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Non-surgical Interventions for Improving Nutrient Absorption in Pediatric Short Bowel Syndrome

Joel Faintuch[1], Andre Dong Won Lee[2], Salomao Faintuch[3], Asher Mishaly[4], Francisco Juarez Almeida Karkow[5]

[1]Department of Gastroenterology, Sao Paulo University Medical School, Sao Paulo, SP, Brazil; [2]Liver and Digestive Organs Transplantation Service, Hospital Das Clinicas, Sao Paulo, Brazil; [3]Interventional Radiology, Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [4]Private Practice, Internal Medicine, Sao Paulo, Brazil; [5]Department of Clinical Nutrition, Fatima Faculty of Nutrition, Caxias do Sul, RGS, Brazil

Correspondence: Joel Faintuch, Senior Professor of Gastroenterology, Hospital das Clínicas, Avenida Eneias C. Aguiar 255, 9th Floor, Rm 9077, Sao Paulo, SP, 05403-000, Brazil, Email faintuchj@gmail.com

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Abstract: As recently as 1990, short bowel syndrome in infants with less than 6 cm of remaining small intestine beyond the ligament of Treitz was defined as irreversibly lethal, and withholding further treatment was considered reasonable at that time (Reference deleted, Reviewer 2 item 1). Intestinal transplantation was already available, however not highly reliable. Nowadays transplantation is associated with long-term survival, even though indications are not expanding. On the contrary, they are shrinking, particularly for children as non-transplant handling. Surgical lengthening of the remaining gut, and more recently by enterohormone supplementation to stimulate diarrhea reversal and gut rehabilitation, is permitting encouraging rates of long-term survival. The purpose of this study was to review current non-surgical interventions aiming at parenteral nutrition weaning and intestinal failure reversal in the short bowel syndrome population, with emphasis on pediatric cases.

Keywords: intestinal failure, gut rehabilitation, enterohormones, GLP-2, GLP-1, food supplements, short bowel syndrome

Introduction

Short bowel syndrome (SBS) is a potentially fatal condition in both children and adults, with vast medical, social and financial repercussions. Even though it is not a malignancy, it was deemed a death sentence until the 1960s, and for severe cases until the 1990s,[1] with virtually no long-term survival. Along more recent years, it has been upgraded to a treatable and even curable condition, particularly in the pediatric setting, although that is not an easy or rapid task. It can take years and cost a fortune till the defective small bowel recovers or acquires sufficient absorptive abilities to sustain life.[2–4]

Home parenteral nutrition (HPN) was the first heroic attempt to maintain life in such circumstances, and it is still obligatory in all severe forms, mostly as the exclusive nutritional prescription, however sometimes as a combined feeding intervention. The central venous catheter is the lifeline in such circumstances.[5–7] It is still the first step conducted at admission in all patients and the definitive one for many, depending on how much intestinal hypertrophy and adaptation along the early months or years will lead to progressive introduction of enteral and oral nutrients, abolishing dependence on intravenous feeding (Figures 1 and 2).

Intestinal transplantation (ITx) was started around 1968[8] however only in the 1990´s was long-term success achieved. Whether alone or multivisceral, combined with liver graft, it has been greeted as the complete and definitive repair; however, it entails all the short- and long-term challenges of major organ transplantation, besides those germane to small bowel idiosyncrasies, notably in children, such as oral aversion, slow psychosocial and educational recovery, and even graft-versus-host disease. Costs can be exorbitant and outcomes remain worse than after other solid organ transplants.[9] Pharmacotherapy, or more specifically enteral hormone therapy, has emerged in the last decades as the most promising non HPN, non ITx alternative, potentially enabling patients to an independent and productive life.

