Redefining short bowel syndrome in the 21st century

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In 1968, Wilmore and Dudrick reported an infant sustained by parenteral nutrition (PN) providing a potential for survival for children with significant intestinal resections. Increasing usage of TPN over time led to some patients developing Intestinal Failure Associated Liver Disease (IFALD), a leading cause of death and indication for liver/intestinal transplant. Over time, multidisciplinary teams called Intestinal Rehabilitation Programs (IRPs) began providing meticulous and innovative management. Usage of alternative lipid emulsions and lipid minimization strategies have resulted in the decline of IFALD and an increase in long-term and transplant-free survival, even in the setting of ultrashort bowel (< 20 cm). Autologous bowel reconstructive surgeries, such as the serial tapering enteroplasty procedure, have increased the likelihood of achieving enteral autonomy. Since 2007, the number of pediatric intestinal transplants performed has sharply declined and likely attributed to the newer innovations healthcare. Recent data support the need for changes in the listing criteria for intestinal transplantation given the overall improvement in outcomes. Over the last 50 y, the diagnosis of short bowel syndrome has changed from a death sentence to one of hope with a vast improvement of quality of life and survival.

In their initial report of utilization of parenteral nutrition (PN) in a child, Wilmore and Dudrick described an infant who was sustained by PN for 44 d (1). This female infant was born with near total small intestinal atresia and two areas of colonic atresia. Her intestine was reanastomosed and her initial nutritional needs were provided with 10% glucose and protein solutions (Figure 1). Her weight declined and subsequently an intravenous catheter was placed to provide adequate calories, vitamins, and minerals intravenously given her significant weight loss. Although glucose and protein were provided, there were no intravenous fat emulsions available at that time. This child demonstrated growth in length, weight, and head circumference over the 44 d with positive nitrogen balance. It was this family's willingness to allow their child to be the first to undergo a catheter placement and the researchers' determination to improve outcomes that led to a rapid expansion of the field of PN and allow hope for long-term survival for children with short bowel syndrome.

Over the last 50 y, the management of these patients has drastically changed given our current knowledge of this complex patient population. Determinants of the severity of intestinal failure have been linked to remnant intestinal length, prematurity with comorbidities including cardiac and pulmonary disease, underlying diagnosis and the development of PN associated liver disease (intestinal failure associated liver disease; IFALD) (2–7). Quiros *et al.* demonstrated that patients with sustained cholestasis >3 mo had <20% survival at 5 y of age (6). In this same cohort, 43% of patients with <15 cm died during the first 3–4 y. Overall during this era, the majority of patients with <30 cm were viewed as unlikely to have long-term survival unless they underwent intestinal transplantation. In 2012, the largest experience of caring for children with intestinal failure at multiple centers in North America was reported through the Pediatric Intestinal Failure Consortium (PIFCON) (8). This consortium consisted of 14 programs caring for patients with short bowel syndrome. They reported that 26% of patients had NEC, 16% had gastroschisis and 10% had intestinal atresia which is similar to other studies (Table 1) (9–12). A smaller percentage of patients had volvulus, motility disturbances, and mucosal lesions. Of the 272 patients in this cohort (2000–2007), 47% achieved intestinal adaptation with 26% and 27% respectively underwent intestinal transplantation or died by 72 mo. Utilizing this same dataset, the factors identified as associated with attaining enteral autonomy were (1); diagnosis of NEC (2), presence of the ileocecal valve, and (3) longer residual length (13). The current management strategies for patients with intestinal failure now lead to better outcomes than those reported for the PIFCON cohort. There is not a large, multicenter dataset describing a more contemporary cohort, and the majority of reports are from single centers (14–16) (Table 2).

