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REVIEW

Multidisciplinary Management in Pediatric Ultrashort Bowel Syndrome

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Abstract: Pediatric intestinal failure (IF) remains a complex and devastating condition resulting in the inability of the gastrointestinal tract to absorb adequate fluids and nutrients to sustain life. The goal in the management of IF is to achieve enteral autonomy and when not possible to avoid and minimize the development of long-term complications. Survival rates for children with IF have continued to improve resulting in an increased population of children with more altered anatomy. While IF remains a rare disease, children with IF secondary to ultrashort bowel syndrome comprise an even smaller patient population. The goal of this article is to review the recent literature related to the impact of multidisciplinary intestinal rehabilitation programs (IRPs) on the management and outcomes of intestinal failure in children with ultrashort bowel syndrome and potential avenues to further improve the long-term outcomes of this patient population.

Keywords: intestinal failure, ultrashort bowel syndrome, short bowel syndrome, intestinal rehabilitation program

Introduction

Intestinal failure (IF) is a challenging and complicated medical condition resulting in the loss of absorptive surface area. Patients with intestinal failure are unable to absorb adequate fluids and nutrients to sustain life.[1] Intestinal failure results in prolonged use of parenteral nutrition (PN) that places patients at risk for multiple complications including central line-associated bloodstream infections (CLABSI), intestinal failure-associated liver disease (IFALD), metabolic bone disease, vitamin and mineral deficiencies, and renal impairment.[2] Intestinal rehabilitation programs (IRPs) have played a significant role in the improvement of outcomes, consolidation of expertise, care coordination and prevention of complications. Ultrashort bowel syndrome (USBS) is a subgroup of patients with IF that have more extremely altered anatomy and were previously felt to have a poorer prognosis, as such the introduction of multidisciplinary management has had a significant impact on this population of patients.

Intestinal Failure Etiology

Intestinal failure is a term used to describe a number of conditions that result in the body's inability to maintain adequate growth or hydration. Historically, mortality rates were estimated at 35–50% of those with IF, but with the medical and surgical advancements over the past 15 years more recent reports show an improvement in survival of 74–93%.[2–8] The causes of pediatric IF (PIF) include short bowel

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syndrome (SBS), mucosal enteropathies and dysmotility disorders. Short bowel syndrome is the most common cause of IF that results in an estimated incidence of 24.5 per 100,000 live births.[4] The majority of individuals who develop SBS have congenital or acquired conditions that occur in the neonatal/newborn period. There are three main anatomical types of SBS that include: 1) SB resection with jejunostomy and no remaining colon, 2) mid small bowel (SB) resection with an intact colon; and 3) SB resection with partial colonic resection and enterocolonic anastomosis.[9]

History and Definition of Ultrashort Bowel Syndrome

Previously, individuals with ultra SBS (USBS) experienced significant mortality due to their inability to wean off PN and development of complications.[10] The reduction in sepsis and advanced cholestatic liver disease has permitted increased time for individuals to achieve EA, even in the setting of more extreme anatomy. For patients who lack the capacity to completely adapt, they are able to survive on long-term PN. At present there remains no consistent definition of USBS; however, many reports in the literature use <10–25cm.[10–12] The importance of multidisciplinary management is paramount for patients living with USBS to prevent development of long-term complications or to reduce the impact when complications develop.

History of Multidisciplinary Management

The role of multi-disciplinary management has been described in the literature in the management of IF since 2000 where Koehler et al described the role of IRPs as an opportunity for practitioners to provide care that is tailored to their patient and family needs.[13] A 2013 systematic review and meta-analysis reported improved outcomes for PIF patients managed by an IRP with respect to survival (22% increase) and reduced septic events when compared to controls. In addition, IRPs were associated with improvements in the coordination of care, tolerance of increased enteral calories and earlier assessment for transplantation.[14,15] There have also been reports describing the importance of IRPs for patients being referred for intestinal transplantation with improvement in survival to transplant and even patients being de-listed due to clinical improvement.[15] The importance of IRPs is often discussed in the context of all patients with IF and not necessarily specific to USBS. Many of the general attributes of multidisciplinary IRPs will be even more relevant to the USBS population as they have the likelihood of prolonged or permanent PN support, development of complications and potential need for transplantation. All of the advantages to a multidisciplinary approach to care for children with USBS will be discussed further.

