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REVIEW

Diagnosis and therapeutic strategies for small bowel vascular lesions

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Abstract

Small bowel vascular lesions, including angioectasia (AE), Dieulafoy's lesion (DL) and arteriovenous malformation (AVM), are the most common causes of obscure gastrointestinal bleeding. Since AE are considered to be venous lesions, they usually manifest as a chronic, well-compensated condition. Subsequent to video capsule endoscopy, deep enteroscopy can be applied to control active bleeding or to improve anemia necessitating blood transfusion. Despite the initial treatment efficacy of argon plasma coagulation (APC), many patients experience re-bleeding, probably because of recurrent or missed AEs. Pharmacological treatments can be considered for patients who have not responded well to other types of treatment or in whom endoscopy is contraindicated. Meanwhile, a conservative approach with iron supplementation remains an option for patients with mild anemia. DL and AVM are considered to be arterial lesions; therefore, these lesions frequently cause acute life-threatening hemorrhage. Mechanical hemostasis using endoclips is recommended to treat DLs, considering the high re-bleeding rate after primary APC cauterization. Meanwhile, most small bowel AVMs are large and susceptible to re-bleeding therefore, they usually require surgical resection. To achieve optimal diagnostic and therapeutic approaches for each type of small bowel lesion, the differences in their epidemiology, pathology and clinical presentation must be understood.

Key words: Angiodysplasia; Angioectasia; Dieulafoy's lesion; Arteriovenous malformation; Obscure gastrointestinal bleeding; Video capsule endoscopy; Deep enteroscopy; Argon plasm coagulation

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Core tip: Angiodysplasia includes a variety of synonymous disease concepts such as angioectasia, Dieulafoy's lesion and arteriovenous malformation. Although these lesions are the most common causes of small bowel bleeding, optimal management strategies have not been established. We propose that these lesions should be addressed separately when determining diagnostic and therapeutic plans because of their clinical heterogeneity. In this review, we focused on differences in their epidemiology, pathology and clinical presentation and discussed the currently available diagnostic and therapeutic options that may be used to control small bowel bleeding, which consequently improve patient quality of life.

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) has been defined as gastrointestinal (GI) bleeding from an unidentified origin that persists despite a comprehensive upper and lower GI evaluation[1]. Although missed lesions during an esophagogastroduodenoscopy or colonoscopy should be considered, most bleeding sources are reportedly identified within the small bowel[2], accounting for approximately 5% of all cases of GI bleeding[3]. Small bowel bleeding can present as overt bleeding, can manifest as clinically evident melena or hematochezia or occult bleeding, and can be associated with iron-deficiency anemia, with or without a positive fecal occult blood test. Additionally, overt bleeding is sometimes further categorized into ongoing and previous. Despite recent developments in endoscopic and radiologic modalities, small bowel bleeding remains a diagnostic and therapeutic challenge because of the difficulty in accessing and performing optimal treatments within the small bowel.

Several types of vascular abnormalities have been identified in the GI tract. Angiodysplasia (AD) is characterized by the focal accumulation of abnormal, dilated and tortuous blood vessels visualized within the mucosal and submucosal layers of the gut and is reportedly the most common cause of small bowel bleeding[4,5]. AD can usually be found in patients with OGIB, and the severity of bleeding may range widely from chronic, well-compensated conditions to acute life-threatening conditions[6]. Since the term AD sometimes includes a variety of synonymous disease concepts, such as angioectasia (AE), Dieulafoy's lesion (DL) and arteriovenous malformation (AVM), careful attention is needed when interpreting epidemiological and clinical data concerning ADs, because several clinical heterogeneities (*e.g.*, the incidence, pathogenesis and distribution of the lesion; bleeding pattern; and patient prognosis) underlie, these vascular abnormalities. However, these differences have not been fully addressed in previous reports. Moreover, the optimal approach to treating these lesions remains unclear because of a lack of large clinical trials. This review will focus on small bowel abnormalities, including AE, DL and AVM, and will assess the differences in their epidemiology, pathology, clinical presentation and management, which may help to establish diagnostic and therapeutic strategies.

METHODS

A comprehensive literature search was conducted using PubMed database. The MeSH terms used were "angiodysplasis" or "angioectasia" or "vascular ectasia" or "vascular lesions" or "Dieulafoy's lesion" or "arteriovenous malformation". The search was limited to manuscripts published in English language only. Subsequently, we manually selected manuscripts regarding lesions located at small bowel.

