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REVIEW

New insights to occult gastrointestinal bleeding: From pathophysiology to therapeutics

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Abstract

Obscure gastrointestinal bleeding is still a clinical challenge for gastroenterologists. The recent development of novel technologies for the diagnosis and treatment of different bleeding causes has allowed a better management of patients, but it also determines the need of a deeper comprehension of pathophysiology and the analysis of local expertise in order to develop a rational management algorithm. Obscure gastrointestinal bleeding can be divided in occult, when a positive occult blood fecal test is the main manifestation, and overt, when external sings of bleeding are visible. In this paper we are going to focus on overt gastrointestinal bleeding, describing the physiopathology of the most usual causes, analyzing the diagnostic procedures available, from the most classical to the novel ones, and establishing a standard algorithm which can be adapted depending on the local expertise or availability. Finally, we will review the main therapeutic options for this complex and not so uncommon clinical problem.

Key words: Obscure gastrointestinal bleeding; Angiodysplasia; Wireless capsule endoscopy; Double balloon enteroscopy

Core tip: This is an invited in depth review of occult gastrointestinal bleeding, addressing its pathophysiology, diagnosis and treatment. Our paper tries to unify in one single manuscript all what a general gastroenterologist should know about those items. From the essentials of pathophysiology, we have tried to build a rational approach to those patients' management depending on the severity of the condition, proposing an evidence-based management algorithm.

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INTRODUCTION

Gastrointestinal bleeding is a term that includes any bleeding originating from the esophagus to the anus. Classically, it has been classified in upper or lower depending on the location of the bleeding source, proximal or distal to the angle of Treitz.

The usual management of gastrointestinal bleeding (GIB) involves an upper endoscopy and colonoscopy in a first attempt to find the bleeding lesion. If those are unsuccessful, and there's a bleeding persistence or recurrence, the entity is called gastrointestinal bleeding of obscure origin or obscure gastrointestinal bleeding (OGIB), being the source of bleeding usually located in the small bowel. This seg-

Table 1 Causes of obscure gastrointestinal bleeding (in order of frequency)

Overlooked lesions in the upper GI tract or in the colon
Upper GI tract (proximal to the angle of Treitz)
Cameron ulcers
Fundic varices
Peptic ulcer
Angiectasia
Dieulafoy lesion
Gastric antral vascular ectasia
Colorectal lesions
Angiectasia
Polyps
Neoplasms
Anal disease
Dieulafoy lesion
Mid-GI tract lesions
< 40 yr
Meckel diverticulum
Dieulafoy lesion
Tumors (GIST, Lymphoma, Carcinoids, *etc.*)
Inflammatory bowel disease
Celiac disease
40-60 yr
Small bowel tumors
Angiodysplasia
Celiac disease
NSAID's related lesions
> 60 yr
Angiodysplasia
Small bowel tumors
NSAID's related lesions
Rare causes (< 1%)
Haemobilia
Aortoenteric fistula
Hemosuccus pancreaticus

GI: Gastrointestinal; NSAID: Non-steroidal anti-inflammatory drug.

ment of the gastrointestinal tract has been impossible to endoscopic exploration for a long time. It has been studied with suboptimal procedures such as small bowel series or enteroclysis in mild cases, or with more aggressive methods in severe cases, such as intraoperative enteroscopy (IE).

But the development of new endoscopic procedures like wireless capsule endoscopy or therapeutic procedures like the new enteroscopes, with different modalities of overtubes and balloons, has allowed an accurate exploration of this part of the GI tract, modifying significantly OGIB patients' management.

From 2006 a new OGIB classification has been proposed, based on the segment of the GI tract where the bleeding source is located, which determines the needed procedures for its diagnosis and treatment. Indeed, upper gastrointestinal bleeding is defined as the one with a bleeding source proximal to the ampulla, therefore accessible to upper endoscopy; mid GI bleeding is established when the causative lesion is between the ampulla and the ileocecal valve. Finally, lower GI bleeding has a colorectal bleeding source accessible to colonoscopy[1].

Therefore, obscure OGIB can be defined as a persistent or recurrent GI bleeding without a bleeding source found after performing upper endoscopy and colonoscopy. OGIB comprises 5% of all GI bleeding cases, constituting a diagnostic and a therapeutic challenge, either because of the morbidity and mortality associated, as well as for the high consumption of health resources for its diagnosis and treatment[2].

In most of OGIB patients (75%), the bleeding source is located in the small bowel[3], being normally a mid-GI bleeding[4]. The rest of the lesions are usually in areas accessible to conventional endoscopy, but overlooked in previous endoscopic procedures.

OGIB refers to two different clinical situations, regarding the onset of the GI bleeding: (1) Obscure-occult GI bleeding refers to the patient with a GI bleeding detected by a positive occult blood fecal test, with or without iron depletion; (2) Obscure-overt GI bleeding, in which an evident GI bleeding is seen, in the form of melena or hematochezia[5]. This review addresses the diagnosis and management of patients with obscure-overt GI bleeding, with a special interest in the different available procedures, establishing a management algorithm.

ETHIOLOGY

Causes of OGIB include overlooked bleeding lesions by upper endoscopy or colonoscopy, as well as the ones that, after an exhaustive endoscopic study, are classified as mid-GI bleeding[6]. The causative condition of OGIB is highly determined by age, being tumors as lymphoma, carcinoids, and GIST more likely in patients of less than 40 years, and vascular lesions as angiodysplasia more usual in elder patients, comprising 40% of all cases[7]. Table 1 contains the main recognized causes of OGIB[5].