Review of the Current Literature

Outcomes

Mortality

As mentioned, there have been significant improvements in patient survival over the last 15–20 years, and the introduction of multi-disciplinary programs has played a large role. Previous estimates of mortality were between 35% and 50% of the pediatric IF patients dying compared to updated estimates of 7–26%.[2–6,8,16] Numerous studies have demonstrated the role that multidisciplinary IRPs have played in the reduction in mortality including Oliveira et al time-series analysis in 2016 highlighting the reduction in mortality after the introduction of an IRP.[17]

Others have also demonstrated reductions within their own centres related to the role of an IRP in improving patient survival.[15,18,19] Significant mortality was reported in a more historical patient population by Quiros-Tejeira et al in 2004 with 43% of the patients with < 15cm of SB dying within the first 3–4 years.[20] In contrast, several more recent reports have demonstrated significant improvement in survival in patients with USBS.[11,12,21,22] Norsa et al evaluated 36 patients with < 40cm of SB and reported that 78% of their cohort remained alive. Eight patients had died post-transplant with all patients on long-term PN remaining alive after a median follow-up time of 17 years.[23] In patients who were diagnosed with necrotizing enterocolitis, Fallon et al reported a mortality rate of 13% of their cohort and in those that died the mean SB length was 27cm.[24] Infantino et al reported survival rates of 96% in their cohort of 28 patients with < 20cm of SB with 4 patients undergoing transplant.[11] Diamanti et al also reported a mortality rate of 18% for their cohort of patients with < 10cm of SB (11 patients) only 1 of whom received a transplant.[12] However, there continues to be significant variation in mortality rates with a recent publication in 2017 by Dore et al who reported mortality in USBS patients with < 10cm of residual SB at 47%. The significant difference in this patient population compared to others relates to

the high rate of transplantation (21/30) with 5 patients dying before receiving a graft.[25]

Enteral Autonomy

The ultimate goal in the management of children with IF is the achievement of EA. This is especially challenging in children with USBS due to the significantly short remnant bowel remaining. Infantino et al reported an EA rate of 48% in their cohort with the median PN time of 1.13 years. They found that children who had an intact ICV and colon were more likely to achieve EA despite having < 20cm of SB.[11] Hong et al evaluated long-term outcomes in children who had USBS secondary to malrotation with midgut volvulus. They found that patients who had associated gastroschisis were less likely to achieve EA compared to those who did not (0 versus 58%).[22] When looking at the role of etiology on achievement of EA, Fallon et al reported the probability of achieving EA in patients with necrotizing enterocolitis based on residual SB length. They reported that the predicted probability of weaning based on having 10%, 20% and 30% of SB remaining was 0.50 (0.25–0.74), 0.67 (0.49–0.81) and 0.81 (0.65–0.91).[24] Other centres have reported rates of EA from 0% to 44%, but there is significant variations in the definitions of USBS and surgical management making comparisons challenging.[12,21,23,25,26] In most studies, the strongest predictor of EA is the residual SB length. A 2017 cohort study evaluating the probabilities of achieving EA based on the residual length of SB and large bowel (LB) showed that unsurprisingly those with >50% SB had an 80–100% chance of weaning from PN despite the length of their LB.[3] Patients with less than 50% of expected SB remaining had a 56% probability of EA as long as their LB remnant was >50% of expected for age. In fact, EA was possible with as little as 10% of expected SB if the colon was intact. Only 8% of the patients with <50% of both SB and LB were able to wean from PN.[3] The percentage of residual small and large bowel expected for age were positively associated with EA (HR = 1.03; 95% CI 1.02–1.03 and HR = 1.01; 95% CI 1.00–1.02) and septic events per 1000 catheter days (HR = 0.95; 95% CI 0.91–0.99) was negatively associated with EA, respectively. It is important to note that there remains no consensus on the definition of IF, SBS or USBS at present. We will discuss the challenges with this in subsequent sections of this paper.

