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Management of small bowel angioectasias diagnosed during video capsule endoscopy

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Abstract

Small bowel angioectasias (SBA) are vascular malformations consisting of thin-walled, dilated capillaries located in the gastrointestinal mucosa. They are responsible for 10% of all causes of gastrointestinal bleeding and 60% of small bowel bleeding pathologies. The diagnosis and management of SBA depend upon bleeding acuity, patient stability and patient characteristics. Small bowel capsule endoscopy is a relatively noninvasive diagnostic approach ideal for non-obstructed and hemodynamically stable patients. It is superior to computed tomography scans in visualizing mucosal lesions, such as angioectasias, as it provides mucosal views. Management of these lesions will depend on the patient's clinical condition and associated comorbidities, and very often consists of medical and/or endoscopic treatment delivered through small bowel enteroscopy.

Keywords Small bowel capsule endoscopy, enteroscopy, angioectasias

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Introduction

Small bowel angioectasias (SBAs) are vascular malformations consisting of thin-walled, dilated capillaries located in the gastrointestinal mucosa. Their thin or absent smooth muscle layer explains their tendency to bleed, which makes them the causative agent for 10% of all gastrointestinal bleeding sources and 60% of small bowel bleeding sources [1] (Fig. 1A). The development of SBAs is likely to be secondary to increased vascular endothelial growth factor (VEGF) expression, which, in turn, is affected by cytokines, growth factors, hormones, and hypoxic states [2].

The Yano-Yamamoto classification for bleeding lesions detected during small bowel enteroscopy classifies SBAs into those smaller than 1 mm, viewed endoscopically as punctuate erythema (type 1a), and those larger than 1 mm with patchy erythema (type 1b). Type 1a and 1b lesions may be oozing or non-oozing [3] (Fig. 1B, 2). The Saurin classification divides lesions visualized on small bowel capsule endoscopy (SBCE) into P0, P1 and P2, ranging from no bleeding potential to high bleeding potential, as summarized in Table 1.

SBAs are mostly located in the proximal small bowel [4] and are often multifocal [5]. Patient characteristics such as advanced age [6] and western origins [7] increase the likelihood of SBA. Medical conditions such as aortic stenosis also increase the tendency to have SBA. The combination of aortic stenosis with SBA is known as Heyde's syndrome [8]. Bleeding from SBAs carries a mortality rate of up to 3.5% [9]. Bleeding from SBAs may manifest clinically as melena, or present with symptoms of anemia, including chest pain, shortness of breath and fatigue. Fig. 3 depicts altered blood on SBCE.

The approach to small bowel gastrointestinal bleeding depends on the acuity of the blood loss as well as patient characteristics. The American College of Gastroenterology recommends SBCE as the first-line investigation for small bowel assessment in non-obstructed, stable patients after endoscopy of the upper and lower gastrointestinal tract to identify the bleeding source [10]. SBCE was approved by the Food and Drug Administration in 2001, yet its history dates to 1981, when Gavriel Iddan identified a deficiency in endoscopic bowel assessment, as the small bowel is not visualized. Through extensive funding and liaison with engineers and physicists, a wireless capsule endoscope was devised and its images were first pooled at a congress in 2002 [11].

SBCE is noninvasive, has few contraindications and a diagnostic yield of up to 78% [12]. This yield is superior to that

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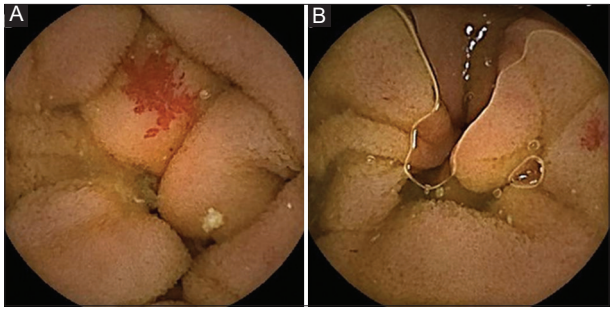

Figure 1 (A) Small bowel angioectasia. (B) Small bowel angioectasia, type 1B without oozing

