Chapter 7
Small Bowel

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Epidemiology and Natural History

The reported prevalence of a SB lesion in patients presenting with either occult or overt GIB is about 5–10% [2]. Regarding occult GIB specifically, combined data from four different studies of patients with IDA (total 381 patients) by *Rockey et al*, found a pooled prevalence of SB bleeding in 3% [3].

As one might expect, occult SB bleeding has been shown to have a lower recurrence rate compared to that of overt bleeding. One study demonstrated a 12-month re-bleeding rate of 19.5% in untreated occult bleeding compared to 38.9% in overt bleeding, as well as lower rates of subsequent hospitalization and blood transfusion in occult bleeding [4]. Use of medications such as anticoagulant and/or anti-platelet agents are a risk factor for recurrent SB bleeding, though interestingly, there is no prospective data to support clinical benefit in discontinuation of such medications. [5]

Etiology

Regarding the etiology of SB bleeding, patient age has been demonstrated to be associated with the type of underlying lesion. Younger patients are more likely to be diagnosed with occult SB bleeding related to inflammatory bowel disease, Meckel's diverticulum, and various polyposis syndromes (e.g., familial adenomatous polyposis (FAP), Peutz-Jeghers), while older patients are more likely to be diagnosed with

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Table 7.1 Etiologies of occult small bowel bleeding

Common etiologies in patients younger than 40 years	Common etiologies in patients older than 40 years	Rare etiologies in all ages
Crohn's disease	Angiodysplasia	Telangiectasias (sporadic or congenital)
Small bowel neoplasia	Small bowel neoplasia	Small bowel varices and/or portal hypertensive enteropathy
Dieulafoy's lesion	Dieulafoy's lesion	Blue rubber bleb nevus syndrome
Polyposis syndromes	NSAID-induced ulcers	Amyloidosis
Meckel's diverticulum		Henoch-Schonlein purpura
		Hematobilia
		Hemosuccus entericus
		Kaposi's sarcoma

NSAID; nonsteroidal anti-inflammatory drug

angiodysplasia and NSAID-induced enteropathy. Patients of any age can develop bleeding related to SB neoplasia (GI stromal tumor (GIST), carcinoid, lymphoma, and adenocarcinoma) and Dieulafoy's lesions [2, 6, 7]. Rarer causes of SB bleeding include Henoch-Schoenlein purpura, blue rubber bleb nevus syndrome, Kaposi's sarcoma, amyloidosis, hereditary hemorrhagic telangiectasias, and hematobilia, among others (see Table 7.1). There is no data available to suggest patient ethnicity is associated with specific SB pathology [2].

Vascular Lesions

Small intestinal vascular lesions, including angiodysplasia, telangiectasia, and Dieulafoy's lesions, are a group of heterogeneous diseases, which are the most common causes of occult SB bleeding [8, 9]. The true prevalence of vascular lesions in occult bleeding has not been well studied, but in patients with possible small bowel bleeding (PSBB), SB vascular lesions are reported in about 40–50% of cases [10, 11].

Angiodysplasia (AD; otherwise known as angioectasia) is the formation of aberrant and abnormally dilated, thin-walled (little or no smooth muscle), and tortuous blood vessels, which form within the mucosa or submucosa of the GI tract and have a propensity to bleed [9]. Studies have suggested that these lesions form due to either mechanical dilation related to vessel congestion, sphincter failure from chronically increased intestinal wall pressure, or increased angiogenesis from overexpression of vascular endothelial growth factor (VEGF) due to hypoxia from chronic low-grade vessel obstruction [8].

Clinical risk factors for development of AD include older age and presence of medical comorbidities, such as chronic kidney disease, valvular or ischemic heart

disease, congestive heart failure, and hypertension [12–15]. Bleeding from AD in patients with aortic valve stenosis is well-described and known as Heyde's syndrome. This association is theorized to be due to an acquired von Willibrand's factor (vWF) deficiency related to loss of high molecular-weight vWF multimers from high shear stress in the aorta [10, 16–18]. Although not limited to the SB, patients with left ventricular assist devices have also been shown to have increased GI bleeding from AD, thought to be related to a similar mechanism of acquired vWF-deficiency [19].

Telangiectasias (otherwise known as arteriovenous malformations, AVMs) are typically larger than AD, thick-walled with excessive smooth muscle, and without capillaries, involving direct connections between arteries and veins. Telangiectasias can be sporadic or congenital [16]. The autosomal dominant vascular disorder, hereditary hemorrhagic telangiectasias (HHT; otherwise known as Osler-Weber-Rendu syndrome), is most commonly associated with presence of telangiectasias, and presents most typically as epistaxis in childhood, with development of chronic GI bleeding (overt or occult) and IDA later in life. Systemic sclerosis (scleroderma) and Turner's syndrome are also associated with telangiectasias (Fig. 7.1) [16].

Dieulafoy's lesion (DL) is another vascular cause of GIB, which can present as occult bleeding or as a life-threatening overt hemorrhage. The etiology of this lesion is poorly understood, but may be similar to that of AD described above. DLs are much more commonly identified in the stomach, rather than the duodenum or jejunum [7, 8, 16, 20, 21].

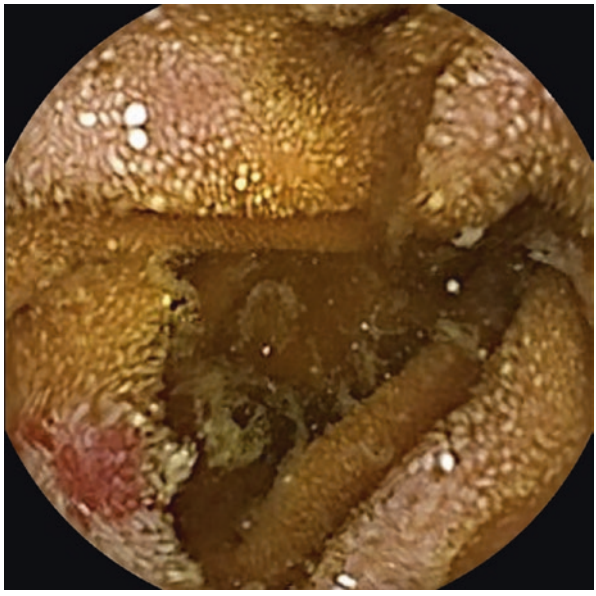

Fig. 7.1 A small bowel telangiectasia (also known as arteriovenous malformation, AVM) identified during video capsule endoscopy in a patient with systemic sclerosis. (Image courtesy of Micheal Tadros, M.D)

Small Bowel Ulcers

One of the most common etiologies for ulcer formation in the small intestines is Crohn's disease (CD), a chronic progressive inflammatory disease which can involve any segment of the gastrointestinal tract [22]. Although its exact etiology remains unclear, it seems to result from the complex interplay between genetic factors, environmental influences, and the gut microbiota. The prevalence of CD is highest in Europe (322 cases per 100,000), Canada (319 per 100,000) and the USA (214 per 100,000) It is equally distributed among men and women and most commonly presents between the second and fourth decades of life [22].