In the infancy of this field, children lived in the hospital their entire lives given the complexity of their medical needs. Care for the intravenous catheter and administration of PN were deemed to require high level inpatient medical attention. Over time given cost constraints and improvement of quality of life for these children, the paradigm has shifted regarding their care. Currently, many of these children now reside at home with parents and skilled home care nursing providing the day-to-day care of their venous catheters, PN administration,

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Received 9 May 2016; accepted 30 October 2016; advance online publication 25 January 2017. doi:10.1038/pr.2016.265

enteral feeding pumps, and at times intravenous medications such as antibiotics. One of the major advancements in this field has been the development of Intestinal Rehabilitation Programs (IRPs). These programs are multidisciplinary in nature and consist of health care providers which may include gastroenterologists, surgeons, nurses, nurse specialists, registered dietitians, social workers, pharmacists, and psychologists. This multidisciplinary approach has improved care and survival compared with historical controls (17,18). In addition to the multidisciplinary care provided by these teams, newer innovations including alternative lipid management (alternate lipid emulsions and lipid lowering strategies), surgical interventions such as the serial transverse enteroplasty (STEP), and ethanol locks have made an impact on morbidity and mortality in this population (17,19–21).

IFALD

Historically, the major causes of mortality in intestinal failure patients are the development of progressive liver disease and cirrhosis (22,23). In fact, IFALD has previously been responsible for the high percentage of pediatric combined liver/intestinal transplants (24). Multiple components of PN have been implicated in this type of liver disease including protein, fat, and micronutrients such as copper (4,25,26). In addition to

PN components; gestational age, absence of enteral feedings, and massive resection have also been linked to IFALD (26). Prior to further understanding of the etiology of IFALD, the outcome was bleak with reported mortality as high as 100% for patients who did not adapt with persistent cholestasis or who were unable to undergo liver/small bowel transplantation (23). Sondheimer *et al.* demonstrated that children who had their first episodes of bacteremia at an earlier age were more likely to develop progressive liver failure (27). Approximately 70% of the pediatric intestinal transplant list in the early 2000's was comprised of children awaiting liver/small bowel transplant with wait list mortality approaching 50% for children < 1 y of age (28).

In the early 1990's, phytosterols, the major component of soy based lipid emulsions, were implicated in the pathogenesis of IFALD. Clayton *et al.* demonstrated elevated phytosterol levels in children receiving long-term PN with soy based lipids (29). One theory was that phytosterols negatively impact bile transport in the liver leading to cholestasis (29). The subsequent decrease in bile secretion may lead to increased red cell breakdown and hyperbilirubinemia. Unlike the United States; European countries and Canada have ready access to five alternative lipid emulsions including a fish oil-based product known as Omegaven which has been used in multiple centers (30,31). However, one obstacle to its use in the United States is lack of FDA approval. In order for this product to be used in the United States, a center must currently have a license from the US Department of Agriculture and an investigational new drug approval (IND) from the FDA. As this drug is considered experimental in the United States, the cost of the product must be absorbed by the hospital or some outside funding agency, not the family. Furthermore, an institutional review board (IRB) protocol must be in place if multiple patients are to be treated with this drug. To date there have not been large-scale prospective studies performed, and this drug is still not approved almost 8 y since the initial case report, despite the product's approval in Europe and Canada. In Europe, it was used more as a supplement to soybean-based lipid products, not sole therapy.

In 2008, the outcome of the first two patients in the United States who received the primarily omega-3 fish oil, containing lipid preparation, Omegaven, under a compassionate usage protocol through the Food and Drug Administration (FDA) was reported (32). This case series demonstrated resolution of cholestasis and improvement in hepatic function in two male

Figure 1. Delivery and collection apparatus. Hypertonic nutrient solution was propelled from reservoir bottle into the superior vena cava at a constant rate. Reproduced with permission from JAMA. 1968. Vol. 203 (10): 860–864. Copyright© 1968 American Medical Association. All rights reserved.

Table 1. Disease entities resulting in short bowel syndrome

A	Disease entity (NR = not reported)						
Author	NEC	Gastroschisis	Intestinal atresia	Volvulus	Combination	Hirschsprung's disease	Other
Columb <i>et al</i> (10) (<i>n</i> = 230, 1980–1999)	48 (16%)	48 (16%)	72 (24%)	NR	NR	39 (13%)	134 (44%)
Demeheri (11) (<i>n</i> = 171, 1988–2013)	82 (43.9%)	42 (22.5%)	40 (21.4)	34 (18.2%)	NR	NR	26 (13.9%)
Nucci <i>et al.</i> (9) (<i>n</i> = 389, 1996–2006)	74 (19%)	78 (20%)	47 (12%)	58 (15%)	NR	31 (8%)	26 (10.1%)
Squires (8) (<i>n</i> = 272, 2000–2007)	71 (26%)	44 (16%)	27 (10%)	24 (9%)	46 (17%)	11 (4%)	48 (18%)
Fullerton <i>et al.</i> (12) (<i>n</i> = 313, 2002–2014)	95 (30%)	72 (23%)	52 (17%)	33 (11%)	NR	NR	22 (7%)