CLASSIFICATION OF SMALL BOWEL VASCULAR LESIONS

Small bowel vascular lesions can be endoscopically classified into four categories based on the Yano-Yamamoto classification[7]. AEs are generally found during

endoscopy as small erythemas and are classified as Type 1a: Punctuate (< 1 mm) or Type 1b: Patchy (a few mm). Histopathologically, they consist of thin, dilated and tortuous veins that lack a smooth muscle layer, explaining their weakness and tendency to bleed. DLs consist of histologically normal but abnormally large arteries that typically protrude through a small mucosal defect and are classified as Type 2a: Punctuate lesions with pulsatile bleeding or Type 2b: Pulsatile red protrusions without surrounding venous dilatation[8]. AVMs are histopathologically diagnosed as aberrant vessels with thickened, hypertrophic walls that vary in thickness greatly and are characterized by the direct connections of arteries and veins without a capillary bed[9]. Some intestinal AVMs are classified as Type 3: Pulsatile red protrusions with surrounding venous dilatation. Meanwhile, congenital intestinal AVMs are relatively large and sometimes appear as a mass or polypoid lesion[10,11], which can be classified as Type 4: Lesions not classified into any of the above categories.

During real-time endoscopic observations, the presence of pulsation can be evaluated, enabling venous and arterial lesions to be distinguished from each other. The presence or absence of arterial components provides important information because it helps in the selection of an optimal treatment approach and can affect a patient's prognosis. However, this endoscopic classification doses not necessarily reflect the histopathologic findings. Distinguishing small bowel vascular lesion can be difficult, and an accurate diagnosis can only be achieved after a post-operative histopathological evaluation. The representative images of each type of small bowel vascular lesion were shown in Figures 1, 2 and 3 respectively.

ETIOLOGY AND PATHOGENISIS

Because of the high incidence of AE in the GI tract, the etiology and pathology of this condition must be addressed. Although the pathogenesis of AE is not fully understood, two developmental mechanisms, termed the "mechanical theory" and the "angiogenic theory", have been proposed. Boley *et al*[12] suggested that increased bowel wall pressures and chronic hypoxia can induce the partial obstruction of submucosal veins, leading to capillary congestion, failure of the pre-capillary sphincters, and eventually the formation of permanent AE. This hypothesis is supported by the fact that AE is frequently identified in the right colon of elderly patients, where the bowel tension is relatively high[13-15]. On the other hand, Junquera *et al*[16] reported the importance of angiogenic factors in the formation of AE. They revealed that the expression of vascular endothelial growth factor (VEGF); a central mediator in the early phases of angiogenesis, was significantly increased in patients with colonic AEs. Mucosal ischemia from chronic hypoxia, which can be due in part to cardiac or renal diseases, reportedly impairs the balance between pro-angiogenic and anti-angiogenic factors, resulting in pathological neovascularization[17,18]. Recently, Randi *et al*[19] reported a close association between von Willebrand factor dysfunction and vascular malformation, suggesting that replacement therapy could be a novel therapeutic approach to controlling refractory bleeding from small bowel AE. Meanwhile, the etiology and pathology of DL is poorly understood. However, the consensus is that ischemic injury, probably related to co-morbidities (*e.g.*, cardiovascular disease) or drugs (*e.g.*, non-steroidal anti-inflammatory drugs and anti-thrombotic drugs), leads to the disruption of the overlying epithelium, then massive bleeding occurred from a large submucosal vessel[20].

The etiology and pathology of AVMs are also not fully understood. According to Moore's classification[21], intestinal AVMs can be classified into three categories. Type 1 AVMs are an acquired disease, occurring mainly in elderly patients and frequently appearing in the right colon. Type 2 AVMs are considered to be a congenital disease, occurring in younger patients and typically appearing in the small bowel. Type 3 AVMs present as GI involvement in patients with hereditary hemorrhagic telangiectasia. Type 1 AVMs, which are considered to be an acquired disease, are predominantly located in the right colon, where the bowel tension is relatively high, suggesting that AVMs might also develop through "mechanical theory", similar to AEs.

DIAGNOSIS

A variety of diagnostic modalities are available to reveal the cause of OGIB. The choice of investigation is strongly affected by the clinical status of the patient. For example, endoscopic investigation is not recommended for patients with hemodynamic instability. In contrast, radiographic examinations are especially useful

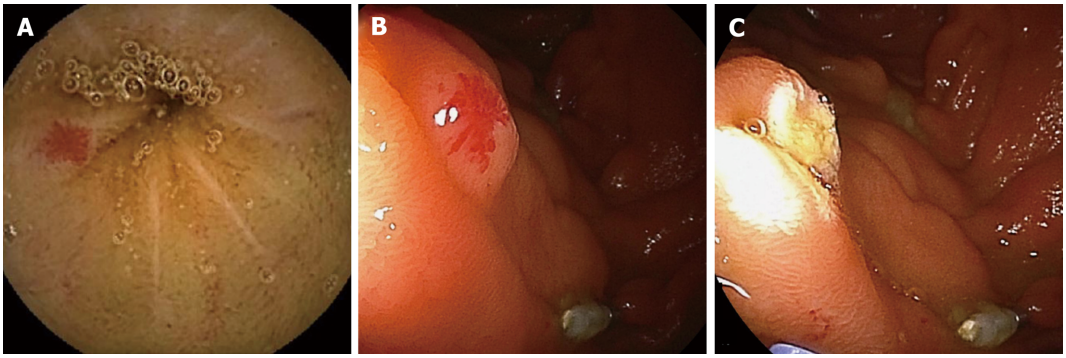

Figure 1 Representative images of angioectasia. A: Video capsule endoscopy confirmed multifocal jejunal angioectasias in patients with chronic anemia; B: Double balloon endoscopy identified an angioectasia classified into Yano-Yamamoto classification Type 1b; C: Argon plasm coagulation cauterization was successfully performed.

for patients with ongoing overt bleeding, but for patients with occult bleeding, because the bleeding rate threshold is relatively high. It is important to understand the characteristics of each diagnostic modalities and adequate timing for clinical application.

