Journal of Pediatric Surgery 55 (2020) 1802–1808

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

STEP improves long-term survival for pediatric short bowel syndrome patients: A Markov decision analysis☆,☆☆

Rashikh A. Choudhury *, Dor Yoeli, Gerard Hoeltzel, Hunter B. Moore, Kas Prins, Mark Kovler, Seth D. Goldstein, Stephan G. Holland-Cunz, Megan Adams, Jonathan Roach, Trevor L. Nydam, Raphael N. Vuille-dit-Bille

[a] University of Colorado Hospital, Department of Transplant Surgery, Aurora, CO
[b] Johns Hopkins Hospital, Department of Pediatric Surgery, Baltimore, MD
[c] Ann and Robert H. Lurie Children's Hospital of Chicago, Division of Pediatric Surgery, Chicago, IL
[d] University Children's Hospital of Basel, Department of Pediatric Surgery, Basel, Switzerland
[e] Colorado Children's Hospital, Department of Pediatric Surgery, Aurora, CO

ARTICLE INFO

Article history:
Received 3 August 2019
Received in revised form 31 January 2020
Accepted 22 March 2020

Key words:
Short bowel syndrome
Intestinal transplant
STEP
Markov

ABSTRACT

Introduction: Increasingly, for pediatric patients with short bowel syndrome (SBS), intestinal lengthening procedures such as serial transverse enteroplasty (STEP) are being offered with the hope of improving patients' chances for achieving enteral autonomy. However, it remains unclear to what extent STEP reduces the long-term need for intestinal transplant or improves survival.
Methods: Based on existing literature, a decision analytic Markov state transition model was created to simulate the life of 1,000 pediatric SBS patients. Two simulations were modeled: 1) No STEP: patients were listed for transplant once medical management failed and 2) STEP: patients underwent STEP therapy and subsequent transplant listing if enteral autonomy was not achieved. Sensitivity analysis of small bowel length and anatomy was completed. Base case patients were defined as neonates with a small bowel length of 30cm.
Results: For base case patients with an ostomy and a NEC SBS etiology, STEP was associated with increased rates of enteral autonomy after 10 years for patients with an ICV (53.9% [STEP] vs. 51.1% [No STEP]) and without an ICV (43.4% [STEP] vs. 36.3% [No STEP]). Transplantation rates were also reduced following STEP therapy for both ICV (17.5% [STEP] vs. 18.2% [No STEP]) and non-ICV patients (20.2% [STEP] vs. 22.1% [No STEP]). 10-year survival was the highest in the (+) STEP and (+) ICV group (85.4%) and lowest in the (-) STEP and (-) ICV group (83.3%).
Conclusions: For SBS patients, according to our model, STEP increases rates of enteral autonomy, reduces need for intestinal transplantation, and improves long-term survival.
Type of study: Economic/Decision Analysis or Modeling Studies
Level of evidence: Level III

For neonates with short bowel syndrome (SBS), long-term mortality remains as high as 30–60% despite significant advances in parenteral nutrition (PN) and central access catheter care [1,2]. Nearly 10–20% of patients will be referred for intestinal transplant (ITx) [3,4]. Although outcomes following ITx have demonstrated increased quality of life, long term survival remains stark, most recently noted at 50% at 5 years for patients who have failed medical management of their SBS [5,6].

For providers managing SBS patients, the optimal decision-making paradigm remains poorly defined. Typically, SBS patients remain on PN until liver failure, lack of central access for PN, experience frequent life-threatening catheter related complications or experience an unacceptable quality of life; after which the option of ITx is considered [7]. In contrast to adult SBS patients, for pediatric SBS patients, particularly those with major intestinal resections in the first few months of life, intestinal lengthening procedures have increasingly been performed and seem to offer great promise [8,9]. Intestinal lengthening procedures

☆ There no disclosures from any of the co-authors.
☆☆ Author contributions: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: RA Choudhury MD, D Yoeli MD, HB Moore MD, PhD, K Prins MD, M Kovler MD, SD Goldstein, MD, MPhil, SG Holland-Cunz MD, M Adams MD, JP Roach MD, TL Nydam MD* RN Vuille-dit-Bille MD, PhD. Drafting the work or revising it critically for important intellectual content: RA Choudhury MD, D Yoeli MD, HB Moore MD, PhD, K Prins MD, M Kovler MD, SD Goldstein, MD, MPhil, SG Holland-Cunz MD, M Adams MD, JP Roach MD, TL Nydam MD* RN Vuille-dit-Bille MD, PhD. Final approval of the version to be published: RA Choudhury MD, D Yoeli MD, HB Moore MD, PhD, K Prins MD, M Kovler MD, SD Goldstein, MD, MPhil, SG Holland-Cunz MD, M Adams MD, JP Roach MD, TL Nydam MD* RN Vuille-dit-Bille MD, PhD. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and Resolved: RA Choudhury MD, D Yoeli MD, HB Moore MD, PhD, K Prins MD, M Kovler MD, SD Goldstein, MD, MPhil, SG Holland-Cunz MD, M Adams MD, JP Roach MD, TL Nydam MD* RN Vuille-dit-Bille MD, PhD.