infants, one with midgut volvulus and one with intestinal perforation, requiring long-term PN. One infant was listed for liver/small bowel transplant by the age of 5 mo. After initiation of Omegaven, cholestasis resolved over time despite both patients requiring 50 and 100%, respectively, of calories via the parenteral route. The authors surmised that using this type of lipid emulsion would reverse liver disease and may be safe as the sole source of lipids. This article heralded the increased usage of this product in children with or at risk for IFALD. This type of liver disease is one of the major risk factors for mortality in this patient population in addition to infection. In 2009, this same group reported the outcomes of 42 patients who received fish oil lipid emulsion monotherapy compared with historical controls. Patients receiving the fish oil lipid emulsion had a sixfold faster decline of serum direct bilirubin and were less likely to undergo intestinal transplantation or die (10 vs. 34%, $P < 0.005$) (33). None of the patients were diagnosed with hypertriglyceridemia, essential fatty acid deficiency, or coagulopathy. Texas Children's Hospital reported a larger group of 97 infants who received Omegaven (31). In their cohort, infants with conjugated bilirubin >10 mg/dl had higher mortality as shown previously (34). The nonsurvivors had higher peak bilirubin and higher mean bilirubin at the time of initiation of fish oil lipid emulsions. This supports the hypothesis that early intervention with fish oil lipid emulsions in the setting of hyperbilirubinemia may improve hepatic dysfunction and survival. Several small series have shown that despite the resolution of hyperbilirubinemia, Omegaven may not be able to halt the progression of liver fibrosis (35–37). However, there are risks associated with using a predominantly omega-3 based fatty acid emulsion. These include the lack of omega-6 fatty acids that may lead to essential fatty acid (EFA) deficiency. Brain development has been linked to EFA and the risk of deficiency may result in a decline in neurodevelopmental outcome, which is especially of concern in high risk premature infants (38). However the data is not conclusive that extra supplementation will improve visual acuity and neurodevelopment (39).

Some hypothesize that the benefit of the fish oil based emulsions may be the use of a lower lipid dose, not simply the fish oil itself. As a result, various centers instituted and have reported on the use of lipid minimization protocols. The term lipid minimization does not refer to one specific method. Centers may withdraw standard lipids for 2–4 wk, decrease the dosage to 0.5–1 g/kg/d daily, and/or decrease the frequency to three times weekly. One of the first pediatric studies to describe lipid minimization and its impact on cholestasis was a retrospective study that demonstrated the resolution of episodes of cholestasis in 10 children when lipid emulsions were withheld (mean 3.6 ± 2.5 mo) or permanently withdrawn (10). These authors warned that to withdraw these lipids was not without potential complications including EFA deficiency, growth failure, and potential hepatic steatosis. Cober *et al.* described a prospective study of 31 infants with IFALD who received the standard soy-based lipids of 1 g/kg/d twice weekly comparing them to age-, birthweight-, and diagnoses-matched historical controls

who received 3 g/kg/d of lipid daily (40). IFALD was defined as a direct bilirubin ≥ 2.5 mg/dl or total bilirubin ≥ 5 mg/dl. These patients demonstrated a similar decline in bilirubin as previously shown in the Omegaven studies. Twenty-three percent of the lipid reduction group received bacterial overgrowth prophylaxis potentially resulting in a greater decline in cholestasis (41,42). The theoretical impact of the prophylaxis is that it may decrease the risk for bacterial translocation which has been linked to bacterial overgrowth; nevertheless, there was no statistical impact of this type of therapy with further analysis. As had been shown previously, the mean serum bilirubin values were higher during episodes of bacteremia supporting the hypothesis that bacteremia worsens cholestasis and liver disease (40). Of note in this publication, the authors reported that 8 of 31 patients were found to have an elevated triene-to-tetraene ratio, but none had a ratio >0.2 which is the biochemical definition of EFA deficiency.