Endoscopy

Video capsule endoscopy (VCE) and deep enteroscopy (DE) play important roles in the diagnosis and treatment of small bowel ADs. While the indications for the use of these modalities are the same, their characteristics are different. VCE enables the visualization of the entire small bowel in approximately 90% of patients[22], and this success rate can be further improved through the use of real-time viewing or an increased battery capacity[23]. A large systematic review that included 227 studies revealed that the diagnostic yield of VCE for OGIB was 59.4% and that more than 50% of the patients had ADs, with a pooled retention rate of 1.4%[22]. The diagnostic yield of VCE was highest when it was performed during ongoing overt bleeding[24], which demonstrating the usefulness of emergent VCE. To note, emergent VCE is useful not only for identifying cause of bleeding, but also for determining subsequent management plan. The detection of ADs using VCE is reportedly higher than that for other diagnostic modalities, such as computed tomography (CT) enterography, mesenteric angiography and DE[25]. Therefore, VCE is currently recommended by GI societies as a first-line test for evaluating the presence of small bowel bleeding[2,26]. However, some limitations of VCE remain to be resolved. The most important limitation is its inability to obtain biopsy samples or to provide endoscopic treatments. Additionally, it is sometimes difficult to distinguish highly relevant lesions from less relevant lesions, even though less relevant lesions, such as tiny red spot or erosion, are considered to be a negative finding[27]. Moreover, the diagnostic yield of capsule endoscopy can be reduced when the visibility of the mucosa is impaired by the presence of air bubbles, food residue, or bile pigments. To overcome these disadvantages, we previously revealed that flexible spectral imaging color enhancement can reduce the effects of bile -pigments and improve the detectability of small bowel AE[28]. Recently, the efficacy of computer-assisted automatic diagnosis using a convolutional neural network has also been reported to increase the detection of small bowel AE[29].

DE enables pathological diagnosis and therapeutic intervention within the small bowel. DE includes single-balloon enteroscopy and double-balloon enteroscopy (DBE), which function using a push-and-pull technique, and spiral enteroscopy (SE), which functions using a rotate-to-advance technique. Of the three types of DE, DBE has been established as the most viable option for the management of small bowel abnormalities. Although no significant differences in the diagnostic yields of the three modalities have been reported, the total enteroscopy rate and the maximum insertion depth of DBE were significantly higher than those of other modalities[30-32]. The diagnostic yield of DBE was lower than that of VCE using a single insertion approach, but the results became comparable when both anterograde and retrograde approaches were used[33]. DBE appears to be an effective and safe endoscopic technique, with a reported pooled complication rate (including pancreatitis and perforation) of 1.2%[34]. However, DBE is an invasive and time-consuming procedure that usually requires sedation; consequently, it can be intolerable for elderly patients with severe co-morbidities.

Overall, CE can be used as a first-line investigation for small bowel ADs because of

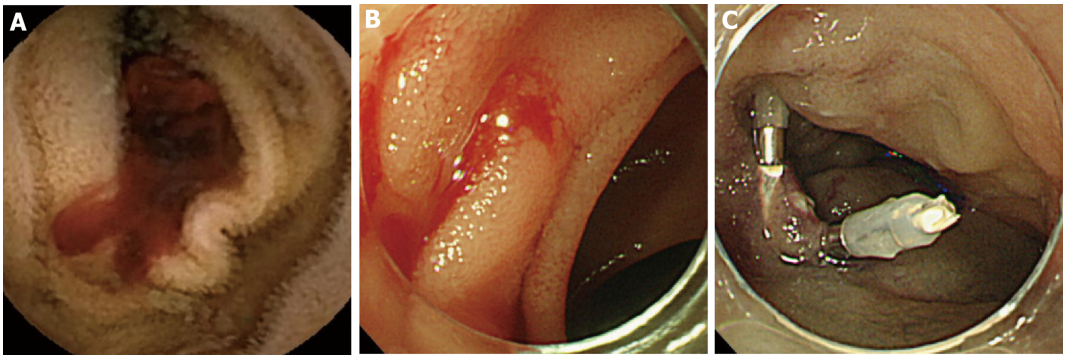

Figure 2 Representative images of Dieulafoy's lesion. A: Video capsule endoscopy confirmed active bleeding from unknown origin in patient with ongoing overt obscure gastrointestinal bleeding; B: Arterial bleeding occurred from a jejunal punctuate lesion classified into Yano-Yamamoto classification Type 2a; C: Successful hemostasis was achieved by combination of argon plasm coagulation cauterization and endoclips.

its usefulness in evaluating the localization, size and number of ADs, providing information on the best insertion route for DE. Since the re-bleeding rate was reportedly high in patients with positive VCE[35], subsequent interventional DE should be conducted even if the overt bleeding is temporarily relieved. On the other hand, there are no clear guidelines for patients with negative findings after an initial VCE examination. Teshima *et al*[36] conducted a meta-analysis and revealed that the diagnostic yield of DBE after a previous negative VCE was only 27.5%. Taken together with the lower re-bleeding rate after a negative VCE result[37], some patients with a stable general condition can probably be managed safely with observation only.