Around 30% of patients with CD have isolated SB disease (Fig. 7.2) [22]. Ulcer formation is one manifestation of the transmural inflammation that characterizes CD, and is not specific to the small intestines. A significant percentage of patients will go on to develop complications from this chronic inflammation, including fistulas, abscess, and strictures [22, 23]. symptoms including abdominal pain, diarrhea, fatigue, weight loss, growth failure, or extra-intestinal manifestations such rash, arthropathy, ocular inflammation, or hepatobiliary disease [22, 23]. IDA which may result from chronic GI blood loss and/or intestinal malabsorption, is not uncommon in these patients (Fig. 7.3).

Non-steroidal anti-inflammatory drug (NSAID) enteropathy is another common but under-diagnosed cause of small bowel ulceration. Patients commonly self-prescribe NSAIDs owing to their well-demonstrated anti-inflammatory and analgesic effects, though frequently underreport their use [24]. While commonly prescribed acid suppressive regimens (e.g., proton pump inhibitors, H2-receptors antagonists) have reduced NSAID-related gastroduodenal complications, more distal small intestinal complications out of reach of a standard upper endoscope are more

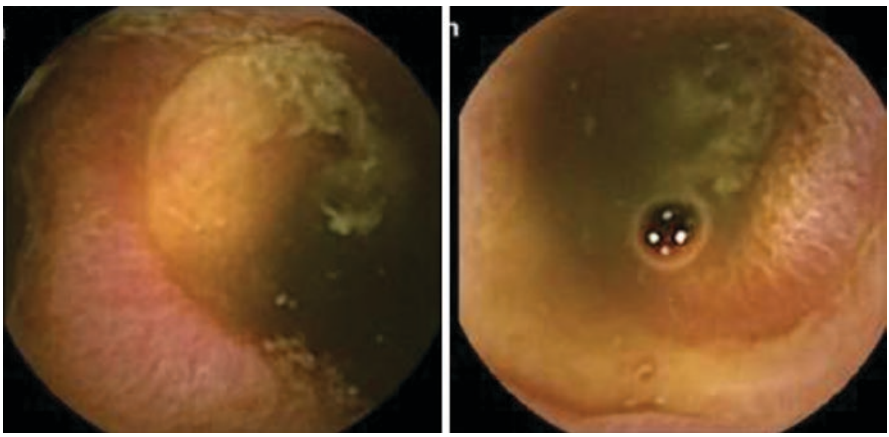

Fig. 7.2 Small bowel ulcerations identified during video capsule endoscopy in a patient with IDA who was ultimately diagnosed with isolated small bowel Crohn's disease. (Images courtesy of Haleh Vaziri, M.D)

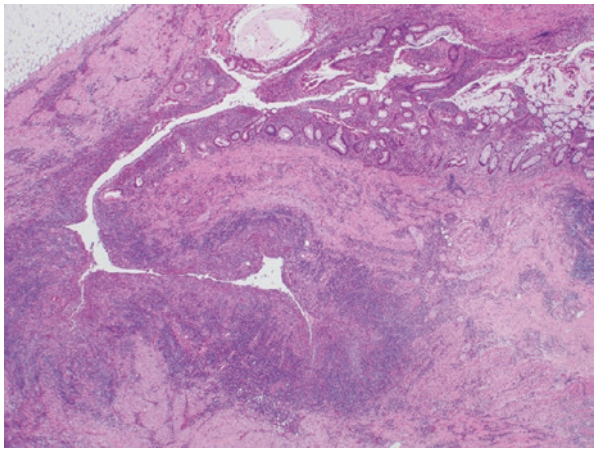

Fig. 7.3 Crohn's disease with fissuring ulcer involving the ileum [Hematoxylin and eosin, x20]. (Image courtesy of Dr. Hwa Jeong Lee)

difficult to diagnose. Studies have demonstrated a high incidence of NSAID enteropathy, occurring in 53–80% of healthy short-term users, and 50–71% of long-term users [24]. Iron deficiency anemia can result from occult or overt blood loss, as well as impaired mucosal iron absorption. Protein-losing enteropathy, NSAID-induced small bowel strictures, and small bowel diaphragm disease (pathognomonic, with predilection for the distal small bowel) can all occur secondary to more chronic NSAID use [24].

Meckel's Diverticulum

Meckel's diverticulum (MD) is a congenital malformation that affects between 2–4% of the general population, and occurs due to incomplete closure of the vitelline duct. Bleeding originating from the MD is generally uncommon, but relatively more common in children than adults, and most often results from ulceration of ileal mucosa due to acid production from ectopic gastric mucosa located within the diverticulum [34] (Fig. 7.4).

Small Bowel Tumors

Small bowel tumors, both benign and malignant, are relatively rare, accounting for only 2–5% of all GI tumors [36]. A large retrospective chart review in 2013 examined the incidence of SB tumor types in patients referred for double balloon enteroscopy (DBE) due to occult GIB. In patients with malignant tumors, SB neuroendocrine tumor (NET, formerly known as carcinoid) was the most prevalent (11.1% of patients), followed by GIST, lymphoma, and adenocarcinoma (8.3% each). In the patients who had benign tumors, adenoma (8.3%) and hamartoma (5.6%) were most common [6].