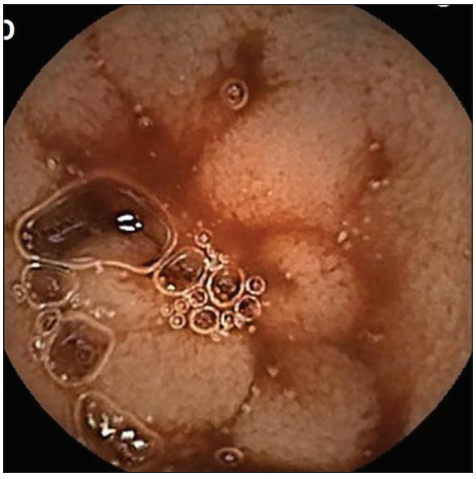

Figure 2 Fresh blood from oozing angioectasias

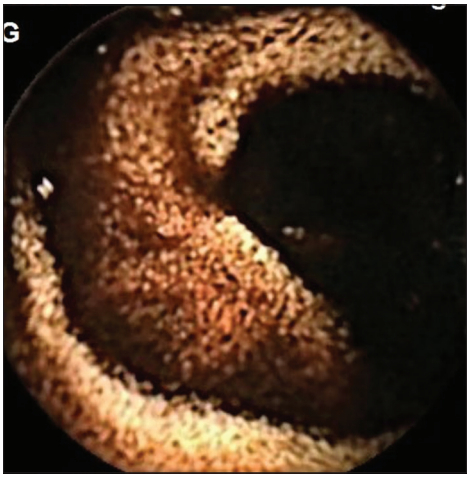

Figure 3 Altered blood on small-bowel capsule endoscopy

of computed tomography (CT) enterography for small bowel bleeding and mucosal lesions [13] as, unlike CT, it provides mucosal views. Factors associated with a higher yield of SBCE are hemoglobin <10 g/dL, duration of bleeding >6 months, more than one episode of bleeding, overt bleeding with SBCE performed within 72 h of the bleed, age above 60 years, male sex, and renal or hepatic impairment [14-20]. Complete visualization can be augmented with real-time viewing and larger battery capacity [21]. Increased detection rates may occur when technology such as flexible spectral imaging color enhancement is used [22].

Table 1 The Saurin classification of small bowel lesions

Lesion type	Bleeding potential	Example
P0	None	Visible submucosal veins diverticula without the presence of blood nodules without mucosal break
P1	Uncertain	Red spots on the intestinal mucosa small or isolated erosions
P2	High	Typical angiomas Large ulcerations Tumors Varices

The management of SBAs diagnosed on SBCE follows the same approach, as treatment modality will depend on the patient profile, comorbidities, frequency of blood loss and fitness for intervention. Thus, management varies and depends on the patient's characteristics. Fig. 4 is a management algorithm for lesions identified on SBCE. Management is also executed keeping in mind the adverse effects of different modalities, as well as their failure rates. Rebleeding is one of the main complications of SBAs, regardless of the treatment modality used [23,24], and heart failure, smoking status and angioectasias >5 mm are amongst the independent factors that increase the rebleeding risk [25]. The latter is outlined in Table 2, which displays data from the available literature for rebleeding rates following treatment of SBAs diagnosed on SBCE. The RHEMITT score anticipates the individual risk of small bowel rebleeding after SBCE and may therefore be utilized by physicians to direct therapy [26].

Conservative management

A universal approach in a stable patient is to transfuse and consider iron replacement in oral or intravenous form prior to more permanent measures. Contributing factors to SBAs, such as medical comorbidities and medications, must be dealt with or optimized. These measures may include aortic valve replacement or transcatheter aortic valve implantation [27], optimization of renal or hepatic function, transfusion of packed red calls, and discontinuation of anticoagulant therapy. These measures are especially crucial in patients who are elderly, have multiple comorbidities with a high Charlson comorbidity score, or are not eligible for the invasive management described below. If the conservative approach does not suffice, and the patient is eligible for invasive measures, one may then proceed to invasive therapy.