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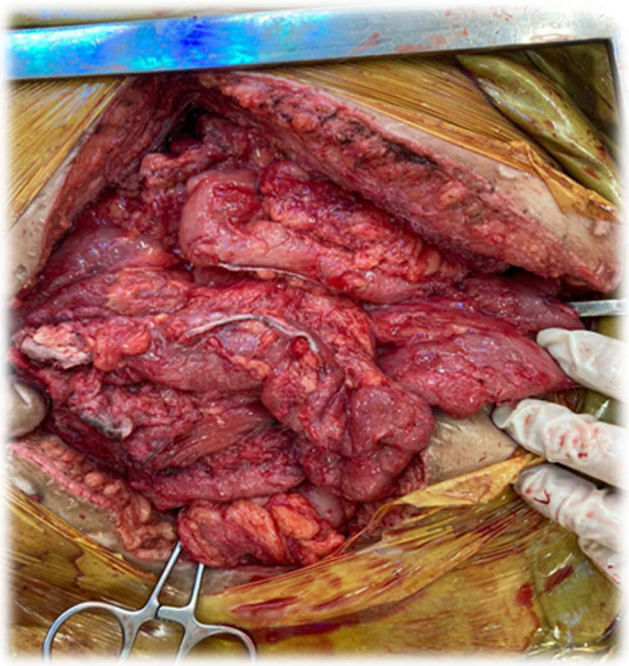

Figure 1 (Intraoperative view). Male, 25 years old. Underwent five operations in another service, for abdominal sepsis and small bowel fistulas, subsequent to an anti reflux procedure and correction of hiatal hernia. By the time of the 6th intervention, here depicted, only 100 cm of the jejunum and about 80% of the colon remained. He underwent jejunum- ascending colon anastomosis and was discharged on home parenteral nutrition (HPN). Three months later a modified oral diet was successfully introduced along with progressive weaning off HPN, which was completed within another three months. Currently lost to follow up. (Image courtesy of author ADWL).

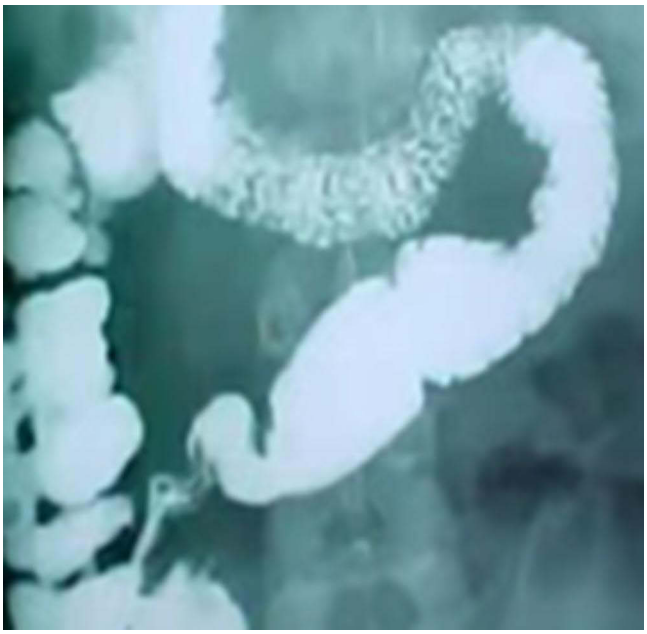

Figure 2 Female, 44 years old, 10 cm remaining jejunum, 10 cm remaining ileum, ileocecal valve and colon in continuity. Since age 12 (during 27 years) on parenteral followed by exclusive enteral nutrition. Weaned off enteral feeding at age 39, with stable nutritional status for an additional five years, on oral diet and micronutrient supplementation. Currently lost to follow up. (Image courtesy of author ADWL).
Note: A radiograph of the same patient and period appeared in Da Rocha,[4] however with a different angle and focus.

