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# Anastomotic ulcers in short bowel syndrome: New suggestions from a multidisciplinary approach☆,☆☆

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ABSTRACT

*Background and aims:* Anastomotic ulceration (AU) is a rare potential life-threatening complication that may occur after intestinal resection. The diagnosis is often delayed after a long-lasting history of refractory anemia. The pathogenesis remains unknown and there are no established therapies. The aim of the study was to analyze the medical history of children with short bowel syndrome (SBS) who were experiencing AU.
*Methods:* Records of SBS children were retrospectively reviewed. Demographics, baseline characteristics, presentation, diagnosis and treatment of AU cases were analyzed.
*Results:* Eight out of 114 children with SBS were identified as having AU. Mean gestational age was 32.5 weeks. Underlying diseases were: 5 necrotising enterocolitis, 2 gastroschisis and 1 multiple intestinal atresia. The mean age at AU diagnosis was 6.5 years (diagnosis delay of 35 months). All but 2 patients had AU persistency after medical treatment. Endoscopic treatment (2 argon plasma coagulation; 1 platelet-rich fibrin instillation; 2 endoscopic hydrostatic dilations) was effective in 3 out of 5 children. Surgery was required in 3 patients.
*Conclusions:* Severe bowel ischemic injury, especially in preterm infant, could predispose to AU development. Medical treatment showed discouraging results. We firstly described that different endoscopic treatment could be attempted before resorting to further surgery.
*Level of Evidence:* IV.

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Short bowel syndrome (SBS) is the most common cause of intestinal failure in childhood. It is a malbsorptive condition following extensive surgical resection of the small bowel causing inability of the gastrointestinal tract to sustain nutrient and hydratation status requiring total or partial parenteral nutrition (PN), to maintain health and/or growth [1]. In the majority of cases, SBS originates during the neonatal period (80% of SBS patients) and its incidence varies from 0.02–0.1% among the all live births, to 0.7% among very low birth weight neonates [2–4]. The leading causes of SBS are necrotising enterocolitis (NEC), intestinal atresia, gastroschisis, and extensive intestinal aganglionosis [5]. Advances in neonatal intensive care, nutrition support and innovative surgical techniques coordinated in a multidisciplinary setting have improved the outcome of children affected by SBS [6,7]. Mortality rates falling from 20 to 40% to 10% in more recent studies [6,7]. Mortality and outcomes are historically linked to the length of residual bowel, the absence of the ileocecal valve, the inability to achieve enteral autonomy and complication related to long-term PN such as sepsis and chronic liver disease [5–8]. Anastomotic ulceration (AU) is a rare and potential life-threatening complication in patients affected by SBS, which may occur insidiously as a chronic anemia or as severe bleeding even after several years of intestinal resection and anastomosis [9,10].

Limited data have been published on AU and there are no definitive therapeutic indications for its management. Both medical and surgical therapeutic strategies have been attempted, but variable and often discouraging results were obtained [9–19].

We describe a series of children with neonatal SBS who have experienced AU. The aim of this case series was to critically analyze our experience in order to provide new possible steps toward understanding, diagnosis and treatment of this rare condition.

## 1. Patients and methods

Medical records of 114 children with SBS referred between 1995 and 2015 to the Intestinal Failure Rehabilitation Groups at Bambino Gesù

*Abbreviations:* APC, argon plasma coagulation; AU, anastomotic ulceration; EGF, epidermal growth factor; EHD, endoscopic hydrostatic dilations; ICV, ileocecal valve; LILT, longitudinal intestinal lengthening and tailoring; NEC, necrotising enterocolitis; PN, parenteral nutrition; PPI, proton pump; PRF, platelet-rich fibrin; pt, patient; SBS, short bowel syndrome; SIBO, small intestinal bacterial overgrowth; WCE, wireless capsule endoscopy.

☆ Case Series With no Comparison Group IV.

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Children's Hospital in Rome, Italy and to the Pediatric Department at Saint Luc Hospital, Université Catholique De Louvain in Brussels, Belgium were reviewed. The study was conducted under the approval of the institutional review board (IRB number 201503 × 003572) at the Bambino Gesù Children's Hospital of Rome.

Detailed data of patients (pts) with SBS experiencing AU were collected: demographics and baseline disease characteristics as well as clinical presentation, diagnosis, treatment of AU cases and their outcome were carefully analyzed.

