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Cycled Enteral Antibiotics in Suspected Small Bowel Bacterial Overgrowth Complicating Short Bowel Syndrome - Experience from a Ter-tiary Neonatal Centre of Canada

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Summary

Background: Short Bowel Syndrome (SBS) poses a major challenge in the clinical and nutritional management of many surgi-cal neonates. Small Bowel Bacterial Overgrowth (SBBO) complicates up to 60% of patients with SBS.

Aim: To describe baseline demographic characteristics of infants with SBS in the last 5 years and identify variables (clinical, laboratory and radiological) associated with the use of cycled antibiotics. Report the major indications and short-term outcomes of starting CEA among infants with SBS treated for presumed SBBO, as continuous quality improvement in our practice.

Methods: Retrospective cohort study in Children´s and Women´s Health Centre of British Columbia NICU.

Results: 52 infants had SBS during the study period, a cumulative incidence of 14 per 1000 NICU admissions. 30 (58%) were treated with CEA for suspected SBBO. NEC represented the most common aetiology for SBS 18/52. Among the infants who received CEA, the most consistent feature identified preceding treatment was poor weight gain (93%) followed by bowel dilata-tion on abdominal radiograph (80%). There was a significant improvement in the trend of stoma outputs and cholestasis among the infants who received 6 weeks of CEA. No difference was however found with regards to change in acid base and electrolytes status, or nutritional parameters over time between the two groups ($p>0.05$).

Conclusion: Our review of CEA use as a therapeutic modality for suspected SBBO revealed an improvement in certain clinical and laboratory parameters, which may make this a promising therapy for this population.

Background

The true incidence and impact of Short Bowel Syndrome (SBS) in the neonatal population has likely been underestimated as a result of inconsistent clinical definitions and reporting criteria, as well as difficulties in diagnosis. Nevertheless, this entity poses a major challenge in the clinical and nutritional management of many surgical neonates, often entailing multidisciplinary involvement, prolonged hospital stays and substantial resource investment [1]. A recent population-based estimate reports the overall incidence of SBS across Canada to be 22.1 per 1,000 Neonatal Intensive Care Unit (NICU) admissions and 24.5 per 100,000 live births [2]. The incidence is much higher in the preterm population. The Canadian Association of Paediatric Surgeons (CAPS) defines SBS as The Need for Total Parenteral Nutrition (TPN) greater than 42 days after bowel resection, or a residual small bowel length of less than 25% expected for gestational age [3]. The most commonly report-ed aetiologies of SBS are Necrotizing Enterocolitis (NEC) (35%), intestinal atresia (10%), abdominal wall defects (12.5%), volvu-lus (10%), and complicated meconium ileus [2]. SBS, along with other rarer entities like motility disorders and enterocyte dysfunc-tion constitute the broader group of Intestinal Failure (IF), defined as 'a severe reduction in functional gut mass below the minimum amount necessary for digestion and absorption adequate to satisfy

the nutrient and fluid requirements for growth' [4]. The management of this condition relies heavily on prolonged Parenteral Nutrition (PN) [5], which provides adequate calories for growth and promotes intestinal "adaptation". Besides PN, additional management strategies have also included the use of elemental hydrolyzed formulas, effective prevention and management of catheter-related sepsis, Autologous Intestinal Reconstruction (AIR) surgery and intestinal transplant [1]. Abnormal colonization of dysmotile bowel leads to Small Bowel Bacterial Overgrowth (SBBO), an entity which has been reported to complicate up to 60% of SBS cases [6]. SBBO can lead to excessive stool output, malabsorption, poor growth, and electrolyte disturbances, particularly among prema-ture infants with functioning stomas post intestinal surgery, who may have stoma outputs in excess of 40-50ml/kg/day [6]. It has been proposed that bacterial.

Translocation across the inflamed intestinal barrier might lead systemic sepsis [7] which is a major cause of morbidity and mortality in this population. Currently the gold standard for diagnosing SBBO is a duodenal aspirate with a confirmed colony count of >105 CFU/mL bacteria or the presence of colonic flora, both of which are technically challenging and generally not feasible in clinical practice. The presence of D-Lactic acidosis, a by-product of bacterial metabolism, may also be used as a surrogate marker, but is often confounded in neonates by other clinical conditions and chronic use of certain medications (e. g. diuretics). Due to the aforementioned limitations, the diagnosis and monitoring of SBBO remains essentially clinical.

