the reduction of functional gut mass below the minimal amount necessary for digestion and absorption adequate to satisfy the nutrient and fluid requirements for maintenance in adults or growth in children.”<sup>4</sup> An umbrella label, intestinal failure includes the surgical short-bowel syndrome (intestinal resection for acquired or congenital gastrointestinal diseases, leading to clinically significant malabsorption and requiring specialized nutritional therapy), as well as disorders of gastrointestinal motility (e.g., intestinal pseudo-obstruction) and congenital enterocyte disorders (microvillus inclusion disease, tufting enteropathy, and others). This review concentrates on the natural history and management of the short-bowel syndrome, although several aspects of management also apply to other forms of intestinal failure.

Amassing data on the incidence of intestinal failure has been difficult because of the condition's rarity and the varied case definitions. (Indeed, the evidence for many treatments of intestinal failure is weak<sup>5-7</sup> because of heterogeneous definitions, low disease prevalence, and reliance on uncontrolled case series to evaluate therapies and outcomes.) One commonly used definition of intestinal failure during infancy is the need for parenteral nutrition for at least 90 days.<sup>8</sup> A population-based estimate, with cases defined as the need for parenteral nutrition for more than 42 days after bowel resection or a residual small-bowel length of less than 25% of that expected for gestational age, yielded an incidence of 24.5 cases per 100,000 live births.<sup>9</sup> The incidence of the short-bowel syndrome among infants with low birth weight (<1500 g) is higher, at 7 cases per 1000 live births.<sup>10</sup>

Pediatric intestinal failure is most often caused by necrotizing enterocolitis.<sup>11</sup> The incidence of necrotizing enterocolitis among very-low-birth-weight neonates increases by 3% for every 250-g decrement in birth weight below 1500 g.<sup>12</sup> As the survival rate among very-low-birth-weight neonates increases, the incidence of necrotizing enterocolitis, and consequent intestinal failure, may also increase. Gastroschisis is another common cause of pediatric intestinal failure,<sup>3</sup> and the prevalence of gastroschisis has increased by 36% — from 3.6 cases per 10,000 births (in the 1995–2005 period) to 4.9 per 10,000 births (in the 2006–2012 period).<sup>13</sup> Other common causes include malrotation and midgut volvulus, intestinal atresia, intestinal aganglionosis, and trauma. The numerous gastrointestinal and nutritional manifestations of intestinal failure (Fig. 1) include malabsorption of nutrients, small-bowel dysmotility and bacterial overgrowth, and intestinal failure–associated liver disease.

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#### INTESTINAL ADAPTATION AND THE CONCEPT OF ENTERAL AUTONOMY

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The management of intestinal failure is aimed at supporting adequate nutrition and minimizing the risk of complications or death, with the goal of independence from parenteral nutrition, or “enteral autonomy.” The process of intestinal adaptation to massive bowel loss has been described as a compensatory process wherein the remaining bowel undergoes substantial structural and functional changes that increase its absorptive capacity.<sup>14</sup> Histologic hallmarks of the compensatory process include increased villous height and crypt depth, with gross anatomical features that include bowel lengthening and dilatation. Such adaptation is promoted by a combination of mechanical, humoral, and luminal factors,<sup>15,16</sup> and putative molecular signaling pathways are being actively investigated.<sup>17,18</sup> It is thought that aggressive enteral therapy enhances adaptation and prevents complications associated with prolonged parenteral therapy.<sup>19</sup>

As the intestine adapts and absorption improves, the growing child also undergoes a progressive reduction in energy, protein, and fluid needs (as expressed per kilogram of body weight). The likelihood of adequate adaptation depends on the severity of gastrointestinal compromise and the absorptive capacity of the intestine. A child

with relatively higher absorptive capacity may require parenteral nutrition for only a year or two. The more severely limited the absorptive capacity, the slower the recovery will be. A child with an ultrashort gut or low absorptive capacity may have limited adaptive potential, with increasing tolerance of enteral nutrition but without the capacity for full independence from parenteral nutrition.