Autologous Bowel Reconstruction

Surgical management in USBS poses significant challenges due to the length of the remnant bowel. Wales & Dutta published on the role of a primary serial transverse enteroplasty (STEP) in neonates specifically presenting with USBS secondary to vanishing gastroschisis and jejunal atresia. Patients had 9–22% of their expected SB length at birth (based on published normative data) and after a delayed primary STEP, they had 26–46% based on age. Two of the 5 went on to achieve EA and the remaining 3 patients were tolerating 40–74% of nutrition enterally at last follow-up.[27] Infantino et al reported 52% of their USBS patients received at least one bowel lengthening procedure (Bianchi or STEP). They did not find an association between bowel lengthening procedures and the achievement of EA.[11] In another report, Sudan et al evaluated outcomes of patients who received a Bianchi compared to the STEP. They reported that surgical lengthening with either the Bianchi or STEP improved enteral nutrition intake and resulted in reversal of IFALD.[28] They did not find significant differences in survival, achievement of EA or complication rates between the two procedures but did report at a trend towards more rapid weaning of PN in those with a STEP.[28] In fact, in most reported series, intestinal lengthening procedures are negatively associated with EA. This is in part due to the fact that these operations tend to be applied to patients with shorter residual SB.

Transplantation

Indications for intestinal transplantation, published in 2001, in an era where there was significant disease mortality from chronic PN, recommended referral for transplantation in children with < 10cm of residual SB due to the poor likelihood of survival.[10,29] Dore et al reported a 72.4% rate of transplantation in their cohort of patients with < 10cm of SB with post-transplantation survival of 62%. However, with the likelihood of survival on home PN approaching 90% at 5 years, exceeding that of intestinal transplantation (60%), there has been a proposal to remove the diagnosis of USBS as an indication for bowel transplantation.[30] A recent publication by Burghardt et al found that in the old era of increased mortality, the diagnosis of USBS was previously strongly predictive of requiring an intestinal transplant (positive predictive value = 100%), but in the current era of improved survival, USBS diagnosis had a decreased positive predictive value of 9%.[30]

Complications

Central Line-Associated Bloodstream Infections

Central venous catheters (CVC) are necessary for delivery of PN, but are a source of complications, including infection, dislodgement and thrombosis. Sepsis is a risk factor for hepatic dysfunction, death and a negative predictor of EA. There is significant variation in rates of CLABSI reported in the available literature. The population of patients with SBS have reported rates between 1/1000 and 11/1000 CVC days.[31–35] Diamanti et al reported a CLABSI rate of <1/1000 catheter days in 10/11 patients with one patient having 3/1000 catheter days.[12] They utilized a taurolidine lock protocol to reduce CLABSIs in their population. Sanchez et al reported significantly higher rates of CLABSIs with patients having 6–9 episodes over a 43- to 62-month period.[21] This significant variation in CLABSI rates has been seen in previous publications and likely relates to the significant variation in practices and it is unclear if underlying bowel anatomy contributes.

Intestinal Failure-Associated Liver Disease

IFALD is traditionally the leading complication in children with IF. It was the most common cause of death in SBS children. It remains a significant complication in children with USBS due to the duration of PN dependence with rates between 63% and 88% in historical reports.[12,21,22,25,26] More recent publications, employing alternative lipid management strategies and improved multidisciplinary care have demonstrated reduced hepatic complications (22–25%).[36,37] In a case series of 5 patients with USBS by Sanchez et al, they reported significant elevation in direct bilirubin in 4/5 patients (range 12–14/mg/dL) with 4 receiving Omegaven© and/or lipid restriction. At the time of analysis, all patients had a normal direct bilirubin with only one patient receiving an intestinal transplantation.[21] Torres et al also reported a significant proportion of patients with liver disease in 21/24 patients with 19 patients having a mean conjugated bilirubin (CB) of 7.5mg/dL with 18/19 patients having normalized liver function after treatment over an 11-week period.[26] Interestingly, 13/21 had a liver biopsy with 8 patients showing grade 3–4 fibrosis.[26] Infantino et al also reported median total bilirubin values of 6.4 and 9.1mg/dL, respectively in their non-adapted and adapted cohort of patients at initial presentation with significant improvement over time with median total bilirubin at final follow-up of 0.3–0.5mg/dL. They did however, report persistent elevation of transaminases in the non-adapted group that may represent continued use of PN.[11] Although significant advances have been made in the outcome of IFALD, the literature still suggests a significant proportion of patients will develop cholestasis that is amenable to lipid management strategies.