* Corresponding author at: University of Colorado Hospital, 1225 N Emerson St. Unit B, Denver, CO, 80218. Tel.: +1 5133752611.
E-mail address: Rashikh.Choudhury@CUAnschutz.edu (R.A. Choudhury).

https://doi.org/10.1016/j.jpedsurg.2020.03.017
0022-3468/

such as serial transverse enteroplasty (STEP) aim to increase rates of enteral autonomy in SBS patients, and as such, to decrease the future need for ITx [10–12].

Beyond small case series, few large-scale studies have explored the complex decision-making paradigm surrounding surgical lengthening procedures for pediatric SBS patients [13–15]. No randomized controlled trials have been performed on the matter likely due to the costly, time-consuming and controversial nature of such a study in the pediatric population. STEP has been increasingly offered for pediatric patients. However, it remains unclear whether the initial short-term improvements in enteral autonomy rates merely delay the need for future transplant. Furthermore, the impact of small bowel length and the presence or absence of the ileocecal valve bias outcomes following STEP procedures and make interpretations of the current available literature difficult. As such, the aim of this study was to create a decision analytic Markov model to quantify, across a spectrum of bowel anatomy, the impact of STEP therapy on rates of enteral autonomy, need for future transplantation, and survival for pediatric SBS patients.

1. Methods

Markov decision analysis is a predictive modeling technique which aims to use data from existing literature to model stochastic processes, as is often present in medicine. Markov models have increasingly been utilized in the healthcare setting, particularly in situations where long-term trial data is lacking. Although limited by their inherit need for extrapolation, Markov models offer the advantage of providing decision makers guidance/forecasts on clinical decisions in a data-driven manner. Our group has previously created Markov models to describe the role of bariatric surgery for kidney and liver transplant candidates [16–18].

For this study, our aim was to build upon our prior Markov experience to create a model in order to quantify the potential utility that STEP offers SBS patients. Although intuitively and anecdotally surgeons are aware that STEP offers benefit, current literature which describes this benefit in a granular, long-term nature is lacking.

As such, a decision analytic Markov state transition model was created in order to estimate the impact of STEP on SBS patients on PN. Medical decision-making software was utilized (DATA 3.5; TreeAge Software, Inc., Williamstown, MA). Base case patients were defined as neonatal pediatric SBS patients (<12 months of age), with 30cm of small bowel length (lowest measured length in patient's history). Base case definitions were created to be reflective of the typical SBS patient who may need an ITx in the future. Baseline characteristics from patients in the included studies for the Markov model approximated that of our base case patient (median age ~1 year, SB length ~ 30cm, no ICV present, ostomy present, and NEC etiology of SBS).

1.1. Decision model structure

A decision analytic Markov state transition model was created in order to simulate the life of 1,000 pediatric SBS patients on parenteral nutrition. Transition probabilities from the initial state (SBS with PN) were to achieve enteral autonomy, or have a "medical failure" requiring either intestinal transplant or intestinal and liver transplant. Waitlist times were assumed to be uniform for all patients. Patients had a mortality risk in every state, as represented by state transition to death. Two simulations were modeled: (1) No STEP: patients were immediately listed for intestinal transplant (intestinal or intestinal/liver) once medical management of SBS failed and (2) STEP: patients underwent STEP therapy followed by transplant listing if enteral autonomy was not achieved (Fig. 1). Three-month cycle lengths were utilized until all patients died. Of note, it was assumed that all patients were surgical candidates for STEP. During the first 3-month cycle, patients faced a postoperative 30-day mortality risk (Table 1). Among patients who did not have enteral autonomy 6 months following STEP, they were re-entered into a re-do STEP arm.

1.2. State transition probabilities

Transition probabilities were extracted from existing, published literature using MEDLINE electronic search (Table 1). As has been previously described by Naughler et al. and utilized by our group previously, transition probabilities available in the literature for various time periods were converted into rates per cycle with the actuarial method for 3-month cycle probabilities [18,19].

1.3. Sensitivity analysis

Sensitivity analysis of initial small bowel length (shortest length in patient's medical history) was performed. Data points for 20 intervals between 10cm and 100cm of small bowel length was simulated in several iterations of the models. Presence of an ICV valve, ostomy, and NEC vs non-NEC etiology of SBS was also altered in each version of the model.

2. Results

2.1. State Transitions (Fig. 2)

At 10 years following initiation of the model, for non-ICV base case patients who did not undergo STEP, 22.1% had required transplantation (either ITx or ITx + LTx) (and were alive), 25% remained TPN-Dependent, and 36.3% were alive with enteral autonomy. In comparison, at 10 years, among such patients who did undergo STEP, 20.2% of patients were transplanted 20.4% remained TPN-Dependent and 43.4% of patients were alive with enteral autonomy.

For base patients with the presence of an ICV and who did not undergo STEP, 18.2% of patients were transplanted 15.6% remained TPN-Dependent and 51.1% of patients were alive with enteral autonomy. In comparison, such patients who underwent STEP, 17.4% of patients were transplanted 13.9% remained TPN-Dependent and 53.8% of patients were alive with enteral autonomy.