Clinical factors relevant to achieving enteral autonomy have not been defined prospectively. However, numerous retrospective studies have identified important factors that affect the chances of attaining this goal, including longer residual small bowel, younger age at the time of intestinal resection, preservation of the ileocecal valve, diagnosis of necrotizing enterocolitis, absence of severe liver disease, and normal gastrointestinal motility. Data from the Pediatric Intestinal Failure Consortium suggest that receipt of care at an institution that does not offer intestinal transplantation predicts successful enteral autonomy (possibly reflecting a difference in the severity of cases according to whether an institution does or does not offer transplantation)<sup>20</sup> and that white race correlates with longer survival.<sup>21</sup>

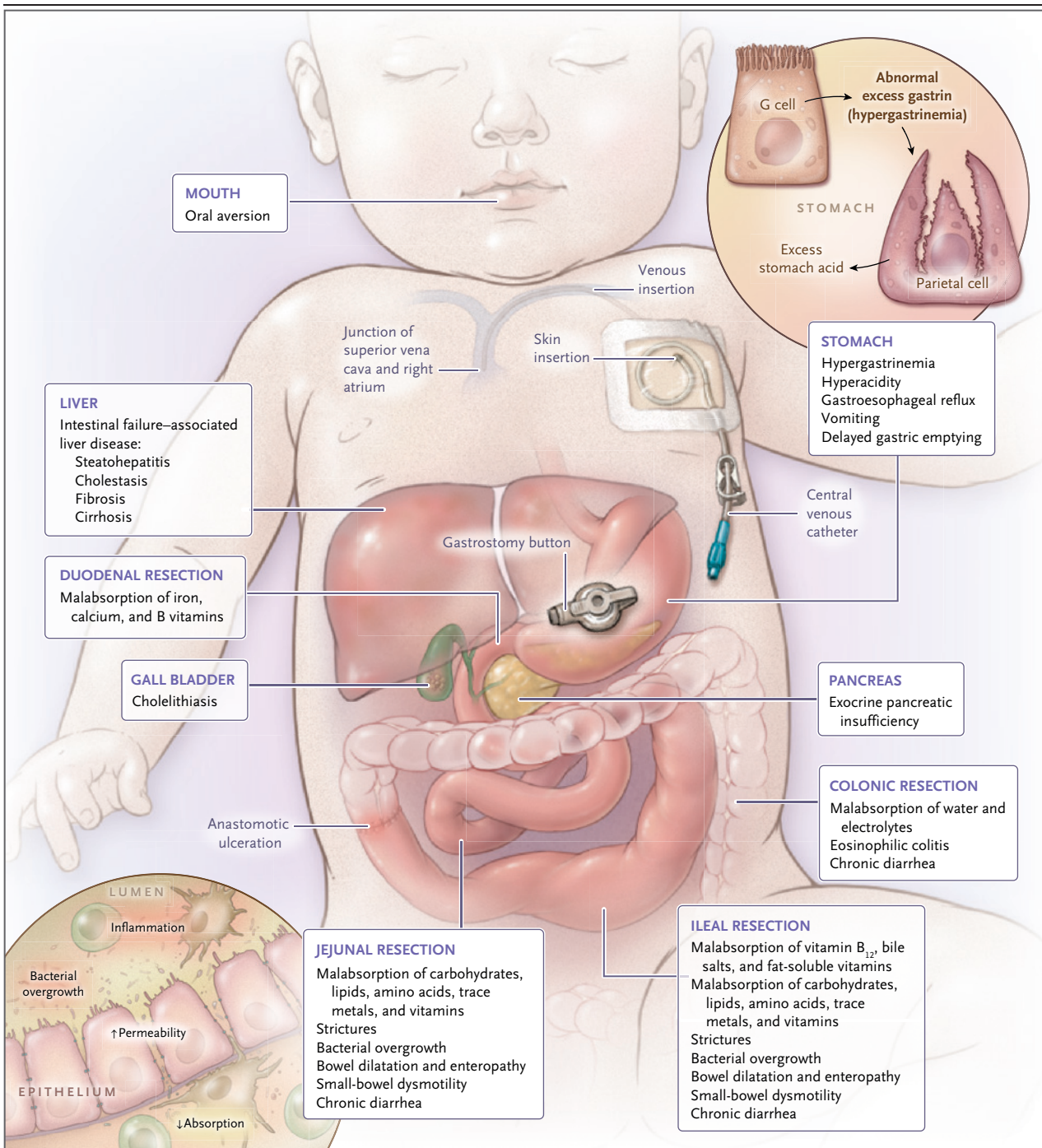
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#### NUTRITIONAL THERAPIES

