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REVIEW

Small bowel bleeding: clinical diagnosis and management in the elderly

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ABSTRACT

Introduction: With the global increase in life expectancy, there is an increase in gastrointestinal presentations in the elderly. Small bowel bleeding (SBB) is a cause of significant morbidity in the elderly requiring multiple hospital visits, investigations, and potentially expensive therapy.

Areas covered: In this review, we will outline the different modalities which are used for the diagnosis and management of SBB. We will also discuss the common causes of SBB in the elderly.

Expert opinion: SBB in elderly has a significant impact on the quality of life of the elderly. Larger randomized studies in the elderly are urgently required to help guide clinicians on the best and most cost-effective treatment algorithm in this challenging cohort.

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KEYWORDS
Small bowel bleeding; capsule endoscopy; enteroscopy; elderly; somatostatin analogues

1. Introduction

The population all over the world is aging and this trend is projected to continue in the future. It is predicted that by 2050 one in four people living in Europe and North America will be over 65 years of age. Approximately 5% of all GI bleeds occur from the small bowel (SB) and vascular lesions like SB angioectasia are the commonest cause of SBB in the elderly [1]. SB bleeding can cause significant impairment in the quality of life of elderly patients. Vascular lesions of the SB are often difficult to identify and treat and hence these patients often require multiple procedures to identify and treat the source of bleeding [2]. SB capsule endoscopy (SBCE) has revolutionized imaging of the SB by providing reliable mucosal images of the entire SB. Prior to the advent of SBCE, radiology was the most commonly used diagnostic modality for investigating the SB, which has a lower diagnostic yield particularly in the detection of vascular abnormalities. Device assisted enteroscopy (DAE) allows clinicians to diagnose as well as treat SBB, although the risks of the procedure are higher when compared to SBCE [3]. With the use of SBCE and DAE it is possible to minimize the number of repeated procedures required for the investigation and management of SBB [4].

Suspected SBB is defined as the loss of blood from anywhere between the ampulla of Vater to the ileocecal valve and where bidirectional endoscopy has been negative [5]. SBB can be subcategorized based on the type of bleeding-either overt bleeding, where the patient has melena or hematochezia or occult bleeding with the presence of anemia or a positive fecal occult test only [3]. Obscure GI bleeding (OGIB) should be reserveD for patients without a clear source even after SB evaluation has been performed [6].

With increasing life expectancy there is an increasing use of oral anticoagulation and antiplatelet drugs to prevent cardiovascular and cerebrovascular disease. The use of these drugs has also been associated with an increased risk of SBB [7,8].

2. Diagnostic modalities

Capsule endoscopy, device-assisted enteroscopy, and SB radiology are important diagnostic modalities in the context of suspected SBB. The modality of choice is dependent on patient factors and the most likely pathology. With the elderly population, it is often important to consider their suitability for invasive investigations.

2.1. Small bowel capsule endoscopy (SBCE)

SBCE is the first-line test in patients with SSB after the upper GI tract and colon have been satisfactorily evaluated [3]. It is also a very safe procedure in the elderly [9]. SBCE allows for direct mucosal visualization of the SB. Studies have shown that the diagnostic yield (DY) of SBCE is significantly higher when performed within the first few days to 2 weeks after the bleeding episode [10,11]. There are several other patient-related factors like advanced age, male sex, and increasing transfusion requirements which are independent predictors of DY in obscure GI bleeding [12]. Antithrombotic therapy use can lead to a two-fold increase in recurrent SBB compared to non-users [13]. Management of patients with obscure GI bleeding can be challenging. In a meta analysis with a total of 3657 patients, the pooled rebleeding rate after a negative SBCE was .19 (95% CI, .14–.25; $P < .0001$) and the pooled rebleeding rate after positive SBCE was .29 (95% CI, .23–.36; $P < .001$) with a significant difference between the groups ($P < .001$) [14]. The pooled odds ratio (OR) of rebleeding was 0.59 after

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Article highlights

- Angioectasias are the most common cause of SBB in elderly.
- NSAID-related SBB is common in the elderly.
- SBCE performed within the first few days to 2 weeks has a significantly higher DY compared to when done after 2 weeks.
- The most common indication for DBE in the elderly is obscure GI bleeding.
- Somatostatin therapy is safe and effective in the elderly with bleeding secondary to angiodysplasia.
- Bevacizumab has promising results for refractory GI bleeding secondary to SB angioectasia.

a negative index SBCE compared with positive SBCE (95% CI, 0.37–0.95;$P < 0.001$). In both cases, it seems reasonable a wait and see strategy and to consider treatment after rebleeding. When comparing patients with and without re-bleeding, advanced age was a predictive factor for re-bleeding after negative SBCE (hazard ratio 1.05 [1.01–1.10], $P = 0.03$) [15]. A recent meta-analysis has shown a significantly higher risk of re-bleeding after a positive SBCE as compared to negative SBCE [16]. These findings support current ECGE guidelines of a watch and wait approach for patients with obscure GI bleeding and a negative SBCE as the rebleeding risk is low. However, if the clinical presentation of the bleeding changes to overt or the hemoglobin drop is >4 g/dl, further investigations would be appropriate [14].