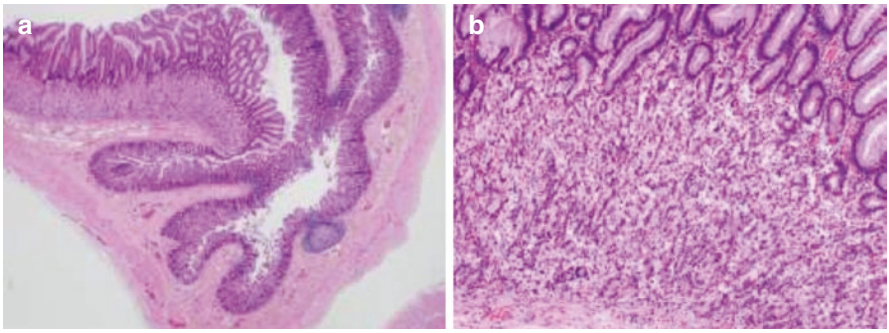

Fig. 7.4 (A on the left & B on the right): (**a**) Meckel's diverticulum of the ileum [Hematoxylin and eosin, x20]. (**b**) Higher magnification of the Meckel's diverticulum showing gastric type oxyntic mucosa within the diverticulum [Hematoxylin and eosin, x100]. (Images courtesy of Dr. Hwa Jeong Lee)

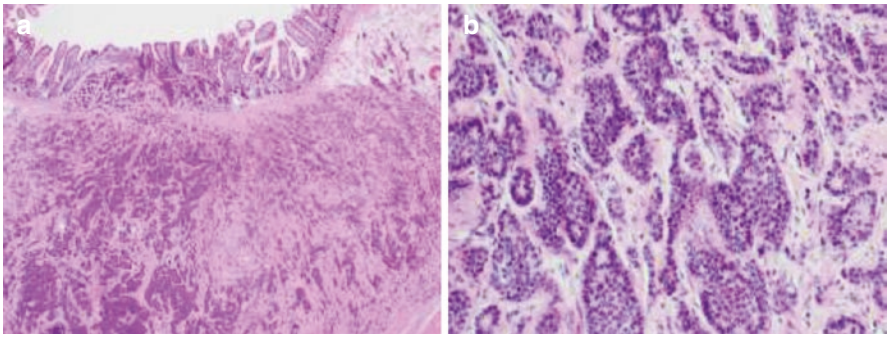

Fig. 7.5 (A on the left & B on the right): (**a**) Well-differentiated neuroendocrine neoplasm of the small bowel [Hematoxylin and eosin, x20]. (**b**) Same tumor under higher magnification showing "salt and pepper" pattern chromatin of the nuclei [Hematoxylin and eosin, x200]. (Images courtesy of Dr. Hwa Jeong Lee)

Neuroendocrine Tumors (NETs)

Neuroendocrine tumors of the small bowel are rare. The SEER (Surveillance, Epidemiology, and End Results) database reported an incidence of jejunal/ileal NETs of 0.67 per 100,000 per year [25]. The median age of diagnosis is 64 years, with most patients presenting with non-specific symptoms. Given their indolent course, 60–80% of patients with SB NETs have metastatic disease to the liver at the time of diagnosis [25]. The overall prognosis for locally advanced and metastatic small bowel NETs is favorable, with 10-year survival rates between 40–70% [26]. Treatment typically involves surgical resection for localized disease and/or somatostatin analogue therapy for metastatic disease [26, 27] (Fig. 7.5).

Sporadic Adenocarcinoma

Sporadic adenocarcinoma of the small bowel is also rare, with the majority of tumors occurring within the duodenum and with incidence decreasing distally throughout the jejunum and ileum. One exception is a significantly higher rate of ileal adenocarcinoma in Crohn's ileitis, though it should be noted that patients with CD in general have a 20–30 times higher rate of developing any SB adenocarcinoma [27]. The molecular phenotype of SB adenocarcinoma has been shown to be similar to that of colorectal adenocarcinoma with several similar molecular mutations involved in their malignant transformation [28]. Similar to NETs, the median age at diagnosis of SB adenocarcinoma is the sixth decade of life. Also, patients typically present with non-specific symptoms and are at an advanced disease stage at the time of diagnosis. Unfortunately, in contrast to NETs, the prognosis is generally poor, with a median 5-year survival of 10–40% for stage-III disease and 3–5% for stage-IV disease [27, 28]. Management typically involves surgical resection, with limited data available to guide adjuvant or neoadjuvant chemotherapy [27, 28].

Other Neoplastic Conditions

Several inherited conditions including Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, MUTYH-associated polyposis, serrated polyposis syndrome, juvenile polyposis syndrome, and Cowden syndrome are associated with an increased risk of SB malignancies, highlighting the importance of prompt disease recognition and initiation of relevant screening protocols [29].

Primary gastrointestinal lymphoma is the most common extra-nodal presentation of lymphoma, with the majority of tumors located within the stomach and, less commonly, the small intestines. Management is typically similar to that of lymphomas arising from outside the GI tract [27].

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumor, up to a third of which occur within the small bowel (most commonly in the jejunum). They are characterized by a positive CD117 antigen with expression of c-kit receptor tyrosine kinase [27]. These tumors are most commonly benign, though tumor size, high mitotic rate, and presence of necrosis increase risk of malignancy. Treatment options include close observation, surgical resection, adjuvant/neoadjuvant imatinib, and/or locoregional therapy for liver metastasis [30] (Fig. 7.6).

Portal Hypertensive Bleeding

Portal hypertension (PH) is very common and develops secondary to a number of disorders, with cirrhosis being the most common etiology in western countries, and schistosomiasis and portal vein thrombosis the most common in non-western

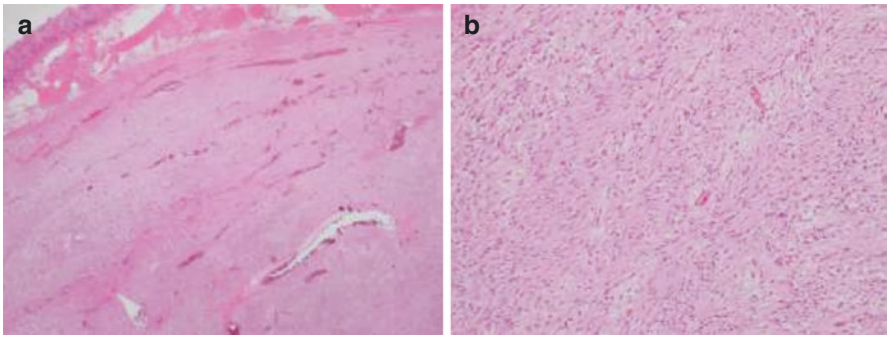

Fig. 7.6 (A on the left, B on the right) (**a**) GIST of the small bowel with involvement of the bowel wall [Hematoxylin and eosin, x40]. (**b**) Higher magnification of the same tumor showing the proliferation of spindle cells [Hematoxylin and eosin, x100]. (Images courtesy of Dr. Hwa Jeong Lee)

countries [31]. PH occurs due to increased resistance to portal blood flow secondary to structural and dynamic changes (vasoconstriction) within the liver and leads to an increase in the portal pressure gradient [31]. Increases in splanchnic blood flow result in systemic hypotension and angiogenesis, and often lead to formation of portosystemic collaterals (varices) and microcirculatory changes within the gastrointestinal mucosa [31–33]. When varices form within the SB, they are referred to as ectopic or SB varices, and though they are rare (only 5% of all variceal bleeding), they may result in life-threatening overt bleeding [32, 33].