Patients were defined as having SBS when intestinal failure resulted from surgical bowel resection leading to loss of intestinal length below the minimal amount necessary for the absorption of nutrients to maintain a normal nutritional status. Children included in our study underwent resection of ≥50% small bowel length according to age-adjusted reference value, or showed ≥60 days of PN dependence with history of intestinal resection.

All AU cases were detected endoscopically during the SBS children's workup for chronic or acute anemia. Endoscopic assessments were performed under deep sedation or general anesthesia according to the standard hospital procedures. Endoscopic equipment were: Olympus GIF Q165 or 160, PCF 160 or 180, SIF Q 140 (Olympus, Tokyo, Japan). Wireless Capsule Endoscopy (WCE; SB2 PillCam, Given Imaging, Yoqneam, Israel) and advance delivery capsule device (US Endoscopy, Mentor, Ohio, USA) were used according to the manufacturers' instructions.

In case of active AU bleeding a therapeutic endoscopy approach with argon plasma coagulation (APC; ERBE APC System, Marietta, Ga, USA) or autologous platelet-rich fibrin (PRF) instillation (Vivostat PRF®, Borupvang, Alleroed, Denmark) was used.

Endoscopic hydrostatic dilations (EHD; G-Flex, 12–15 mm, Atlanta, Ga, USA) were performed in presence of narrow stricture at the anastomotic site.

Surgery was reserved in case of medical and endoscopic treatment failure.

Positive outcomes were defined as a stable increase in hemoglobin levels with fecal occult blood disappearance and no further need of blood transfusions or iron replacement during the follow-up.

## 2. Results

Of 114 patients affected by SBS, 8 children (7%) were identified as having AU. Demographic and baseline disease characteristics are summarized in Table 1, while clinical presentation, diagnosis, treatment and outcome are detailed in Table 2.

### 2.1. Demographics and baseline disease characteristics

Five out of 8 children were male. Mean gestational age was 32.5 weeks (range 30–38 weeks) and median birth weight was 1988.7 g (range: 1500–3650 g). All but one patients were preterm (<37 weeks), two of them were very preterm (<32 weeks).

Causes leading to SBS were: five necrotizing enterocolitis (NEC; pts. 2, 3, 4, 5 and 8), two gastroschisis complicated by bowel ischemia (midgut volvulus of gastroschisis: pt. 1; vanishing gastroschisis: pt. 6) and one multiple intestinal atresia complicated by volvulus (pt 7). The median age at first resective surgery was 10.3 days of life (range 1–40 days). All anastomosis were end-to-end type and they were made by interrupted absorbable sutures (5 ileocolonic, 2 ileoileal and 1 colo-colonic). The mean residual intestinal length was 58.4 cm (range 27–120 cm). Ileocecal valve was preserved in 3 patients. Mean residual colon length was 87.5% (range 50%–100%).

Three patients underwent further surgical procedures because of severe bowel dilatation proximally to AU site: one underwent longitudinal intestinal lengthening and tapering (LILT) procedure (pt 6), one had simple tapering (pt 4), and the last one had partial resection (pt 3).

All patients required PN for a median time of 21.3 months (range: 2–51 months). At the time of the data collection, 2 patients were still on PN (pts 5 and 6).

### 2.2. Revealing symptoms and signs of AU

Clinical history of seven out of 8 children showed a chronic iron-deficiency anemia refractory to oral iron supplement. Four of them presented a chronic occult gastrointestinal bleeding revealed by a positive fecal occult blood test while the other 3 children experienced also a sentinel episode of acute gastrointestinal bleeding (1 melena, 2 rectal bleeding) leading to hemodynamic instability. One patient had a sudden onset life-threatening intestinal bleeding episode requiring emergency treatment. All patients received at least one blood transfusion (1 to 3).

The median age at AU diagnosis was 6.5 years (range 12 months–18 years). The median delay between symptoms onset and AU diagnosis was 35 months (range 2–156 months).

### 2.3. AU diagnosis

In all cases, AU was identified by endoscopy: 3 ileocolonoscopy (pts 2, 3 and 8) (Fig. 1), 3 deep enteroscopy (pts 4, 5 and 7), and 2 small bowel wireless capsule endoscopy (WCE; pts. 1 and 6) (Fig. 2). The mean number of endoscopic procedures was 4.3 (range 3–6).