More recently, Lam *et al.* reported nine patients who were treated with lipid minimization, <1 g/kg/d (mean dose of 0.61 g/kg/d) of soy-based lipid, upon entry into their IRP program (43). No patient was found to have biochemical evidence of EFA deficiency with a median triene-to-tetraene ratio of 0.026. Admittedly this cohort received more lipid than the Cober study (0.3 g/kg/d) (40). There was one patient with a low serum linolenic acid, and two had low serum mead acid levels which resolved with reintroduction of lipids. The mean height-for-age z-scores (HAZ) increased from -2.6 to -0.5 with mean weight-for-age z-scores increasing from -1.4 to -0.6 . These results suggest that growth can occur despite lipid minimization.

There was one randomized controlled trial that compared the safety and efficacy of a fish oil-based intravenous fat emulsion to a soy-based fat emulsion (44). Both groups received 1 g/kg/d of either lipid preparation. Due to the lower incidence of cholestasis than predicted overall, this study was terminated early. Authors concluded that fish oil was safe and found no risk of impairment to growth, infection, or neurodevelopmental outcomes. As they had previously demonstrated there was no coagulopathy, elevated triglycerides, or EFA deficiency noted. Nevertheless, there is no conclusive data showing the superiority of one therapy over the other when the identical doses are administered.

Regardless of which type of lipid strategy is implemented, there is the potential risk to develop EFA deficiency. Docosahexaenoic acid (DHA) is the predominant omega-3 polyunsaturated fatty acid (PUFA) and EFA in the body, that comprises $>90\%$ of PUFA in the brain (38). Multiple studies have shown the impact of EFA on brain development and cognition but the impact of supplementation in formula is unclear (45,46). Premature infants may be lacking in DHA because of their shorter gestation during which DHA is usually transferred from the mother. The effect of DHA has been linked to a variety of neural events and cognition (38). Patients treated with lipid minimization may become EFA deficient resulting in dampening of brain development and subsequent function, but to what exact degree is unclear. We do know there is a

large body of evidence that has clearly demonstrated that DHA improves cognition (38). One trial of preterm infants receiving human milk supplemented with DHA and arachidonic acid found that the supplemented infants had higher cognition at age 6 mo based on neurodevelopmental testing (47).

Recently, Blackmer *et al.* examined 25 of the eligible 62 patients who had been treated with lipid minimization in the Cober study (40,48). The neurodevelopmental scores were similar to patients not receiving lipid minimization when controlling for gestational age (48). This is one of the first studies to examine the impact on lipid minimization on outcomes using several parental surveys. Limitations of this work are that >60% ($n = 37$) patients did not enroll in the follow-up study and that there is missing data such as EFA levels. The patients who had not enrolled may have had worsened neurodevelopmental outcomes, and this was simply not captured in the follow-up neurodevelopmental study. Further elucidation of the effect of lipid minimization on neurodevelopmental outcomes is definitely needed in a larger, multicenter study.

The emerging arena of newer combination lipid emulsions is also growing with early results suggesting these products may be beneficial in preventing IFALD (49,50). One of these newer generation lipids is SMOF, a soy-, medium chain triglyceride-, olive oil-, and fish oil-based product. The potential benefit of this preparation is the presence of antioxidants and less phytosterols. A randomized trial revealed infants with intestinal failure who received SMOF had lower serum mean conjugated bilirubin at the conclusion of the 12 wk study (49). The SMOF treated infants were more likely to have a serum conjugated bilirubin of 0 $\mu\text{mol/l}$ compared with those who received soybean based lipids (hazard ratio 10.6, $P = 0.03$).

Omegaven and lipid minimization protocols are assumed to be having the greatest impact on decreasing the rates of IFALD and thus the number of pediatric intestinal transplants globally. SMOF has recently been approved for use in adults requiring IV lipid emulsions in the United States. There are ~4 pediatric studies that are completed or currently recruiting according to clinicaltrials.gov to investigate the use SMOF lipid in children. Little data is published on the impact of lipid minimization or Omegaven in neurodevelopmental outcomes, so this is an area that requires further investigation.