It would be desirable to announce that this last initiative is progressing by leaps and bounds, given its advantages as a conservative, non-invasive alternative. Indeed, one seminal preparation, a glucagon-like peptide 2 (GLP 2) analog, has been in the market for several years (teduglutide), and some consider it a paradigm shift[2] (Reviewer 2, ítem 2),

potentially as much as HPN and ITx were in the last century. Two other hormone analogs of the same family are waiting in the pipeline, as highlighted later on in the ítem Long-term GLP-2 analogs, in addition to a variety of alternative pathways currently being explored. However, only incremental advances are to be expected in the near future, not veritable breakthroughs. In order to extend effective pharmacologic therapy to all SBS patients in need of it, including perhaps borderline cases that are only partially dependent on HPN, a number of challenges exist which will demand more daring initiatives.

In the current article, recent achievements notably targeting improved intestinal nutrient absorption by means of non-surgical interventions will be reviewed, and areas for future research will be highlighted.

Methodology

The authors used different keywords to conduct a literature search for this narrative review, namely short bowel syndrome, intestinal insufficiency, intestinal rehabilitation, extensive intestinal resection, enterohormones and intestinotrophic agents. Subtitles *pediatric (children), adult, and home therapy* were interspersed as well. Papers from Scopus, Web of Science, and PubMed databanks were collected during the period of March-May 2024. (Reviewer 2, ítem 3). Texts were curated according to quality of scientific and experimental background, timeliness, effectiveness, and relevance for clinical application in adult and particularly pediatric short bowel syndrome. Randomized controlled trials are uncommon in the field, given the relatively low numbers of SBS in the population, and a single meta analysis was encountered, dealing with teduglutide efficacy.[10] As a consequence, other modalities of articles were accepted. Nevertheless, very small series and single-case reports were avoided, as well as preclinical studies, with rare exceptions.

Absorptive Essentiality

The small bowel was considered mostly expendable and treated with relatively little respect by early surgeons in the XIX and first half of the XX century. Whereas parenchymatous abdominal organs, particularly liver and pancreas, were handled with care and preserved as much as possible, partly because they could also be a source of life-threatening hemorrhage, hollow viscera, specifically the short bowel were deemed of scarce relevance and thus easily sacrificed. Indeed, reconstruction techniques for the esophagus, stomach, biliopancreatic routes, colon and rectum, urinary system and even neovaginas are used or continued to use intestinal segments.[11–14] Effectively about one meter of small bowel, in and otherwise healthy and undamaged adult abdomen, can be guiltlessly removed or transposed, whenever surgically indicated. In morbidly obese adult and adolescent patients undergoing bariatric surgery, as much as half of the small bowel is taken out (2–3 m) by some groups.[11] The fact that in such context, as little as 1.2 m of total intestinal loops (jejunum plus ileum) are left to handle the whole task of nutrient absorption, has been severely criticized; nevertheless, the procedure still finds advocates.[11]

Exceptional evidences notwithstanding, trouble can emerge when 40–80% of the bowel is not available in animal models,[15] or even less in circumstances of disease or malfunction of the remaining gut. In particular, resections removing the ileum, the ileocecal valve, or additionally excluding/resecting large segments of the colon are prone to ominous outcomes. SBS can strictly be a medical condition as well, not a sequela of surgical resection or bowel atresia, when it entails no previous congenital anatomical catastrophe or abdominal operation, and the whole length of the intestine is maintained. Examples are congenital diseases of enterocyte development with severe malabsorption or disabling motility disorders like chronic intestinal pseudo-obstruction. Within such circumstances, some prefer to call it intestinal insufficiency (II) or intestinal failure (IF), because the bowel has normal length.

It is relevant to emphasize that insufficiency or failure is inherent in all modalities of SBC, independent of the length of the remaining intestine, as in all of them absorption is impaired, and the patient becomes dependent on artificial nutrition. To clarify the conflicting nomenclature, some designate II or IF as the functional arm of SBC, with or without an anatomically shortened bowel (SBC).