Similar endoscopic appearance of AU was observed in all cases: single round or oval well-delineated lesion (1 to 3 cm) surrounded by healthy mucosa localized within a few centimeters from anastomotic site (Figs. 1 and 2). Histological evaluation from endoscopic biopsies (6 patients) and surgical specimens (3 patients) showed features of non-specific inflammation characterized by polymorphous lymphocytic infiltrate.

Tagged red blood cell scintigraphy was performed in 3 children with positive fecal occult blood test (pts 4, 5 and 8); only in one case (pt 5), the scan showed an abnormal focus of increasing activity in the right iliac region evocative of a gastrointestinal bleeding. Afterward, in this patient, a WCE confirmed AU diagnosis. In two of these patients (pts 4 and 8), selective angiography was also performed, but failed to localize any source of bleeding.

**Table 1**
Demographics and disease characteristics.

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Gestational age | 33 | 30 | 32 | 31 | 32 | 34 | 38 | 33 |
| Gender | M | F | M | F | M | M | M | F |
| Birth Weight (gr) | 1830 | 1600 | 2080 | 1500 | 1500 | 2150 | 3650 | 1600 |
| Underlying condition | Midgut volvulus of gastroschisis | NEC | NEC | NEC | NEC | Vanishing gastroschisis | Intestinal atresia | NEC |
| Age at surgery (days) | 1 | 10 | 18 | 9 | 40 | 1 | 2 | 2 |
| Anastomosis sites | I-C | C-C | I-C | I-C | I-I | I-C | I-C | I-I |
| Length of remnant bowel (cm) | 60 | 100 | 27 | 35 | 30 | 35 | 120 | 60 |
| Presence of ICV | No | Yes | No | No | Yes | No | No | Yes |
| Residual colon length (%) | 70% | 100% | 90% | 90% | 100% | 50% | 100% | 100% |
| Need for PN (months) | 22 | 14 | 51 | 12 | 18 (Still on PN) | 49 (Still on PN) | 2 | 5 |
| Further surgical procedures | / | / | resection | tapering | / | LILT | / | / |

C-C, colo–colic; I-C, ileocolic; I-I, ileoileal; ICV, ileocecal valve; LILT, longitudinal intestinal lengthening and tapering; NEC, necrotizing enterocolitis; PN parenteral nutrition.

**Table 2**
AU: clinical presentation, diagnosis, treatment and outcome.

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Clinical presentation | | | | | | | | |
| Main revealing symptoms/signs of AU | IDA, (FOBT +) | IDA, rectal bleeding | IDA, (FOBT +) | IDA, melena | rectal bleeding | IDA, (FOBT +) | IDA, rectal bleeding | IDA, (FOBT +) |
| Blood transfusions (nr) | 1 | 1 | 1 | 3 | 2 | 1 | 1 | 1 |
| Age at AU symptoms/signs onset (years) | 6.3 | 1.2 | 10.6 | 0.3 | 0.7 | 1 | 5 | 6.3 |
| Age at AU diagnosis (years) | 8.7 | 1.4 | 11 | 2.4 | 1 | 1.5 | 18 | 8 |
| Delay from symptom onset to AU diagnosis (months) | 57 | 2 | 9 | 27 | 3 | 6 | 156 | 20 |
| Diagnosis | | | | | | | | |
| Endoscopic procedures (nr) | | | | | | | | |
| Total | 6 | 6 | 6 | 4 | 4 | 3 | 3 | 3 |
| Upper GI endoscopy | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 1 |
| Ileocolonoscopy | / | 3* | 4* | 1 | 1 | 1 | / | 1* |
| Deep enteroscopy | 1 | / | / | 2* | 2* | / | 2* | / |
| WCE | 2* | / | / | / | / | 1* | / | 1 |
| Endoscopic finding of AU | | | | | | | | |
| Active bleeding | No | Yes | Yes | No | No | No | No | Yes |
| Stricture | No | No | No | Yes | Yes | No | No | No |
| Tagged RBC scintigraphy | / | / | / | Negative | Positive | / | / | Negative |
| Selective angiography | / | / | / | Negative | / | / | / | Negative |
| Treatment | | | | | | | | |
| Medical treatment[a] | | | | | | | | |
| PPIs | 0 → | 0 → | 0 → | 0 → | 0 → | 0 → | 0 → | 0 → |
| Antibiotics | 0 → | 0 → | 1 → | 0, 1→ | 0 → | 1,2 | 0, 1 → | 1, 2 |
| Cholestyramine | 0 → | / | / | / | / | / | / | 0 |
| Budesonide | 1 → | / | / | / | 1 → | / | 1 → | 1,2 |
| Mesalamine | / | / | 1 | / | / | 1 | / | / |
| Endoscopic treatment | | | | | | | | |
| EHD | / | / | / | **X** | **X** | / | / | / |
| APC | / | **X** | / | / | / | / | / | **X** (failed) |
| PRF instillation | / | / | **X** | / | / | / | / | / |
| Surgical treatment | / | / | / | resection | / | resection | / | resection |
| Outcomes | | | | | | | | |
| Age at last evaluation (years) | 11.2 | 2.6 | 12.4 | 5 | 1.6 | 5.6 | 20.5 | 19.2 |
| Follow-up (years) | 3.5 | 1.2 | 1.4 | 2.6 | 0.6 | 4.1 | 2.5 | 11.2 |
| Last hemoglobin level (gr/dl) | 13.7 | 10.6 | 9.6 | 12.2 | 10 | 9.8 | 11.8 | 12.6 |