Alternatively, microcirculatory changes within the SB can occur secondary to portal hypertension and are referred to as portal hypertensive enteropathy (PHE). PHE commonly leads to occult bleeding [33]. The reported prevalence of PHE is variable (15–82% of cirrhotic patients), and should be suspected in advanced cirrhosis (Child-Pugh class C) in the presence of portal hypertensive gastropathy [33]. Endoscopically, PHE has a variable appearance, including mucosal edema, loss of vascularity, friability, mosaic-like pattern, inflammatory polyps, and angiodysplasia-like lesions. Unfortunately, histopathologic findings are non-specific and the diagnosis must be made in conjunction with other clinical data [33]. There is insufficient evidence to guide management at this time, though vasoactive medications (beta-blockers, octreotide), argon plasma coagulation, transvenous intrahepatic portosystemic shunting (TIPS), surgical resection of affected SB segment, and liver transplantation have all been described [33].

Celiac Disease

Though celiac disease has previously been thought to be a potential cause for occult SB bleeding with IDA, more recent data has suggested otherwise. A 2006 study using radiolabeled red blood cells, found no evidence of significant gastrointestinal blood loss in patients with untreated celiac disease, and at this time, IDA seen in patients with celiac disease is thought to be a result of intestinal iron malabsorption, rather than occult SB blood loss [37].

Diagnostic Work Up

Second-Look Endoscopy

A long list of factors can potentially influence the quality of any given endoscopic exam, including the endoscopist's experience, skill level or fatigue; the patient's clinical stability and movement; type of anesthetic used and complications related to anesthesia; the quality of bowel preparation and presence of food/blood within the lumen; as well as procedure environment, presence and quality of support staff, and the available equipment. Given these potential limitations, it is not surprising that a significant number of upper and lower GIB sources may be missed during initial endoscopic workup for occult GIB.

The incidence of a missed lesion within reach of a standard endoscope is between 10–40%, while that within reach of a standard colonoscope is between 2–14% [38–42]. The most commonly reported missed lesions are vascular lesions, but others include Cameron ulcers, portal hypertensive gastropathy, peptic ulcer disease, erosive mucosal disease (esophagitis, gastritis, duodenitis), and malignancy [38, 41, 42].

The decision regarding whether to perform a repeat upper and/or lower endoscopy before proceeding with a SB evaluation is complicated. As stated above, repeat upper endoscopy has been shown to have a higher diagnostic yield than repeat lower endoscopy. Factors which may affect this decision include the timing and quality of the prior procedure, the presence of blood or food in the upper GI tract, the quality of the prior colon preparation and the type and severity of bleeding. Repeat colonoscopy should always include an examination of the terminal ileum, to evaluate for a more proximal source of SB bleeding [42].

If the decision is made to repeat an evaluation of the proximal GI tract, consideration should be given to performing a push enteroscopy, where either a specialized commercially-available endoscope or pediatric colonoscope is used to perform a more extensive proximal SB evaluation (including the distal duodenum and proximal jejunum). Studies have demonstrated repeat evaluation with push enteroscopy to have a 38–70% higher diagnostic yield when compared with EGD alone [38, 39]. While a pediatric colonoscope can typically advance 45–60 cm beyond the ligament of Treitz, a push enteroscope may be advanced 70–90 cm beyond the ligament of Treitz if variable stiffness design is utilized [43, 44].

Video Capsule Endoscopy

Up until 2001, the SB was studied non-invasively using relatively ineffective radiographic and nuclear medicine modalities such as SB follow-through (SBFT), SB enteroclysis, CT, MRI, and radionuclide imaging. While CT and MRI without enterography can visualize abdominal masses, vasculature, and solid organs with high sensitivity and specificity, they are unable to provide adequate information

regarding the small intestinal wall and the etiology for occult PSBB in most instances [45]. SBFT and SB enteroclysis specifically have been found to have low sensitivity and specificity in diagnosing SB sources of occult bleeding [46]. The introduction of video capsule endoscopy (VCE) in the United States in 2001 drastically changed the field of gastroenterology by allowing for near-complete non-invasive visualization of the entire SB mucosa in the majority of patients [45].

VCE is a procedure that involves swallowing or having endoscopically deployed a small capsule which contains a wireless camera programmed to take thousands of pictures as it traverses the GI tract. The size of a VCE varies by model but typically measures between 10–13 mm in diameter by 24–31 mm in length [47]. Most models incorporate a single camera lens associated with a 140–170-degree field of view, though one model has four different laterally-placed cameras with a reported 360-degree field of view. The capsule emits light and images are taken either at a predetermined frequency or, more recently, at an adaptive rate with fewer images taken during slower transit to avoid redundant imaging. Images are transmitted by radiofrequency to a wireless recorder carried by the patient and later interpreted by a physician [47].

Though most VCE manufacturers recommend a 12-hour clear liquid diet leading up to the study, a 2008 meta-analysis demonstrated superior SB visualization and diagnostic yield in patients who had undergone a bowel purge prior to VCE [48]. Low volume bowel purges provide a similar preparation quality when compared with higher volume preparations [49]. Medications that can cause gastroparesis, such as narcotics, anticholinergics, and antihistamines, should be discontinued 2–3 days prior to VCE administration. If this is not possible, pro-kinetic agents can be prescribed to reduce the risk of delayed gastric passage and an incomplete study [47].

A complete study is defined as the capsule reaching the cecum within the available recording time. Battery life ranges from 8–15 hours, with studies demonstrating an overall completion rate of 79–90% [45, 47]. The most important VCE complication to consider is capsule retention, defined as non-passage within 2 weeks, and which occurs in only 1–2% of those being evaluated for SB bleeding [47]. Though known SB luminal obstruction or ileus are the only absolute contraindications to VCE, caution should be exercised in patients with a history of abdominal radiation, heavy NSAID use, or a history of IBD, specifically Crohn's enteritis and bowel strictures, with a reported capsule retention rate of up to 13% in these cases. In patients at increased risk for capsule retention, luminal patency should first be demonstrated with either SB imaging or a patency capsule [47, 50]. Finally, intestinal perforation due to capsule impaction is very rare, with only a few cases reported [51–53].

PSBB remains the most common indication for performing VCE with a higher diagnostic yield observed in overt compared to occult SB bleeding [2, 54]. Other factors found to be predictive of a positive capsule study include test performance within 2 weeks of bleeding episode, male sex, age >60 years, cardiac and renal comorbidities, and inpatient status [2, 55, 56]. It should be noted that recent guidelines have supported a trial of oral iron supplementation prior to routine use of VCE in asymptomatic patients with IDA, though this recommendation is based upon very low quality evidence [35].