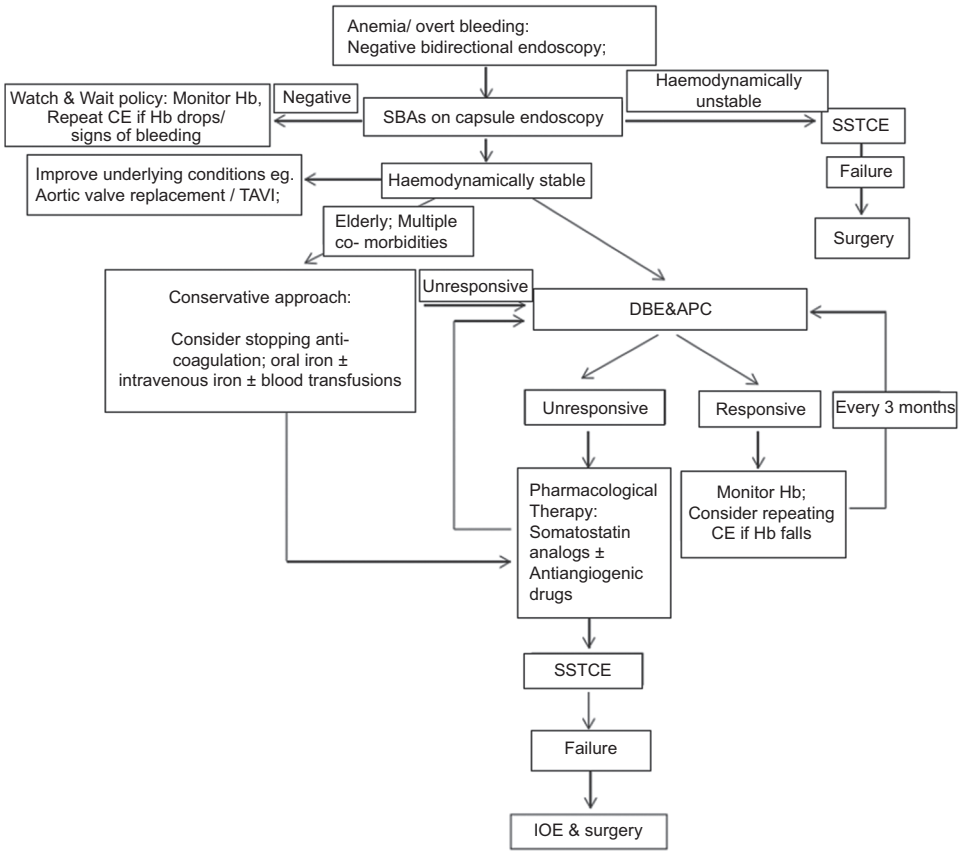

Figure 4 Management of SBAs diagnosed on capsule endoscopy
SBAs, small bowel angioectasias; APC, argon plasma coagulation; Hb, hemoglobin; CE, capsule endoscopy; Hb, haemoglobin; SSTCE, super selective transcatheter embolization; DBE, double balloon enteroscopy; IOE, intraoperative enteroscopy; TAVI, transcatheter aortic valve implantation

Invasive management

Endoscopic therapy

Device-assisted enteroscopy (DAE) has a therapeutic role in the management of SBAs. DAE allows a larger length of small bowel to be examined compared to push enteroscopy, because of the anchorage provided by the balloon [28]. However, push enteroscopy has an overall better tolerability and may be considered in patients with proximal SBAs who may not be ideal candidates for deeper sedation. Double-balloon enteroscopy (DBE) and single-balloon enteroscopy have similar diagnostic and therapeutic yields, as well as complication rates, but DBE provides better anchorage [28]. In addition to better anchorage, small bowel visualization is more complete using DBE. Although the latter observation achieved statistical significance, its clinical significance remains controversial [29]. Another technique that does not use a balloon system is spiral enteroscopy, which employs a rotatory technique [30]. Complications of enteroscopy include perforation, acute pancreatitis, bleeding and aspiration pneumonia. Complication rates vary between different centers, with perforation being the commonest complication (0.4%) in a US-based study, whilst pancreatitis was the most reported complication (0.34%) in a German study [31,32]. The complication rate has been described more frequently in therapeutic DBE compared with diagnostic DBE, yet in both it amounts to less than 5% [33]. There are also reports that it is very safe in elderly patients [34]. Patients with SBA are very often elderly with multiple comorbidities.