2.2. Survival

Markov simulation of long-term survival was completed across a spectrum of bowel anatomy (Fig. 3). Outcomes of base case patients (SB length 30cm) were modeled, with variation in presence of ICV, ostomy, and NEC vs. non-NEC etiology of SBS simulations (16 total scenarios).

Among patients with an ICV, the highest 10 year survival was observed with patients who underwent STEP, did not have an ostomy and had a NEC SBS etiology (86.5%). Lowest survival was observed amongst patients who did not undergo STEP, had an ostomy and had a non-NEC SBS etiology (84.5%).

Survival trends for non-ICV patients followed similar trends. The highest observed 10 year survival was among patients who underwent STEP, did not have as ostomy, and had a NEC SBS etiology (85.6%); while the lowest survival was observed amongst patients who did not undergo STEP, had an ostomy, and had a non-NEC SBS etiology (83.2%).

2.3. Small bowel length, sensitivity analysis

Sensitivity analysis of small bowel length (among patients with + ostomy and + NEC, and +/- presence of ICV) demonstrated that undergoing STEP and retaining ICV was associated with improved survival regardless of initial small bowel length (Fig. 4).

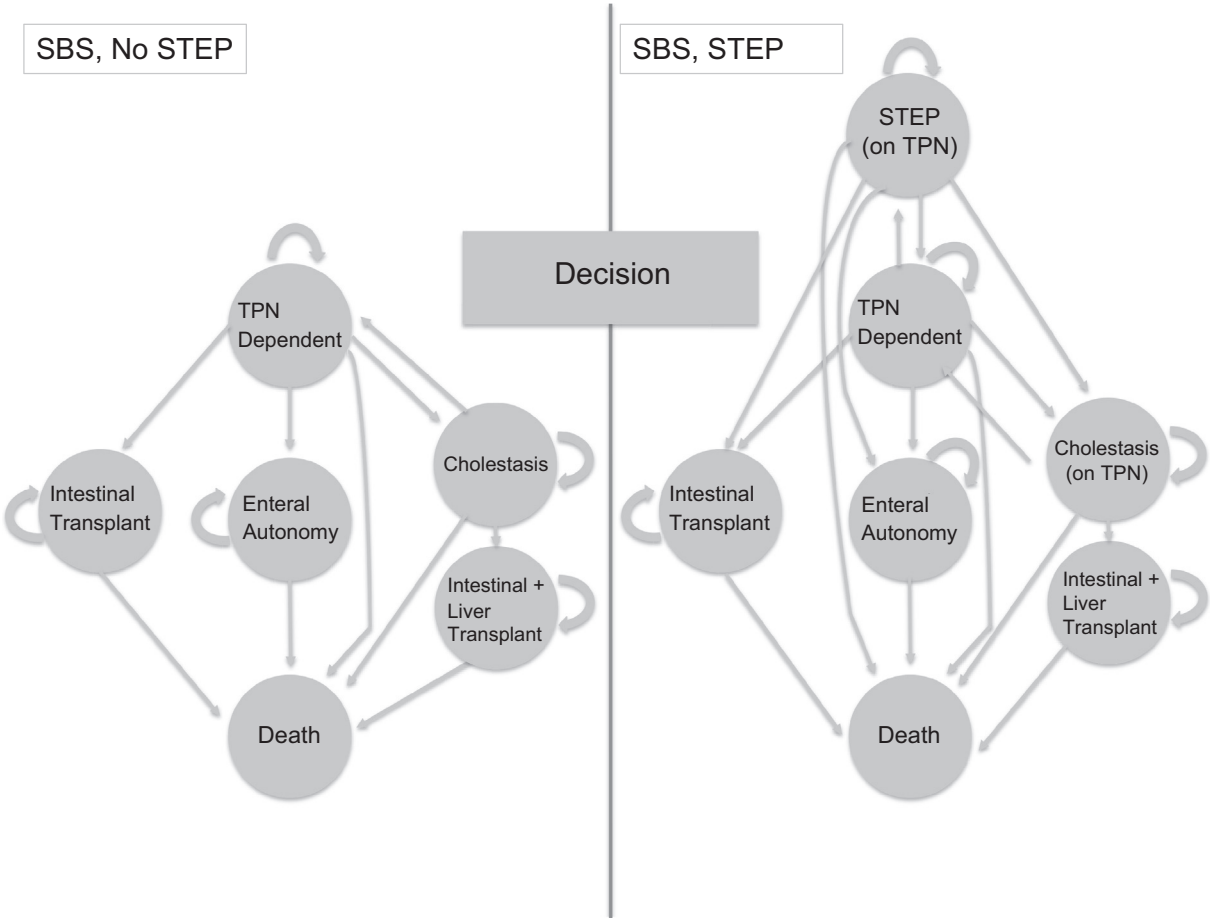

Fig. 1. Markov model bubble diagram.

2.4. STEP timing, sensitivity analysis

Timing of STEP while patients (base case: 30cm, -ICV, +ostomy, +NEC) were TPN dependent was altered to estimate the impact of delay/inability to perform STEP immediately (Fig. 5). Compared to Non-STEP patients, patients who immediately underwent STEP has improved rates of enteral autonomy at 10 years (43.4% [STEP] vs 36.3% [Non-STEP]. Longer delay to STEP was associated with lower rates of enteral autonomy. Of note, STEP continued to improve rates of enteral autonomy compared to No-STEP up and until 54 months of delay.