Current Management Strategies for Short Bowel Syndrome- Lack of Consensus [8-10]

Management of SBS has been focused mainly on three phases; the acute, the recovery or intermediate phase and the late phase with each posing its own challenges. In the acute phase, the management focuses on treating fluid, metabolic and electrolytes imbalances. During the recovery phase some of the strategies that have been implemented to reduce the risk of complications include the use of new mixture of ω-6 and ω-3 fatty acids, MCT, long chain triglycerides, structured triglycerides, fish oil and olive oil lipids. The use of lowest aluminum containing products, low or removal of trace elements in PN, cycling PN are some strategies to help minimize the neurologic and hepatic injury. Novel thera-pies in SBS to improve bowel adaptation being tested actually in humans include the use of Teglutide (GLP-2), growth hormone, oral insulin supplementation, epidermal growth factor. Treatment of SBBO should be focused on modifying the gastrointestinal flora with judicious use of antibiotics against aerobic and anaerobic en-terobacteria although there is still no consensus on the best regime. In children carbohydrate restriction with increase in protein and fat may be useful to decrease gas related symptoms and osmotic diarrhoea [10].

Major pharmacological strategies aimed at preventing or treating abnormal gut colonization and SBBO in recent years have focused on the use of probiotics and Cycled Enteral Antibiotics (CEA) [11]. CEA is a regimen of orally administered antibiotics in cycles with alternating periods off antibiotics in order to allow the gut a recovery period. Literature regarding regimens and ef-ficacy of CEA is scant and guidelines for use are largely institu-tion-dependent. The aim of the current study was to review the demographic characteristics of patients diagnosed with SBS in The Neonatal Intensive Care Unit (NICU) of Children´s and Women´s Health Centre of British Columbia over the past five years, and to report the major indications and short-term outcomes of starting CEA among infants with SBS treated for presumed SBBO, as part of continuous quality improvement in our practice.

Objectives

- To describe the baseline demographic characteristics of infants diagnosed with short bowel syndrome in our NICU over the last 5 years.
- To compare clinical, laboratory and radiological data between the cohorts of patients who received enteral cycled antibiotics and those who did not.
- To identify variables (clinical, laboratory and radiological) as-sociated with the use of cycled antibiotics over the last 5 years among SBS patients.

Setting, Materials and Methods

This was a retrospective study carried out in the NICU of Children´s and Women´s Health Centre of British Columbia, a large tertiary care unit in Western Canada which serves as the main referral center for high risk and surgical newborns in the province of British Columbia (BC). The rate of neonatal admissions in our unit is approximately 700 per year. This study was approved by the Research and Ethics board of the BC Children's and Women's Hospital under the University of British Columbia. The medical records and charts of all patients with SBS admitted from May 2009 - December 2014 were reviewed to collect clinical, laboratory, and radiologic data reports. Patients with SBS are followed in the post-operative period by an interdisciplinary team of neonatologists, surgeons, paediatric gastroenterologists and nutritionists which has been in operation since 2007. Records kept by this team were also reviewed to collect information regarding Parenteral Nutrition (PN) duration, trials of elemental formula and growth. Treatment with CEA for presumed SBBO was started at the discretion of the responsible medical and/or interdisciplinary team. The current regime for treatment of suspected SBBO followed in our unit is oral Gentamicin 5 mg/kg/dose BID for 7 days, oral Metronidazole 10 mg/kg/dose BID for 7 days, followed by no antibiotics for 7 days; the cycle is typically repeated if clinically indicated. Infants with

SBS were classified based on their residual small bowel length ac-cording [12] into three categories: 1) residual small bowel length 100-150 cm, 2) residual bowel length 40-100 cm 3) residual Small Bowel (SB) <40 cm.