APC, argon plasma coagulation; AU, anastomotic ulceration; EHD, endoscopic hydrostatic dilations; FOBT, fecal occult blood test; IDA, iron deficiency anemia; PPIs, proton pump inhibitors; PRF, platelet-rich fibrin; RBC, red blood cell: WCE, wireless capsule endoscopy.

* Endoscopic procedure that led to AU identification.

[a] The numbers indicate the sequence in which the treatments were administered (0, therapy ongoing before the diagnosis; 1, treatment started after the diagnosis →, repeated treatment cycles).

### 2.4. AU treatment

All patients were on proton pump inhibitor (PPI) therapy before AU diagnosis and received empirical cycle of antibiotic therapy (metronidazole and/or nebicine, and/or fluconazole) either before or after AU diagnosis. Anti-inflammatory agents have been administered in 6 patients; four received budesonide (pts 1, 5, 7 and 8) while 2 had mesalamine (pts 3 and 6). Two patients received also cholestyramine (pts 1 and 8).

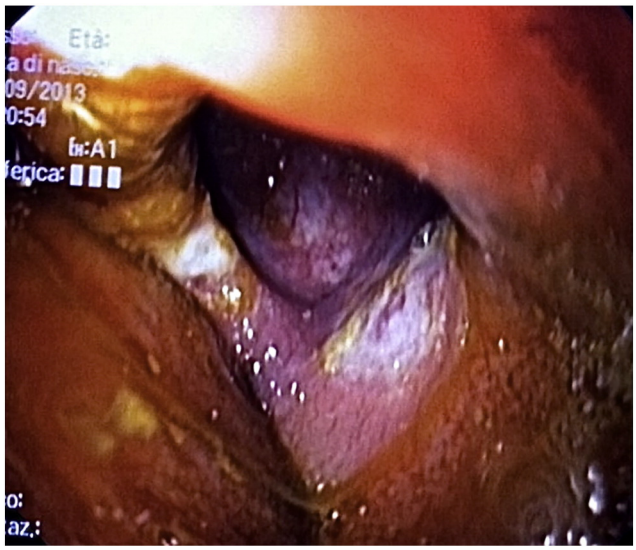


**Fig. 1.** Endoscopic appearance of ileocolonic anastomotic ulcer.

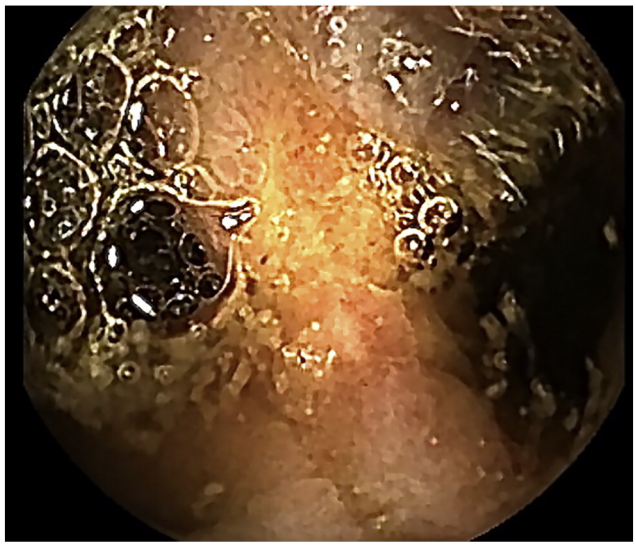

**Fig. 2.** Ileoileal anastomotic ulcer detected by wireless capsule endoscopy.

A favorable long-term clinical response to medical therapy was observed in 2 patients (pts 1 and 7).