The Crucial Tennis Court

It is classically admitted that the surface of the 3–7 m long adult small bowel often reaches 250 square meters (2700 square feet), equivalent to a tennis court.[12] More modest assessments in the range of 50 m^2, akin to a small residential apartment,

are available as well. The area is still superlative compared to other specialized surfaces, such as the gas-exchanging lung epithelium, the blood-filtering and urine-manipulating epithelial surfaces of the kidneys, or the multifunctional whole body skin. Of course, intestinal performance further benefits from natural mucosal valves or *plicae circulares*, and notably from cellular villi and microvilli, which exponentially elevate available absorptive surface. So much so that most meals are believed to be absorbed within the first one meter of the jejunum, rendering the majority of the small bowel redundant. Nevertheless, the ileum should never be overlooked. Even though distally located and thus barely participating in routine digestion of macronutrients, it is indispensable because vitamin B12, bile acids, and much of the fluid absorption occur in this site.

Intestinal Adaptation

Anatomical and functional changes after massive resection engage and activate all regenerative abilities of the gut remnant. Prominent responses include progressive length, diameter and thickness increase,[3,12,16] motility reduction to favor absorption (following initial acceleration),[4] hypertrophy of villi, microvilli and crypts, cell differentiation and improved angiogenesis.[3,5,12,16] Enzyme activity and carrier protein enhancement do not lag behind,[3,12,16,17] partially making up for the vast anatomical loss of bowel mucosa. Nevertheless, the changes with the most therapeutic potential, actively explored in recent years, deal with enteral hormones and their potential role in parenteral nutrition weaning.[18–20]

The small bowel is not only the largest interface between the human body and the environment (or at least the ingested environment), as well as the number one immune organ. It is also the endocrine powerhouse, with over 100 reported bioactive peptides and other signalling molecules.[17] Gastrin, cholecystokinin, motilin, glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY), glucagon-like peptide-1 (GLP-1) and glucagon-like peptide 2 (GLP-2) are among the best known. GLP-2 analogs will be mostly addressed, in agreement with the current literature, even though incretin hormone GLP-1 analogs and other hormones could be complementary and are the target of trials.

GLP-2 Analog (Teduglutide)

This recombinant analog of human glucagon-like peptide-2 is internationally licensed for the treatment of short bowel syndrome (SBS), in children >one year old and adults. It is secreted by the L-cells distributed at the terminal ileum and right colon, however production in the proximal small bowel also occurs.[16] It is endowed with multiple regulatory and motor effects that favor gut absorption, gastrointestinal slowing (better digestion and absorption), less fluid and nutrient loss and, as a result, partial or total TPN weaning. It is believed to collaborate in the orchestration of intestine-microbiome-immune system crosstalk as well, germane to barrier function and metabolic homeostasis.[17] It can be defined as the state of art pharmacological therapy for intestinal adaptation, obviously complemented by oral supplements,[4,21] yet with significant shortcomings. A meta analysis with follow-up till two years or more encountered growing weaning rates off TPN along time, yet still modest: 11%, 17% and 21% after, respectively, 6 months, 1 year and ≥2 years. Patients with preserved colon exhibited a higher final weaning rate, as usually reported, despite lower initial responses.[10]

Financial Concerns

James Carville, the strategist for Bill Clinton´s successful presidential campaign in 1992, coined the rude and aggressive, however, widely cited expression: "it´s the economy, stupid". Obviously, any complex, prolonged medical treatment will be costly; however, SBS carved a niche for itself. Home TPN can reach expenses up to 150,000 dollars a year in the USA, as estimated by Medicare.[22] Intestinal transplantation does not lag much behind, at least during the first year. A Belgian study estimated the mean cost for adults during the first, second and third-year post ITx as approximately 172,000, 41,000 and 16,000 euros, respectively.[23] And what about teduglutide? A staggering disbursement of 400,000 US dollars a year is published for both adults and children and what is worse, for life.[24,25] Even though teduglutide is classified as a trophic hormone and indeed stimulates enterocyte proliferation, with heightened intestinal weight and absorptive surface, such intestinal hypertrophy is rarely sustained. Symptoms may recur upon drug discontinuation, which as a consequence is advised for permanent use.[24,25]