Table 1
Transition probabilities for Markov model.

Variables	Estimate (time)	Reference
Parenteral nutrition related mortality rate (no medical failure)	35% dead in 35 years	Colomb et al., 2007 [41]
Intestinal transplant related long-term mortality rate	41% dead in 5 years	Lao et al., 2010 [42]
Intestinal and liver transplant related long-term mortality rate	52% dead in 5 years	Lao et al., 2010 [42]
Intestinal transplant rate if failure to achieve enteral autonomy	26% transplanted in 6 years	Squires et al., 2012 [43]
Failure to achieve enteral autonomy, requiring ITx for SBS patients on PN (small bowel length, NEC, ostomy, and ileocecal valve sensitivity analysis parameters)	10cm of SB length: 57% at 60 months; 20 cm: 44%; 30 cm: 31%; 40 cm: 21%; 50 cm:13%; 60 cm: 8%; 70 cm: 5%; 80 cm: 3%; 90 cm: 2%; 100 cm: 1%; lack of ICV, HR-2.86; Non-NEC SBS etiology, HR = 2.84; presence of ostomy, HR = 2.55	Fallon et al., 2014 [34], Demehri et al. 2015 [30], Khan et al., 2015 [43]
Liver disease requiring liver transplant listing for SBS patients on PN	18% with clinically significant cholestasis in 3 years; 2% need for liver transplant in 6 years if history of cholestasis	Squires et al., 2012 [44], Puder et al., 2009 [34]
Survival rate once/if enteral autonomy achieved	98% alive in 5 years	Fullerton et al., 2016 [45]
Improvement rate in enteral autonomy after STEP	21% reduction in need for transplant following STEP	Avitzur et al., 2015 [46]
Procedure related mortality rate of STEP	0% mortality rate after 30 days	Mercer et al. 2014 [47]

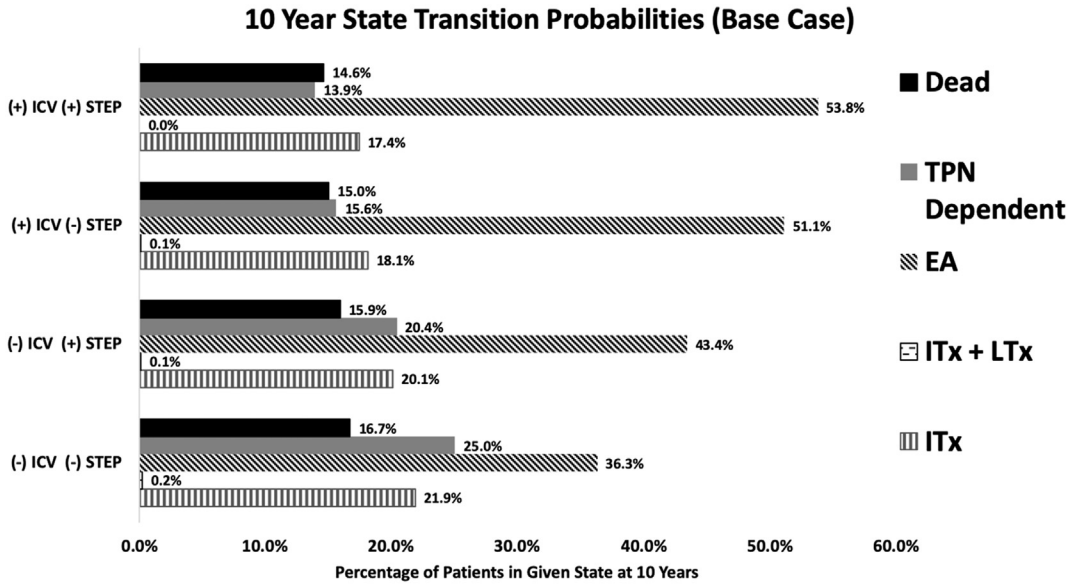

Fig. 2. State transition diagram (base case patient: 30 cm SB length, +ostomy, +NEC).

3. Conclusions

In the present study, Markov decision modeling was used in order to assess outcomes such as long-term survival and need for intestinal (and liver) transplant following STEP in pediatric patients suffering from SBS. For the majority of SBS patients modeled, STEP therapy improved rates of enteral autonomy, reduced need for subsequent transplant and increased long-term survival.