A scoring system called the RHEMITT score (Renal disease; Heart failure; Endoscopic findings; Major bleeding; Incomplete SBCE; Tobacco; Treatment by enteroscopy) has been developed to predict the rebleeding risk in patients with a negative SBCE and obscure bleeding. In a prospective study, the sensitivities and specificities of the score are, 0% (0–10%) and 28.8% (21.1–36.5%) for low risk patients; 23.3% (8.2–38.4%) and 72% (64.3–79.7%) for intermediate-risk patients; 76.7% (61.6–91.8%) and 99.2% (97.7–100%) for high-risk patients [17]. Further studies are required to compliment and validate this scoring system.

Several studies have investigated the use of CE within the emergency care setting as a triage tool for non-hematemesis GI bleeding (NHGIB). In a study by Mayra et al., the likelihood of localization of bleeding was greater for patients who ingested a CE as soon as they presented to hospital (64.3%) as compared with the standard care arm where patients underwent endoscopic investigations as directed by the gastroenterologists based on clinical presentation ($P < 0.01$) [18]. CE is not only able to correctly identify source of bleeding but also adds the value of SB examination with a potential of reduced length of stay.

Panenteric capsule has also been used in the emergency setting. A pilot study by Mussetto et al showed that in 12 patients with melena and negative gastroscopy who underwent a pan enteric capsule (both SB and colonic examinations), the diagnostic yield was 83%. Significant findings were found in the SB 41%, colon 33% and both 8.3%. DBE was required in 50% and re-bleeding at 30 days was 0% and 18% at 12 months [19]. Whilst this is a proof of concept study, patient selection needs clarification and the elderly would seem a suitable choice for this pathway.

One of the main limitations of SBCE is the inability to obtain histology samples or provide therapy. However, SBCE can be used as a guide when planning for DAE. By identifying the location of the pathology, the route of DAE can be determined [20,21].

2.2. Push enteroscopy

Push enteroscopy allows examination up to 120 cm beyond the ligament of Triatz. It can be performed using an enteroscope or a pediatric colonoscope. It is a more widely available technique as it is not limited by the availability of specialized equipment; however, it is limited by the depth of insertion. Push enteroscopy has largely been superseded by DAE. Although push enteroscopy has high accessibility, ESGE does not recommends it as a first-line investigation because of a low diagnostic yield when compared to SBCE. DY is reported to be within the range of 24–56% in SBB [22].

2.3. Device-assisted enteroscopy (DAE)

The increased detection of SB pathology has led to an increased need to access the SB for obtaining histology or providing therapy. Device-assisted enteroscopy (DAE) is used for complete SB evaluation and encompasses double balloon, single balloon, and spiral enteroscopy. DBE is the most published DAE method. It can be used as a diagnostic as well as a therapeutic modality. However, the completion rates of DBE are lower than that of SBCE, and it is more invasive. DBE is often performed after a positive SBCE. A study by Teshima et al shows that the pooled diagnostic yield of DBE performed after a previously positive SBCE was 75% (95%CI 60.1% – 90%). In that same study, the pooled diagnostic yield when DBE was performed after a previously negative SBCE was 27.5% (95%CI 16.7% – 37.8%) [23]. In a retrospective single center study older patients (≥65 years) showed statistically higher rates of clinically relevant findings than adult patients (18–65 years) ($p = 0.001$) on DBE [24]. The reported complete enteroscopy rates for DBE was 44% with pooled minor and major complication rates as 9.1% and 0.72%, respectively [25]. Advancing age has been related to extended procedure times and higher risk of complications [26]. The complication rates increase when therapeutic interventions are included in the procedure, from 0.72% to 4.3% [27]. An anterograde (via the oral cavity) or retrograde (via the anus) approach can be undertaken based on location of pathology identified on SBCE or imaging, and the two approaches can be combined to give full visualization of the SB [28]. DBE has also been noted to have a comparable diagnostic yield to SBCE [23,29]. The main indication of performing DAE in the elderly is obscure GI bleeding [30]. In the setting of overt bleeding, urgent DBE has an improved DY if carried out as close to the bleeding episode and it is recommended that DAE is performed within 48–72 hours of the bleeding episode [3,31,32].