Argon plasma coagulation (APC) is the most used and thus the most studied endoscopic treatment modality in relation to SBAs [34]. It has very few side-effects, and initial research reported a positive outcome in terms of transfusion requirements and hemoglobin levels. However, a systematic review demonstrated a 42.7% rebleeding rate following endoscopic therapy, only slightly less than the 49.2% rebleeding rate in patients who did not receive any therapy at all. This percentage increases with time, as rebleeding rates of 63% have been reported at 5 years post-endoscopic therapy.

The risk of rebleeding is higher in patients with certain characteristics, such as a history of blood transfusion, several angioectasias, medical conditions such as chronic kidney disease and valvular heart disease, and anticoagulant use [35]. Patients with left-ventricular assist devices may experience small bowel bleeding rates of up to 31%, and although DAE

Table 2 Rebleeding rates following treatment of SBAs diagnosed on SBCE

Study [ref.], year	Type of study	No. of patients with SBAs	Treatment modality	Primary Aim/Definition of Re-bleeding	Follow up/ months	Outcome
Endoscopic						
Saurin *et al* [37], 2004	Retrospective analysis of previous prospective study	7	APC	Rebleeding defined as presence of persistent anemia, transfusion requirement, or oral iron requirement	12 (mean)	No rebleeding
Lai *et al* [56], 2006	Retrospective	12	Laparotomy and push enteroscopy – treatment not defined	Not defined	19 (median)	7 (58.3%)
Fujimori *et al* [38], 2007	Prospective	6	APC and clipping	Not defined	12 (minimum)	1 patient experienced rebleeding 70 days after treatment
May *et al* [39], 2007	Retrospective cohort	50	44 patients treated with APC	Not defined	55	Not all 50 diagnosed on SBCE. Re-bleeding in 21 patients (42%)
Gerson *et al* [40], 2009	Prospective cohort	40	APC	Not defined	12 (mean)	17 (43%) reported no recurrence of bleeding or need for iron/transfusion therapy, 11 (28%) reported recurrent overt bleeding, and 12 (30%) reported ongoing need for iron or transfusion therapy during the mean follow-up period
May *et al* [41], 2011	Prospective	63	APC	Melena, hematochezia, or a decrease in the hemoglobin level in occult bleeding of more than 1 g/dL	55 (mean)	blood transfusions were administered in only 8 of the 50 patients (16%), whereas transfusions had been necessary in 30 of the patients (60%) before APC
Samaha *et al* [48], 2012	Prospective	112	APC in the majority, clipping in 2 patients, other hemostatic techniques in 3 patients	Not defined	22.6 (median)	Rebleeding rate was 46% (45/98 patients) at 36 months
Rahmi *et al* [42], 2014	Prospective	183	APC	The need for red blood cell transfusion, the presence of overt digestive bleeding (melena, hematemesis, or hematochezia), or a decrease in the hemoglobin concentration of more than 2 g/dL, after exclusion of all other causes of anemia	12 (total)	35% recurrence, 65% no recurrence
Bizid *et al* [43], 2015	Retrospective observational	69	APC	Not defined	12.3 (mean)	Recurrence of bleeding -33.3% of patients after a mean time of 12.3 months

(Contd...)

