Journal of Translational Gastroenterology **2025** vol. 000(000) | 000–000 Epub
DOI: 10.14218/JTG.2025.00021

Letter to the Editor

Procedural versus Pharmacological Therapeutic Approaches for Gastrointestinal Bleeding Due to Small-intestinal Angiodysplasia

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Received: May 13, 2025 | **Revised:** July 18, 2025 | **Accepted:** July 29, 2025 | **Published online:** September 03, 2025

Dear Editors,

Bleeding from the small intestine accounts for approximately 5% to 10% of all patients presenting with gastrointestinal (GI) bleeding. The most common cause is small-intestinal angiodysplasia (SIA), primarily affecting elderly patients.[1] Despite significant improvements in the diagnosis of SIA due to recent advances in small bowel imaging, there is no consensus on the management of SIA.[2] Selecting the optimal therapeutic approach for patients with SIA, especially those with recurrent or refractory bleeding, remains challenging.

Currently, both invasive procedural (or surgical) and non-invasive pharmacological (medical) approaches are explored and applied in clinical practice. Procedural approaches include angiographic embolization, endoscopic intervention, and surgical operation, whereas pharmacological approaches include thalidomide, hormones, somatostatin analogues, and other antiangiogenic therapies (Table 1, Fig. 1).[1–9]

Angiographic embolization has been reported to both stabilize the patient's hemodynamics and localize the lesion before surgery.[10] However, its main limitation is that bleeding rates greater than 0.5 mL/m are required for angiography to accurately localize the bleeding site.[1] Furthermore, bleeding recurs in approximately 20% of patients with lower GI bleeding after embolization, despite its high immediate hemostatic effectiveness.[3,4] Thus, angiographic embolization is generally considered for patients with hemodynamically significant bleeding (systolic blood pressure < 90 mm Hg, heart rate > 100 beats per minute, or orthostatic changes). Endoscopic treatment is usually applied to patients with a few vascular lesions that are accessible to the endoscope. The most commonly used and clinically evaluated endoscopic modalities for SIA include argon plasma coagulation, electrocoagulation, photocoagulation, injection sclerotherapy, and mechanical hemostasis such as endoscopic clipping and rubber band ligation.[4,11–13] However, their clinical application is limited due to variable efficacy and various disadvantages.[14] Rebleeding rates after endoscopic intervention range from 34% to 60% across studies, likely attributable to differences in follow-up durations. Nevertheless, these rates remain comparable to those expected without therapy,[1,5] possibly due to lesions that are not detected during endoscopy or newly formed lesions. Before the availability of enteroscopy, right hemicolectomy was performed as the treatment of choice for recurrent GI bleeding, as right-sided diverticulosis was presumed to be the source of bleeding. Accurate preoperative or intraoperative localization of the target lesion is essential for successful surgical resection. Currently, surgical operation is considered the last procedural resort for GI bleeding that is uncontrollable by other therapeutic modalities, following advances in angiographic embolization, endoscopic intervention, and pharmacological treatment.

Due to the limitations of procedural approaches described above, current guidelines recommend considering pharmacological or medical treatment with somatostatin analogues or antiangiogenic therapy if bleeding persists, recurs, or a lesion cannot be localized.[1,15]

Hormonal therapy was initially used in the 1980s but is now rarely applied for bleeding due to SIA, as a multicenter randomized clinical trial in 2001 demonstrated no clinical benefit of continuous estrogen-progestogen treatment in reducing bleeding episodes or blood transfusions.[16] In the 1990s, somatostatin analogues began to be used for treating SIA. Several observational studies have shown their beneficial effect in reducing bleeding from SIA.[1,17]

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How to cite this article: Tang M, Wu S, Chen H, Gao Z, Gong S, Li D, *et al*. Procedural versus Pharmacological Therapeutic Approaches for Gastrointestinal Bleeding Due to Small-intestinal Angiodysplasia. *J Transl Gastroenterol* 2025;000(000):000–000. doi: 10.14218/JTG.2025.00021.

Table 1. Procedural versus pharmacological therapeutic approaches for gastrointestinal bleeding due to small-intestinal angiodysplasia