Quality of Life

At present, there are no studies specifically evaluating the quality of life (QOL) in USBS. However, publications of children and caregivers on home PN are relevant as the majority of children with USBS will be dependent on long-term PN indefinitely. Tran et al in a recent pilot study of children on home PN evaluated and found that QOL was significantly impacted with increased dependency related to activities of daily living, as well as their ability to cope with daily life and issues related to having a social life.[38] They reported that QOL was not affected when it related to school attendance, general fatigue, pain and body image and overall QOL was rated high at 8/10.[38] Gottrand et al also reported similar findings of high QOL scores in children on home PN with scores similar to a reference population of healthy children/adolescents.[39] Lower QOL scores were related to domains around hospital, health, doctors, medication and other obligations. Interestingly parents and caregivers reported significant impairment in QOL. These studies suggest that there is an integration of coping strategies to ensure children's QOL is not significantly impacted that may be resulting in significant impairment of caregivers QOL. This is an important area of future research.

Discussion

Pediatric IF is a rare condition. Much of the literature is based on single-centre experience with small sample sizes in very heterogeneous patients. There are no consensus definitions for PIF outcomes. As a result, interpretation of the literature is difficult. However, despite these limitations, there has been consistent reporting regarding the positive impact on clinical outcomes with management by a formal IRP. These advantages are related to aspects widely impacting patient management that deserves further discussion.

Surgical Management of USBS

A critical aspect of management in USBS is related to surgical decision-making. Decisions made at the time of initial surgery then again when considering autologous reconstruction have life-long implications. These decisions include both timing of surgery and strategies for bowel preservation based on a patient's clinical symptoms and anatomy.

Various surgical strategies have been described to preserve as much bowel as possible in children who present with diagnoses requiring urgent and/or emergency intervention. This can include second look laparotomies where bowel that is questionable is preserved and evaluated at 24 to 48 hrs later to determine its viability.[40] Less conventional surgical strategies include transluminal stenting for patchy infarction from necrotizing enterocolitis or type 4 intestinal atresia's. In our experience, transluminal stenting was associated with a final SB length of 63.9cm representing 40–50% of expected bowel length based on age.[41] The bowel preserved with transluminal stenting increased the residual SB length by 79% (range 52–96%) avoiding more extreme SBS.[41]

Autologous bowel reconstruction including procedures such as the longitudinal intestinal lengthening procedure (LILP) or serial transverse enteroplasty (STEP) have been reported extensively in the literature. They exploit bowel dilatation and taper and lengthen the residual bowel while maintaining maximum mucosal surface area for absorption. The surgical gains are in part based on the initial caliber of the SB. The STEP is not technically difficult to perform; however, patient selection is key. Typically, failure to further advance enteral feeds, or development of complications such as refractory bacterial overgrowth or IFALD may signal that a patient could benefit from bowel reconstruction. Fluoroscopic studies that demonstrate residual small and large bowel length as well as caliber and transit time help determine the appropriate reconstructive procedure. For patients with USBS, it may not be feasible to achieve EA, but optimizing adaptive potential to minimize PN exposure and maximizing quality of life are very important goals. Surgical decisions should be made under the umbrella of a multidisciplinary IRP.