Spiral enteroscopy (SE) was introduced in 2008, it is a rotational enteroscopy and pleats the SB allowing for SB examination via the anterograde approach [33]. The first motorized spiral enteroscopy was introduced into clinical evaluation in 2015 [34]. In patients with SBB, the overall DY of

motorized SE was 74.2%; with 68.2% of procedures requiring some form of endotherapy [35]. In the same study, anterograde panenteroscopy was achieved in 10.6% of the cases and adverse events were reported in 14.4% with major complications in 1.5% [35]. It has the advantage of a significantly lower procedural time when compared with DBE and similar DY [36]. This is a promising technology but requires more safety and feasibility studies in the elderly population.

2.4. Radiology

The use of SB follow through and conventional enteroclysis for the diagnosis of SBB is obsolete as it has a very low diagnostic yield [37]. CT angiography is a useful diagnostic and treatment modality in elderly patients with significant active bleeding (>0.5 ml/minute), who are unstable for endoscopy or in those where the lesion is endoscopically inaccessible. It is performed by selective catheterization of the vessel which is feeding the bleeding lesion and injecting an embolizing agent [38]. The development of multiphase CT enterography has improved imaging of the SB and the surrounding structures. A good SB distention is essential to obtain adequate views. It is better at visualizing localized lesions like SB tumors, in comparison with flat lesions like ulcers and angiodysplasias [39,40]. However, there is a risk of high radiation exposure. Radiological investigations are more widely available and hence can be used in an acute setting for elderly patients with overt bleeding.

3. Pathology

The most common cause of SBB in the elderly is bleeding from vascular abnormalities like angioectasia [41]. Other causes include SB ulceration and SB tumors. However, SB tumors, Dieulafoy lesions and Crohn's are more common in adults under the age of 50 [41,42].

3.1. Angioectasia

Angioectasias (Figure 1) are commonly found in the proximal SB [43], but can be distributed with multiple lesions along the length of the SB [44]. Risk factors for angioectasia include conditions such as ischemic heart disease, valvular heart disease, heart failure, chronic kidney disease, previous thromboembolic conditions, chronic respiratory disease, and the use of long-term anticoagulation [45]. As these conditions are commoner with advancing age, it puts elderly patients at a greater risk of having angioectasias.

3.2. Telangiectasia

Telangiectasias can occur throughout the GI tract and in the SB they usually present as occult bleeding. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder which manifests as recurrent epistaxis, mucocutaneous telangiectasia, and visceral arteriovenous malformations [46]. Most patients have recurrent epistaxis which predates the development of GI bleeding which usually presents in the fifth decade of life [47].

Figure 1. Small bowel angioectasia.

3.3. Dieulafoy lesions

This is a rare cause of SBB in the elderly. However, these lesions can sometimes cause massive life-threatening bleeds [48].

Small bowel ulceration

Ulceration of the SB is a common cause of SBB. NSAID are widely prescribed in the elderly for their analgesic and anti-inflammatory properties. Many elderly patients tend to use these drugs on a long-term basis including regular over the counter preparations [49]. Long-term NSAID use risk the development of NSAID enteropathy with ulceration, structuring disease, protein loss, and anemia. The other causes of SB ulceration include Crohn's disease and drugs such as nicorandil [50].

3.4. Tumors

SB tumors can be found in the elderly although commoner in patients below the age of 50 years and account for 5–10% of all SBB [51,52]. These are often identified using radiological methods which are complementary to SBCE as they can be missed through direct visualization given their submucosal location [40].

4. Management and treatment

4.1. Vascular abnormalities

Treatment of SB bleeding in the elderly is challenging. Majority of elderly patients with SBB would be supported by iron, either oral or intravenous iron and transfusions as required which leads to multiple hospital visits.