The widespread use of VCE as the initial diagnostic modality in PSBB is largely related to its high positive (94–97%) and negative predictive value (83–100%), though this data pertains to both occult and overt bleeding with data specific to occult bleeding not available [2, 54, 57]. The overall reported diagnostic yield of VCE in occult bleeding specifically following initial negative bidirectional endoscopy is variable and has been reported to range between 32–76% [58–61].

One possible explanation for this reported variability is that studies performed soon after introduction of VCE in 2001 included many patients with longstanding history of obscure GIB, associated with significant anemia and repeated negative testing due to limited diagnostic options. This likely resulted in a higher pre-test probability for SB lesions in this cohort of patients undergoing VCE. Recent larger studies showing a diagnostic yield of 50% is likely a more accurate reflection of current everyday clinical practice [45, 59].

Patient selection, including clinical factors such as type of bleeding (overt versus occult), presence of IDA, minimum hemoglobin value, previous transfusion requirements, and duration of suspected bleeding, have also been shown to significantly impact the diagnostic yield of VCE [62].

Several studies, including a large 2017 systematic review and meta-analysis, have demonstrated a low overall re-bleeding rate in GI bleeding following a negative VCE [63]. The indications or clinical benefit of a repeat VCE in the setting of occult bleeding following an initial non-diagnostic VCE remain controversial. Patients who may benefit from a repeat VCE include those with a further drop in hemoglobin >4 gm/dL, and/or a transition from occult to overt bleeding [64, 65]. In the absence of these criteria, there also has been no demonstrated improvement in the diagnostic yield of VCE when repeated immediately following an initial negative study [66].

Limitations of VCE include a moderate false positive rate, with findings reported in ~15% of healthy individuals [67] and a false negative rate between 10–36% [56, 68]. Of note, VCE has been reported to miss up to 56% of clinically important lesions within the duodenum and proximal jejunum, probably due to the greater transit speed of the capsule within the sharply angulated duodenal sweep and active peristalsis [69]. This known limitation lends additional support to performing push enteroscopy during second-look endoscopy to obtain a more thorough evaluation of the proximal SB.

Radiography of the SB

Despite the medical advances related to VCE described above, there is still no clear consensus on how best to proceed following non-diagnostic or ambiguous VCE results. While several older radiographic techniques (SBFT, SB enteroclysis, radionuclide imaging) offer limited diagnostic utility, more recent developments in cross-sectional imaging have helped CT enterography (CTE) and MR enterography (MRE) to emerge as useful diagnostic tools in certain clinical situations [59].

CTE has been shown to possess diagnostic utility in patients with SB bleeding. A large meta-analysis has shown an overall pooled diagnostic yield of about 40%, with a range between 13–83% for this modality in combined occult and overt PSBB, which is lower than that reported for VCE (see above) [59]. Given the significantly lower diagnostic yield, in the absence of contraindications to VCE, CTE has been utilized mostly as second-line diagnostic test for this indication.

In occult PSBB following a non-diagnostic VCE, the diagnostic utility of CTE is somewhat uncertain, but probably low. Following non-diagnostic VCE, several small studies have demonstrated a diagnostic yield between 0–15% in patients with occult bleeding specifically, whereas patients with overt bleeding were found to have a significantly higher yield between 50–67% [70, 71].

While VCE has been demonstrated to be superior to CTE in diagnosing SB vascular lesions [72–75], studies have shown CTE to be more accurate in diagnosing SB masses [73, 75, 76]. Specifically, studies of patients simultaneously undergoing both CTE and VCE have identified CTE to have a higher sensitivity and VCE to have a higher false positive rate in the evaluation of SB tumors [75, 76].

In general, while data have shown CTE and VCE to be complimentary diagnostic modalities in occult PSBB (i.e., CTE superior in diagnosing masses; VCE superior in diagnosing vascular abnormalities), the overall diagnostic yield of CTE is greater in overt compared to occult bleeding, and several studies have challenged the clinical necessity of reflexively following-up a non-diagnostic VCE study with CTE. Ultimately, clinical judgement must be used to guide study selection, with consideration given to patient age, persistent/progressive anemia, likelihood of SB malignancy, and patient preference.

Very few studies have investigated the use of MRE in evaluating SB sources of bleeding, but this modality may have a role in patients who have a contraindication to CT or when trying to limit radiation exposure. [72, 73]

Deep Enteroscopy

Deep enteroscopy is a combined diagnostic and therapeutic procedure involving an endoscopic evaluation of the proximal and distal SB, accomplished either by an oral or rectal approach. Deep enteroscopy is accomplished with either of two techniques: (i) balloon-assisted enteroscopy, including double-balloon enteroscopy (DBE) and single-balloon enteroscopy (SBE); and (ii) spiral enteroscopy (SE). This section will review the technique, diagnostic utility, and potential complications of these two approaches.

Balloon-Assisted Enteroscopy

DBE was first reported in 2001 by *Yamamoto et al*, and introduced in the United States for clinical practice in 2004 [77]. Shortly thereafter, SBE was introduced in the U.S. in 2007 [78]. A single- and double-balloon enteroscope can be inserted to

a depth of 240–360 cm distal to the pylorus using the antegrade (oral) approach, and alternatively, up to 140 cm proximal to the ileocecal valve using the retrograde (rectal) approach. The standard accessory channel within each scope allows for passage of nearly all standard diagnostic and therapeutic endoscopic equipment [2]. DBE includes two latex balloons, one positioned on the distal end of an overtube and the second, on the distal end of the enteroscope. The SBE includes a silicone balloon at the distal end of an overtube but utilizes the tip of the enteroscope to anchor in place of a second balloon in DBE. Patients with a latex allergy should not undergo DBE [2].

Both DBE and SBE utilize the technique of push and pull enteroscopy, effectively shortening the SB to prevent looping, accomplished by drawing/pleating the SB back onto the enteroscope using the balloons, overtubes, and, in SBE specifically, enteroscope tip deflection [77].

Unfortunately, the overwhelming majority of studies investigating the diagnostic yield of balloon-assisted enteroscopy do not distinguish between occult and overt bleeding. However, based upon the select few studies which do specify outcomes, the diagnostic yield of DBE in occult bleeding following negative bidirectional endoscopy and VCE appears to range between 60–80% (Fig. 7.7) [79–82]. While there is conflicting data regarding the difference in diagnostic yield between occult and overt bleeding, several studies have demonstrated an overall lower diagnostic yield of DBE in patients with occult bleeding [2, 83–92].