Table 2 *(Continued)*

Study [ref.], year	Type of study	No. of patients with SBAs	Treatment modality	Primary Aim/Definition of Re-bleeding	Follow up/ months	Outcome
Igawa *et al* [50], 2015	Retrospective	64	11 type 1a: No intervention, 24 type 1a and 17 type 1b: PDI, 12 type 1b: PDI+APC/ clipping	Recurrent visible gastrointestinal bleeding (melena or hematochezia) with recent negative upper and lower gastrointestinal endoscopies and/or a subsequent decrease in the hemoglobin level by >2 g/dL from baseline	12 (total)	Diagnosed on SBCE or DBE. Type 1a: rebleeding in 2 cases (1 treated conservatively), mean time 23 days, bleeding occurred from lesions other than those treated. Type 1b: Re-bleeding in 5 cases (17%), 4 treated with PDI, and 1 who had been initially treated with PDI combined with APC, mean time 123 days
Pinho *et al* [44], 2016	Retrospective single-center series	26	APC	Need for blood transfusion, or the presence of overt bleeding (melena, hematemesis, or hematochezia), or a decrease in hemoglobin >2 g/dL, after exclusion of all other causes of anemia	23 (median)	More than half of the patients had rebleeding after 5 years of follow up, although transfusion requirements decreased. Patients with high-risk comorbidities are more likely to rebleed
Igawa *et al* [51], 2016	Prospective	12	PDI	Evidence of recurrent visible GI bleeding (melena or hematochezia) on recent negative upper and lower GI endoscopies and/or a subsequent decrease in hemoglobin level>2 g/dL from baseline	65 (median)	1 patient experienced rebleeding (9%, diameter=10 mm) 7 days after the first PDI and was managed endoscopically with additional PDI. The final hemostasis rate was 100% (12/12), and the adverse event rate related to PDI was 0% (0/12).
Seong Ran Jeon *et al* [45], 2017	Retrospective multicenter study	66	Endoscopic therapy (APC in 87.2%)	Evidence of bleeding at least 30 days after BAE	24.5 (mean)	45 treated, 21 not treated. ET and non-ET groups had rebleeding rates of 15.6% and 38.1% respectively (P=0.059)
Ana Ponte *et al* [46], 2018	Retrospective double-center study	37	Second endoscopic therapy (APC monotherapy in 81.1%, or APC combined with clips or adrenaline in 18.9%)	Need for a blood transfusion, the presence of overt bleeding or a decrease in hemoglobin ≥2 g/dL	44 (maximum)	Fifteen patients (40.5%) of the 37 patients who underwent a second endoscopic therapy experienced rebleeding
Al-Bawardy *et al* [47], 2018	Retrospective	4	APC	Recurrence of overt bleeding after initial BAE or after small bowel diagnostic imaging	28 (median)	40% of patients with left ventricular assisted device with small bowel bleeding (of different etiologies) managed with device-assisted enteroscopy re-bled
Lio *et al* [52], 2022	Retrospective cohort study of systemic sclerosis patients	65	PDI	When bleeding observed again from the treated lesions	6 (maximum)	No post-treatment rebleeding

(Contd...)

Table 2 *(Continued)*

Study [ref.], year	Type of study	No. of patients with SBAs	Treatment modality	Primary Aim/Definition of Re-bleeding	Follow up/ months	Outcome
Somatostatin Analogs						
Scaglione *et al* [63], 2007	Prospective	13	Octreotide	primary endpoint: presence of hemoglobin values>12 g⁄dL with repeated negative fecal occult blood test at 1 year in the absence of any blood transfusions. Rebleeding not defined.	33 (mean)	9 of 13 patients (69%) had their hemoglobin levels normalized, and did not need blood transfusions and iron supplementation, partial response in 1 patient, no response in 3 patients
Molina Infante *et al* [64], 2009	Prospective	11	Octreotide-LAR	Not defined	15 (median)	2 patients remained transfusion-free, however, octreotide reduced transfusion requirements [14 (9-49) vs. 4 (0-9), *P*=0.002] and hospital admissions related to gastrointestinal bleeding
Riccioni *et al* [65], 2010	Retrospective cohort	51	60 mg IM lanreotide-frequency and duration not stated	Not defined	12 (mean)	In 15 of 46 patients with angioectasias IDA spontaneously resolved without any treatment. 10 patients healed after lanreotide administration
Bon *et al* [66], 2012	Prospective	10	Octreotide in APC-refractory SBA	Not defined	14 (median)	Complete lack of response (hemoglobin drop and transfusion requirement) in 1 patient. Significant drop in pooled number of blood units required and frequency of transfusion
Nardone *et al* [67], 2014	Prospective	86	Octreotide	Overt blood loss from the gastrointestinal tract; loss of at least 2 g/dL of hemoglobin without any other identifiable cause; ferritin concentration below 12 mg/L	78 (mean)	30 patients fully responded, 30 patients relapsed and 26 patients did not respond
Chetcuti Zammit *et al* [68], 2017	Retrospective cohort	12	SC lanreotide given at 60 mg, 90 mg, 120 mg at 4-6 weeks for 19 months in patients treated with APC	Not defined	42	Improvement in mean hemoglobin, bleeding episodes and packed red cells. Patient required less DBE and APC (P=0.048)
Del Cueto-Aguilera *et al* [62], 2022	Prospective randomized study	52	Octreotide 100 µg/24 h SC, for at least 6 months	Decrease of hemoglobin >2 g/dL compared with the baseline values; visible blood in stools; blood transfusion requirement (serum hemoglobin levels <8 g/dL); and iron parenteral requirement (when hematocrit was <25%)	12.9 (mean)	36 not treated, 16 treated. 4 (25%) treatment group patients and 26 (72.2%) non-treatment group patients presented with rebleeding (P=0.002)