Radiographic examination

Radiographic examinations include multiphase CT angiography, radionuclide scanning and mesenteric angiography; these modalities are useful for detecting the bleeding source in patients with active overt GI bleeding. When interpreting the results of radiographic examinations, the bleeding rate threshold and the intermittent nature of bleeding from small bowel ADs should be considered.

In patients with overt GI bleeding, multi-phase CT angiography can accurately localize the bleeding area as an extravasation when the bleeding rate is over 0.3 mL/min[38]. A recent meta-analysis revealed that CT angiography had a pooled sensitivity of 89% and specificity of 85% for the detection of active bleeding[39]. Meanwhile, CT enterography has been developed to identify the specific cause of small bowel bleeding, although large volumes of a neutral enteric contrast material are needed to distend the intestine. Using a modified, multiphase CT enterography technique, Huprich *et al*[40] found that small bowel vascular lesions can be classified into several categories. Interestingly, the morphology and enhancement pattern seen on CT enterography are well correlated with the aforementioned endoscopic classification[7]. AE can be detected as a focal enhancement that is brightest during the enteric phase and gradually fades during the delayed phase. Arterial lesions, including DL and AVM, are enhanced most brightly during the arterial phase and become invisible during the enteric and delayed phases. Most small bowel AVMs are congenital, appear as relatively large lesions, and sometimes harbor an early draining vein during the arterial phase. VCE reportedly had a significantly higher pooled OGIB diagnostic yield than CT enterography (53% *vs* 34%), mainly because of the higher detection rate for vascular lesions[41]. In contrast, CT enterography was superior to VCE for the detection of small bowel tumors[42]. Although there are concerns regarding radiation exposure and nephrotoxicity from the intravenous contrast agents, CT enterography can be used as a complemental modality to small bowel VCE, possibly enabling the identification of missed small bowel lesions.

Radionuclide scanning using technetium-99m-labeled red blood cells can be used to localize the bleeding source when the bleeding rate is over 0.1 mL/min. The accuracy of a positive test result is reportedly as high as 66%[43]. Despite its sensitivity at detecting bleeding and its noninvasive nature, radionuclide scanning includes difficulty in accurate localization of the bleeding site. Additionally, this technique can only be used for diagnostic purposes; thus, a subsequent endoscopic or angiographic examination is required.

The sensitivity of mesenteric angiography is relatively low[44], because it requires an active bleeding rate of over 0.5 mL/min at the time of the examination to enable diagnosis and treatment. Nevertheless, this technique allows accurate localization and subsequent selective embolization during the same examination. The successful

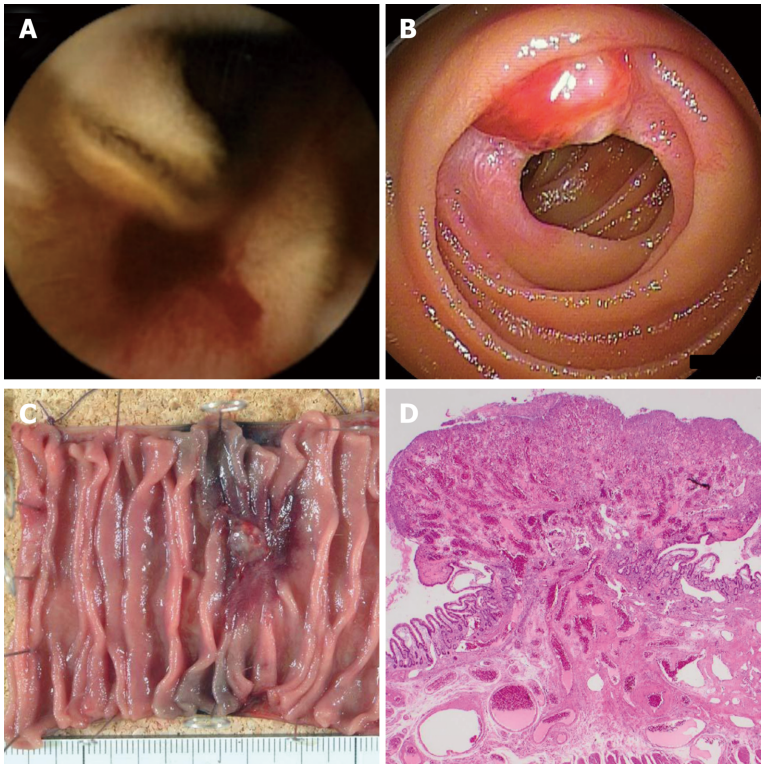

Figure 3 Representative images of arteriovenous malformation. A: Video capsule endoscopy confirmed active bleeding from jejunum in young patient with ongoing overt obscure gastrointestinal bleeding; B: Double balloon endoscopy identified pulsating subepithelial tumor classified into Yano-Yamamoto classification Type 4; C: Subsequent to endoscopic tattooing, surgical resection was performed; D: Pathological examination revealed a vascular malformation in the submucosa.

localization of bleeding is highly dependent on the rate of bleeding, which may be especially useful for patients with hemodynamic instability requiring a large blood transfusions[45].