Dietary proteins and carbohydrates are absorbed in the small intestine after enzymatic digestion via specific enterocyte transporters [20–24]. The importance of the intestinal nutrient absorption becomes evident in situations of intestinal failure. Intestinal failure reflects the reduction of functional bowel below the minimum necessary for digestion and absorption to maintain growth in children. Short bowel syndrome describes a reduction in functional bowel length and is the most common etiology of intestinal failure in children [25]. Several diseases of the gastrointestinal tract including necrotizing enterocolitis, intestinal atresias, midgut volvulus, and long-segment Hirschsprung's disease may lead to excessive intestinal resections ending in short bowel syndrome and intestinal failure [26]. These patients are mostly dependent on long-term parenteral nutrition with its inherent morbidity and mortality and may require intestinal transplant in the future. Factors affecting intestinal failure include length of the remaining small bowel [27], as well as the presence or absence of an ileocecal valve; as published in 1972 in a cohort of 50 patients following extensive small bowel resection at least 40cm small bowel without ICV or 15cm of small with an

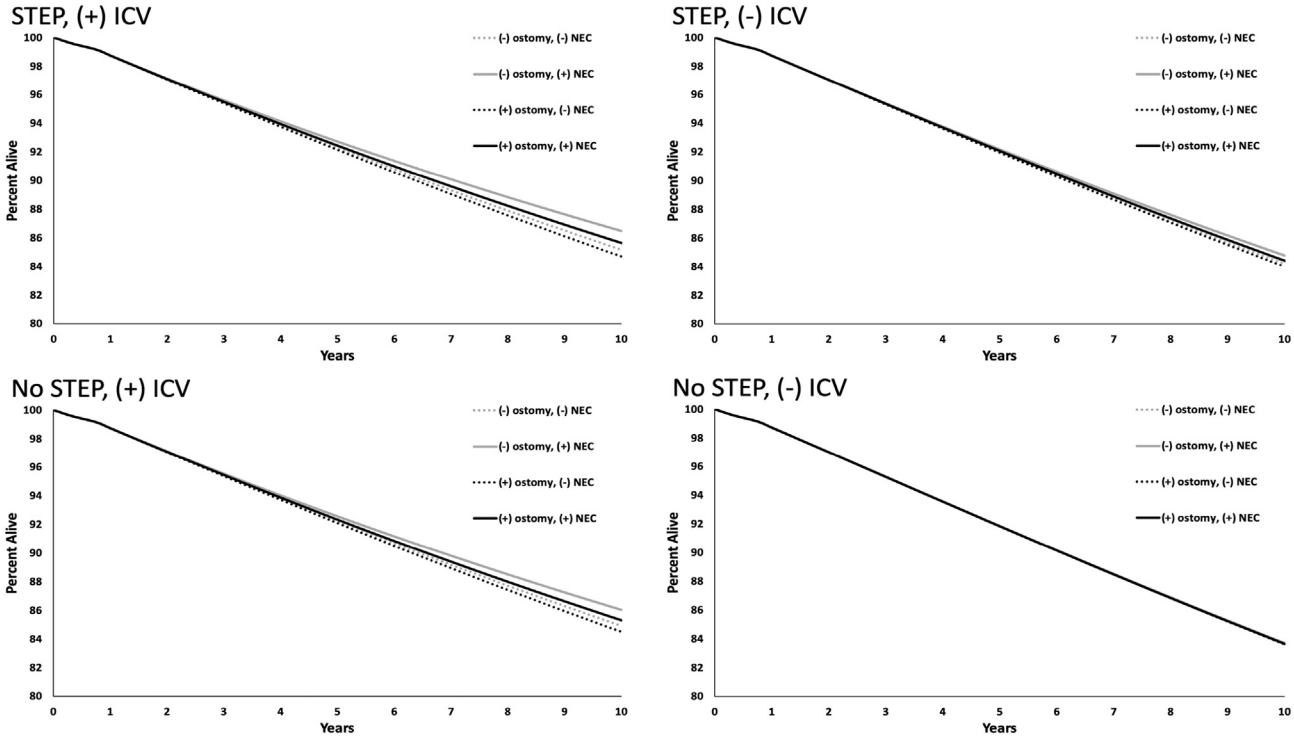

Fig. 3. Monte-Carlo simulation; 10 year survival (base case: SB length 30 cm).