Ethanol Lock Prophylaxis

Another newer, increasingly standard practice is the use of ethanol locks. This technique consists of 70% ethanol solution being instilled in the central venous catheter for durations ranging from 2 to 12 h. The antimicrobial and antifungal properties of ethanol are thought to reduce the number of catheter line-associated blood stream infections (CLABSI) without subsequent antibiotic resistance. The initial data regarding this type of prophylactic therapy has been studied in the pediatric hematology and oncology population (51). CLABSI may lead to prolonged hospitalizations for intravenous antibiotics, loss of the catheter if the infection is unable to be cleared, and increased cost/charges associated with patient care (52,53). It has also been shown that there is a relationship between the

number of CLABSI and earlier age of onset to the development of cirrhosis (35). These adverse effects strengthen the case for the use of ethanol lock therapy and numerous studies have concluded that the use of ethanol locks is safe and effective in decreasing the number of blood stream infections in children on PN despite the uniformity of the protocols (19,21,54). Centers have used variable ethanol strengths, dwell times, and frequencies of instillation. Adura *et al.* described a protocol for ethanol lock prophylaxis, and confirmed a decrease in CLABSI from 7/1,000 d to 0.64/1,000 d after initiation of therapy ($P < 0.004$) (19). Patients receiving ethanol locks were noted to have fewer hospitalizations for fever and blood stream infection ($P < 0.003$) and fewer catheter replacements ($P < 0.001$). Catheter dysfunction has been a concern with the use of this type of lock, but multiple studies support that there is little difference in complications with or without ethanol lock therapy (19,21,54,55). More recent data argues that catheter dysfunction may be more common than previously reported (56). Single center studies have demonstrated the reduction in CLABSI in patients receiving ethanol lock prophylaxis but the reports are mixed with regard to the degree of catheter dysfunction related to therapy. With the loss vascular access being an indication for intestinal transplantation, larger multicenter trials would be beneficial in defining the risk of catheter dysfunction and subsequent loss in the setting of ethanol lock usage and in general (57).

Surgical Management of Short Bowel Syndrome

The surgical management of short bowel syndrome has also changed over time (58). This review will focus on the two more commonly known procedures, longitudinal intestinal lengthening procedure (LILT) or the “Bianchi procedure” and the serial transverse enteroplasty (STEP). A thorough review of the surgical literature is beyond the scope of this article. As part of the adaptive process after intestinal resection, the intestine may lengthen and dilate. In some settings, the bowel dilatation may lead to complications from stasis including recurrent bacteremia, plateau in advancement of enteral feedings, vomiting, and refractory D-lactic acidosis (59–61). In 1980, Bianchi described the LILT in which dilated loops of bowel are divided longitudinally along the mesenteric border leading to the creation of two hemi-loops with preserved vasculature (Figure 2) (62). These hemi-loops are then reanastomosed end to end preserving the surface area of the bowel but decreasing the diameter by roughly half. Bianchi reported his own series of the first 20 children who underwent a LILT during 1982–1997 (63). Patient survival was 45% with a mean follow up of ~6 y. Patients who had >40 cm of bowel and minimal hepatic dysfunction fared better.

In 2003, Kim *et al.* described a newer surgical procedure called a STEP in a pig model (64). This procedure consists of serial firing of staples perpendicular in a zig-zag pattern along the dilated loops of bowel without disturbing the vasculature (Figure 3). Unlike the LILT, this procedure can be performed on the duodenum and is thought to be less technically challenging. In 2013, the STEP registry published its data on 111

Figure 2. The Bianchi procedure. Reprinted from *Surgery*, 135 (5), Thompson JS, Surgical rehabilitation of intestine in short bowel syndrome, 465–470, 2004, with permission from Elsevier.

patients with dilated segments of bowel who underwent STEP procedures, the largest series to date of these patients. Of the 97 patients who were analyzed, 47% achieved full enteral autonomy within a median of 21 mo (59). The post-STEP mortality was 11% with the risk of death being associated with elevated bilirubin and shorter remnant length ($P = 0.05$ and $P < 0.001$ respectively). Most interestingly, almost 30% of children with a pre-STEP bowel length between 0 and 30 cm also eventually adapted supporting the fact that this type of surgery is a viable option even in the setting of ultrashort bowel. A more recent meta-analysis that evaluated data from 86 patients, suggests that the STEP procedure increases the likelihood of attaining enteral autonomy up to 87% (95% CI 77–95%) (65,66).