Two patients with active acute bleeding underwent APC treatment (pts 2 and 8) that was effective in one (pt 8).

One patient underwent PRF instillation (pt 3) and long-term remission was achieved.

A stricture associated to AU was observed in two children (pt 4 and 5). All patients were treated by EHD. In one (pt 5) after dilation, five cycles of budesonide was administered, and a long-term remission was observed.

Overall, endoscopic treatment was performed in 5 patients and has been effective in 3 of them (60%).

Three patients unresponsive to medical and/or endoscopic treatment required surgery (37,5%). In one (pt 6), after failure of medical treatment, surgery was the only therapeutic alternative because the altered bowel anatomy related to prior surgery (LILT) did not allow performing operative endoscopy. The remaining two patients underwent surgical resection of the anastomotic site because of bleeding recurrence after both medical and endoscopic treatment (APC pt. 8; EHD pt. 4).

All patients were free of symptoms at a mean follow-up of 3.3 years (range 0.6–11.2); their last hemoglobin determination revealed a mean value of 11.2 g/dl (range 9.6–13.7).

## 3. Discussion

Patients undergoing bowel resection, notably those affected by SBS, are at risk of developing AU, a rare, often unrecognized and sometimes life-threatening complication that may also appear several years after surgery. Over the last two decades, several descriptions have been reported in children with SBS, but AU incidence and etiology remain unclear, the diagnosis is generally delayed and no relevant amelioration in medical or surgical management has been acquired [9–19].

Few and small case series in both adults and children reported that AU incidence varies from 0.3 to 8% [17,20]. In our cohort of 114 SBS children, we found an incidence of 7% of AU.

As already pointed out by previous authors [9–19], the diagnosis of AU is often delayed. In our series we observed a mean delay of 35 months. The reasons behind this might arise from two factors: first, the history of iron deficiency anemia secondary to AU occult bleeding is generally misattributed to an iron malabsorption that is common in SBS children; second, the standard endoscopic procedures may be ineffective to detect an uncommon source of gastronintestinal bleeding [17,19]. Thus, in SBS children with a history of iron deficiency anemia and negative upper and lower endoscopy it is advisable to look for AU as cause of gastrointestinal occult blood loss and the endoscopic diagnostic work-up should be extended to small bowel assessment (WCE and deep enteroscopy).

Recently, Charbit-Henrion et al. published the largest pediatric case series on this topic and failed to find any correlation between the development of AU and potential risk factors such as the underlying disease, the length of remnant bowel and the ICV preservation [17].

In our case series all children have experienced a severe bowel ischemic injuries: 5 pan-enteric NEC, 2 gastroschisis complicated by massive bowel ischemia (midgut volvulus and vanishing gastroschisis), and 1 multiple intestinal atresia complicated by volvulus. This observation, in opposition to the study of Charbit-Henrion et al. [17] but in accordance with other reports [9,12], may suggest a possible role of the massive ischemic damage in promoting AU development.

NEC is the leading cause of SBS in infants and its outcome is variable [21–23]. Although the exact etiology of NEC onset remains uncertain, it has been demonstrated that ischemia has a primary role in its pathogenesis. Severe ischemic injuries may result in a massive transmural necrosis with complete loss of epithelial and muscular architecture [24,25]. Newborns presenting Bell's stage III pan-enteric NEC requires multiple staged surgical interventions aiming to remove gangrenous bowel and to preserve as much bowel length as possible. However, because of pan enteric extension of ischemic injury, the preserved residual bowel may not be fully healthy [26]. This key concept could be translated to other cases of severe bowel ischemic injuries such as volvulus and vanishing gastroschisis. Anastomoses of bowel segments with questionable blood supply may result in impaired tissue healing that in turn may lead to complications such as leakages, strictures or ulcers. Although there are no conclusive evidence and conflicting results arise from previous studies, examining our series, it appears that severe ischemic injuries could be a risk factor for AU development in SBS patients.