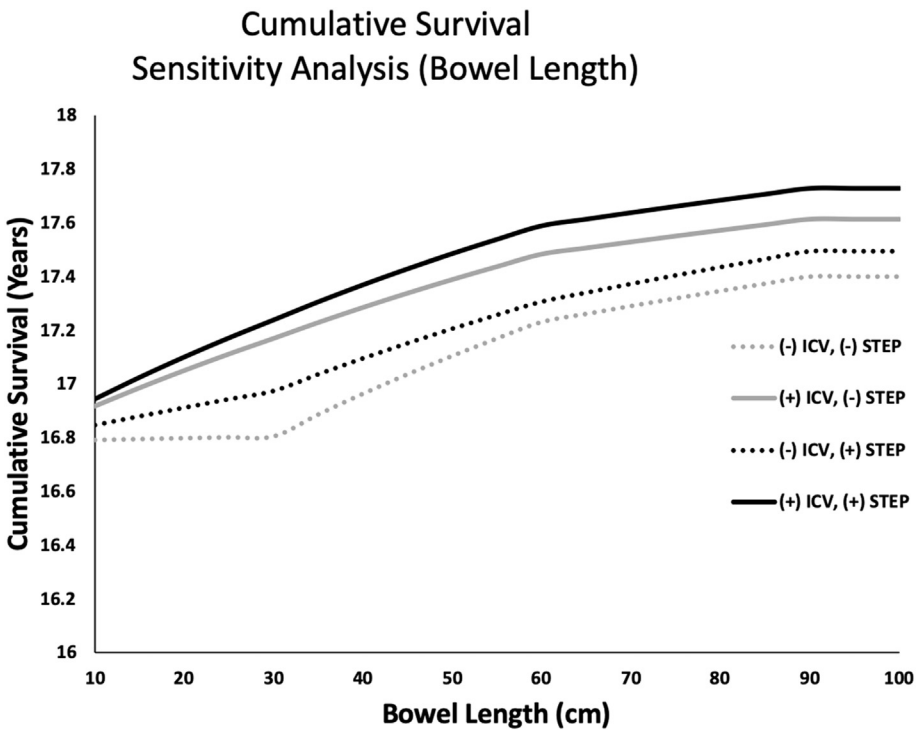

Fig. 4. Small bowel length sensitivity analysis (+ostomy, +NEC).

intact ICV are needed for survival [28]. However, these criteria were questioned by later studies [27,29]. Nevertheless, shorter intestinal length and the absence of an ICV have been repeatedly demonstrated to be predictors of intestinal failure, TPN-related complications, poor outcomes following transplantation, and thereby poor long-term survival [28–32]. Children without an ICV and small bowel length <30 cm are at especially high risk for poor outcomes, and many centers are increasingly advocating for STEP in this population, however randomized controlled trials are lacking to support such a paradigm. Our model suggests that there is indeed a survival benefit with STEP for these patients. The model demonstrated that for patients with an ICV, regardless of small bowel length, STEP therapy decreased need for transplantation and improved survival. Previously, Lopushinksky et al. utilized Markov analysis to explore the optimal timing of ITx for SBS

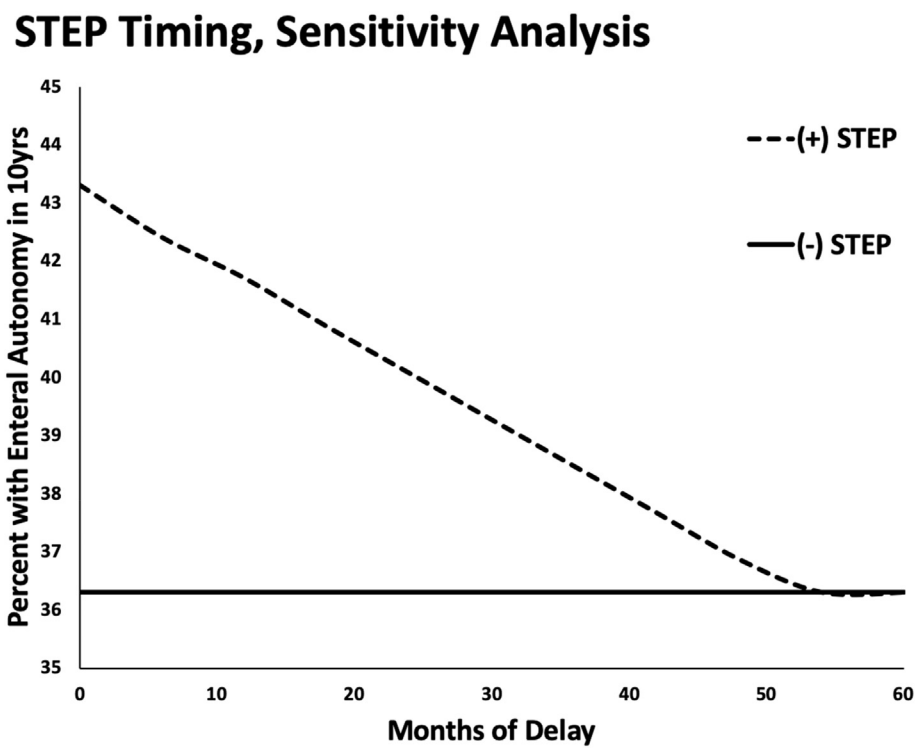

Fig. 5. STEP timing, sensitivity analysis (base case patient: 30 cm SB length, -ICV, +ostomy, +NEC).

patients; however, this model did not consider whether or when procedures like STEP should be attempted prior to needing to list a patient for ITx [33].

Although this study supports the current practice paradigm to aggressively refer SBS patients early for STEP evaluation, the magnitude of long-term survival benefit that STEP was estimated to offer in the model was muted. Although significant improvements were observed for rates of enteral autonomy, the survival benefit of STEP was <1yr across a spectrum of bowel lengths and anatomy. Fish-oil/SMOF lipid formulations of PN have drastically reduced liver injury thereby improving long-term survival on PN, which thereby offers SBS patients a longer time horizon to achieve enteral autonomy without a bowel lengthening procedure. Indeed as PN formulations/strategy continue to improve in the future, the true advantage of STEP appears to be in its ability offer an expedited path to enteral autonomy rather than improved survival. Increasingly, ITx has been offered as a quality of life surgery in the setting of frequent hospitalization for TPN-catheter related complications. The current lack of published long-term, broad based quality of life assessments of SBS patients prevents the current model from addressing/quantifying this potential future demand of ITx.