Therapeutic approach	Indication	Dose and duration	Efficacy	Adverse events
Angiographic embolization[1,3,4]	Ongoing overt GI bleeding	Not applicable	Diagnostic yields for angiography ranging from 20% to 77%; Success rates ranging from 80% to 90%, but with rebleeding rates ranging from 12% to 20%	AEs: renal failure, thromboembolism, infections, or bleeding at the catheter site
Endoscopic intervention[1,4,5]	GI bleeding with a known source and significant ongoing anemia or active bleeding	Not applicable	Rebleeding rates ranging from 34% to 60%	Not reported
Somatostatin analogues[6,9]	Recurrent GI bleeding	40 mg octreotide long-acting release, intramuscular injection every 28 days for 12 months	Reduced number of transfusion units: 10.2 (95% CI, 2.4–18.1)	AEs: GI symptoms, pain at the administration site, and glucose intolerance; SAEs: acute cholangitis, hypoglycemia with loss of consciousness
Thalidomide[7]	Recurrent GI bleeding	100 mg or 50 mg, daily oral for 4 months	Effective response rate: 100 mg: 68.6%, 50 mg: 51.0%	AEs: constipation, peripheral neuropathy, somnolence, fatigue, rash, edema, tremors, ataxia
Bevacizumab[8]	Recurrent GI bleeding	IV with an initial dose of 5 mg/kg every 2 weeks for a total of 4 doses. Complete response: continue with 5 mg/kg IV monthly for 4 doses; Partial response: continue with 5 mg/Kg IV every 2 weeks for 2–4 more doses; No response: 7.5 mg/kg IV every 2 weeks for 4 doses	Positive treatment response: 90% at 6 months, 86% at 12 months	AEs: hypertension, epistaxis

AE, adverse event; CI, confidence interval; GI, gastrointestinal; IV, intravenous injection; SAE, serious adverse event.

A recent multicenter, open-label, randomized controlled trial in 2024 involving 62 patients with GI angiodysplasia-related bleeding demonstrated that treatment with 40 mg octreotide long-acting release by intramuscular injection every 28 days significantly reduced the total number of transfusions (11.0; 95% Confidence Interval, 5.5–16.5) compared to standard care (21.2; 95% CI, 15.7–

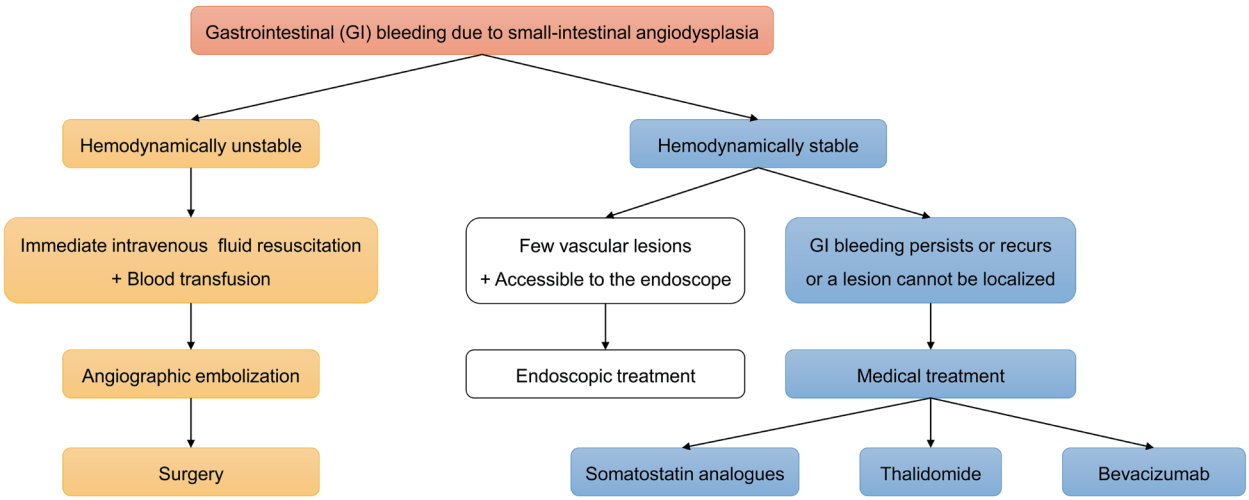

Fig. 1. Algorithm for gastrointestinal (GI) bleeding due to small-intestinal angiodysplasia.[1–4]

26.7).[6] Drug-related adverse events (AEs) were reported in 65% of patients but were mild and self-limiting. Therefore, somatostatin analogues, especially octreotide, appear effective with a good safety profile for treating SIA.