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##### PARENTERAL NUTRITION

Meticulously administered fluid, electrolyte, and nutritional therapy, with both specialized parenteral and enteral nutrition, is the mainstay of treatment for pediatric intestinal failure.<sup>22</sup> Infants who have undergone massive bowel resection should receive parenteral nutrition early in the postoperative period, and enteral nutrition (discussed below) should be initiated shortly thereafter. Safe and successful parenteral therapy begins with a comprehensive multidisciplinary assessment of the child’s water, electrolyte, energy, and macronutrient and micronutrient requirements. Ideally,<sup>23</sup> the treatment team should include a registered dietician to objectively measure nutritional status, a nutritional support nurse to evaluate venous-access use, a nutritional pharmacist to oversee the sterile and safe preparation of parenteral-nutrition components, and a supervising physician specializing in nutrition.<sup>24</sup> Close communication with the referring surgical and neonatal intensive care team is critical. Important considerations include the cause of intesti-



**Figure 1. Gastrointestinal Manifestations of Intestinal Failure.**

After intestinal resection, malabsorption of several classes of nutrients ensues (depending on the site of resection) and numerous inflammatory complications (e.g., bacterial overgrowth, colitis, anastomotic ulcerations, peptic disease with hypergastrinemia, and increased intestinal permeability) occur. Water and electrolyte losses are also commonly observed. Intestinal failure–associated liver disease has multiple manifestations.

nal failure, the underlying nutritional status (as it relates to factors such as prematurity, low birth weight, or appropriate size for gestational age), gastrointestinal anatomy (length of the residual small and large bowel), vascular access, concomitant medical and surgical illnesses, family medical history, and social history (e.g., living conditions and employment of parents).

Prolonged parenteral nutrition is lifesaving but nevertheless may lead to numerous complications, including central catheter-associated bloodstream infections, mechanical catheter-associated complications (breakage or thrombosis), metabolic bone disease, and intestinal failure-associated liver disease. Detailed considerations of these complications are found elsewhere,<sup>22</sup> but several unique aspects of intestinal failure-associated liver disease deserve mention.

Parenteral preparations themselves may lead to problems. For example, parenteral exposure to proinflammatory n-6 fatty acids or phytosterols (e.g., stigmaterol) contained in soy-based intravenous fats have been implicated in the development of intestinal failure-associated liver disease.<sup>25</sup> The commonly recommended dose of intravenous fat emulsion for infants receiving parental nutrition was previously 2 to 3 g per kilogram of body weight per day; however, in an effort to reduce the incidence or severity of intestinal failure-associated liver disease, more recent data support routine restriction of the dose to 1 g per kilogram per day in infants with severe gastrointestinal disease who are likely to require long-term parenteral nutrition.<sup>26,27</sup> Essential fatty acid deficiency may occur if fat emulsion is administered at a level below 1 g per kilogram per day. For example, in a study providing an average of 0.3 g of intravenous fat per kilogram per day, mild essential fatty acid deficiency developed in 8 of 13 infants.<sup>26</sup> Thus, regular clinical and biochemical monitoring (total fatty acid profile, including the ratio of triene to tetraene) is essential for children receiving restricted amounts of intravenous fat emulsion.