Both procedures have known complications including gastrointestinal (GI) bleeding and repeat bowel dilatation (65–68). In one series of 20 STEP procedures in 16 patients, bowel dilatation was associated with prolonged PN usage (41 vs. 3 mo in nondilated patients, $P < 0.006$) (69). Only 11% of the redilated patients achieved enteral autonomy as compared with 85% of those who did not. In another series of 16 patients, eight patients had redilation of the bowel and only one of these patients attained enteral autonomy (67). Of note, two of the eight patients redilated after their LILT and underwent a STEP. Patients undergoing > 1 STEPs are less likely to achieve enteral autonomy (67). Similarly in the STEP registry, of the 11 patients whose bowel redilated three attained enteral autonomy, two died, and two underwent a third STEP.

Gastrointestinal bleeding involving ulcerations around the staple lines have also been described as a late complication of patients undergoing STEP at single centers (65–68). Treatment for these patients varied including surgical resection,

Figure 3. Serial transverse enteroplasty (STEP). Reprinted from *Surgery*, 135 (5), Thompson JS, Surgical rehabilitation of intestine in short bowel syndrome, 465–470, 2004, with permission from Elsevier.

antibiotics, bowel rest, and luminal steroids. A meta-analysis by Frongia *et al.* reviewed outcomes of 363 LILT patients and 109 STEP patients obtained from 39 articles (69). Bleeding was reported in 16.1% (0–71.4) of LILT patients and 22.2% (7.1–33.3%) of STEP patients. The authors did not elaborate on the nature of the bleeding or the time period after the initial procedure that the bleeding occurred.

Few would disagree with the statement that STEP and LILT procedures have made a positive impact on clinical outcomes of patients with intestinal dilatation. Enteral autonomy has been shown in patients with ultrashort bowel syndrome. Unfortunately, we do not know the incidence of complications such as redilation and GI bleeding given the small number of patients overall.

Another aspect of surgical care is related to catheter placement and management. As loss of vascular access is an indication for intestinal transplant, techniques to minimize thrombosis are needed. Conventional practice has been that for short term usage, <3 mo, peripheral inserted central catheters (PICCs) or safe while Broviac or Hickman catheters for longer term PN usage. There are no randomized trials in pediatrics to suggest that one type of catheter is superior to another but one series suggested that PICCs may be beneficial and avoid loss of access (70). The European Society of Parenteral and Enteral Nutrition (ESPEN) position statement emphasizes that aseptic technique for insertion and care of the catheter and ultra sound guidance for placement are important but they conclude the data is weaker for other interventions such as the use of routine heparin prophylaxis (71).

Micronutrient Deficiency

Now the children with short bowel syndrome have longer life expectancy, they require monitoring of micronutrient deficiencies as identified in two cohorts of children followed in large IRPs (Tables 3) and (4). Yang *et al.* reported a series of 30 children with a median PN duration of 23 wk (73). During the transition to full EN over the course of 12 wk, 33% of the patients had one vitamin deficiency whereas 77% had one mineral deficiency. Upon transition to full EN, there was a further increase in vitamin deficiency to 70% and no change in mineral deficiency. The one modifiable variable the authors found was the use of a multivitamin prevented deficiency. In a larger cohort of 178 patients, there was a high prevalence of micronutrient deficiency reported during the transition to EN and once on full EN (73). In this study, PN duration was the only significant variable associated with micronutrient deficiency in the multivariable analysis. The most common deficiency identified was iron with >90% of the patients in both groups being anemic during the transition to full EN (Table 3). Vitamin D and zinc deficiencies were also prevalent in both cohorts. When analyzing anthropometric measurements, children in the Yang cohort with lower HAZ were more likely to have a mineral deficiency during the transition period (73). Conversely in the Cincinnati cohort, children with HAZ ≥ 2 were more likely to have a mineral deficiency as compared with those who did not (36.4 vs. 56% respectively, $P = 0.04$) (74). This strengthens the need for close monitoring regardless of the anthropometric values as they do not appear to correlate with deficiency status. As evidenced in both cohorts, the

large number of potential micronutrient deficiencies require close monitoring in these high-risk patients despite the ability to obtain enteral autonomy.