Cancer Risk

If teduglutide is markedly trophic, however, with temporary effects on normal small intestinal mucosa, what about cancer cells? This has been a concern since the first prescriptions reached the market, given the lifelong nature of the intended use. So far the record is clean, with experimental evidence, however, not a single human case.[26]

Successful Rehabilitation

According to manufacturer´s advertisements, teduglutide is able to induce at least 20% reduction in TPN consumption. The drug should actually be discontinued if such goal is not achieved. Many patients reach the improvement threshold within weeks, and after a year up to 60% less intravenous support is observed in certain cohorts. Can this be called success? The most feared complications of home TPN are central line-associated blood stream infections (CLABSI), catheter-related thrombosis (CRT), and intestinal failure associated liver disease (IFALD). IFALD seems at least partially volume-dependent, as large amounts of intravenous lipids, particularly soybean oil-derived omega-6 fatty acids and plant sterols, have been linked to its appearance. Plenty of carbohydrate calories might also play a deleterious role, along with micronutrient imbalances.[27] With less food by vein (TPN weaning) and more via the enteral route (dietary transition), such hurdles might be minimized.

CLABSI and CRT look less sensitive to partial TPN withdrawal compared to the exclusive modality. As long as a central catheter is used, these risks do not disappear. By the same token, quality of life can only be stated as adequate, when complete TPN weaning occurred and independent life is possible. How often does total weaning materialize after teduglutide introduction? Among adults, 11%, 17% and 21% of the population become free of home TPN after, respectively, 6 months, 1 year and ≥2 years.[10] The response in children can be more precocious and encouraging, in the range of 32% after 48 weeks.[28] These numbers suggest that also within the realm of full therapeutic rehabilitation, teduglutide is a valuable routing beacon, however not a floodlight yet.

Long-Term GLP-2 Analogs

One of the inconveniences of teduglutide, notably in children, is the need for daily subcutaneous injections. Longer acting analogs are in the pipeline like Glepagludide from Zealand Pharma (Soborg, Denmark) and Apraglutide from VectivBio (Ironwood Pharmaceuticals, Boston, MA, USA). Lipidated GLP-2r agonists,[18] biased GLP-2 agonist with strong G protein-coupling but impaired arrestin recruitment and receptor desensitization,[19] as well as computer designed selective d-peptide agonists GLP-2r[29] are on various stages of development, for higher potency or longer action.

GLP-1 Analogs

GLP-1 is the archetypal incretin hormone, inducing insulin secretion by pancreatic beta-cells, as a response to food ingestion. Analog use by diabetics was already successful when it was demonstrated that some molecules, nominally semaglutide but more recently also GIP-combined tirzepatide, were associated with expressive weight loss in overweight and obese diabetic and non-diabetic subjects. Are any of these compounds endowed with intestinotrophic properties? Since 2013 it is informed, on the basis of a small pilot study, that this hormone reduces diarrhea in SBS patients.[20]

More recently, a small controlled prospective study with liraglutide in adult cases of SBS[30] was consistent with a significant reduction in ostomy or fecal output after six months. Energy intake dependent on parenteral prescription could thus be reduced, in favor of more enteral calories.

Though the authors do not elaborate, two hypotheses for the response could be considered. Insulin exhibits widespread anabolic effects, and as an incretin GLP-1 analog liraglutide could rely on such pathway, with possible benefits for gut anatomy and physiology. Such possibility notwithstanding GLP-1 is not listed as a true trophic hormone, and absorptive intestinal surface does not seem to increase.

The other alternative[31] is GLP-1 ability to inhibit gastrointestinal motility and secretion (enterogastrone feature), thus reinforcing the ileal brake response. The incompletely understood ileal brake is theoretically elicited by the arrival of undigested food, especially lipids, to the ileum, as well as by certain enterohormones, partially blocking appetite and intestinal physiology. Robust appetite is not undesirable for SBS patients, and even mildly diminished

peristalsis could be an advantage for the severe malabsorptive syndrome, allowing more time for digestion and absorption.