Laboratory data (pH, anion gap (AG), urea, conjugated bili-rubin [an indication of cholestasis], electrolytes), abdominal x-ray reports and weights were collected if available at 3-time points. For those who were treated with CEA, these included: 1) at 2 weeks prior to starting CEA, 2) within 1 week of starting CEA, and 3) after 2 CEA cycles (6 weeks post-CEA). For those who did not receive CEA, data were collected at: 1) half full enteral feeds (80mL/kg/d), 2) within 2 weeks of reaching half full feeds, and 3) at full feeds (160mL/kg/d) if attained. Laboratory and ra-diologic studies were requested by the responsible medical team during routine clinical care (at least once weekly for laboratory in-dices, and per clinical indication for radiologic studies which were subsequently reported by a radiologist); weights (kg) and stoma/ stool outputs (mL/kg/day) were collected and recorded daily by bedside nursing. Laboratory data, namely, (urea, pH, conjugated bilirubin, anion gap (AG), and electrolytes,), abdominal x-ray re-sults, and weights were collected at 3 chosen time points. - In those who were treated, the chosen time points were at 2 weeks prior to starting CEA, within 1 week of starting and after 2 CEA cycles (6 weeks post-CEA). Similar data were collected in the cohort who did not receive CEA at half full enteral feeds (80mL/kg/d), within 2 weeks of reaching half full feeds and at full feeds (160mL/kg/d) if attained. Exclusion criteria: Infants with surgical SBS who were started on CEA due suspected SBBO, but which were stopped be-cause of culture proven sepsis.

Statistics

Analyses were carried out using SPSS software, version 22.0. Data were tested for normality using the Shapiro-Wilk test. Comparison of median values (with IQRs) of growth (calculated as weight gain in grams/day), serum bilirubin levels (mmol/L) and stoma outputs (mL/kg/ day) across the two groups were analyzed using the Mann-Whitney U test with an accepted significance level of $p<0.05$ presuming non-parametric distribution of data across the groups. To analyze the influence of factors contributing to the deci-sion of starting CEA, stepwise binary logistic regression was used.

Results

Between 2009 and 2014, there were a total of 3708 admis-sions to the NICU, of which 52 patients were diagnosed with SBS and included in our study. The cumulative incidence of SBS was 14 per 1000 NICU admissions during the study period. Of these infants, 30 (58%) were treated with CEA for suspected SBBO. The most commonly used antibiotics were Gentamicin (initial antibi-otic in treatment cycle for 84%) and Metronidazole (16%). The basic demographics of the two groups are depicted in (Table 1).

Demographics	Received CEA (n=30)	Did not receive CEA (n=22)
Male	19 (63%)	12 (55%)
Female	11 (37%)	10 (46%)
GA (Median, IQR)	32 (23,41)	35 (23,47)
Birth weight (g)	1922 (490, 3520)	2055 (585,3826)
Diagnosis (n, %)		
-NEC	10 (33%)	8 (36%)
-Gastroschisis	8 (27%)	3 (14%)
-Intestinal atresia	4 (13%)	5 (23%)
-Volvulus	2 (7%)	2 (9%)
-Others	6 (20%)	4 (18%)
Ileocecal valve present (n, %)		
-Yes	28 (93%)	15 (68%)
-No (p=0.18)	2 (7%)	7 (32%)
Stoma present (n, %)		
-Yes	16 (53%)	20 (91%)
-No (p=0.004)	14 (47%)	2(9%)
Type of SBS (n, %) <40 cm	8 (27%)	5 (23%)
40-100 cm	10 (33%)	10 (45%)
>100 cm	9 (30%)	6 (27%)
N/A	3 (10%)	1 (5%)

Table 1: Demographic characteristics of patients.

Mortality and short-term morbidity outcomes between the two groups are presented below (Table 2).

	Treated with CEA	Did not receive CEA
Mortality	1	3
Median PN days	100	97
Discharged on PN	9/30 (30%)	3/22 (13.6%)
Median NICU stay	117	123

Table 2: Morbidity Outcomes.

The absence of Ileo-cecal valve (ICV) has been considered to be a predictor of poor outcome in the cohort of short bowel syndrome patients. We looked at the differences in morbidity between those who had intact ICV and those who did not (Table 3).

	ICV intact (n=43)	ICV resected (n=9)
Discharged on PN	12-Nov	1/12 (11.1%)

Residual bowel <40cm	13-Nov	13-Feb
Mortality	2	2

Table 3: Morbidity outcomes based on presence of ileocecal valve (ICV).

Analysing the aetiology of SBS, NEC (35%) was the predominant cause of SBS in both groups, followed by abdominal wall defects namely gastroschisis (21%) (Figure 1).