The advent of intravenous fat preparations enriched with n-3 fatty acids has had a substantial effect on the severity of intestinal failure-associated liver disease and has probably reduced mortality rates among infants with the short-bowel

syndrome.<sup>28,29</sup> Children in whom intestinal failure-associated liver disease develops may have cholestasis. The involvement of such patients in open-label studies of various agents strongly suggests that switching from an emulsion containing predominantly n-6 fatty acids to one that contains predominantly n-3 fatty acids and that is also low in phytosterols reduces biochemical measures of cholestasis. Fish oil preparations have relatively low concentrations of the essential fatty acids (linoleic and alpha-linolenic acids); however, in a study involving 30 children with intestinal failure who were treated with fish oil emulsion as the sole source of intravenous fat for a median of 4.6 years, essential fatty acid deficiency (as defined by a serum triene:tetraene fatty acid ratio >0.2) did not develop in any of the children. In this series, the mean percentage of enteral calories ranged from 20 to 30%.<sup>30</sup>

Newer intravenous fat emulsions, one containing a four-lipid combination of soy, olive, fish, and medium-chain oils (Smoflipid, Fresenius Kabi) and the other containing olive and soy oils (Clinolipid, Baxter Healthcare), were approved for use in adults by the Food and Drug Administration in 2016 and 2013, respectively. The four-lipid product has undergone preliminary evaluation in infants with early intestinal failure-associated liver disease (mean direct bilirubin level, 1 to 3 mg per deciliter [17 to 50  $\mu$ mol per liter]). In a multicenter pilot study (a blinded, randomized, controlled trial comparing the four-lipid product with a soy-based lipid emulsion [Intralipid, Fresenius Kabi]), the conjugated bilirubin level was significantly lower in 11 infants who received the four-lipid product than in 13 infants treated with the soy-based lipid emulsion, each for a mean duration of 8 weeks.<sup>31</sup> Long-term follow-up studies are needed to compare fat emulsions and examine the risk of hepatic cirrhosis (which can develop despite improvements in cholestasis markers) and other features of intestinal failure-associated liver disease, as well as growth rates, body composition, and neurodevelopment.

#### ENTERAL NUTRITION

The composition and timing of enteral feeding can affect the achievement of enteral autonomy. Prompt initiation of enteral feeding after bowel

resection has been reported to improve the rate of enteral autonomy<sup>8</sup>; such findings provide little justification for prolonged “gut rest.” For infants with the short-bowel syndrome, human milk is often chosen for enteral nutrition, but data to support this choice are limited. Human milk contains growth factors, amino acids, immunoglobulins, and other immunologically important compounds that may promote intestinal adaptation.<sup>32</sup> It has been hypothesized that the use of human milk may result in fewer days of dependence on parenteral nutrition<sup>33</sup> and may reduce the risk of intestinal failure–associated liver disease.<sup>34</sup> When human milk is unavailable, amino acid–based formulas, which have been associated with more favorable outcomes than protein hydrolysate formulas,<sup>33,35</sup> are commonly used. It is thought that decreased intestinal barrier function<sup>36</sup> may predispose infants with intestinal failure to allergic gastrointestinal diseases.<sup>37</sup> Studies in animals suggest that intact macronutrients (e.g., long-chain fatty acids) lead to better intestinal adaptation than do medium-chain fatty acids,<sup>38</sup> but data in humans are limited.

In children with chronic diarrhea, enteral nutrition delivered by continuous drip has been shown to improve intestinal absorption and weight gain,<sup>39</sup> and in adults with intestinal failure, tube feedings improve energy and macronutrient absorption as compared with oral (bolus) feeding.<sup>40</sup> However, bolus enteral feeding results in cyclical changes in plasma levels of gastrointestinal hormones such as insulin, pancreatic polypeptide, gastric inhibitory polypeptide, gastrin, motilin, enteroglucagon, and neurotensin, which may be important for adaptation and growth.<sup>41</sup> In our experience, a combined approach (e.g., continuous feeding at night and bolus feeding during the day) is feasible.<sup>19</sup> There is evidence that using protocols for enteral feeding can shorten the duration of parenteral nutrition and lower the rates of intestinal failure–associated liver disease.<sup>42</sup> The introduction of oral boluses of human milk or formula as soon as they are tolerated postoperatively appears to help stimulate oral motor development and may help prevent long-term feeding aversion.<sup>4</sup> The American Academy of Pediatrics guidelines<sup>43</sup> suggest the introduction of complementary, age-appropriate foods between 4 and 6 months of age. We have followed this practice with intestinally challenged infants to apparently good effect.