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Table 2 *(Continued)*

Study [ref.], year	Type of study	No. of patients with SBAs	Treatment modality	Primary Aim/Definition of Re-bleeding	Follow up/ months	Outcome
Immuno-modulation						
Bauditz *et al* [71], 2004	Retrospective	3	Thalidomide	Not defined	33 (mean)	Hemoglobin reached normal levels without further transfusions and remained stable during a mean follow up of 34 months
Ge *et al* [72], 2011	Prospective	48	Thalidomide	Not defined	39 (median)	4-month interval bleeding episodes progressively decreased from 4.90 +/- 0.62 to 2.30 +/- 0.45 after treatment until month 8, and then remained low afterward in the thalidomide group
Multiple modalities						
Endo *et al* [23], 2008	Retrospective	13	4 patients treated endoscopically, 2 surgically, 1 medically and 6 not treated	Visible passage of blood or positive fecal occult blood testing with a drop in hemoglobin after the CE examination	11.6 (median)	2/4 patients treated endoscopically re-bled, 2/6 patients not treated re-bled, no rebleeding in those with surgical and medical management
Tan *et al* [24], 2015	Retrospective	92	Thalidomide, embolization or endoscopic treatment	Not defined	48 (median)	Re-bleeding rate was 52 (56.5%)

SBAs, small bowel angioectasias; APC, argon plasma coagulation; SBCE, small bowel capsule endoscopy; PDI, polidocanol injection; SC, subcutaneous; DBE, double balloon enteroscopy; IDA, iron deficiency anemia; LAR, long acting; IM, intramuscular; BAE, balloon-assisted enteroscopy

is safe in this cohort of patients, it has a moderate therapeutic yield of around 64% and does not improve long-term clinical outcomes such as rebleeding rates and mortality compared to conservative treatment [36]. Further studies portraying rebleeding rates of SBAs diagnosed on SBCE and treated with APC are listed in Table 2 below. [37-47].

Other less used endoscopic techniques for angioectasias are hemostatic clips and polidocanol solution [48]. Clips have mostly been described in gastric and colonic angioectasias. In the small bowel, clips, with or without epinephrine injection, were used in managing Dieulafoy's, lesions [49]. Polidocanol (PDI) is a fatty acid-derived sclerosant used by Igawa *et al* for the treatment of SBAs in 64 patients, either on its own or in combination with APC or endoclips [50]. It was more effective in combination with APC in terms of rebleeding rates; 4 of 5 patients who re-bled (17% of cohort) had been treated with PDI alone [51]. A study conducted last year involving systemic sclerosis patients reported no rebleeding in SBAs managed with PDI [52]. The literature regarding sclerotherapy is limited, and there are no studies focusing on Hemospray and radiofrequency ablation in the context of SBAs.

Some challenges with DAE remain, including the requirement for deep sedation to improve tolerability of such long procedures and the fitness for these patients for anesthesia. Moreover, there is a need to repeat these procedures due to the recurrent formation of SBAs and the persistent comorbidities that predispose to their formation. There is a paucity of data regarding the time interval between repeat procedures, as well as the number of procedures required to prevent any further drops in hemoglobin.