4.1.1. Double balloon enteroscopy (DBE)

SBB is most commonly seen because of bleeding from angioectasias and the first-line therapy is argon photocoagulation (APC) during DAE, which has a very good response rate

[53]. A recent meta analysis has shown that DBE is a safe procedure for the elderly with a higher diagnostic yield (DY) when compared to young patients [54]. A comparison of DBE between elderly (369 patients) and young patients (1208 patients) showed a DY of 1.74 (95% CI: 1.34, 2.27; $p = 0.0001$) [54]. In patients undergoing DBE (214 elderly vs 537 young patients), the risk of major events was 1.41 and there was no statistical difference between the 2 groups (95% CI: 0.29, 6.76, $p = 0.67$) [54]. However, rebleeding is a relatively common occurrence. A study by Kim et al [55] looked at a cohort of 141 patients with obscure GI bleeding who had undergone a DAE. 31.1% of these patients presented again at 36 months with rebleeding. Factors which were deemed likely to be responsible for increasing likelihood of rebleeding included comorbidities of chronic disease such as cirrhosis or chronic kidney disease, or patients who are on anticoagulants and antiplatelets for indications such as secondary prevention of coronary artery disease. These factors are much more prominent in the elderly population given their increased probability of a higher comorbidity burden. Kim et al concluded that patients with ulcerative lesions, multiple lesions, and bleeding lesions, who require more than five units of packed red cell transfusion, were at the highest risk of a rebleeding [55]. Elderly patients are more likely to have multiple lesions given their higher prevalence of vascular conditions such as angiodysplasia, making them more prone to rebleeds. Rebleeding rates from the published literature post endoscopic ablation remain high. In a systematic review by Romagnuolo et al., patients who received endoscopic therapy for SBB 209/490 (42.7%; 95% CI, 38%-47%) rebled, and the patients who did not receive any therapy, 64/130 (49.2%; 95% CI, 40%-58%) rebled, which is not dissimilar [56]. Hence, it is important to risk stratify elderly patients before they undergo invasive procedures to treat angioectasias. It is also important to take into consideration the degree of frailty of elderly patients before making a decision on the type of therapy to be used. A prospective study which looked at the five-year survival of patients with SBB showed that the five-year survival was 64.0% (80/125) compared to 70.4% (88/125) in those with a normal SBCE and patients with significant cardiac or vascular comorbidity had a poorer survival (52.9% (37/70) at 5 years [57]. Interestingly, the use of blood thinners or need for endoscopic therapy did not change survival.

4.1.2. Medication

Somatostatin analogues have been increasingly used to treat SB bleeding caused by SB angioectasia, the most common cause in the elderly population [58]. Their mechanism of action in treatment of SB bleeding is thought to be a combination of decreased blood flow to splanchnic circulation [59], improved platelet aggregation for plug formation [60], and prevention of further angiogenesis [61]. They also act systemically to increase vascular resistance [62]. These are typically used for patients who present with refractory anemia which is transfusion dependent [63]. They are well-olerated medications with a low side effect profile [39] and are often deemed a preferable treatment option in the elderly population as they prevent the need for a physical intervention. A systematic review and meta analysis by Goldstein showed that somatostatin analogues reduced transfusion requirements from 12.8 transfusions in a year to 2.3 transfusions when on treatment with somatostatin analogues [64]. Octreotide also faired better than lanreotide in this study. A study by Zammit et al [58] has shown that the use of somatostatin analogues in combination with endoscopic therapy was more effective than endoscopic therapy used on its own. It has shown to improve hemoglobin levels, reduce the number of transfusions, and also reduce the number of bleeding episodes. Although somatostatin analogues are expensive drugs, a study by Klimova et al reported a reduction of approximately 60% in annual treatment costs of patients who used somatostatin analogue therapy [65].

Thalidomide can be utilized in the management of SBB due to its anti-angiogenic properties. It is usually employed after other therapies have failed given its side effect profile such as peripheral neuropathy [66], teratogenicity [67,68], and thromboembolism [69]. Thalidomide can also be used in combination with somatostatin analogues to treat refractory bleeding [70]. When considering drug therapies in SBB, somatostatin analogues are the preferred drug of choice.

Linalidomide is a thalidomide analogue with anti-angiogenic properties. Its use has been described in a case reports and a small case series for the treatment of recurrent bleeding secondary to vascular malformation in hereditary hemorrhagic telangiectasia (HHT) and Von Willebrand's disease (VWD) [71,72]. There studies have shown that the use of lenalidomide reduces the number of endoscopic interventions and also has a much better side effect profile when compared to thalidomide [72]. It is widely used in the management of multiple myeloma and myelodysplastic syndrome [73].

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). In a few case studies on patient with HHT, it has shown to significantly reduce transfusion requirements in those who fail to respond to endoscopic therapy, angiographic embolization, and somatostatin analogues [74,75]. In a case series, bevacizumab has also been used to treat refractory GI bleeding secondary to SB angioectasias and gastric antral vascular ectasia (GAVE) with promising results [76].