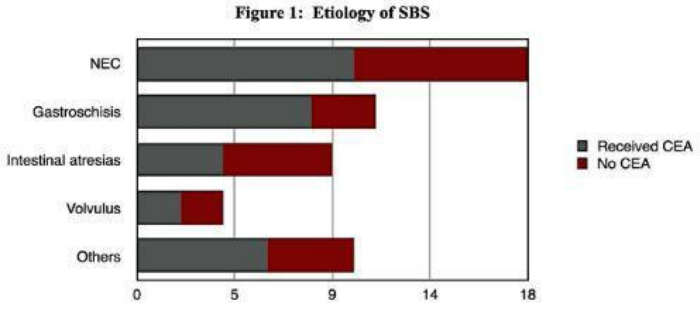

Figure 1: Frequency distribution of SBS aetiologies.

The median gestational age of the infants who received CEA was slightly less than those who did not, probably indicating an in-creased severity of intestinal disease among the lower gestational ages. Among the infants who received CEA, the most consistent morbidity identified preceding treatment was poor weight gain (93%) followed by radiographic evidence of intestinal loop dila-tion (80%) and nearly a quarter had all indications present prior to the initiation of CEA (Table 4).

Indication	Frequency
Poor weight gain (<20g/day)	28
Dilated bowel loops on x ray	24
Failure of elemental formula trial	19
Ostomy output >40mL/kg/d	15
All criteria	7

Table 3: Indicators of SBBO in patients treated with CEA.

Median stoma/stool outputs were significantly higher among the infants who were treated with CEA at time point 1 (p= 0.018) (Figure 2),

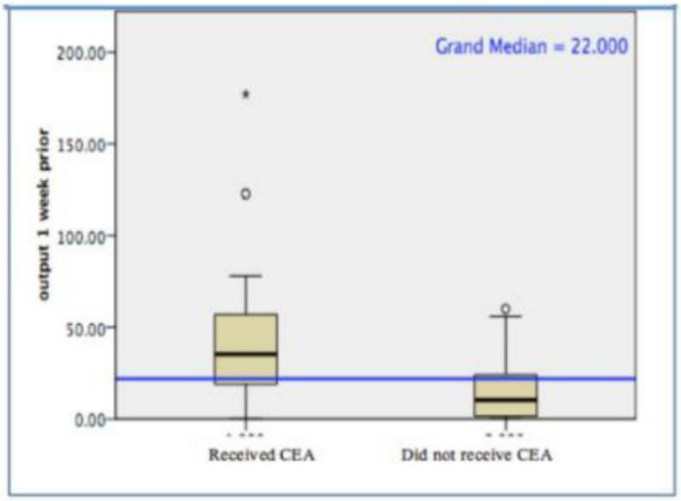

Figure 2: Median stoma outputs at time point 1.

Again, reflecting the fact that this group were probably sick-er. The median stoma outputs at time point 3 were also signifi-cantly different among groups (p=0.038) with the median outputs in the treatment group being significantly less (figure 3),

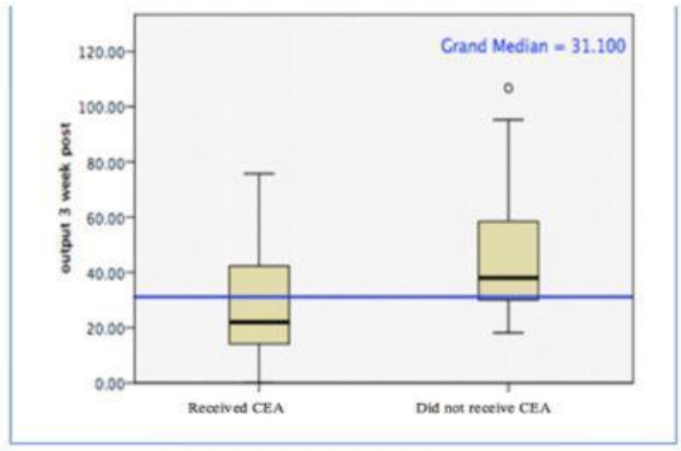

Figure 3: Median stoma outputs at time point 3.

showing a greater decrement in output among them after 6 weeks of treatment. The median and ranges of weight gain at each time point however did not significantly differ between the two

groups. Among infants diagnosed with SBS treated with CEA, a significant decrease in conjugated bilirubin was observed over time ($p<0.05$) (Figure 4),