Surgical management

Segmental small intestine resection has been described historically following exact localization by intraoperative enteroscopy and capsule endoscopy [53]. Capsule endoscopy and intraoperative enteroscopy have a 70% concordance rate in patients with small bowel bleeding [35]. Although small intestine segmental resection would be a permanent measure for small bowel bleeding resolution, procedure-related mortality equates to 5% and postoperative complications occur in 21% [54]. The latter figure excludes intraoperative

complication rates, which may include hemorrhage, hematoma, ischemia, serosal or vascular rupture and perforation. In view of this, surgical management is not considered first-line and is used only if the cause of small bowel bleeding is unresponsive to other treatments. A recent case report describes multiple angioectasias identified during an exploratory laparotomy, treated with full thickness sutures under guidance of intraoperative enteroscopy [55]. Lai *et al* also report on SBAs treated surgically [56].

Radiological embolization

Small bowel bleeding has been managed with selective transcatheter embolization and its 20% failure rate often responds to repeat embolization [57]. Embolization is performed using agents such as microcoils, absorbable gelatin sponges and polyvinyl alcohol. Microcoils are easier to maneuver and have a more permanent effect in comparison to sponges and particulate agents. N-butyl cyanoacrylate has been used effectively in very small caliber arteries. Particulate agents may reflux or spread to non-target arteries, risking bowel infarction [57]. Bowel infarction risk is higher if more than 3 *vasa recta*, or a single *vas rectum* with more than 2 branches, are embolized. However, this is often asymptomatic and self-limiting [58]. The radiological approach must be considered in unstable patients who would otherwise benefit from other therapy once stable.

Noninvasive management

Somatostatin analogs

Somatostatin analogs reduce splanchnic blood flow, enhance platelet aggregation and exert anti-angiogenic effects. Long-acting octreotide (octreotide-LAR) can be administered at a starting dose of 20mg monthly, intramuscularly, for a minimum of 6 months. Lanreotide is the more expensive of the 2 and, unlike octreotide, can be administered subcutaneously in addition to intramuscularly; this is especially useful in patients on anticoagulant treatment. Intramuscular lanreotide is formulated in 30 mg vials administered at 28-day intervals. Somatuline Autogel is the subcutaneous form of lanreotide, available in 60-mg, 90-mg, and 120-mg vials [27]. Unlike octreotide, lanreotide requires dose adjustments in renal impairment.

According to a recent systematic review of 11 studies with moderate-to-high quality evidence, somatostatin analogs reduce the red blood cell transfusion requirement in patients with angioectasias. Patients included were solely on somatostatin analog therapy for SBAs, and previous treatment with APC was recorded. They were studied for a median treatment period of 12 months and followed-up for a year after treatment. One study used short-acting somatostatin analogs administered subcutaneously t.i.d., while others used the long-acting formulations described above. The primary endpoint in most of the studies was a reduction in red blood cell transfusion requirement compared to baseline: 83% of patients had a reduction of more than 50%. Octreotide was found to be superior to lanreotide in terms of treatment response (P=0.02). Pasireotide is mentioned in one study included in the systemic review, and is inferior to octreotide as it binds least to the somatostatin receptor type 2. Unfortunately, most studies describe the use of somatostatin analogs following a failure of endoscopic therapy. There are also, until the time of writing, no available studies directly comparing octreotide to lanreotide. The side-effect rate for octreotide and lanreotide has recently been reported as 38%. The commonest reported adverse events are loose stools, cholelithiasis, flatulence, and administration site reaction [59].

Somatostatin analogs may be used as sole agents, but are also administered as additional therapy following APC. One small study noted that the need for DBE was reduced significantly in patients on different doses of lanreotide. Patients on lanreotide also experienced a decrease in bleeding episodes and transfusion requirements, as well as an improvement in hemoglobin. These findings did not correlate with either the dose of lanreotide administered or the timing of initiation of lanreotide [60]. Prior to this study, Jackson *et al* identified 4 studies of somatostatin analog use for the management of SBAs refractory to endoscopic therapy. All 4 studies administered octreotide at different doses and dosing intervals. Bleeding cessation rates increased significantly following the introduction of somatostatin analogs, with a pooled odds ratio of 14.52 [61].

Further studies are required to shed light on the use of somatostatin analogs as monotherapy, especially in patients ineligible for DAE. A study published in 2022 included 16 patients with untreated SBAs treated solely with subcutaneous octreotide at 100 μg daily. The results are promising, as they demonstrated a significant reduction in rebleeding rates (P=0.002), hemoglobin reduction and transfusion requirements [62]. Future research will also need to concentrate on dosing and duration of treatment with somatostatin analogues, since trials so far have not been uniform, making it difficult to draw a comparison [63-68].