Dual GLP-2/GLP-1 Administration

Also, paired GLP-1 and GLP-2 injections have been conducted as early as 2013.[30] The aim was to maximize the absorptive potential of GLP-2 with the anti-diarrheal effect of GLP-1. The synergy seemed to materialize as the two drugs were superior to each of them alone, however the idea remained dormant for many years. Dapiglutide, a molecule combining the two hormones,[15] as well as individual injections of the two analogs[32,33] are being tested. There are reasons to believe that only specific doses of each will be able to enhance intestinal growth and slow transit time, without impairing appetite, gastric emptying or glucose metabolism.[33]

Oral Food Stimulation of GLP-2 and GLP-1 Production by the Ileum

It has been recognized for many decades that the presence of oral nutrients in the gut of SBS patients is a powerful stimulant for metabolic stabilization and gut regeneration. Exclusive TPN markedly delays the advent of enteral autonomy, whereas luminal contents including nutrients seem to incentivize adaptation.[16] Indeed, non-digested macronutrients that reach the ileum, such as lipids and proteins and, to a lesser extent, carbohydrates are known to stimulate secretion of GLP-2 and other enterohormones.[16,34] Physiologically both GLP-1 and GLP-2 are secreted by L-cells in the intestine whenever induced by food intake. Such postprandial output is triggered by nutrient-sensing receptors and is also believed to be part of the ileal brake mechanism.[16,35]

The oral option has entered daily practice decades ago, in the form of carefully titrated prescriptions of enteral nutrition, along with oral electrolytes whenever tolerated. It is indispensable for intestinal adaptation and weaning off parenteral support, and in the case of infants, breast milk is highly encouraged. Yet injectable fluids and drugs, such as teduglutide, represent the mainstay of SBS management during the first year, and potentially for life in severely mutilated cases (anenteric syndrome). Of course, the parenteral route elicits more predictable responses, even though it is not necessarily the most sustainable or most conducive to intestinal rehabilitation. Some SBS patients lack the ileum and sometimes the colon as well, raising concerns about diet-induced hormonal output and regenerative ability of the proximal gut only. Nevertheless, the oral route is inexpensive, safe, well accepted by patients, and compatible with good quality of life compared to any parenteral alternative, therefore it should deserve more interest.[3,4]

Soluble Fibers and Slowly Digestible Alpha Glucans

Partially hydrolyzed guar guam, a soluble fiber, or mixed soluble/insoluble fibers, has been validated by a meta analysis in the prevention of enteral nutrition associated diarrhea.[36] Indeed, soluble fibers represent a rather classic prescription for diarrhea- affected children, in many parts of the world. The enterohormonal advantage of soluble fibers in comparison to standard food is that small amounts could be able to initiate a response, not necessarily full meals, as no substrate losses to digestion would occur along the upper digestive tract. Such difference could be critical for SBS subjects with limited food tolerance. As enzyme-resistant molecules, soluble fibers integrally reach the ileum and colon, where fermentation by the microbiome occurs. The ileum (and to a smaller extent the colon) is considered a crucial site for GLP-2- and GLP-1- secreting L-cells.[15,18–20,33,35]

Experimental evidence for α-glucan, a soluble fiber, is available. Goto et al observed in rats after a 10-day dietary supplementation that villus length and mucosal thickness increased in the jejunum and the ileum. At the same time, an elevated concentration of GLP-2 was demonstrated in portal vein plasma.[36] A study by another group had already pointed out that α-glucan fiber elicits a GLP-1 response in the small intestine of rats.[37]

Fungal α-Glucan

Alpha glucans are available in vegetable starch-derived molecules, such as isomaltodextrin and resistant maltodextrin.[36,37] They can also be found in certain algae and in virtually all fungi. Edible supplements such as standardized extract of *Lentinula edodes* mycelia, nominally AHCC® (Amino Up, Sapporo, Japan), could be an attractive

alternative. Rich in α-glucan and low in insoluble fiber, it fulfills the requirements for a potential trigger of GLP-2 and GLP-1 endogenous secretion,[38–42] as a complement to or in partial replacement of pharmacologic injections, in patients with less severe diarrhea or fistula output, already beginning to accept small amounts of oral food. This might diminish the superlative rehabilitation costs of SBS, and enhance their quality of life.