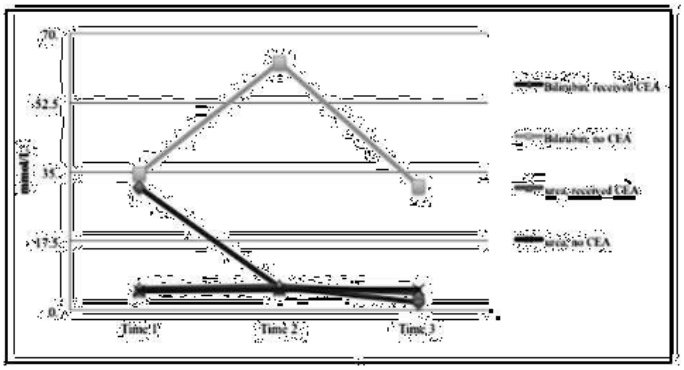

Figure 4: Comparison of median laboratory values among infants with SBS.

though no change in serum pH, urea, or weight gain after treatment was found. There was no difference among the groups with regards to change in bilirubin, pH, urea, or weight gain over time ($p>0.05$). Use of ursodiol was also similar in each group (40% of CEA-treated infants, 38% of non-treated infants). Step-wise binary logistic regression was used to determine the impact of antecedent factors namely poor weight gain, stoma outputs, pres-ence of dilated bowel loops, or failed trial of elemental formula on the decision to initiate CEA among SBS patients. Lack of ad-equate weight gain (defined in our population as < 20g/day) in the preceding 2 weeks was found to be a significant predictor of CEA use (p=0.007, OR- 0.069, CI=0.10- 0.488), as did failure of an elemental formula trial (p=0.049, OR= 4.42, CI=1.008- 19.4). The model overall however was found to poorly explain the associa-tions between the above variables and the initiation of antibiotics due to insufficient sample size (R2= 0.24).

Discussion

This study aims to review the characteristics of the cohort of infants diagnosed with SBS at our institution over the past five years, including those treated with cycled enteral antibiotics for presumed SBBO, one of its most challenging complications. Ap-proximately 20,000 Americans, including both children and adults are affected by SBS. Data from a large tertiary NICU in Canada showed an overall incidence of SBS as 22.1/1000 admissions and 24.5/100000 live births [2]. The SBS case fatality rate reported in the same review was 37.5%. Incidence rates among hospitalized neonates range from 0.7 to 1.1% depending upon birthweight [14]. The incidence of SBS in our center (14 per 1000 NICU admis-sions) over the past 5 years was less than that reported [2]. The latter study however presented data now over a decade old, and continuing advances in neonatal care, particularly with respect to NEC prevention among preterm infants, have likely contributed to this reduced incidence. Furthermore, SBS case fatality in our cohort was only 5.8%, a dramatic reduction from that reported by Wales et al. Data from the Center for Advanced Intestinal Rehabil-itation at Children´s Hospital in Boston showed that in their cohort of more than 200 children, NEC was the primary etiology (35%) underlying SBS; intestinal atresias were second (25%) followed by gastroschisis (18%) as well as malrotation and volvlus (14%). We found a similar pattern in our cohort, where NEC was the most common etiology of SBS among 18/52 infants (35%), followed by gastroschisis (21%), intestinal atresia (17%) and volvulus (8%).

In their study about outcome and long-term growth in children with SBS, Goulet et al., demonstrated that PN duration is influenced by residual small bowel length and presence of the Ileocecal Valve (ICV), with small bowel length <40 cm and/or absence of the ICV representing poor prognostic factors for achieving intestinal autonomy and normal growth [12,15]. In our cohort, the majority of infants with residual small bowel length of <40 cm was treated for suspected SBBO; many were also discharged home on PN (Table 2), which aligns with massive bowel resection being a prognostic factor for morbidity. Among the infants lacking an ICV in our cohort, the somewhat longer residual bowel length among these particular patients may have contributed to their lower rates of SBBO treatment and home TPN. Bacterial overgrowth occurs as a result of dysmotility in the dilated areas of the bowel which promotes an increase in colony counts of Gram negative aerobes and anaerobes in particular which tend to migrate from the large to the short bowel [16,17]. In our 5 years review we found that 58% of the infants with SBS were treated for suspected SBBO, which approximates the reported occurrence of SBBO among SBS pa-tients in the literature (60%) [6].