The length of the remnant bowel and the presence of ICV have been classically advocated as a possible predisposing factor for AU development [17]. Infants with very short bowel length are those who have experienced a severe ischemic damage; therefore we can draw on the previous discussion. Despite a slight prevalence of very SBS children and patients without ICV, our findings along with others [10,17] do not suggest that shorter length bowel and absence of ICV should be definitively considered as risk factors for AU development.

Examining our series, a further possible risk factor could be identified: all patients but one were preterm and very preterm newborn (<32 weeks). It is conceivable that, as described in animal models, the age-related immature physiological state might result in an unfavorable local intestinal immunologic, microbial and metabolic environment that may influence negatively the repair process leading to a poor quality of scar tissue of intestinal anastomosis predisposing to stricture or mucosal inflammatory injury and possibly AU development [14,27–29].

Regardless of these fascinating speculations, to date the AU pathogenesis is largely unknown and is probably multifactorial. Consequently, no targeted therapy is available and different empirical treatments have been proposed according to hypothetical underlying pathophysiologic mechanisms. Gastric acid hypersecretion, bile acid malabsorption and small intestinal bacterial overgrowth (SIBO) following extended small bowel resection including the ICV have been advocated as possible causes of the AU development. Antisecretory agents, as histamine-2 receptor antagonists (ranitidine) and proton pump inhibitors (PPIs), and bile acid sequestrants (cholestyramine) have been described without clear evidence of efficacy [10–17]. Our study is in accord with the non-protective role of these agents because all children received PPIs and 2 had also cholestyramine before AU diagnosis [17].

It has been widely reported that SIBO occurs commonly in children with SBS because of the altered bowel anatomy that may lead to intestinal dilation and associated motility alteration, which in turn promote stasis and bacterial overgrowth [30,31]. SIBO usually responds to antibiotics treatment [32]. It has been speculated that SIBO promoting local inflammation could participate to AU development and almost all patients described in previous reports received empirical antibiotics therapies [10,14,15,17]. In our series, all children received antibiotics either before or after AU diagnosis without clear effectiveness on AU. This observation do not allow to establish a clear causal link between SIBO and AU, it is likely that the condition of bacterial overgrowth may contribute to other factors to the AU occurrence and then a cyclic antibiotic therapy could be administered according to clinical need.

Following the observation that all histologic specimens showed nonspecific polymorphous inflammatory infiltrate at AU level, several anti-inflammatory agents have been proposed [9,14,17]. In our series, 6 children received anti-inflammatory agents (budesonide or mesalamine) and 2 of them (pts 1 and 7) achieved stable clinical and endoscopic remission after cycles of budesonide treatment combined with metronidazole. Therefore, we cannot draw definitive conclusion about the role of these agents in treating AU, however based on our experience, we can suggest that a trial with anti-inflammatory agents should be tested prior to consider the invasive treatments.

At our knowledge this is the first pediatric series where the role of endoscopic treatment of AU is analyzed.

All children experiencing ischemic intestinal injury and notably those surviving of the acute phase of NEC may develop an intestinal

stricture secondary to an impaired healing process [33,34]. Bowel strictures can lead to severe and prolonged morbidity in infants because of intestinal obstruction, septicemia, and/or perforation. The risk to develop intestinal strictures is increased at the level of the intestinal anastomosis. Indeed, as previously stated, surgical strategies aimed at preserving bowel length might increase the probability to leave poor vascularized tissues at the end of the preserved intestinal segments leading to fibrotic scarring and stricture development. Bowel dilation, stasis, bacterial overgrowth and local inflammation secondary to anastomotic stricture may promote AU development and reoccurrences. Traditionally, stricture management requires a surgical resection [33] but in order to avoid further sacrifice of the residual bowel length in SBS condition, endoscopic hydrostatic dilation (EHD) should be considered. This technique has been widely described as a successful alternative in the management of intestinal strictures secondary to several conditions such as Crohn's disease and SBS [34,35]. In our series, a narrow anastomosis surrounded by ulcers was detected in 2 patients with SBS secondary to NEC; both of them have been firstly treated by EHD with relief of the obstruction. In one case, following dilation, both antibiotics and budesonide were administered and long-term remission was achieved. In the second case, after the attempt of EHD, because of stricture recurrence, persistent anemia and hemodynamic instability an anastomotic surgical resection was performed.