4.2. Small bowel mass lesions (SBML)

DBE plays an important role in the management of SBML. In a recent multicenter study of 218 patients with SBML identified on DBE, 73.3% of the patients (median age of 63 years) presented with iron deficiency anemia or bleeding [77]. Almost half of these patients were either discharged or advised endoscopic surveillance only (benign histology/successful endoscopic resection) after DBE and DBE was also used to place a tattoo in 65.6% of the cases. It has been shown that tattooing of lesions in the colon minimizes localizing errors during surgery [78]. There is limited literature about the role of tattoo in SBML [79,80]. The European Society of Gastrointestinal Endoscopy recommends placing a tattoo in the SB to mark and identified lesion during DAE [3]. A small

study supports tattooing during DBE as it facilitated laparoscopic SB resection which in turn was associated with shorter recovery time and reduced morbidity [81].

4.3. Small bowel ulceration

SB ulceration is a common cause of SBB. Regular NSAID use is common in the elderly and can cause occult bleeding secondary to NSAID enteropathy [82]. Discontinuation of NSAIDS has shown to reduce complication rates to 4.3% in a mean follow up period of 15.9 months [83]. SB Crohn's disease is another cause of ulceration in the SB. Patients with proximal/extensive SB Crohn's have been shown to have a worst prognosis [84]. It is important to identify these patients and initiate biologic therapy early to reduce complication.

5. The future

Artificial Intelligence (AI)

There is a growing interest in the use of AI in capsule endoscopy. Several computer-aided diagnostic systems and AI models have been developed to diagnose bleeding lesions in the SB. In a meta-analysis on the use of AI in SBCE, it has been shown that the pooled sensitivity and specificity for bleeding lesions is 0.98 (95% CI, .96–.99) and 0.99 (95% CI, .97–.99), respectively [85]. In future prospective, multicenter studies are necessary for this technology to be implemented in clinical use.

6. Conclusion

Management of SBB in the elderly remains challenging. A combined approach including endoscopic therapy and medical management should be considered in selective patients with transfusion-dependent SBB.

7. Expert opinion

Elderly population all over the world is increasing and is expected to rise further. SB bleeding has a significant impact on the quality of life of an elderly patient. The examination of the SB has been challenging in the past, however with the advent of SBCE it is now possible to directly visualize the SB mucosa which has led to an increased detection of SB pathology. It is also very well tolerated by the elderly. DBE is used to evaluate the entire SB and can provide targeted therapy when a lesion is identified. It can also obtain histological samples. It is a safe procedure and has a positive impact in the management of SBB in the elderly. It is well known that angioectasias are the most common cause of SBB in the elderly and often present as multiple lesions throughout the SB. The lesions are more frequently in the proximal SB. Multiple clinical factors such as increasing age, cirrhosis, chronic kidney disease, or patients who are on anticoagulants and antiplatelets are known to increase the diagnostic yield of both modalities. The relationship between vascular endothelial growth factor and comorbidity manifests in the SB with proliferation of SB angioectasia. In a proportion of patients, bleeding can be also more troublesome as the patient becomes more comorbid with increasing age. Timing remains key to find the source of bleeding. Ideally a SBCE should be performed within two weeks and a DAE within 72 hours of suspected SBB. However, this may not be possible in smaller hospitals due to the lack of service provision. The use of panenteric CE would be a useful tool for investigation of bleeding in the elderly in the acute setting providing views of both the small and large bowel in one sitting and reducing the number of procedures. A significant proportion of elderly patients with SBB require multiple hospital visits for blood transfusions, iron infusions or further investigations. The literature informs us that the rebleeding rate secondary to angioectasia is high despite endoscopic ablation. Whilst studies have demonstrated that medical therapy such as somatostatin analogues with or without endoscopic ablation are helpful to transfusion requirement and rebleeding, which cohorts would benefit the most, remains key unanswered questions. These drugs are well tolerated but also with a significant cost. There are no randomized studies that have compared somatostatin analogues, endoscopic ablation, or conservative management alone with blood and iron. The meta analysis informs us that DAE is safe in the elderly in this setting; however, it is important to risk stratify elderly patients before putting them through invasive procedures. In small case control studies monoclonal antibodies like Bevacizumab have been used successfully for refractory SBB. AI is rapidly benign incorporated in multiple aspects of healthcare and there is a growing interest in the use of AI in SBCE. Studies have shown high sensitivity and specificity of AI for diagnosing SBB lesions. Larger randomized studies in the elderly are urgently required to help guide clinicians on the best and most cost-effective treatment algorithm in this challenging cohort. This ultimately will result in better quality of life for elderly patients with bleeding.

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