More studies are needed to identify factors associated with the achievement of adequate oral intake.

Micronutrient (vitamin and mineral) supplementation is a critical aspect of nutritional therapy. The human gastrointestinal tract absorbs nutrients at numerous anatomical locations, and the location of bowel resection in infants with intestinal failure helps determine the frequency and severity of micronutrient deficiencies (Fig. 1). Common nutrient deficiencies that develop include deficiencies of vitamin D, zinc, iron, and vitamin B<sub>12</sub>; deficiencies of these and other nutrients can be observed even with the use of full or “total” parenteral nutrition, especially during the weaning from parenteral to enteral nutrition.<sup>44,45</sup> Even infants with normal somatic growth and few gastrointestinal symptoms may have important micronutrient deficiencies,<sup>46</sup> so regular biochemical monitoring is indicated. Enterally administered, water-soluble preparations of fat-soluble vitamins are helpful for ensuring adequate intake and absorption. In patients who have undergone terminal ileal resection, parenteral vitamin B<sub>12</sub> may be necessary; sublingual and intranasal vitamin B<sub>12</sub> preparations are available, but data on their efficacy are sparse.

#### PHARMACEUTICAL AGENTS

Numerous medical therapies with various mechanisms of action, including antisecretory, antimotility, and proabsorptive agents (Table 1), are used in children with intestinal failure. Antacid therapies are important for combatting the gastric hypersecretion that is known to follow massive bowel resection.<sup>47</sup> The optimal duration of postoperative antacid therapy in affected patients is unknown, but histamine H<sub>2</sub> blockers, proton-pump inhibitors, or both are often administered.<sup>3</sup> Since there are data that suggest a link between acid blockade and infections of the respiratory and gastrointestinal tracts<sup>48</sup> (presumably including bacterial overgrowth in the small intestine), it is worthwhile to wean patients from antacid therapy as soon as possible. Other antisecretory agents, including loperamide, bile acid sequestrants, and octreotide, have not been extensively studied in children with intestinal failure.

Bacterial overgrowth of the small intestine is a common finding in patients with the short-bowel syndrome and is thought to be due to

**Table 1. Medical Therapies for Pediatric Intestinal Failure.**

Class and Examples	Comments
Antisecretory agents	
Histamine H <sub>2</sub> receptors (e.g., ranitidine)	Used to reduce hyperacidity after massive resection
Proton-pump inhibitors	Used to reduce hyperacidity after massive resection
Loperamide	Used to slow intestinal transit
Bile acid sequestrants (e.g., cholestyramine)	Used for bile salt malabsorption after terminal ileal resection; use may reduce absorption of fat-soluble nutrients
Octreotide	Has not been evaluated for intestinal failure
Racecadotril	Has not been evaluated for intestinal failure; not available in the United States
Crofelemer	Has not been evaluated for intestinal failure; indicated for adults with antiretroviral therapy–induced chronic diarrhea
Adjunctive absorptive agents: pancreatic enzyme replacement therapy	For pancreatic atrophy and exocrine insufficiency, which are rare complications of intestinal failure
Prokinetic agents	
Cisapride	For delayed gastric emptying in patients with gastroschisis and other foregut anomalies
Erythromycin, clarithromycin, amoxicillin–clavulanic acid	Antibiotics used for their promotility effect in intestinal failure
Cyproheptadine	Improves gastric accommodation and stimulates appetite
Antibiotic agents: many available	Helpful in the treatment of small-intestinal bacterial overgrowth; indiscriminate use may result in fungal infections, antimicrobial resistance, or <i>Clostridium difficile</i> infection
Probiotic agents: many available	No evidence of benefit in small studies; risk of sepsis
Growth factors: glucagon-like peptide 2 analogues (e.g., teduglutide)	Teduglutide is licensed for use in adults with intestinal failure; trials in children are ongoing