An alternative endoscopic approach with argon plasma coagulation (APC), was used in two children (pts 2 and 8). APC is the best technique for hemostasis of intestinal superficial diffuse vascular lesions [36]. One patient (pt 2) achieved a long-term remission; the second (pt 8) underwent surgery because of bleeding recurrence after APC and several attempts of medical treatment.

The age-related immaturity of the intestinal repair process has been considered for purposes of facilitating innovative treatment of AU [14]. Ulceration of the intestinal mucosa induces into the crypt close to the ulcers the development of a novel cell lineage from stem cells. This "ulcer-associated cell lineage" secretes epidermal growth factor (EGF) that plays an important role in intestinal cell proliferation promoting ulcer healing [37]. It has been speculated that, newborns that experienced a massive bowel resection, may have a defective development of this cells with decreased production of EGF. To support this hypothesis, further studies have demonstrated that in SBS administration of EGF can promote intestinal adaptation [38] while drugs such octreotide, used to control secretory diarrhea in SBS, may inhibit this process by suppression of the EGF production [39]. Following this hypothesis, we have supposed that the topical administration of autologous platelet-rich fibrin (PRF) as a source of growth factors might have a role in managing the healing process of the AU. PRF is derived from autologous blood with a high platelet concentration in a small volume of plasma. Although, its mechanism is poorly understood, it seems that the delivery of growth factors in high concentrations to the injury site could enhance tissue recovery. PRF contains intra and extra-platelet components, other than several growth factors that could contribute to the regeneration of tissue. Despite that the studies aimed to evaluate its efficacy are not conclusive, the application of PRF in different tissues has given favorable results in several conditions, such as orthopedics, ophthalmology and healing therapies [40–42]. In gastroenterology, promising results have been found in the treatment of perianal fistulas [43,44]. Based on this hypothesis, we have utilized PRF in one patient (pt 3) with hemorrhage observing prompt resolution of bleeding and long-term remission.

In our series, surgery was required in three out of eight patients (37.5%). One underwent to surgical re-do (pt 6), after failure of several attempts of medical treatment, and because of the impossibility to reach endoscopically the AU site because of the bowel torsion secondary to surgical lengthening procedure (LILT). In the other two (pts 4 and 8), surgery was performed after failure of both medical and endoscopic treatment.

## 4. Conclusions

In summary, it is difficult to draw any definitive conclusion from our small series, however the critical analysis of our results may give some new suggestions in the management of SBS patients with AU.

First, AU should be kept in mind as cause of chronic or acute anemia in children with a history of massive intestinal resection. Although, the etiopathogenesis of AU is still poorly understood and is most likely multifactorial, the observation of our population allows to identify some possible risk factors. Severe ischemic injury of the bowel, especially if experienced by preterm infant, might be considered a predictive factor for AU development. Environmental factors such as SIBO, local inflammation and age-related immaturity of the repair process may act synergistically amplifying unknown pathogenic mechanisms. In our experience medical treatment has been effective in controlling AU bleeding in two cases that were showing a quite long-term remission (3.5 and 2.5 years) upon receiving cyclical course of both antibiotics and budesonide.

The main addition, in terms of treatment, coming from our experience has been the use of the endoscopy as a therapeutic tool that has never been described in AU management. The environmental conditions above-mentioned could be exacerbate in case of anastomotic stricture, then all children with AU should be investigated for its possible presence. We display that stricture resolution through EHD procedure in association with medical treatment may result in long-term AU remission. Moreover, we successfully achieved a bleeding control by the endoscopic application of APC and by the topical administration of autologous PRF, a new innovative and promising therapeutic option. In experienced hands, the endoscopy is an essential diagnostic tool and it represents an important therapeutic option in SBS patients where the preservation of bowel length is critical in determining the outcome. In a referral center for intestinal failure patients, a combined medical–endoscopic–surgical management represents the suggested approach for SBS patients with AU. Larger multicentric series with longer follow-up are still needed to better define the roles of each therapeutic option and define the best algorithm to manage SBS children experiencing AU.

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