TREATMENT

Endoscopic treatment

Since the intestinal wall of the small bowel is thin, endoscopists should be cautious of the possibility of perforation. Argon plasma coagulation (APC) involves the use of a jet of ionized argon gas that is directed through a probe that in turn passes through the endoscope, allowing the transmission of the gas to the target lesion without any direct contact with the mucosa[46]. The depth of coagulation is limited to the superficial mucosa and can be controlled using the power setting, gas flow and the duration of coagulation. Optionally, the submucosal injection of a saline and adrenaline solution can be applied for the treatment of Type 1b lesions to avoid muscular damage caused by the long duration of coagulation[47]. Because of its lower incidence of complications[48], APC has become the most widely used method for treating small bowel AEs. APC has enabled favorable outcomes for the treatment of colonic AE, with rebleeding rates of only 2% and 10% at 1- and 2-year follow-ups, respectively[49]. Meanwhile, its efficacy for small bowel AE is controversial, since the pooled rebleeding rate estimated by a recent meta-analysis was 43% in patients with small bowel AEs after endoscopic treatment[50]. Instead, there is a consensus that endoscopic treatment can stabilize the blood hemoglobin level and reduce the need for transfusion, thereby improving the patient's quality of life[51].

Other endoscopic modalities that can be applied in the management of small bowel ADs include endoclips and injection with sclerotherapy. Mechanical hemostasis using endoclips can be attempted for the management of large AEs or arterial lesions such as DL and AVM. Meanwhile, Igawa *et al*[52] reported that a combination of APC and endoscopic injection sclerotherapy with polidocanol was useful for achieving the successful hemostasis of large AEs in the small bowel. Because of the limited clinical data that is currently available, whether coaptive and noncontact cauterizing

therapies differ in efficacy or whether mechanical hemostasis is better for selected lesions remains uncertain.

Radiological embolization

Radiological embolization is generally considered for patients with active GI bleeding in whom endoscopic therapy has failed or is contraindicated because of hemodynamic instability. Subsequent to the detection of the bleeding vessel by mesenteric angiography, superselective transcatheter embolization is performed using microcoils, which have been recommended for small bowel bleeding[53]. Importantly, microcoils can also be used as a radiographic marker to indicate the localization of the bleeding source during surgery[54]. Although the rate of successful immediate hemostasis achieved by embolization is reportedly high (96%), early recurrent bleeding can occur in approximately 20% of patients with lower GI bleeding[43,55]. The reported incidence of severe complications, including arterial dissection and bowel infarction, was 17%, and this high incidence is a major limitation of angiographic embolization[43]. Since mesenteric angiography requires a higher bleeding rate for detection, the benefits of this technique are more notable for DL or AVM, and less so for AE.

Surgical treatment

Now that endoscopic or angiographic treatment has become widely available, surgery is expected to play a minor role and is often the final therapeutic option for uncontrollable bleeding after other treatments, including endoscopic hemostasis or angiographic embolization, have failed. The preoperative or intraoperative localization of the target lesion is necessary to achieve successful surgical resection.

Pharmacological treatment

Even after invasive therapeutic interventions for patients with small bowel ADs, recurrent bleeding can occur since it is usually difficult to determine the locations of all lesions and to detect the true bleeding origin[56]. Pharmacological treatment can be considered as an alternative strategy for such patients.

At present, hormonal therapy is not recommended for patients with ADs, since the results of a large prospective, double-blind randomized trial showed no clinical benefits in terms of reducing the number of bleeding episodes or blood transfusions between patients treated with a combination of ethinyl estradiol and norethisterone and a placebo group[57]. Instead, the efficacy and safety of thalidomide and somatostatin analogs have been investigated in patients with refractory anemia after failed endoscopic treatment for intestinal ADs.

Thalidomide has been shown to reduce bleeding from ADs by suppressing the expression of VEGF[58]. Subsequent to the favorable clinical outcomes that were confirmed in several case reports[59-61], Ge *et al*[58] conducted a randomized open-label trial that included 55 patients with recurrent bleeding from ADs. They found a significant reduction in bleeding episodes in the thalidomide group, compared with the control group after a mean follow-up period of 39 months. Similarly, Chen *et al*[62] reported that a significant reduction in bleeding episodes was confirmed in approximately 80% of the patients who received a course of 100 mg/d of thalidomide for 4 mo during a follow-up period of at least one year. However, previous clinical trials reported high rates of adverse events including fatigue, constipation, peripheral neuropathy, leukopenia and liver toxicity[62,63]. Together with the risk of birth defects associated with the use of thalidomide, these findings suggest that the clinical usefulness of thalidomide is likely to be limited to a small number of patients.