Multidisciplinary IRP Experience

Intestinal failure is a rare disease; therefore, consolidating management in dedicated centres of excellence improves the quality of care. Established programs may have increased resources and experience that permits an enhanced ability to achieve adaptive potential and minimize comorbidities.[42] As with many rare and complex medical conditions, there is often a relationship between the volume of patients and the outcome. Experienced and well-resourced programs should provide comprehensive care that is current and optimizes medical outcomes, as well as, QOL for the child and family. An IRP should provide pediatric surgery, gastroenterology, nutrition, nursing, physiotherapy, occupational therapy, social work and pharmacy support. An IRP also needs a relationship with an intestinal transplant program for easy flow of patients as required. The actual construct of most IRPs in North America varies significantly, as do the protocols and guidelines employed by each. The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) published guidelines of the minimum requirements for an IRP membership supporting the minimum involvement as surgical, gastroenterology, dietetic and nursing support, as well as suggested team members as highlighted above.[43]

Care Coordination

USBS patients are at a disadvantage and will likely require prolonged if not lifelong PN support. Coordinating care is essential to minimize potential complications. Through an IRP, practitioners can optimize bowel function and preservation through both medical and surgical management that includes a variety of enteral feeding variations, promotion of oral feeding skills and when necessary surgical interventions. The role of an IRP is also essential in monitoring and preventing the development of complications that can include IFALD, CLABSI, SB bacterial overgrowth, nutritional deficiencies, renal impairment and metabolic bone disease.

IRPs often have internal protocols and guidelines that are built on years of experience and available literature to provide patients and caregivers with consistency and standardization of care. It is critical, however, to tailor the management to each individual's needs depending on their response to interventions.

A multidisciplinary approach is essential for communication with patients and families. Anecdotally, patients and caregivers often report being overwhelmed. Due to the large number of services and support required, coordination of care by an IRP provides the family with access to a large number of health care individuals to address all aspects of their child's care in a streamlined fashion.

Through the development of a therapeutic relationship with the IRP, the child and caregivers can receive ongoing support and education in the hospital before primary discharge and then ongoing as an outpatient with one point of contact.[15,42,44]

Transitions of Care

Patients with USBS experience a number of transitions in their lives. These include transitioning from hospital to home, from care in the home to attending school and eventually transition to adult care. There is limited literature available on these transitions, but they are important aspects to consider as survival rates continue to improve, and more patients will be navigating through these events. A significant amount of effort is needed to prepare a patient and caregiver to provide the necessary supports in the home setting. In our experience, there are often limited resources available to support families in the home. Hughes at al. presented data showing caregivers in their program woke between 1 and 8 times at night to provide for the needs of their children.[45] This represents a significant burden of care on the caregiver and must be accounted for. Children with USBS will require prolonged home PN making the caregivers at risk of burn out. Determining the supports that best decrease the strain on caregivers is paramount for us to understand as a community providing medical care for this population.

Changing Attitudes

Another aspect of the management of USBS is changing the perspectives of care providers who are often the first ones to encounter these patients and families. A recent study by Pet et al highlighted the fact that many neonatologists and pediatric surgeons continue to recommend comfort care for infants who have had massive bowel loss.[46] This does not reflect the improved survival rates of >90% and highlights the need for further education to promote the current practice changes and decreased mortality. It also highlights the need to promote expert care and management of these patients and ensure early transfer to centres with more experience.

Where Do We Go from Here?

In spite of improvements in outcome for children with IF, patients with USBS represent a more extreme phenotype. One can anticipate prolonged or permanent PN and therefore, potential complications. There are initiatives that would enhance clinical and academic understanding of these patients that will be explored in more detail below.

Definitions

One of the challenges in the IF literature remains the lack of consensus definitions for almost all key outcomes. It is surprising, but there are no standardized definitions for IF, SBS (including USBS), IFALD, EA, etc. As a result, published studies are difficult to compare as outcome variables are often defined differently. Currently, the Pediatric Intestinal Failure working group of the American Society for Parenteral and Enteral Nutrition (ASPEN) is drafting a manuscript to address the gap.