Immune Stimulation

AHCC is endowed with additional qualities not encountered after conventional macronutrient intake, namely significant immune enhancing and inflammation attenuating abilities.[38–42] These have been elicited in contexts such as experimental models, healthy volunteers, liver inflammatory aggression, respiratory infections and cancer-associated virus. The array of responses encompasses modulation of cytokines, natural killer cells, various T-cell categories, immuno globulin, intestinal toll-like receptors, and viral clearance rates.[38–42]

Immune Deficiency in SBS Patients ?

Reports about impaired or inadequate immune response in SBS patients are hardly available, and the hypothesis of immune deficiency is rarely entertained. Indeed, SBS is nor listed among immune diseases, and typically affects previously healthy organisms. Occasional exceptions such as SBS associated with advanced Crohn's disease, a condition with known immune derangements, do not invalidate the paradigm. The most deadly infection in the SBS population, specifically CLABSI, can be explained by frequent venous-line manipulations, not by primary or acquired immune dysfunction.

Moreover, basic dietary and supplementary micronutrient optimization are a priority for SBS teams, and therefore nutritional deficits risky for immune incompetence tend to be routinely corrected and prevented.[4,21] Additionally, as soon as medical or surgical rehabilitation begins, attenuation of most nutritional and metabolic derangements ensues, thus relieving potential anxieties concerning undernutrition-triggered impaired immunity.

Yet not all patients promptly and completely respond to therapeutic and rehabilitation protocols. In a series of 64 children followed for a median of 11.4 years, data are stratified according to surgical (various modalities of autologous intestinal reconstructive surgery) vs conservative (nutritional/metabolic/ pharmacologic) management.[43] The two groups are not perfectly matched because surgical indication depends on length and nature of the remaining intestine, as well as the experience of the surgeon. Moreover, some complications are inherent in the operative approach, being absent in medically handled cases, such as anastomotic/staple line ulcerations or strictures. Nevertheless, it is worth emphasizing that more than a decade after the interventions, significant numbers of patients in both groups were still not fully healthy, with worse results in the surgical population.

This applies to symptoms of intestinal dysfunction (39% vs 5%), small intestine bacterial overgrowth (53% vs 24%), histological liver steatosis (50% vs 24%), and impaired bone health (26% vs 6.7%).[43] Immunological profile is not reported; however, one would expect it to follow the functional, nutritional and metabolic health.

Pitfalls more directly suggestive of altered immune status have been registered as well, for instance as complications of rotavirus vaccination.[44] In this sense, supplementation with an immune enhancing functional food would not be inappropriate in this setting.

Personal Experience

One of the authors (FJAK) has experience with off-label prescription of AHCC to patients with advanced Crohn's disease including SBS (unpublished data). Decrease of diarrhea has been observed along with improved general health, whereas no case of supplement intolerance was registered. These findings are consistent with a small retrospective study of supplementation of GLP-2 (teduglutide/Gattex), to patients with Crohn's disease and intestinal failure requiring parenteral nutrition. After one-year intravenous fluid requirements decreased, and the majority was weaned off parenteral support.[45] It is emphasized that these not-yet validated observations are here included as an incentive for further investigations.

Study Limitations

This review aimed to consider only papers with sufficient objective informations, clearly described and analyzed. All the authors participated in the selection in order to enhance the selection, as well as reduce the risk of personal bias. Yet less than ideal communications such as case reports or short series were occasionally included, when submitted by reputable centers, germane to the topic, and without better alternatives. In order to minimize such shortcomings, discussions preferably targeted the dynamic field of enterohormones and intestinal compensation, avoiding as much as possible anecdotes and unusual episodes.