Somatostatin analogs can reduce bleeding from ADs, probably because of a combination of improved platelet aggregation, decreased splanchnic blood flow, increased vascular resistance and the inhibition of angiogenesis[64]. Although several prospective cohort studies have shown the efficacy of somatostatin analogs for the management of recurrent bleeding from ADs[65,66], differences in study design, patient characteristics, therapeutic schedule and follow-up periods complicate assessments of these results. In a recent meta-analysis, a significant effect of somatostatin analogs on bleeding cessation was confirmed, with a pooled odds ratio of 14.5 (95% confidence interval, 5.9-36)[67]. Long-acting release octreotide (OCT-LAR) harbors a significant advantage in reducing the burden of treatment and thus may improve patient compliance. Nardone *et al*[68] showed that the number of bleeding episodes was significantly reduced and that 73.4% of patients with recurrent bleeding from AD achieved a stable hemoglobin level without requiring a blood transfusion after one to three cycles of intramuscular OCT-LAR administration. As for cost-effectiveness, Klímová *et al*. confirmed a reduction in costs of 61.5% before and after the start of OCT-LAR administration[69]. Although the rate of serious adverse events was reportedly low[68], Holleran *et al*[70] expressed some concern regarding the safety of

OCT-LAR, since treatment was discontinued in 30% of the participants. Despite the promising utility of somatostatin analogs, prolonged use is potentially associated with an increased risk of adverse events. Consequently, the efficacy of lanreotide, which is thought to be less toxic and better tolerated, has been recently evaluated for the management of bleeding from intestinal ADs[71].

Overall, pharmacological therapy can be considered as a therapeutic option in patients who have failed or who are not candidates for other invasive therapies. However, most previous studies were performed using retrospective cohorts, included relatively small sample sizes, had short follow-up periods, and were not focused only on small bowel ADs. Multicenter randomized controlled trials are therefore needed to confirm the utility and safety of pharmacological therapy for the management of bleeding from small bowel ADs.

DIAGNOSTIC AND MANAGEMNET STRATEGIES FOR EACH TYPE OF SMALL BOWEL VASCULAR LESION

The choice of examination and treatment method depends on the epidemiology, pathology, and clinical presentation, which should be determined considering the aforementioned differences among each type of small bowel vascular lesion. Proposed diagnostic and therapeutic algorithms are presented in Figures 4 and 5, respectively.

AE

AE is the most common causes of small bowel bleeding and is frequently seen in elderly patients with multiple comorbidities[72]. They are considered to be venous lesions, and they usually manifest as a chronic, well-compensated condition. When OGIB occurs in such patients, VCE should be conducted to confirm the presence of lesions in the small bowel. Prior CT examination may be useful for detecting arterial bleeding caused by DLs or AVMs. Since multiple lesions are reportedly identified in up to 63% of patients[25], observation of the entire small bowel is desirable to determine a suitable insertion route for subsequent DE. For patients with positive VCE, endoscopic intervention is usually conducted to treat target lesions, considering the higher rate of re-bleeding after a positive VCE result[35]. Meanwhile, watchful observation can be applied to patients with a negative VCE result. However, a repeat VCE should be considered if the disease presentation changes from occult to overt or if a rapid decrease in the serum hemoglobin level is confirmed, providing an opportunity to identify missed lesions and to initiate changes in patient management[73,74]. Mesenteric angiography remains as an alternative diagnostic and therapeutic tool, especially for patients with hemodynamic instability.

Endoscopic treatment can be applied to control active bleeding or to stabilize the blood hemoglobin level and reduce transfusion requirements. The decision to proceed with interventional treatment depends on the size, distribution and number of AEs as well as the severity of bleeding. Since it can be difficult to distinguish true bleeding origins from other incidentally identified lesions, the therapeutic target may consist of multiple lesions. Additionally, tiny AEs can also cause active bleeding and anemia requiring transfusions[75]. According to previous reports, initial APC, sometimes in combination with the injection of a saline and adrenaline solution, was successful for hemostasis in most cases[76-79]. Nevertheless, small bowel AEs were prone to recurrent bleeding in up to 43% of cases, even after successful endoscopic treatment[50], with the incidence of recurrent bleeding reportedly increasing to 63% at 5 years[80]. These recurrences may arise from the re-occurrence of AEs, driven by persistent underlying comorbidities, or missed AEs that were beyond the reach of DE. Therefore, small bowel AE remains a diagnostic and therapeutic challenge for gastroenterologists. Meanwhile, endoscopic treatment can be avoided in elderly patients with severe comorbidities, since bleeding from small bowel AEs can stop spontaneously. A conservative approach with iron supplementation remains an option for such patients with mild anemia.