As a Markov analysis, the implications of this study are limited by the extrapolatory nature of the model. Although, promising short-term results have been reported, the rapid expansion and innovation in relation to STEP have not yet been well reported in a comprehensive manner [25,34,35]. The inherit small volume nature of STEP, and need for long-term follow-up portend that the true/maximal effect of STEP on long-term enteral autonomy and reduced need for transplantation is likely underestimated in the currently available literature. As this Markov extrapolates upon existing published data, it is likely that the predicted positive effect of STEP is also underestimated. As such, future prospective studies will be required to validate the findings of this model.

Additionally, a significant assumption of the model was that all patients, if they did not spontaneously achieve enteral autonomy while PN-dependent, were surgical/medical candidates for STEP. Often, due to either medical illness, or technical considerations, such as altered anatomy or recent surgery related to the initial cause of SBS, STEP must be delayed or altogether abandoned for certain patients. Our sensitivity analysis of STEP timing suggests that STEP offers utility up to 54 months of delay. However, due to lack of granular data in the literature on the matter, the model was not able to simulate specific causes of delay (technical vs. access to care etc.…).

Different intestinal lengthening procedures have been described in the literature including longitudinal intestinal lengthening and tailoring (referred to as LILT or Bianchi procedure) [36] and intestinal spring expansion [37,38]. Whereas the latter has only been tested in animal models, LILT was described in 1980, before STEP was developed. Whereas serial transverse enteroplasties are performed in STEP without need for an intestinal anastomosis, the dilated small intestine is divided longitudinally into two intestinal halves that are fashioned into two narrower tubes, which are anastomosed together to increase the length of the original intestinal segment during the Bianchi procedure. Due to comparative technical simplicity, most surgeons use STEP as their intestinal lengthening procedure of choice rather than Bianchi in the modern era [39,40]. As such, we therefore only included STEP in this study.

In the current model, for SBS patients with or without an ICV, STEP increases rates of enteral autonomy, reduces need for intestinal transplantation, and improves long-term survival. When technically feasible, intestinal lengthening procedures like STEP should generally be encouraged for all SBS patients who fail standard medical management strategies. Additional studies are needed to identify additional characteristics associated with STEP success vs. failure to further stratify which patients with SBS should undergo STEP and which patients should be directly listed for transplantation in order to optimize outcomes in this unique patient population.