Therapeutic Summary

Table 1 briefly lists routinely adopted or occasionally considered non-surgical therapeutic interventions for hospitalized and outpatient cases of short bowel syndrome. As pointed out in the review, actual protocols will to some extent depend on financial availability and regulatory condition of the items. Certain items are expensive, not licensed in many markets, or the utilization is discouraged because of off-label status and insufficient literature endorsement. Another consideration is the experience of each team. Some services consistently achieve acceptable results with nutritional therapy only, others acquired much expertise, with small bowel lengthening surgery or intestinal transplantation, many more trusting pharmacotherapy instead (Table 1).

Areas for Future Research

In the light of the previous discussions, a couple of pharmacological priorities can be anticipated:

Low cost, long acting enterohormonal analogs: Either GLP-2 alone or in association with GLP-1 should be available in the form of more user-friendly and pocket-friendly preparations. The model is insulin, an indispensable hormone for many diabetics that years ago offered few and inadequate options, seriously hampering quality of life. Now, of course, it is compatible with self-administration even during backpackaging.

Oral specialized supplements for enhancing endogenous enterohormonal output: This has been a neglected area in SBS studies, most authorities relying on the regenerative powers of oral feeding alone. The importance of early introduction of enteral and oral alimentation should not be minimized, as the gut critically needs access to local nutrients, not just to intravenous ones. Nevertheless, this is typically a slow and hesitant journey, with frequent false starts interrupted by episodes of diarrhea and malabsorption. The possibility of oral stimulation of GLP-2 output by the remaining intestinal mucosa induced by specialized soluble fibers could represent a temporary scaffold for epithelial build up, until conventional macronutrients are tolerated.

Conclusions

Treatment of short bowel syndrome has gone a long way since the first case of extensive small bowel resection was reported in 1881.[13] In children, particularly newborn or prematures, if initial survival occurs and some small gut remains, the perspectives for intestinal regeneration are substantially better than in adults. Overall, the response to conservative management and to autologous reconstructive surgery has been increasing so that indications for transplantation substantially diminished in recent years.[14] The pillar of intestinal rehabilitation after life-threatening sepsis, dehydration, malnutrition and metabolic aberrations

Table 1 Non- Surgical Therapeutic Interventions for Short Bowel Syndrome (Reviewer 1, Item 4)

Basic feeding therapy	Intravenous, enteral, oral (sequentially or combined)
Complementary nutrients	Fluids and electrolytes, vitamins, minerals, essential fatty acids, soluble fibers
Gastrointestinal modulation	Antidiarrheal drugs, motility agents, proton-pump inhibitors (mostly off-label use[4])
GLP-2 analogs	Teduglutide, other GLP-2/ GLP- 1 analogs
Oral hormone/ immune stimulators	Slowly digestible fungal alpha-glucans (experimental use)

Abbreviations: GLP-2, Glucagon-like peptide-2; GLP-1, Glucagon-like peptide 1.

is under control continues to be GLP-2 analog teduglutide, however more promising alternatives are on the pipeline, including GLP-1/GLP-2 combination. Oral stimulation of endogenous GLP-2 secretion along with immune enhancement by means of an α-glucan enriched fulgal extract is another hypothesis to be considered.

Data Sharing Statement

The reviewed datasets that support the findings of this review are indicated in the article.

Ethical Considerations

Approval of the article by the Ethical Committee of Hospital das Clínicas (CAPPESQ) was not requested because according to CAPPESQ rules, review texts are exempt. Patient approval for picture reproduction was not possible due to loss of follow-up (Figures 1 and 2).

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The authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work, and have given final approval for the version to be published.

A radiograph of the same patient and period depicted in Figure 2 appeared in Da Rocha,[4] however with a different angle and focus.

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Disclosure

The authors report no conflicts of interest in this work.

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