Several meta-analyses have demonstrated similar diagnostic yields between VCE and DBE. One meta-analysis demonstrated pooled diagnostic yields in VCE and DBE of 61.4% and 56.3%, respectively [93]. Other data has shown that VCE and DBE diagnose vascular, inflammatory, and mass lesions in similar percentages of patients (24%/24%, 18%/16%, and 11%/11%, respectively) [1]. Given VCE commonly precedes DBE, with its result being available to the endoscopists performing DBE, one might expect a detection bias to affect the reported diagnostic yields of DBE. However, in two small studies comparing the diagnostic yields of VCE and DBE in which the endoscopists were blinded to the results of VCE, the

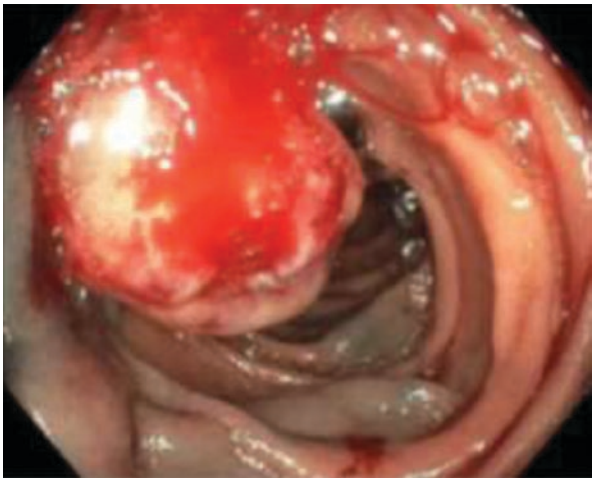

Fig. 7.7 A friable, ulcerated, and bleeding proximal small bowel tumor identified during double-balloon enteroscopy in a patient with iron-deficiency anemia and prior negative EGD, colonoscopy, and video capsule endoscopy. Biopsies confirmed the diagnosis of GIST. (Image courtesy of Micheal Tadros, M.D)

pooled data demonstrated no significant difference in diagnostic yield between the two methods [94–96].

The diagnostic yield of DBE in combined overt and occult bleeding has been shown to increase significantly when preceded by a positive VCE, a diagnostic sequence referred to as 'VCE-guided DBE' or 'targeted DBE' [88, 96]. On the other hand, data has demonstrated significantly lower diagnostic yields in DBE following a non-diagnostic VCE, ranging between 27.5–39.6% [88, 97].

Given the similar diagnostic yields of VCE and DBE, the high positive and negative predictive value of VCE in preceding DBE, along with the more invasive nature of DBE, VCE should be performed first in the vast majority of patients with occult PSBB.

Similar to DBE, there is very little data describing outcomes of SBE in patients with occult PSBB, specifically. Based upon the few studies that do specify outcomes in occult bleeding, the diagnostic yield ranges between 52–67% [98–100]. When evaluating patients with occult or overt PSBB, SBE has been demonstrated to have a similar diagnostic yield compared to DBE [99–106]. Interestingly, the diagnostic yield of enteroscopy has not been shown to correlate with length of SB visualized and complete enteroscopy is often unnecessary [103, 106].

The main limitations of both DBE and SBE are their invasive nature, prolonged procedural time, and need for additional endoscopic personnel [2]. However, these procedures have been demonstrated to have low rates of complication overall [2, 86, 87]. Most of the available data regarding frequency of adverse events is based upon DBE, which may also apply to SBE. According to the ASGE technology committee, the most common adverse events experienced following DBE include pancreatitis, bleeding, ileus, and perforation, occurring in between 1.2–1.6% of cases. Specifically, pancreatitis has been reported in 0.3% and perforation in between 0.3–0.4% of cases, most often occurring following large polypectomies. Complication rates can be higher (up to 4%) when therapeutic interventions are performed or with a history of surgically altered anatomy. Complications following SBE are also rare and include abdominal pain, fever, mucosal tears, bleeding, pancreatitis, and perforation. Perforation, specifically, has been reported in about 0.3% of SBE cases [2, 87]. A 2017 meta-analysis comparing DBE and SBE showed no significant difference in complication profiles [86].

Spiral Enteroscopy

Developed in 2007, SE is a unique method of examining the SB, which utilizes a disposable overtube with soft raised spiral ridges rather than balloons. A single- or double-balloon enteroscope can be used along with this overtube, though the enteroscope balloons are not needed during the procedure. The enteroscope is advanced through the SB with the assistance of a second person, who continuously rotates the spiral overtube in a clockwise fashion, slowly drawing the SB over the overtube, while the endoscopist keeps the enteroscope tip centered within the intestinal lumen.

As with DBE and SBE, this procedure can be performed via both the antegrade (oral) or retrograde (rectal) approach [2, 87].

In studies looking at both occult and overt bleeding, SE has a reported diagnostic yield of between 33–59% [87, 107, 108]. Despite this lower reported yield, a 2017 meta-analysis comparing balloon enteroscopy (DBE and SBE) and SE found no significant difference in diagnostic yield between these techniques [109].

Although pooled data has identified no significant difference between balloon-assisted and SE in depth of maximal insertion, significantly shorter procedural time has been reported with SE [109, 110]. Similar to balloon-assisted enteroscopy, SE has been very well tolerated overall. More common potential adverse events include mucosal tearing and abrasions. Perforation has been reported in about 0.3% of cases. There have been no reported cases of pancreatitis [2, 87].

In patients with occult PSBB, there are several indications for pursuing deep enteroscopy, including a positive VCE requiring endoscopic intervention or tissue sampling, unclear diagnosis with contraindication to VCE, and negative VCE with high clinical suspicion for SB pathology [2]. While the management of patients with occult bleeding following a negative VCE study remains largely unclear at this time, with some data supporting close observation or repeat VCE study, total enteroscopy with DBE/either balloon-assisted or spiral enteroscopy may be pursued if there is a high clinical suspicious for a SB lesion.

Radionuclide Imaging of the SB

Although much less commonly utilized in the workup of obscure PSBB, radionuclide imaging techniques can be considered under proper circumstances. Generally, radionuclide imaging is the generation of images that detect the radioactive emissions (scintigraphy) of an injected radionuclide tracer that is taken up into different tissues at differing rates [111].

Occult SB bleeding occurs infrequently due to a bleeding Meckel's diverticulum (MD), which is typically worked up with the technetium-99 m (^{99m}Tc) pertechnate scan (commonly referred to as the Meckel's scan). This type of scintigraphy is effective because of the tracer's ability to concentrate within ectopic gastric mucosa, often present within a MD. Due to this tracer quality, Meckel's scans will typically be falsely positive in gut duplication cysts [34]. As bleeding is more common in children than adults with MD, the scan has a higher diagnostic yield in children [34, 112, 113].