When repeat endoscopic treatments were conducted to manage re-bleeding, special caution is needed for patients with multiple lesions, chronic kidney disease, valvular heart disease, and a history of anticoagulant use, since these factors are closely associated with re-bleeding from small bowel AEs[51,81]. Pharmacological treatments can be considered for patients who have not responded well to other types of treatments including APC or in whom endoscopy is contraindicated. Somatostatin analogs are promising drugs for the management of bleeding from small bowel AEs; however, these drugs are still being introduced as salvage therapy[82]. Recently, additional benefits of somatostatin analogs were confirmed in patients who received endoscopic treatment for small bowel AEs[83], and somatostatin analogs may be useful

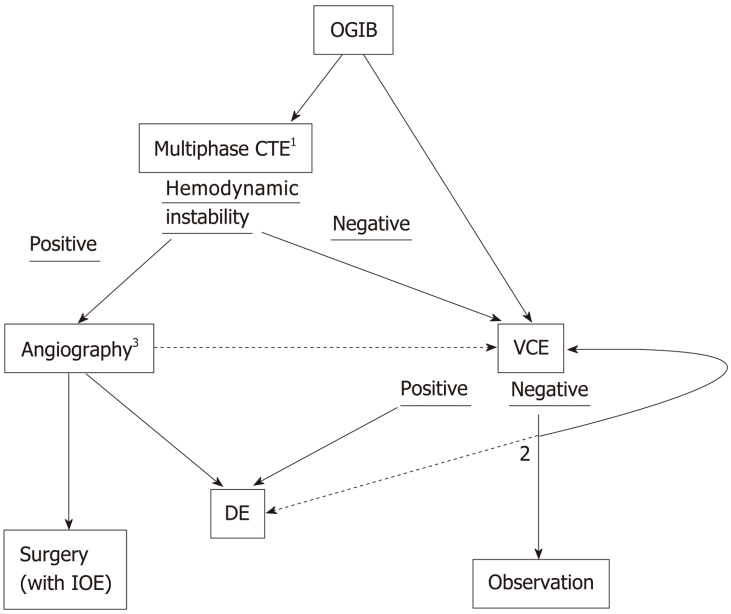

Figure 4 Diagnostic algorithm for small bowel vascular lesions. Note: [1]Computed tomography (CT) scan is especially recommended for patients with ongoing overt obscure gastrointestinal bleeding (OGIB). CT enterography can be replaced to multiphase CT or radionuclide scanning, considering patients general condition; [2]Repeated video capsule endoscopy is recommended if the disease presentation changes from occult to overt or if a rapid decrease in the serum hemoglobin level is confirmed. Urgent deep enteroscopy may be useful to reveal the bleeding source in patients with recurrent overt OGIB; [3]Surgical intervention with intra-operative endoscopy will be conducted when superselective transcatheter embolization was failed. Meanwhile subsequent endoscopic examination is recommended to reveal bleeding origin, even if hemodynamic instability was relieved. OGIB: Obscure gastrointestinal bleeding; CTE: Computed tomography enteroscopy; VCE: Video capsule endoscopy; DE: Deep enteroscopy; IOE: Intra-operative endoscopy; CT: Computed tomography.

as an adjunct therapy, especially for patients with a high risk of re-bleeding.

DL

Although DL is frequently found in the proximal stomach on the lesser curvature, especially within 6 cm of the gastroesophageal junction[84], advances in endoscopic modalities have increased the identification of DL in the small bowel. Using DBE, Dulic-Lakovic *et al*[85] revealed that DL in the small bowel was identified as the source of OGIB in 3.5% of patients, with most of these lesions located in the jejunum. Of note, almost all the patients with small bowel DLs presented with overt bleeding and severe, transfusion-dependent anemia. Similar results have also been confirmed in other previous reports[86-89]. These results suggest that most cases of bleeding from small bowel DL require therapeutic intervention. Nevertheless, bleeding from DL can be easily overlooked despite careful endoscopic examination because of the intermittent nature of bleeding; therefore, a mean of 1.3 to 1.9 endoscopic sessions were reportedly required to reach an exact diagnosis[90,91]. Therefore, VCE should be performed during ongoing overt bleeding. Importantly, the re-bleeding rate from overlooked DL is reportedly high[92]. Although repeated EDG or VCE examinations can be performed to reveal obscure bleeding sources, an urgent anterograde DE may be useful for identifying small bowel DLs, since they are predominantly located in the proximal small bowel. When endoscopic examination fails to localize the bleeding source, a radiographic examination should be considered as a subsequent diagnostic or therapeutic approach[93].