Immunomodulatory therapy

Thalidomide downregulates the expression of VEGF at both protein and mRNA levels [69]. It has been used in the management of SBAs at doses of 50-200 mg daily via the oral route [70]. In terms of re-bleeding rates, thalidomide has demonstrated promising results [71,72]. Adverse events are reported in around 70% of patients receiving thalidomide and lenalidomide, and include length-dependent neuropathy, teratogenicity and thromboembolic events [27]. In view of these adverse event rates, thalidomide and lenalidomide are not used routinely in daily clinical practice.

Bevacizumab

Bevacizumab is an anti-VEGF monoclonal antibody. It has been used successfully to treat refractory SBAs in 2 patients diagnosed with Glanzmann's thrombasthenia. Its use has also been described in patients with hereditary hemorrhagic telangiectasia. Its most severe adverse effect is bowel perforation, which is estimated to have an incidence of 5.4% [27]. More recently, a small series involving 21 patients demonstrated that bevacizumab is useful for refractory SBA, as well as gastric antral vascular ectasia, as it reduced transfusion, intravenous iron and endoscopy requirements. Decreased blood pressure control was reported as an adverse effect [73]. In view of the side-effect profile, one should be cautious in its prescription.

Antifibrinolytic agents

Tranexamic acid and aminocaproic acid stabilize clots by binding to plasminogen and are widely used in upper gastrointestinal bleeding. Two case reports identified the use of tranexamic acid in small bowel bleeding. These agents' commonest adverse events are nausea and diarrhea, and they are associated with a mildly increased risk of thromboembolic events and acute kidney injury [27]. They are used mainly in the acute setting, in combination with radiological or endoscopic management, and it is recommended that they should only be used for a short time.

Hormonal therapy

Estrogen and progesterone have both been used to treat SBAs in isolated case reports [74]. However, other trials conducted in 2001 and 2002 have not shown them to significantly reduce bleeding episodes. Both trials included control groups who received a placebo. Even though combined estrogen and progesterone therapy was used at different dosages in both trials, the calculated odds ratio for remaining free from rebleeding at one year was 69% for the treatment group (CI 50%-87%) and 55% for the placebo group (CI 36%-74%) [75]. Furthermore, clinicians must be wary of the risk of thrombosis and endometrial cancer associated with hormonal therapy [76].

A recent meta-analysis of 25 studies revealed that somatostatin analogs, hormonal therapy, thalidomide and angiogenesis inhibitors all reduced bleeding episodes (OR 0.08, 95%CI 0.04-0.18), transfusion requirements (OR 0.03, 95%CI 0.03-0.07), and hemoglobin drops, and no pharmacological treatment was superior to the others (P=0.83) [77]. However, the choice of pharmacological agent should be guided by a knowledge of patient characteristics and side-effect profile.

Concluding remarks

SBAs are vascular malformations whose etiology lies in an angiogenic factor imbalance precipitated by medical conditions or medications. Their implications are paramount, as they may prove to be life threatening, and if not, may be the cause of recurrent hospitalization and symptomatology. Investigation by SBCE in stable patients following upper and lower gastrointestinal endoscopy may disclose the diagnosis. Management of bleeding SBAs needs to be executed on an individual basis. Different treatment modalities may be combined, depending on the clinical picture and response. Most evidence so far suggests the use of endoscopic therapy with the early introduction of somatostatin analogs if anemia recurs.

The recent surge in research into small bowel bleeding will hopefully prompt the identification of novel therapeutic modalities as well as monitoring techniques, and possibly scores or systems to identify patients at high risk for SBAs. Progress has already been made in SBCE, in terms of increased battery life as well as the use of real-time viewing. The availability of chromoendoscopy has also improved the visualization of lesions on SBCE. The use of artificial intelligence will also increase detection rates, as well as reducing physician burden [78]. Serum biomarkers such as Ang-2 may play a role in identifying patients at high risk of SBA and thus possibly patient selection for SBCE [79]. The use of SBCE in a timely manner in carefully selected patients will ensure management is goal-directed, cost-effective and patient-oriented.

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