The efficacy of thalidomide for treating GI bleeding due to angiodysplasia has been explored since 2003 in case reports.[18] Between 2003 and 2007, our team conducted a single-center, open-label, randomized trial in patients with recurrent bleeding who received either 25 mg of thalidomide four times daily or 100 mg of iron daily for four months, demonstrating a benefit of thalidomide.[19] More recently, we conducted a multicenter, double-blind, randomized, placebo-controlled trial involving 150 patients. The primary endpoint was defined as an effective response (a reduction of bleeding episodes by ≥50% during the first year of follow-up). Effective response rates were 68.6% (35/51), 51.0% (25/49), and 16.0% (8/50) in the 100-mg thalidomide, 50-mg thalidomide, and placebo groups, respectively ($P < 0.001$). Secondary endpoints, including transfusion volume of red cells, duration of bleeding (in days), hemoglobin levels, number of hospitalizations due to bleeding, length of hospital stays (in days), and number of bleeding episodes during the one-year follow-up, were all better with thalidomide than with placebo.[7] Additionally, 42 (42%) patients in the two thalidomide groups experienced no further bleeding within one year after treatment completion, suggesting that thalidomide may have lasting efficacy. AEs, including constipation, peripheral neuropathy, somnolence, fatigue, rash, edema, tremors, and ataxia, were observed in 68.6% and 55.1% of patients in the 100-mg and 50-mg thalidomide groups, respectively, but these were mild and resolved with symptom management.[7] Therefore, thalidomide treatment is beneficial for patients with GI bleeding due to SIA, with lasting efficacy and no major safety concerns. Moreover, studies have reported that thalidomide may be beneficial for hemodialyzed patients, those in palliative care, patients with liver cirrhosis and multiple GI angioectasias, and patients with significant comorbidities suffering from refractory bleeding due to SIA.[20,21]

Additionally, a retrospective study reported that intravenous administration of bevacizumab, a monoclonal antibody angiogenesis inhibitor, significantly reduced the rates of RBC transfusions, intravenous iron infusions, and endoscopic interventions in patients with GI bleeding due to SIA and gastric antral vascular ectasia[8]; however, well-designed clinical trials are needed to confirm efficacy. Common adverse effects of bevacizumab include hypertension, bleeding, proteinuria, thromboembolic events, and GI perforation. In this study, hypertension and epistaxis were the reported adverse effects.

Taken together, over the past decades, invasive procedural approaches have been used less frequently in the treatment of GI bleeding due to SIA, while many clinicians increasingly apply non-invasive pharmacological approaches such as somatostatin analogues and thalidomide. Somatostatin analogues were initially trialed with daily doses, followed by monthly long-acting formulations. Long-acting somatostatin analogues may represent a viable option for managing patients with recurrent bleeding due to SIA. However, the results of studies have been limited by small sample sizes, heterogeneous patient populations, variable inclusion criteria, and differing study designs. Thalidomide has proven efficacious for recurrent GI bleeding due to SIA, as demonstrated in our randomized placebo-controlled clinical trials and confirmed by subsequent reports. Therefore, thalidomide should be considered when selecting a medical treatment approach, especially in countries where long-acting somatostatin analogues are difficult to obtain. Regarding concerns about thalidomide-related AEs, it has been established that their incidence correlates with dose and duration of therapy,[22] although the optimal dose and duration have yet to be determined. We recommend a dose of 100 mg or 50 mg and a treatment duration of four months, as this regimen has been associated with a low rate of mild and self-limited drug-related Aes.[7,19]

In clinical practice, angiographic embolization may be considered for patients with massive acute bleeding and unstable hemodynamics. Endoscopic treatment is particularly suitable for patients with a single lesion. In contrast, pharmacological therapies are more beneficial for patients with multiple lesions and recurrent GI bleeding, mainly including somatostatin analogues and thalidomide. Bevacizumab may also be effective. Given the limited availability of long-acting somatostatin analogues in many countries, thalidomide stands out as a cost-effective and accessible alternative; however, careful monitoring for potential adverse drug reactions during thalidomide treatment is essential.

Further research is needed to directly compare the efficacy of somatostatin analogues and thalidomide in the treatment of recurrent GI bleeding due to SIA. Additionally, the optimal doses and treatment durations for both somatostatin analogues and thalidomide remain to be established. Well-designed randomized controlled trials comparing the efficacy of different thalidomide doses (*e.g.*, 50 mg vs. 100 mg) or assessing the effects of prolonged treatment with thalidomide would help address these questions. Moreover, since patients with severe complications such as agranulocytosis or other contraindications cannot tolerate antiangiogenic therapies, it is worthwhile to explore whether long-acting release formulations could improve patient tolerance. Finally, the development of novel and more efficacious medical therapies with fewer adverse drug reactions is needed.

Acknowledgments

We thank personnel at Medjaden for their proofreading of an earlier version of the manuscript.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 82200710 and No. 82372849) and the Project of the State Key Laboratory of Oncogenes and Related Genes (KF2128-93).

Conflict of interest

None.

Author contributions

Study concept and design (MYT, HMC, ZZG), acquisition of data (HYC, ZFG, DL), analysis and interpretation of data (SW, QWZ, SG), drafting of the manuscript (MYT, HMC), critical revision of the manuscript for important intellectual content (YJG). All authors have made significant contributions to this study and have approved the final manuscript.

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