Ultrashort Bowel Syndrome Outcome in Children Treated in a Multidisciplinary Intestinal Rehabilitation Unit

Mariela Dore¹ Paloma Triana Junco¹ Ane Andres Moreno¹ Vanesa Nuñez Cerezo¹ Martha Romo Muñoz¹ Alba Sánchez Galán¹ Alejandra Vilanova Sánchez¹ Gerardo Prieto² Esther Ramos² Francisco Hernandez¹ Leopoldo Martínez Martínez¹ Manuel Lopez Santamaría¹

¹Department of Pediatric Surgery, Hospital Universitario La Paz, Madrid, Spain ²Department of Pediatric Gastroenterology, Intestinal Rehabilitation Unit, Hospital Universitario La Paz, Madrid, Spain


Abstract

Aim Short bowel syndrome (SBS) is the leading cause of intestinal failure (IF) in the pediatric population. Our aim was to review long-term outcome of ultrashort bowel syndrome (USBS) in an Intestinal Rehabilitation Unit (IRU).

Patients and Methods Retrospective study of patients with USBS (defined as < 10 cm of remnant small bowel) treated between 2000 and 2015. Demographic data, clinical, and treatment variables including parenteral nutrition (PN), surgical techniques, and intestinal transplantation (IT) were analyzed.

Results Out of 250 children, 30 referred to the IRU met inclusion criteria. Upon first assessment, patients had a median age of 3 (1–217) months and had undergone 3 (1–6) previous laparotomies that left 5 (0–9) cm of remnant small bowel. The main cause of USBS was neonatal midgut volvulus (50%). Follow-up was 28 (4–175) months. Advanced IF-associated liver disease (IFALD) was documented in 63%. None of the patients achieved digestive autonomy and was consequently considered for IT. One patient was excluded, five died before IT, and three are still on the waiting list. Six patients received an isolated IT, 6 a combined liver IT, and 18 a multivisceral graft. Digestive autonomy was achieved in 71% after 31 (14–715) days after IT and currently 62% are alive and off total PN. A significant drop in IFALD progression prior to IT was observed with the introduction of new lipid emulsions in 2010 (SMOF or Soy oil MCT (mid-chain triglycerides) Olive oil Fish oil).

Conclusion A multidisciplinary IRU including an IT program offers a comprehensive approach for patients with IF and is crucial to improve survival rate of USBS. New PN lipid emulsions had an impact on IFALD progression and may eventually reduce overall mortality.

Keywords

► intestinal transplantation
► ultrashort bowel syndrome
► intestinal failure

Introduction

Short bowel syndrome (SBS) is the leading cause of intestinal failure (IF) in the pediatric population, usually due to necrotizing enterocolitis, intestinal atresia, midgut volvulus, or gastrochisis.¹ With an incidence of three to five per 100,000 births per year, SBS is associated with a reduced quality of life and significant morbidity, which results in a mortality rate of 10 to 15% over 5 years.²–⁴ A multidisciplinary approach to SBS-associated IF most likely improves its
outcome by optimizing medical and surgical care of these patients. The relentless search of predictive factors for PN weaning has resulted in the knowledge that the remnant bowel plays a crucial role in digestive autonomy, and therefore, the development of parenteral nutrition (PN)-related complications and overall survival.\textsuperscript{3,5}

After massive intestinal loss, acquired or congenital, there is a small percentage of patients who end up with very few centimeters of residual small bowel. Ultrashort bowel syndrome (USBS) has been defined as approximately 10 to 25 cm of remaining small bowel.\textsuperscript{1,6} The length of the remaining bowel after initial surgery has been closely associated with overall patient outcome including PN duration and overall survival; in fact, it defines its severity and it predicts the possibility of intestinal adaptation.\textsuperscript{3,5,7} One of the main issues when treating patients with USBS is the fact that the adaptation phase is usually long and slow, increasing the risk of one of the most severe and prevalent complication of prolonged PN: hepato-biliary dysfunction commonly referred to as IF-associated liver disease (IFALD).\textsuperscript{8} The successful management and prognosis of USBS depends on many variables besides remnant small bowel length. Small bowel anatomy, localization, quality, and motility are important features to consider when assessing these patients.\textsuperscript{3–11} Basal clinical situation and exhaustive medical management are essential before deciding adequate surgical rehabilitation techniques or transplantation.\textsuperscript{12}

In spite of its relevance, there is very few published data regarding management options for USBS. In light of this finding, we aimed to review long-term outcome of USBS in an Intestinal Rehabilitation Unit (IRU) with 15-year experience of treating IF in pediatric patients who will most likely aid physicians in patient care and counseling.