altered intestinal motility and anatomy, resection of the ileocecal valve, and possibly the use of antacids. In a detailed study involving 10 infants with the short-bowel syndrome, the odds of the development of a central catheter–associated bloodstream infection was approximately 7 times as high among those with small-intestinal bacterial overgrowth as among those without such overgrowth.<sup>49</sup> Cyclical use (1 week per month) of broad-spectrum antibiotics (e.g., metronidazole or ciprofloxacin) is the mainstay of therapy for small-intestinal bacterial overgrowth at many centers.<sup>3</sup> Endoscopic sampling and quantitative cultures of duodenal fluid may be helpful in diagnosing the disorder, allowing appropriate tailoring of antibiotic therapy.<sup>50</sup>

Although it has been proposed that probiotics may improve intestinal permeability, this has not been confirmed in patients with intestinal failure,<sup>51</sup> and there have been reports of bacteremia with the use of probiotic supplements.<sup>52,53</sup> In one case, lactobacillus sepsis developed in an 11-month-

old child with the short-bowel syndrome due to necrotizing enterocolitis who was receiving parenteral nutrition. Pulsed-field gel electrophoresis showed an identical pattern in the isolates from his blood and the probiotic supplement he had been receiving,<sup>53</sup> suggesting that bacterial translocation occurred across a permeable gastrointestinal mucosa as a complication of probiotic use. Data are not sufficient to make a recommendation, but it may be reasonable to avoid the use of probiotics in patients who have central venous catheters in place. The role of the gut microbiome in affecting intestinal adaptation, nutrient absorption, and other clinical outcomes is an area of active research.

Therapy with gastrointestinal hormones to induce intestinal adaptation shows promise as a medical therapy for intestinal failure. Glucagon-like peptide 2 (GLP-2) is a naturally occurring hormone secreted by enteroendocrine cells in the distal ileum and colon. GLP-2 induces small-bowel epithelial proliferation and delays gastric

emptying.<sup>54</sup> In a series of studies involving adults with the short-bowel syndrome, subcutaneous administration of the GLP-2 analogue teduglutide reduced intestinal malabsorption, increased villous height and crypt depth,<sup>55</sup> and reduced the need for parenteral nutrition.<sup>56,57</sup> A recent randomized, open-label, 12-week trial involving 42 children compared daily treatment with teduglutide, administered at three dose levels (0.0125 mg per kilogram in 8 children, 0.025 mg per kilogram in 14, or 0.05 mg per kilogram in 15) with the standard of care (in 5 children).<sup>58</sup> Treatment with teduglutide at a dose of either 0.025 or 0.05 mg per kilogram was associated with a trend toward a reduction in parenteral nutrition. A 24-week trial is under way (ClinicalTrials.gov number, NCT02682381) to determine the efficacy of these two higher doses of teduglutide in children.

#### SURGICAL THERAPIES

The preservation of as much intestine as possible, particularly small bowel, is the cardinal goal of surgical management in patients at risk for intestinal failure. Such intestinal sparing is accomplished by salvaging all viable intestine during the initial procedure and, when necessary, performing a “second look” operation within 12 to 24 hours to ascertain whether gut that was marginally viable is recovering. Colonic salvage of malabsorbed nutrients is important for nutrient balance in patients with the short-bowel syndrome,<sup>59</sup> and reestablishment of bowel continuity through ostomy closure, or refeeding distal stomas,<sup>60</sup> is thought to be associated with more rapid attainment of enteral tolerance<sup>61</sup> and a lower incidence of liver disease.<sup>33,60</sup> The placement of feeding gastrostomy tubes may allow for continuous feeding or intestinal decompression as needed. Gastrostomy tubes can also be converted to gastrojejunostomy devices, which permit both nutrient administration directly into the small bowel and gastric drainage.<sup>62</sup>