References

[1] Modi BP, et al. Improved survival in a multidisciplinary short bowel syndrome program. Journal of Pediatric Surgery 2008;43(1):20–4.
[2] Hess RA, et al. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. Journal of Surgical Research 2011;170(1):27–31.
[3] Norsa L, et al. Long term outcomes of intestinal rehabilitation in children with neonatal very short bowel syndrome: Parenteral nutrition or intestinal transplantation. Clinical Nutrition 2019;38(2):926–33.
[4] Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. Seminars in Pediatric Surgery 2017;26(5):328–35.
[5] Amin A, Farmer DG. Current outcomes after pediatric and adult intestinal transplantation. Current Opinion in Organ Transplantation 2019;24(2):193–8.
[6] Abu-Elmagd KM, et al. Long-term survival, nutritional autonomy, and quality of life after intestinal and multivisceral transplantation. Annals of Surgery 2012;256(3):494–508.
[7] Mittal NK, Kato T, Thompson JF. Current indications for intestinal transplantation. Current Opinion in Organ Transplantation 2000;5(3):279–83.
[8] Georgeson K, et al. Sequential intestinal lengthening procedures for refractory short bowel syndrome. Journal of Pediatric Surgery 1994;29(2):316–21.
[9] Sommovilla J, Warner BW. Surgical options to enhance intestinal function in patients with short bowel syndrome. Current opinion in pediatrics 2014;26(3):350–5.
[10] Hernandez F, Andres AM, Lopez-Santamaria M. Long-term results of surgery for bowel lengthening: how many transplants are avoided, for which patients? Current Opinion in Organ Transplantation 2018;23(2):207–11.
[11] Oh PS, et al. Improved tolerance for enteral nutrition after serial transverse enteroplasty (STEP) in infants and children with short bowel syndrome; A seven-year single-center experience. Journal of Pediatric Surgery 2014;49(11):1589–92.
[12] Wester T, et al. Serial transverse enteroplasty to facilitate enteral autonomy in selected children with short bowel syndrome. The British journal of surgery 2014;101(10):1329–33.
[13] Garnett GM, et al. First STEPs: Serial transverse enteroplasty as a primary procedure in neonates with congenital short bowel. Journal of Pediatric Surgery 2014;49(1):104–8.
[14] Rege A. The surgical approach to short bowel syndrome – autologous reconstruction versus transplantation. Viszeralmedizin 2014;30(3):179–89.
[15] Lobos PA, et al. Neonatal serial transverse enteroplasty (STEP): case report. Transplantation Proceedings 2016;48(2):528–31.
[16] Bromberger B, et al. Weight loss interventions for morbidly obese patients with compensated cirrhosis: a markov decision analysis model. Journal of Gastrointestinal Surgery 2014;18(2):321–7.
[17] Choudhury RA, et al. Sleeve gastrectomy compared with gastric bypass for morbidly obese patients with end stage renal disease: a decision analysis. Journal of Gastrointestinal Surgery 2020;24(4):756–63. https://doi.org/10.1007/s11605-019-04225-w.
[18] Choudhury RA, et al. Roux-en-Y gastric bypass compared with aggressive diet and exercise therapy for morbidly obese patients awaiting renal transplant: a decision analysis. Surgery for Obesity and Related Diseases 2014;10(1):79–87.
[19] Naugler WE, Sonnenberg A. Survival and cost-effectiveness analysis of competing strategies in the management of small hepatocellular carcinoma. Liver Transplantation 2010;16(10):1186–94.
[20] Verrey F, et al. Kidney amino acid transport. Pflugers Arch 2009;458(1):53–60.
[21] Camargo SM, et al. The molecular mechanism of intestinal levodopa absorption and its possible implications for the treatment of Parkinson's disease. J Pharmacol Exp Ther 2014;351(1):114–23.
[22] Vuille-dit-Bille RN, et al. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. Amino Acids 2015;47(4):693–705. https://doi.org/10.1007/s00726-014-1889-6.
[23] Meier CF, et al. Intestinal IMINO transporter SIT1 is not expressed in human newborns. Am J Physiol Gastrointest Liver Physiol 2015.
[24] Meier CF, et al. Mucosal monosaccharide transporter expression in newborns with jejunoileal atresia and along the adult intestine. J Pediatr Gastroenterol Nutr 2019;69(5):611–8. https://doi.org/10.1097/MPG.0000000000002425.
[25] Batra A, et al. Epidemiology, management and outcome of ultrashort bowel syndrome in infancy. Arch Dis Child Fetal Neonatal Ed 2017;102(6):F551–6.
[26] Mangalat N, Teckman J. Pediatric intestinal failure review. Children (Basel) 2018:**5**(7).
[27] Spencer AU, et al. Pediatric short bowel syndrome: redefining predictors of success. Ann Surg 2005;242(3):403–9 discussion 409-12.
[28] Wilmore DW. Factors correlating with a successful outcome following extensive intestinal resection in newborn infants. J Pediatr 1972;80(1):88–95.
[29] Kurkchubasche AG, Rowe MI, Smith SD. Adaptation in short-bowel syndrome: reassessing old limits. J Pediatr Surg 1993;28(8):1069–71.
[30] Demehri FR, et al. Enteral autonomy in pediatric short bowel syndrome: predictive factors one year after diagnosis. Journal of Pediatric Surgery 2015;50(1):131–5.
[31] Kaji T, et al. Predictors of a successful outcome for infants with short bowel syndrome: a 30-year single-institution experience. Surgery Today 2017;47(11):1391–6.
[32] Barros GG, et al. Is maintenance of the ileocecal valve important to the intestinal adaptation mechanisms in a weaning rat model of short bowel? Pediatric Surgery International 2018;34(11):1215–24.
[33] Lopushinsky SR, et al. The optimal timing of intestinal transplantation for children with intestinal failure: a Markov analysis. Annals of Surgery 2007;246(6):1092–9.
[34] Fallon EM, et al. Neonates with short bowel syndrome: an optimistic future for parenteral nutrition independenceneonates with short bowel syndromeneonates with short bowel syndrome. JAMA Surgery 2014;149(7):663–70.
[35] Puder M, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Annals of Surgery 2009;250(3):395–402.

[36] Bianchi A. Intestinal loop lengthening – a technique for increasing small intestinal length. J Pediatr Surg 1980;15(2):145–51.
[37] Stark R, et al. Development of an endoluminal intestinal lengthening capsule. J Pediatr Surg 2012;47(1):136–41.
[38] Dubrovsky G, et al. Intestinal lengthening via multiple in-continuity springs. J Pediatr Surg 2019;54(1):39–43.
[39] Sudan D, et al. Comparison of intestinal lengthening procedures for patients with short bowel syndrome. Ann Surg 2007;246(4):593–601 discussion 601-4.
[40] Frongia G, et al. Comparison of LILT and STEP procedures in children with short bowel syndrome – a systematic review of the literature. J Pediatr Surg 2013;48(8):1794–805.
[41] Colomb V, et al. Long-term outcome of children receiving home parenteral nutrition: a 20-year single-center experience in 302 patients. Journal of Pediatric Gastroenterology and Nutrition 2007;44(3):347–53.
[42] Lao OB, et al. Outcomes in children after intestinal transplant. Pediatrics 2010;125(3):e550–8.
[43] Khan FA, et al. Predictors of enteral autonomy in children with intestinal failure: a multicenter cohort study. The Journal of Pediatrics 2015;167(1):29–34 e1.
[44] Squires RH, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. The Journal of pediatrics 2012;161(4):723–8 e2.
[45] Fullerton BS, et al. Enteral autonomy, cirrhosis, and long term transplant-free survival in pediatric intestinal failure patients. Journal of pediatric surgery 2016;51(1):96–100.
[46] Avitzur Y, et al. Impact of intestinal rehabilitation program and its innovative therapies on the outcome of intestinal transplant candidates. Journal of Pediatric Gastroenterology and Nutrition 2015;61(1):18–23.
[47] Mercer DF, et al. Serial transverse enteroplasty allows children with short bowel to wean from parenteral nutrition. The Journal of Pediatrics 2014;164(1):93–8.