**Patients and Methods**

All patients with IF assessed as potential transplantation candidates in the IRU in the past 15 years were retrospectively studied. Focus was aimed at patients with \( \leq 10 \) cm residual bowel, which we defined as USBS.

Basal nutritional status, liver function (biochemical panel and biopsy), vascular access, as well as a comprehensive study of the remnant intestine (upper gastrointestinal (GI) contrast series, contrast enema, and ultrasound imaging) were evaluated as part of the transplant candidate assessment protocol.

A comprehensive review of the clinical charts of patients with IF registered in the IRU was performed. After careful review of surgical protocol, referral history, and imaging techniques, patients with remnant bowel of \( \leq 10 \) cm were included. Demographic data, as well as previous medical records, primary diagnosis, and associated congenital anomalies were recorded. The nutritional status was assessed upon first evaluation by anthropometric data and PN dependence situation. Liver function tests were performed, in addition to imaging and biopsy procedures, classifying the hepatic function in mild, moderate, and severe, according to the IFALD.\textsuperscript{13} IFALD was defined as the persistent elevation of serum transaminases 1.5 times above the normal upper limit in the presence of short bowel.\textsuperscript{8}

Different changes in patient treatment protocol were seen over the years, thus making comparisons difficult. In 2010, the new lipid emulsions were introduced as part of the PN support. Patients were thus classified according to pre-SMOF introduction and post-SMOF introduction. Liver enzymes, total bilirubin, and coagulation parameters upon first assessment, 6- and 12-month follow-up were compared. Other changes in practice included a shift in recent years toward multivisceral grafts over combined liver–intestinal graft when a composite graft was indicated. This change is probably multifactorial as the result of the complex technique and poor outcomes of the latter. Furthermore, late referrals, sepsis, and long-term outcomes were evaluated by means of PN dependence, liver disease progression, intestinal transplantation (IT) (isolated, combined intestinal–liver, and multivisceral), complications, morbidity, and survival rates.

Data are expressed in medians and ranges. Nonparametric tests were used to compare data \((p < 0.05\) deemed significant). IBM SPSS Statistics program for windows version 20, IBM Corp., was used for statistical analysis.

**Results**

In a 15-year time frame, the IRU has assessed a total of 250 patients with IF (131 males/119 females). Patients presented with a mean age of 25 ± 7 months upon first assessment and up to 89% were referrals from other institutions for potential intestinal transplant consideration.

After careful review of clinical charts, 30 out of 250 children met the inclusion criteria. Upon first evaluation, patients presented with a median age of 3 (1–21) months and weight of 4.35 (2.6–59) kg. Eighty percent of the patients were below the fifth of weight for age with 42% of them below the first percentile (\( \sim \) Table 1).

Surgical protocols revealed that they had undergone 3 (1–6) previous laparotomies that left 5 (0–9) cm of remnant small bowel. Neonatal onset of USBS was seen in 73% of the patients. The main cause of massive intestinal loss resulting in USBS was neonatal midgut volvulus (50%). Other causes of USBS were necrotizing enterocolitis in five patients, three patients of gastroschisis with associated intestinal atresia, two patients of extensive Hirschsprung’s disease, as well as one patient of superior mesenteric artery thrombosis and a teratoma.

All patients were on total PN (TPN), and despite medical efforts to wean them off, they all continued PN dependent after a 1-year follow-up. The proteic content of the PN solution in all patients was the Primene 10% amino acids intravenous infusion that contains essential and nonessential L-amino acids. Lipid content, however, changed throughout the years, initial lipid content was mainly olive and soybean oil emulsions with some emulsions also containing medium and long chain triglycerides (ClinOleic 20% or Lipofundin 10–20%). However, in 2010, a lipid emulsion-containing fish oil was first introduced (SMOFlipid) as an effort to minimize IFALD.

The first chemical panel revealed serum bilirubin levels of 3.2 (0.2–14) mg/dL which ascended to 5.2 (0.1–20) and 14.6 (0.2–31) mg/dL after 6 and 12 months of first evaluation. A...
similar tendency was observed with liver enzymes serum levels of aspartate aminotransferase (AST) of 88.5 (30–532) U/L and alanine aminotransferase (ALT) of 82.5 (18–560) U/L on the first assessment with AST of 282 (13–878) and 366 (29–1,041) U/L and ALT of 229 (43–532) and 237 (91–591) U/L at the 6- and 12-month follow-up (►Figs. 1 and 2).