Scintigraphy using ^{99m}Tc–labeled red blood cells (commonly referred as a 'tagged red blood cell scan') has been commonly utilized to workup suspected overt GI bleeding, though has a limited role in the workup of occult bleeding. Advantages of ^{99m}Tc-labeled RBC scintigraphy include non-invasive nature, identification of both arterial and venous bleeding, recognition of delayed bleeding through use of delayed imaging, and detection of very slow rates of active bleeding (as low as 0.1 mL/minutes in some studies). Studies investigating the clinical utility of this test

have reported a wide range of sensitivity (33–93%), specificity (30–95%), and diagnostic yield (26–87%) in the workup of GI bleeding, with increased difficulty localizing bleeding sources within the stomach or SB [2, 111, 114]. Furthermore, all studies investigating diagnostic yield have been performed in patients with acute or overt GI bleeding, rather than chronic occult bleeding, [115–120] and given the slower rate of chronic blood loss in occult GIB, the overall clinical utility of the scan would be very limited.

Missed Lesions of the SB

While recent advances in small bowel diagnostics have revolutionized our ability to identify and treat symptomatic and otherwise worrisome small bowel lesions, physicians need to remain aware of the potential for missed lesions. While VCE does have a high negative predictive value, it also carries a false negative rate of between 10–36% [68]. Missed lesions with VCE can occur in a few ways: the video capsule may not reach the cecum (incomplete study or capsule retention), the capsule may fail to capture necessary images, and/or physicians may misinterpret the images obtained. CT enterography has also been demonstrated to have higher sensitivity for small bowel luminal masses, and should be pursued following negative VCE, if appropriate clinical suspicion exists for such a mass [73, 75, 76]. While the sensitivity and negative predictive value of balloon- and spiral-enteroscopy for occult bleeding have not been reported, these procedures carry a wide (likely operator-dependent) diagnostic yield.

Overall, as there is limited literature available to guide when to repeat a diagnostic study following an initial negative result, providers should use their clinical suspicion to direct subsequent workup. Close attention should be paid to the quality of the index diagnostic test, patients' clinical presentation, laboratory abnormalities, disease course, and response to therapy, patient risk factors for alternate potential underlying etiologies, and development of overt GI bleeding or other new GI symptoms.

Treatment of Occult Bleeding of the SB

Given the broad array of possible diagnoses that can lead to SB bleeding, treatment options are typically tailored to specific pathology, and as a result are equally variable. Potential treatment options for small bowel neoplasia include surgical resection, chemotherapy, radiation, and palliation, with specific management recommendations dependent upon tumor type, metastasis, complications, and patient factors [27]. The management of small intestinal Crohn's disease involves a shifting balance between immunosuppressive therapy and surgical resection, while the treatment of choice for a symptomatic MD is surgical excision [34]. This section

will focus on the treatment of vascular lesions within the SB, the most common etiology of occult SB bleeding. While SB vascular lesions thought to be the source of blood loss can be treated with endoscopic therapy, pharmacologic therapy, or close observation, there is very limited data on efficacy of these treatment modalities, with available studies demonstrating overall disappointing reduction in rates of subsequent bleeding [2].

The natural history of occult GIB due to untreated small bowel angiodysplasia (SBAD) has been difficult to define, partly because it is challenging to define an occult bleeding event, and also due to the unethical nature of withholding potentially life-saving therapeutic procedures from patients with bleeding. However, data from the placebo arm of a 2010 trial found rebleeding rates of only 18–21% within 12 months in untreated patients initially presenting with occult bleeding [121]. This is compared with a much higher recurrence rate of 49.2%, reported in a cohort of patients with SBAD presenting with either occult or overt bleeding [122].

Endoscopic Therapy of SB Lesions

While the advent of VCE has significantly improved our diagnostic ability in occult PSBB, the subsequent introduction of balloon-assisted and SE has enabled physicians to intervene upon vascular lesions in the SB. Double-balloon, single-balloon, and spiral enteroscopes are capable of passing nearly all standard diagnostic and therapeutic endoscopic through-the-scope equipment, enabling the endoscopist to perform tissue biopsy, tattoo, hemostasis (using argon plasma coagulation (APC), electrocautery, hemostatic clips), snare polypectomy, balloon dilatation, and foreign body removal (Fig. 7.8) [2].

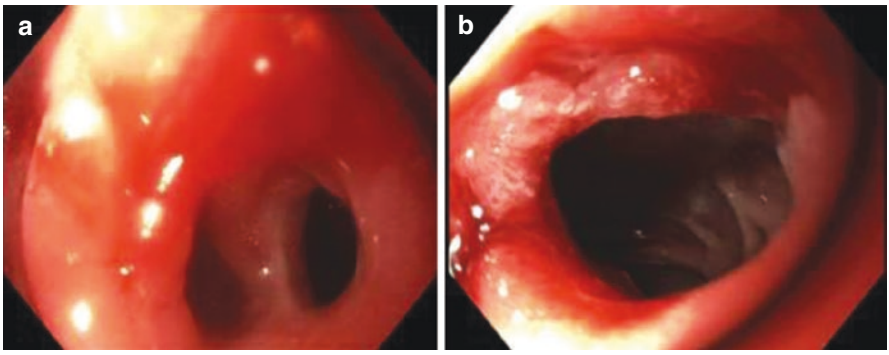

Fig. 7.8 (A on the left, B on the right): (**a**) NSAIDS induced diaphragm-like small bowel stricture identified during double balloon enteroscopy in a patient with occult GI bleeding and a history of heavy chronic NSAID use. (**b**) The same stricture after successful through-the-scope balloon dilation. (Images courtesy of Micheal Tadros, M.D)

The overall therapeutic yield for DBE has been reported to be between 15–55% which is similar to what has been reported for SBE (7–50%) [87]. Pooled data has also shown no significant difference in therapeutic yield between balloon-assisted and spiral enteroscopy [109].

Most studies have used 'recurrence of bleeding' as an indicator to assess the efficacy of the interventions, with disappointing results. A recent systematic review demonstrated a high rate of recurrent bleeding, with no significant difference in recurrence following endoscopically-treated AD (42.7%) versus untreated AD (49.2%) over a mean follow-up of almost 2 years [122, 123]. Risk of recurrent bleeding is greater in the presence of multiple vascular lesions and also appears to increase with time elapsed since endoscopic therapy [124, 125].