Although the optimal therapeutic approach for small bowel DL has not been evaluated in any large clinical trial, endoscopic intervention has been recommended as the treatment of first choice. Since DL can cause arterial bleeding, mechanical hemostasis should be applied. Dulic-Lakovic *et al*[85] reported that re-bleeding episodes occur in 20% (2/10) of patients with small bowel DL after epinephrine injection therapy and/or APC cauterization[85]. To achieve successful hemostasis for small bowel DLs, they recommended combining two endoscopic techniques, one of which should be a clip application. Similarly, Lipka *et al*[94] showed the efficacy of bipolar electrocoagulation combined with additional clips for the treatment of small bowel DLs. Multiple lesions are rarely reported in small bowel DL[85,94], suggesting that initial

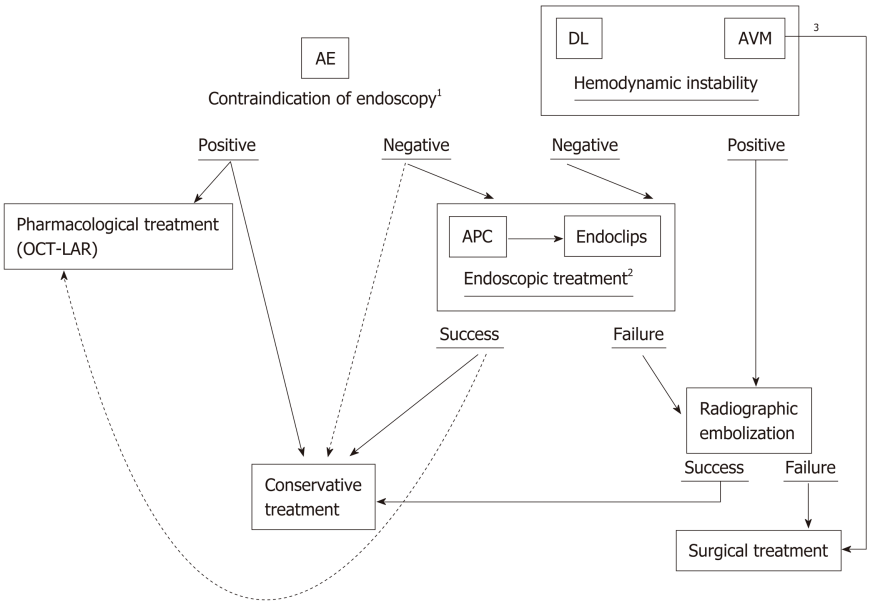

Figure 5 Therapeutic algorithm for small bowel vascular lesions. Note: [1]Pharmacological treatment is recommended for patients whom endoscopy is contraindicated. Meanwhile conservative approach with iron supplementation remains an option for patients with mild anemia; [2]Subsequent pharmacological treatment after successful endoscopic treatment may be useful as an adjunct therapy, especially for patients with a high risk of re-bleeding; [3]Arteriovenous malformation usually requires surgical resection because of their relatively large size and tendency to re-bleed. AE: Angioectasia; DL: Dieulafoy's lesion; AVM: Arteriovenous malformation; APC: Argon plasm coagulation; OCT-LAR: Long-acting release octreotide.

endoscopic treatment is important for reducing the re-bleeding rate and improving patient prognosis. Meanwhile, the efficacy of pharmacologic treatment has not been confirmed in patients with small bowel DLs. Surgical intervention can be considered after other treatment approaches, including radiographic embolization, have failed.

AVM

Similar to DLs, intestinal AVMs can also cause life-threatening bleeding[10,11,54,95]. Although the incidence of small bowel AVMs is quite low, such lesions can be identified as the bleeding source in patients with overt OGIB harboring severe, transfusion-dependent anemia. Since most causes of AVM are congenital, special caution is needed for younger patients. VCE is useful diagnostic modality for detecting small bowel AVMs. Considering the high detection rate, CT enterography is also recommended for detecting small bowel AVMs[42]. Similar to DLs, small AVMs that present endoscopically as flat or mildly elevated hemorrhagic spots can be treated using mechanical hemostasis with endoclips during subsequent DE examinations[7]. However, most small bowel AVMs require surgical resection because of their relatively large size and tendency to re-bleed. In patients requiring surgical interventions for small bowel AVMs, identifying the location of the lesion can be difficult during surgery[95]. Mesenteric angiography and subsequent microcoil embolization are reportedly effective for primary hemostasis and preoperative localization[95]. Additionally, endoscopic tattooing[10] or marking clips[96] and intraoperative indocyanine green injections[54] are reportedly useful for localizing the target lesion.

CONCLUSION

Advances in endoscopic modalities have increased the identification of small bowel abnormalities. Small bowel vascular lesions are the most common causes of small bowel bleeding. The term "AD" is usually used to describe vascular abnormalities including AE, DL and AVM. As shown in this review, the epidemiology, pathology, clinical presentation and optimal management approaches differ widely according to lesion type, and the diagnosis and treatment of these lesions should thus be considered separately. Since the choice of diagnostic and therapeutic investigation is strongly affected by the clinical presentation of the patient, clinicians should understand the characteristics of each modality and select adequate method and

timing for clinical application. Yano-Yamamoto classification enables real-time endoscopic diagnosis of small bowel vascular lesions and helps in the selection of an optimal treatment approach. Although pharmacological treatments have been applied to manage bleeding from small bowel vascular lesions, multicenter randomized controlled trials are needed to confirm the utility and safety of them.

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