Central catheter placement is commonly required for intravenous nutrition and hydration in children with intestinal failure.<sup>63</sup> Avoidance of the ligation of major veins during surgical placement of such catheters and the introduction of interventional radiologic techniques has greatly enhanced the preservation of long-term venous access.<sup>63</sup> The majority of children in the United States who receive parenteral nutrition at home

are successfully treated with tunneled central venous catheters.<sup>64</sup>

Because children with intestinal failure generally require intravenous access and parenteral nutrition for a prolonged period, they are at high risk for central catheter–associated bloodstream infections. Critical preventive measures include strict adherence to aseptic technique, the use of standardized protocols for central catheter management, and caretaker education.<sup>64</sup> The infusion of 70% ethanol, which is both antimicrobial and fibrinolytic, to fill the catheter during intervals between use (called an “ethanol lock”) in patients receiving cycled parenteral nutrition also seems to be beneficial in preventing bloodstream infections.<sup>65,66</sup> Such infections are also a risk factor for intestinal failure–associated liver disease,<sup>67</sup> so prevention of central catheter–associated bloodstream infections may help improve liver outcomes as well.

The endogenous process of intestinal adaptation includes bowel lengthening and dilatation to increase the mucosal surface area. Autologous intestinal reconstruction surgery aims to taper and lengthen the remaining bowel in order to improve motility, enhance absorption, and limit bacterial overgrowth.<sup>68,69</sup> The longitudinal intestinal lengthening and tailoring procedure (LILT), commonly referred to as the Bianchi operation, was first described in 1980.<sup>70</sup> A simpler operation, serial transverse enteroplasty (STEP), was developed more recently.<sup>68</sup> Data from the International STEP Registry indicate that among patients in whom standard bowel rehabilitation is not successful, 66% have improved enteral tolerance and 47% are fully weaned from parenteral nutrition after undergoing the initial STEP procedure.<sup>71</sup> These two procedures have not been directly compared, although limited data<sup>72</sup> appear to support the STEP procedure, which is less technically difficult than LILT and can be repeated.<sup>73,74</sup>

Some children with intestinal failure are candidates for intestinal or multivisceral transplantation. For a child with progressive, severe intestinal failure–associated liver disease, loss of venous access, recurrent central catheter–associated bloodstream infections that are life-threatening, complete mesenteric thrombosis, or extremely short residual bowel (i.e., little or no chance of enteral autonomy), transplantation may be an alternative to lifelong dependence on parenteral

nutrition.<sup>75</sup> Early referral of candidates to a transplantation center is mandatory. There are currently more than 1000 living intestinal-transplant recipients in the United States, nearly half of whom underwent transplantation as children.<sup>76</sup> As of 2015, the 5-year rate of patient survival was 75% for children receiving an isolated intestinal graft and 62% if both liver and intestine were transplanted.<sup>76</sup> A 25% reduction in the number of intestinal transplantations in the United States was reported for the period from 2007 to 2012,<sup>77</sup> probably as a result of the improved outcomes of intestinal rehabilitation.

## CONCLUSIONS

The past few years have seen dramatic improvements in survival among children with intestinal failure. A multidisciplinary approach to the care of this complex disorder has been associated not only with increased survival but also with lower rates of central catheter-associated bloodstream infections and other improved outcomes.<sup>78-80</sup> With advances in intestinal rehabilitation, intestinal transplantation may not be required in some patients; furthermore, survival with prolonged parenteral nutrition has become more common.

Future therapies for intestinal failure are likely to include newer approaches to parenteral and enteral nutrition; hormonal and other medical therapies to facilitate residual gut growth, which will probably target molecular mechanisms of intestinal adaptation; gene therapy targeting intestinal stem cells<sup>81</sup>; the application of tension-induced growth devices to lengthen autologous intestine<sup>82-84</sup>; and the creation of tissue-engineered bowel.<sup>85</sup> Effective management will require the identification of valid and reliable biomarkers for monitoring gastrointestinal function. A focus on the quality of life,<sup>86</sup> neurodevelopmental outcomes, and cost-effective therapies<sup>87</sup> will also be important.<sup>88</sup> Multicenter clinical trials, better definitions of exposure and outcome variables, and longer follow-up are all needed to further improve the quality of the evidence supporting current and future therapies for children with intestinal failure.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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