Although there is no consensus on the most effective type of endoscopic therapy in treatment of SBAD, argon plasma coagulation (APC) is the most commonly utilized technique [126]. APC is a non-contact thermal coagulation technique utilizing a stream of ionized argon gas directed through an endoscopic probe, resulting in superficial coagulation at a depth of 0.5–3 mm [126]. Rates of recurrent bleeding following APC therapy in SBAD have also been shown to be high (42%) [127]. Electrocautery of AD, where current is delivered through tissue to achieve coagulation, was the standard of care in the 1980s prior to the introduction of APC, but is now mainly used as a second line treatment modality for SBAD, due to the reported increased risk of perforation (~3%) [126, 128]. Hemostatic clip placement for treatment of AD in the stomach or colon has been described in case reports, though not in SBAD specifically. Hemostatic clips can be used alone or in combination with other techniques [129, 130]. To this point, there are no prospective, randomized studies comparing the different techniques described above, though expert opinion favors APC as first line endoscopic therapy [126].

Medical Therapy of SB Occult Bleeding

A significant proportion of patients with occult SB bleeding due to AD will have associated IDA. This can be addressed with iron supplementation, although some patients may need packed red blood cell (pRBC) transfusion and/or correction of underlying coagulopathies, with the ultimate goal being normalization of hemoglobin and iron stores [126]. Oral iron therapy should be considered in patients with normal intestinal absorptive capacity and absent intestinal inflammation, though patients need to be monitored closely for treatment failure. Intravenous iron supplementation should be considered in patients with suspected intestinal inflammation and/or malabsorption, side effects to oral iron, or when rapid repletion of iron stores is needed [126]. As would be expected, data from the placebo arm of a single randomized controlled trial showed little to no improvement in frequency of recurrent bleeding from vascular lesions in patients who received oral iron administered four times daily [131]. Transfusions of pRBC can be essential and should be considered in acutely ill or symptomatic patients (especially those with cardiovascular

comorbidities), patients who have failed other medical or endoscopic therapy, and patients who require medical optimization prior to scheduled endoscopic procedures.

Several studies in the 1990s demonstrated conflicting evidence regarding the clinical benefit of hormonal therapy for the treatment of bleeding gastrointestinal AD, generating some interest in their use at that time [132–134]. However, a well-designed study performed in 2001 demonstrated hormonal therapy to be ineffective, with no significant reduction in rates of recurrent bleeding, total number of bleeding episodes, or transfusion requirements between patients on ethinylestradiol or norethisterone versus placebo [135]. Hormonal therapy is not currently recommended for the treatment of SB bleeding from AD [2].

Somatostatin analogs were first investigated as treatment for bleeding AD in 1999 and are thought to work by decreasing splanchnic blood flow, decreasing angiogenesis, and increasing platelet aggregation [136, 137]. Several other studies have demonstrated promising findings since. A 2012 study showed significantly lowered rates of recurrent bleeding from gastrointestinal AD in a small cohort of patients with refractory bleeding treated with long-acting somatostatin analog therapy (73% pre-treatment vs. 20% during treatment) [138]. In a more recent 2016 study, 70% of patients with refractory bleeding from SBAD demonstrated a complete response (no re-bleeding or transfusion requirements) and 20% a partial response (>50% reduction in re-bleeding/transfusion) while on long-acting somatostatin analog therapy, with a significant rise in median hemoglobin levels [139]. Systematic reviews performed in 2010 and 2014 support these findings and restate the importance of somatostatin analog therapy in refractory disease, while at least one multicenter, randomized superiority study (the OCEAN trial) is underway at this time, [123, 140, 141].

Thalidomide has recently generated interest as a treatment for refractory SBAD, despite concerns related to its side effect profile. The mechanism of action in the treatment of bleeding AD is thought to be due to antiangiogenic properties related to suppression of VEGF [131, 142]. In a 2011 randomized controlled trial of patients with refractory bleeding due to gastrointestinal AD, more than 70% of patients treated with thalidomide achieved the primary end point of >50% reduction in bleeding episodes, compared with only 4% of patients treated with iron supplementation. Serum levels of VEGF were significantly reduced during treatment with thalidomide, supporting the proposed mechanism of drug action [131]. The same study group went on to report the long-term outcomes of thalidomide therapy from the above patient cohort. Over a median follow-up period of 46.2 months, a greater than 50% reduction in bleeding episodes was reported in 79.5% of patients [143].

Surgical Therapy of SB Occult Bleeding

Surgical management of occult SB bleeding is now rarely indicated. However, prior to the introduction of VCE and deep enteroscopy, intraoperative enteroscopy (IOE) was considered a gold-standard first-line investigation in patients with PSBB,

achieving complete SB evaluation in the majority of patients [144]. Several studies recommend IOE as a crucial step in localizing bleeding site, sometimes in combination with VCE, prior to performing a targeted endoscopic intervention or surgical resection [2, 145, 146]. Published patient series have demonstrated higher diagnostic yields in ongoing overt bleeding (100%), when compared with previous overt bleeding (70%) and occult bleeding (50%), with IOE leading to an endoscopic or surgical therapeutic intervention in between 40–100% of cases [144]. Reported mortality rates have varied between 2–17%, though considerable morbidity related to surgical and non-surgical complications can also occur [144, 147, 148].

There are limited data on long-term outcomes for patients undergoing IOE. One study described a 30% re-bleeding rate in patients with both occult and overt bleeding [149]. Similar re-bleeding rates may be expected even when endoscopic techniques such as APC are employed during IOE to achieve hemostasis [2]. Given the similar rate of re-bleeding and higher procedure-related morbidity and mortality, IOE is reserved for those patients with recurrent severe SB bleeding who have failed less invasive methods. In patients with Heyde's syndrome – the presence of aortic valve stenosis and gastrointestinal AD – there may be a role for performing aortic valve replacement [123].

Conclusions

Occult small bowel bleeding remains a relatively uncommon condition. While vascular lesions are the most common etiology, the differential diagnosis is long. Few studies have focused specifically on the diagnosis and treatment of occult bleeding in particular, and though the workup is similar to that of overt bleeding, including second-look endoscopy, push enteroscopy, VCE, and deep enteroscopy as appropriate, the diagnostic and therapeutic yields are typically lower than what has been reported with overt bleeding. As the risk for recurrent bleeding following appropriate endoscopic therapy remains significant, concomitant medical therapy, such as iron supplementation, pRBC transfusion, somatostatin analogs, and thalidomide, need to be considered in some cases, although additional prospective data will be helpful in the future to better define its role. Surgical management should be reserved for those patients with disease refractory to endoscopic and medical therapy.

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