Liver function tests were compared before and after the introduction of fish oil-based lipid emulsions. After the routine use of SMOFlipid was implemented, a tendency toward a slower progression or even regression of cholestasis and liver disease was observed (see ►Table 2). Consequently, although a difference in overall survival rate was found before and after the change in PN was found (44.4 vs. 66.6%), these were not statistically significant (p > 0.05).

A liver biopsy was indicated in 86.7% of the patients upon first assessment. Liver disease, ranging from mild fibrosis to cirrhosis, was found in 96% of the patients. Advanced IFALD was documented in 63%. Vascular access complications such as venous thrombosis of at least two vascular regions were found in one-third of the patients (33.3%) and at least one episode of catheter-related sepsis was registered in 66.6%.

After multidisciplinary committee evaluation (pediatric gastroenterologists, surgeons, psychologists, hepatologists, and social workers), one met surgical rehabilitation criteria and after the change in PN was found (44.4 vs. 66.6%), these were not statistically significant (p > 0.05).

Table 1 Patient characteristics upon intestinal transplantation assessment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first assessment, mo: median (range)</td>
<td>3 (1–217)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/13</td>
</tr>
<tr>
<td>Follow-up mo: median (range)</td>
<td>28 (4–175)</td>
</tr>
<tr>
<td>Age of USBSa mo: median (range)</td>
<td>0 (0–204)</td>
</tr>
<tr>
<td>Etiology: n (%)</td>
<td>Midgut volvulus, n = 15 (50%)</td>
</tr>
<tr>
<td></td>
<td>Necrotizing enterocolitis, n = 5 (16.7%)</td>
</tr>
<tr>
<td></td>
<td>Intestinal atresia, n = 3 (10%)</td>
</tr>
<tr>
<td></td>
<td>Gastrochisis, n = 3 (10%)</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung's disease, n = 2 (6.7%)</td>
</tr>
<tr>
<td></td>
<td>SMA thrombosis, n = 1 (3.3%)</td>
</tr>
<tr>
<td></td>
<td>Teratoma, n = 1 (3.3%)</td>
</tr>
<tr>
<td>Previous laparotomies: median (range)</td>
<td>3 (1–6)</td>
</tr>
<tr>
<td>Remnant bowel length, cm: median (range)</td>
<td>5 (0–9)</td>
</tr>
<tr>
<td>Ileocecal valveb presence: n (%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Native colon presence: n (%)</td>
<td>23 (76.7%)</td>
</tr>
<tr>
<td>Weight, kg: median (range)</td>
<td>4.35 (2.6–59)</td>
</tr>
<tr>
<td>AST (U/L): median (range)</td>
<td>88.5 (30–532)</td>
</tr>
<tr>
<td>ALT (U/L): median (range)</td>
<td>82.5 (18–560)</td>
</tr>
<tr>
<td>INR: median (range)</td>
<td>1.15 (0.8–1.9)</td>
</tr>
<tr>
<td>Prothrombin time (%): median (range)</td>
<td>79 (50–105)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL: median (range)</td>
<td>3.2 (0.2–14)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; SMA, superior mesenteric artery; USBS, ultrashort bowel syndrome.

![Fig. 1](Liver enzymes median values at the time of first assessment, 6- and 12-month follow-up are shown.)

![Fig. 2](Total bilirubin median values at the time of first assessment, 6- and 12-month follow-up are shown.)
and a Bianchi procedure was performed. Intestinal adaptation was not achieved, and thus, the patient was considered for IT along with the remaining patients. After full IT workup, one patient was excluded because of poor neurological prognosis. Five patients died while waiting for a suitable donor, and three are currently on the transplantation waiting list. Finally, 21 patients received a graft (transplantation rate in USBS of 72.4%): 6 patients received an isolated intestinal graft; another 6 a combined liver IT, and 9 a multivisceral graft. Composite grafts were indicated in patients with advanced liver disease. A second graft (retransplantation) was required in four patients, all of them due to acute exfoliative rejection. Technical complications included a case of anastomosis dehiscence, severe hemorrhage, and biliary stenosis. Shortly after IT, 71% of the patients were weaned completely off PN in 31 (14–715) days. Currently, 62% are alive and off TPN. Isolated IT yielded a survival rate of 83% with at least 9 (7–13) years survival. We found that although combined liver–intestinal grafts yielded a 33% survival (two survivors with 10- and 12-year follow-up), multivisceral grafts allowed a 67% survival rate with 2.5 (1–10)-year follow-up.

Overall survival rate of patients with USBS was 53% with a median follow-up was 28 (4–175) months (Fig. 3).