Intestinal Transplant

Given the dramatic changes in the care of these patients there has been a significant impact on the dynamics of the intestinal transplant list. The criteria for pediatric intestinal transplant include recurring sepsis, impending loss of central venous access, extreme short bowel syndrome, congenital mucosal disorders, liver disease, and intestinal failure with high morbidity and poor quality of life (57). During the time period of October 1987 to October 2004, ~71% of the patients awaiting intestinal transplant were <18 y of age with 81% also listed for a liver transplant compared with 43% of adults (28). Analysis of the United Network of Organ Sharing (UNOS) registry yielded pediatric survival data at 61 and 51% at 12 and 36 mo respectively. More recent analysis of Intestinal Transplant Registry (ITR) has demonstrated far fewer patients being listed for liver/bowel or multivisceral transplant with a subsequent decrease in transplants being performed overall since 2007, likely due to changes in medical and surgical management (75). Current data strengthens this conclusion (14,17,75). A single center study showed that intestinal transplant candidates cared for during 2006–2009 were more likely to have clinical improvement resulting in removal from the waiting list ($P < 0.0005$) and to have decreased mortality on the waiting list than those cared for during 1999–2005 (15 vs. >60%, $P = 0.0005$) (17).

Given the increasing ability for patients to be rehabilitated, some speculate there needs to be significant changes in the current listing criteria. A single center study analyzed outcomes of patients in two eras, 1998–2005 to the current era, 2006–2012 (75). This work refutes the current listing criteria by demonstrating that advanced liver disease had a sensitivity of 65% in the current era as compared with 84% previously reported with regard to outcome. Whereas ultrashort bowel had a positive predictive value of 100% in the prior era, it was only 9% in the current era. The authors also suggest newer criteria including ≥ 2 ICU admissions, persistent bilirubin >75 mmol/l (4.3 mg/dl) despite alternative lipid management, and loss of ≥ 3 central venous catheter sites; the odds ratio of these factors were 23.6, 24, and 33.3 respectively in their cohort ($P \leq 0.0005$). Patients in this series who had two or more of these newer criteria had a 98% probability of requiring intestinal transplant. Other comorbid conditions, such as congenital heart disease and

Table 2. Ultimate outcomes of patients with short bowel syndrome.

Author	Outcome (NR = not reported)				
	Enteral autonomy	Transplant	Death	Still on PN	Unknown status
Columb <i>et al.</i> (10) ($n = 230$, 1980–1999)	127 (55%)	14 (6%)	21 (9%)	69 (30%)	NR
Demehri (11) ($n = 171$, 1988–2013)	110 (64.3%)	26 (15.2%)	5 (2.9%)	61 (35.7%)	NR
Nucci <i>et al.</i> (9) ($n = 389$, 1996–2006)	42 (10.8%)	119 (35.2%)	109 (32.2%)*	23 (6.8%)	20 (6%)
Squires (8) ($n = 272$, 2000–2007)	47%	26%	27%	NR	NR
Fullerton <i>et al.</i> (12) ($n = 313$, 2002–2014)	174 (55.5%)	17 (5.4%)	18 (5.8%)	104 (33.2%)	NR

*Includes patients who died after transplant.

Figure 4. This is a graph depicting the number of pediatric intestinal transplantations performed from January 1, 2002, through December 31, 2015, based on UNOS data.