Radiological evidence of dysmotility such as dilated bowel loops and/or clinical evidence of dysmotility are reported to be a common occurrence in patients with SBBO [18]. We found dilated bowel on abdominal x-ray to be the second most frequent feature present preceding initiation of CEA among those treated, second only to poor weight gain. The former was not found to be independently associated with CEA use, however, possibly due to many non-treated infants also having dilated loops noted on abdominal films at the first-time point. This may simply be a reflection of the bowel pathology underlying SBS, radiographs ordered for other clinical indications, or possibly reflect inconsistency in practice in diagnosing and/or treating SBBO with CEA. The diagnosis of SBBO can be difficult to make, as it is primarily a clinical one with signs and symptoms which may overlap SBS itself; it is possible that in our cohort, some infants with SBBO may not have received antibiotic treatment, and vice versa. Growth deficits are concerning in patients with SBS [1,14] and can be surrogate signs of SBBO.

In our cohort, 93% of infants had less than optimal average daily weight gain prior to the start of CEA therapy, and this was found to be an independent predictor of CEA treatment.

This number decreased to 50% by the end of 6 weeks post CEA initiation, an effect which may be contributed in part by re-establishment of healthy bacterial flora, reduced stool output (also found to decrease significantly over time for CEA-treated infants and differ between treated and non-treated SBS cases) and sub-sequent improved feed tolerance and absorption after treatment. In the group that did not receive CEA, 59% remained with sub-optimal growth throughout the study period. The other indepen-dent predictor of CEA use identified in our cohort - a preceding failed trial of elemental formula - likely relates to the degree of feed intolerance and malabsorption exhibited as a result of SBBO. Its prominence could also represent a degree of overlap or con-fabulation of the features of SBBO and SBS itself in causing feed intolerance. Hepatic dysfunction in patients with SBS results from prolonged parenteral nutrition use and exposure to a constant in-flux of micro-organisms secondary to SBBO or bacterial trans-location [19]. The presence of cholestasis has been identified by Spencer et al as a strong predictor of mortality in patients with SBS [20]. Infants with SBS treated with CEA for suspected SBBO in our cohort showed a significant decrease in conjugated bilirubin over the 6-week study period ($p<0.05$); however, it is likely that the establishment of enteral nutrition also contributed towards this effect and thus it cannot be attributed to CEA therapy alone. Ur-sodeoxycholic acid was use was similar among those treated with CEA and those not.

One of the complications of SBBO includes the deconju-gation of bile acids and generation of toxic by products such as D-lactic acid by pathogenic bacteria. As this was a retrospective study, it was not possible to specifically assess for the presence of the D-lactate isomer. We also did not find a significant change in pH over time among infants treated CEA or a difference in pH among treated and non-treated groups. This is likely because of the confounding influence of multiple factors on pH, including venti-lation, acetate presence in PN and diuretic use probable for many SBS infants. Sepsis, a major complication of SBBO leading to potential mortality, has been reportedly reduced among pediatric patients on long-term PN with SBS who received CEA treatment
[21]. Though not significant, the incidence of post-surgical cul-ture-positive sepsis was less among the SBS infants who received CEA in our cohort. Failure to reach significance may be related to small sample size, or in part due to prescribing inconsisten-cies. The economic burden of managing patients with SBS and its complications is considerable due to prolonged hospital stays and resources for home PN when required [1]. Despite the improve-ments in weight gain, stoma output, and cholestasis observed over time among CEA-treated infants, there was no difference in mean hospital stay after first surgery until discharge. There was also no difference in the median days of parenteral nutrition use or number of infants discharged home on TPN between groups. The presence of confounding factors like prematurity and chronic lung disease likely affected these outcomes.

Our study was limited by its small sample size and retrospec-tive nature, which relied upon review of investigations ordered and timed as per the treating medical team, and a complete clinical picture at the time of deciding to treat with CEA (or not) was dif-ficult to ascertain. Nonetheless, it adds a single centre experience to a body of literature which is relatively scant. Inspite of its limi-tations, this study also highlights likely inconsistencies in diagnos-ing and treating SBBO adding to the overall challenge. This un-derscores the need to improve our diagnostic capabilities for this disease, such as via non-invasive hydrogen breath testing or other objective parameters, and for larger prospective studies in order to establish the efficacy of CEA as a successful adjunct to TPN in managing the complex paradigm of short bowel syndrome.

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