### Discussion

In this single-center study, we found that the multidisciplinary IRU treated a large number of patients with SBS over the past 15 years, with 12% presenting with less than 10 cm of small bowel remnant (USBS). Although the relationship between remnant bowel length and probability of PN weaning is known, there is an ongoing debate as to what is the length of the remaining bowel at which IF should be considered irreversible and more aggressive treatment plans offered.\(^1\)\(^3\)\(^7\) Goulet et al found a probability of 0.43 (0.19–0.70) in patients with 10 or less centimeters of small bowel, excluding however those patients with IT and mortality.\(^3\) In our study, none of the patients with this small bowel length was able to wean off PN and was considered for IT. These findings are similar to those found by Demehri et al in a recent study where patients with < 10% expected bowel length are significantly less likely to wean off PN than those with > 10% of the remaining bowel length. These findings suggest that a 10-cm cutoff might select patients with irreversible IF, and thus, an early offer of other treatment modalities such as IT might reduce mortality rates.

One of the main problems in treatment of USBS is complete PN dependence during long periods of time resulting in several complications associated with prolonged PN. Efforts toward finding a PN that can be administered during longer periods of time with minimum metabolic repercussions are ongoing. In this study, we found that the introduction of fish oil-containing lipid emulsions in the PN was associated with tendency toward a slower progression of IFALD liver function tests \((p < 0.05)\) and a lower mortality rate \((p > 0.05)\). This allows time to either continue efforts to wean off PN or find a suitable transplantation donor with less postoperation complications.

In fact, a composite graft was necessary in 71% of the patients versus 29% of isolated bowel graft. A possible explanation is the rapid progression of liver disease due either to the use of inadequate lipid emulsions, sepsis, late referrals (when end-stage liver disease is imminent) or most likely multifactorial. These data support the need of multidisciplinary rehabilitation units to optimize medical treatment and avoid the otherwise inevitable IT.\(^14\)\(^–\)\(^16\)

USBS is associated with a great number of morbidity and higher mortality rates than those reported for SBS. It is well known that patients with USBS present with high risk for

<table>
<thead>
<tr>
<th>Liver function test median values</th>
<th>Before fish oil-based lipid emulsions</th>
<th>After fish oil-based lipid emulsions</th>
<th>p-Value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0 mo</td>
<td>6 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>57</td>
<td>296</td>
<td>825</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>58.5</td>
<td>247.5</td>
<td>372</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>2</td>
<td>8.25</td>
<td>23</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>84</td>
<td>67.5</td>
<td>63</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.
multiple morbidities due to IF management such as infectious and mechanical complications related to prolonged use of central venous catheters, multifactorial liver disease progression, metabolic imbalance due to GI electrolyte losses, mechanical and functional bowel disorders. All of these complications result in a lower quality of life due to frequent and prolonged hospital admissions and thus missed school and work.4

A mortality rate reduction from 30% of patients over 5 years17 to 10 to 15% over 4 years18–21 likely reflects the impact of multidisciplinary intestinal rehabilitation programs on patient outcomes.4 However, mortality rates for the special cohort of patients with less than 10 cm are often not reported. The overall mortality rate in this study was 47%, which is higher than reported rates for SBS. This finding shows that these patients require earlier and more aggressive treatment plans to attempt to reduce morbidity as well as mortality. In agreement with other authors, an intestinal rehabilitation program is essential; however, an early referral and optimal treatment plan is even more important to achieve better outcomes.14,15 Most studies have demonstrated improved outcomes with early referral. However, Khan et al found that an early referral was associated with lower rates of enteral autonomy, the most likely explanation is possibly because of selection bias (tendency to refer only the most severely ill children to sites with transplant capacity).14 Efforts should be focused to centralization of SBS to specialized centers, where either rehabilitation or transplantation can be offered if necessary.

Comprehensive review of patients with USBS also allows optimization of parental counseling that is otherwise difficult due to the relatively unpredictable course of the disease and its natural history. Prolonged PN dependence as well as high risk of morbidity and mortality rates should be taken into account in the management of these patients.

Limitations in this study arise from its retrospective design and heterogeneous and scarce number of patients included. Prospective multicenter studies are necessary to acquire patient volume and thus making significant statistical analysis. Given the wide variations in patterns of clinical practice, new focuses should be aimed toward enhancing and optimizing patient care by searching enteral autonomy predictors, prevention of central line complications, and early referral guidelines.

Conclusion

In our series, a 10-cm residual small bowel cutoff might aid in patient treatment and counseling plan. We believe that a multidisciplinary IRU including an IT program offers a comprehensive approach for patients with IF. Our review found that early and careful assessment of patients for IT is crucial and might help improve survival rates. The recent introduction of fish oil-containing PN lipid emulsions had an impact on liver disease progression and may eventually aid in overall mortality reduction.

References