With respect to reporting residual bowel length, we have stated several times in previous literature that residual bowel length should be presented as a percentage of expected bowel for age. This is because of the bowel's inherent ability to grow in the first several years of life. A term newborn has a mean bowel length of 160cm that increases to 425cm at 5 years of age.[47] Therefore, adjusting remaining bowel length for patient age is important to understand adaptive potential and prognosis.

Research

The main challenges with conducting research in pediatric IF include the small patient populations treated by single centers, significant patient heterogeneity and lack of standardized reporting of outcomes. The field will not continue to grow without contemporary multicenter studies. Multicenter observational registries can be helpful in understanding numerous outcomes. For instance, the Intestinal Transplant Registry initiated at the University of Toronto more than 2 decades ago and now administrated by the Taresaki Foundation has been instrumental in our understanding of intestinal transplant outcomes. An initial attempt at gathering multi-centered data came from the Pediatric Intestinal Failure Consortium (PIFCon) that collected data from 14 established IRPs in North America and published its first manuscript in 2012.[2] They were able to assess clinical outcomes, define important research questions and demonstrate collaboration between multiple centres. The recent establishment of the Intestinal Failure Registry will "piggyback" on the Intestinal Transplant Registry and will promote collaboration between centres. This will address some of the key limitations mentioned above and facilitate interventional trials.

A recent publication from our centre proposed a SBS disease severity score to predict EA.[8] The score predicts

the probability of EA and accounts for residual anatomy and clinical status at 6 months post bowel resection including conjugated bilirubin level < 34mmol/L and tolerance of >50% enteral nutrition. Based on a maximum score of 8, patients are stratified into mild, moderate or severe disease that provides predictions on whether or not they will achieve EA. A prediction score will allow for early prognostication and long-term planning for clinicians and families and may assist in research endeavours by adjusting outcome reporting or stratifying recruitment.

Creation of such infrastructure will permit completion of interventional studies that can provide higher level evidence. For instance, evaluation of trophic peptides, manipulation of the microbiome, composite lipid emulsions at conventional doses versus lipid minimization strategies for prevention of IFALD and comparison of various catheter locking solutions are all examples of interventional studies best answered with a multi-institutional approach.

Long-Term Surveillance

The prolonged PN support required by patients with USBS places them at risk for significant complications that can include IFALD, vascular complications, CLABSIs, renal dysfunction, metabolic bone disease and nutritional deficiencies. There have been considerable advancements in the prevention of IFALD and CLABSIs, but there is still many complications and comorbid conditions that we do not completely understand and therefore monitoring for their presence or development is increasingly important both to further our knowledge and understanding, but also to protect our patients. Many programs have their own guidelines for monitoring that can include abdominal, renal and vascular ultrasounds, bone density scans, nutritional bloodwork and transient elastography; however, there remains no consensus on the frequency of monitoring or exactly what to monitor for. The role of the IRP in understanding and monitoring these complications is crucial to avoid the late diagnosis of comorbidities that may necessitate or even preclude a transplant assessment. In addition, we also advocate for close monitoring of patients with a history of liver disease that resolved using lipid management strategies. We suspect that we will likely see the increase of non-cholestatic liver disease in IF patients on long-term PN who experienced initial resolution of cholestasis, but progressive fibrosis that continued due to ongoing PN exposure or recurrent sepsis. Again, this is a crucial role that IRPs will play in the management of these patients to ensure timely referral for transplant when the need arises.

Conclusion

For the last 15 years the field of intestinal failure has been a part of bring about significant improvement in the outcomes for pediatric patients with intestinal failure. As outlined in this paper, these advances have also benefited patients with USBS who may experience a more severe course. Multidisciplinary IRPs have been a major reason for improved survival. With the reduction in mortality, IRPs need to focus on the prevention of comorbidities that have become more apparent now that children are surviving longer, especially in patients with more significantly altered anatomy such as that present in USBS. IRPs will continue to be pivotal in pushing the research agenda and ensuring that our understanding and knowledge continue to grow. Further advancement will be dependent on institutions collaborating and being willing to share knowledge and expertise.

Disclosure

The authors report no conflicts of interest in this work.

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