Table 3. Frequency of micronutrient deficiencies reported in children transitioning from parenteral nutrition to enteral nutrition

A	Micronutrient deficiency						
	Author	Anemia	Iron deficiency anemia	Iron	Vitamin D	Zinc	Copper
	Yang <i>et al.</i> (73) (<i>n</i> = 30, 1999–2008)	29 (97%)	6 (20%)	12 (40%)	6 (20%)	9 (31%)	17 (56%)
	Ubesie <i>et al.</i> (74) (<i>n</i> = 178, 2007–2012)	168 (93%)	66 (37%)	149 (84%)	61 (35%)	36 (20%)	51 (29%)

Table 4. Frequency of micronutrient deficiencies reported in children once attaining enteral autonomy

B	Micronutrient deficiency						
	Author	Anemia	Iron deficiency anemia	Iron	Vitamin D	Zinc	Copper
	Yang <i>et al.</i> (73) (n = 30, 1999–2008)	26 (87%)	11 (37%)	10 (32%)	20 (68%)	20 (68%)	7 (22%)
	Ubesie <i>et al.</i> (74) (n = 178, 2007–2012)	77 (43%)	52 (29%)	72 (24%)	54 (30%)	41 (23%)	14 (8%)

chronic lung disease, rather than the historical risk factors of liver failure resulted in patient deaths (17). Despite this being a single center study, these results lend credence to the fact that change is needed.

What was not been extensively studied in this patient population is racial disparities. Analysis of outcomes utilizing the PIFCON dataset based on race, white (n = 206) vs. nonwhite (n = 46), revealed that nonwhite children had a higher cumulative probability of dying (40 vs. 16% for white children) and were less likely to undergo intestinal transplantation (7 vs. 31% for white children, *P* = 0.003) (78). These outcomes persisted even when controlling for birth weight, underlying diagnosis, and care at an intestinal transplant center. This area of the field is probably one of the most difficult to study given that disparities may also be impacted by socioeconomic status,

educational status, and proximity to an intestinal transplant center. Controlling for socioeconomic status, we may find that these disparities may lessen or even resolve.

Intestinal transplant will always be needed albeit at a lower rate than previously performed given patients with motility disorders and mucosal lesions who develop complications from TPN usage. Analysis of the outcomes of both pediatric and adult intestinal transplant recipients at the University of Pittsburgh Medical Center, who survived for at least 5-y had conditional survival of 75 and 61% at 10- and 15-y survival (77). The most recent analysis of the ITR reveals patient survival at 76, 53, and 43 at 1-, 5-, and 10-y survival (75). It is difficult to compare this survival of patients who successfully achieve intestinal adaptation to those who require intestinal transplantation, who by definition have more complications

from their underlying condition. In the setting of dysmotility and mucosal lesions with resultant liver disease and loss of vascular access, intestinal transplant may be the only hope for long-term survival for some patients.

Intestinal Adaptation: The Final Frontier

A newer therapy for the promotion of intestinal adaptation is the usage of synthetic growth agents such as synthetic glucagon-like peptide 2 (GLP-2), Teduglutide. When used over 24 wk, Teduglutide was found to decrease volume and days of PN required for adult patients with intestinal failure (79). More recently, Schwartz *et al.* further supported the effectiveness of this therapy by reporting sustained response over the course of 24–30 mo (80). This product has been approved for adults in the United States and in Europe. There are currently studies underway in pediatrics to determine the safety and efficacy of this drug. Longer term questions include the risk of polyps or cancer development in actively growing children treated with this drug.

In conclusion, the field of intestinal failure and rehabilitation has made tremendous strides since Wilmore and Dudrick placed the first intravenous catheter in 1968 (1). The definition of short bowel syndrome has been redefined with regard to intestinal length and overall outcomes. It is unlikely that one single factor can be attributed to the improvement of outcomes, the newer therapies including ethanol lock prophylaxis, lipid minimization and alternative lipid strategies, autologous bowel reconstructive surgeries, and the advent of the IRPs have all had an impact. The care and quality of life of these patients has dramatically improved over the last 50 y with the number of those receiving intestinal transplants have declined over the last 9–10 y (Figure 4). Hopefully, the increasing number of IRPs will allow for more collaboration between centers especially those with high risk patients.

STATEMENT OF FINANCIAL SUPPORT

No financial assistance was received to support this study.

Disclosures: There are no financial ties or conflicts of interest to disclosure.

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