PATHOPHYSIOLOGY OF THE MOST USUAL CAUSES OF OGIB

Angiodysplasia

Angiodysplasia is one of the most usual causes of over OGIB in patients older than 40 years, and the most frequent cause in patients older than 60 years[7]. They are also known as arteriovenous malformations or vascular ectasia, more frequently found in the stomach, duodenum, cecum and ascending colon. Most of them are acquired but some may be present at birth, or as a part of some hereditary syndromes[8]. Pathogenesis is uncertain and four theories have been proposed: (1) Some attribute angiodysplasia to a mild chronic venous obstruction. This hypothesis is concordant with the observation of a higher number of these lesions in the right colon, where the wall tension is higher; (2) They could be a complication of mucosal chronic ischemia, which could appear in episodes of bowel obstruction or after tough straining when defecating; (3) Some authors think they could be a complication of local ischemia in patients with heart, vascular or lung disease[9]; (4) Some of them, usually in younger patients, could be congenital or associated to hereditary syndromes; (5) It has also been suggested a pathogenic relation between aortic ste-

nosis and angiodysplasia, caused by the haemodinamic abnormalities determined by the valvular disease (Heyde Syndrome)[10]. Therapy is controversial, but some studies have shown a reduction in bleeding episodes after valvular replacement; and (6) In terminal cardiac failure, left ventricular assisted devices have been associated with increased bleeding episodes from angiodysplasia. In these cases, pathogenesis seems related with anticoagulant therapy, vascular malformations, loss of activity of Von Willebrand factor and mucosal ischemia[11].

Small bowel tumors

Despite infrequent, GI bleeding is the usual clinical onset, being more frequent in benign tumors as leyomioma than in malignant lesions as leyomiosarcoma[12]. Bleeding is caused by erosion of the tumor surface or by the rupture of aberrant vascular structures within the lesion.

Meckel diverticulum

This is a relevant condition in patients of less than 25 years old. Despite rare, it is the most frequent congenital abnormality in the GI tract. They are caused by the incomplete obliteration of the vitelin duct during embryogenesis, which leads to the formation of a true small bowel diverticulum[13]. Meckel diverticulum has all the bowel wall layers, and in 12%-21% of cases it may contain ectopic tissues (gastric or duodenal mucosa or even pancreatic ducts). They are usually asymptomatic, but may also cause abdominal pain or OGIB. Bleeding is caused by an ulceration of the small bowel due to acid secretion by heterotopic gastric mucosa contained within the diverticular layers. Bleeding can be chronic and insidious, or acute and massive, but transfusion is hardly ever required. The main anatomical risk factor that makes bleeding more likely is diverticula size of more than 2 cm[14].

Dieulafoy's lesion

Etiology is unknown. Lesions are normally found in the proximal stomach, in the lesser curvature, near de esophago-gastric junction. It is usually a submucosal, dilated, aberrant vessel that erodes the overlaying mucosa without a previous ulcer[15]. This is caused by the lack of ramification of the submucosal artery which makes its diameter ten times the normal diameter of a mucosal capillary. Triggering causes are unclear and it usually appears in male patients with comorbidities such as cardiovascular diseases, arterial hypertension, chronic kidney disease, diabetes or alcohol abuse. It is important to mention that this lesion can be overlooked in an endoscopic exam[16], given that quite frequently the aberrant vessel cannot be seen unless it bleeds actively.

Celiac disease and inflammatory bowel disease

GI bleeding is usually associated to complications in both conditions, which can be ulcers or tumors like adenocarcinoma or lymphoma.

At lasts, we would like to emphasize three rare OGIB causes, associated to a high mortality and a difficult diagnosis[17].

Haemobilia: It consists in the bleeding from the biliary tree caused by a communication with vascular structures. The most frequent causes are a closed traumatisms, hepatic artery or portal vein aneurisms, liver abscesses, neoplasms or secondary to procedures such as liver biopsy or bile duct stones extraction[18]. Diagnosis is always difficult[19]. It should be suspected in the anamnesis, when the patient presents upper right quadrant pain, jaundice and OGIB, but this is an unusual form of presentation. Diagnosis can be confirmed by direct endoscopic visualization of blood passing through the papilla. Angiography is a therapeutic option but, despite a successful embolization or surgical treatment of the originating vessel, mortality is high.

Aortoenteric fistula: It is an exceptional but severe cause of OGIB, usually related to a previous aortoiliac surgery. The most common cause of primary aortoenteric fistula is an arteriosclerotic aneurism, infectious aortitis or tuberculosis[20]. The most common cause of secondary aortoenteric fistula is an abdominal vascular graft infected, usually some years after its positioning. Pathophysiology involves a graft and surrounding tissue infection of low aggressiveness, usually caused by *S. aureus* or *E. coli*, with causes erosion and communication between the graft and the lumen of the GI tract[21]. Other secondary causes are penetrating ulcers, tumor invasion of the aorta, trauma or radiation. The onset is usually a self-limited premonitory bleeding episode followed, days or weeks later, by a second episode typically massive and life-threatening.

Pancreatic hemosuccus: It is usually caused by the erosion of the splenic artery by a pseudocyst which causes a pseudoaneurysm communicated with the pancreatic duct. Suspicion is arisen by the observation of blood emerging from the ampulla, in a plausible clinical scenario. Angio-CT scan can be diagnostic. Angiography can help to establish a diagnosis, and it can be also therapeutic, but frequently surgery is needed for bleeding control[21].

OGIB AND ANTICOAGULATION

Oral hypercoagulation therapy has been described as a factor increasing OGIB incidence, worsening prognosis and changing management. In a 2014 study the risk of a severe bleeding episode increased up to 4%-23%, being higher when INR was above 4[22]. Despite this, anticoagulants did not seem to modify the type of lesion that caused the bleeding[23,24].

Risk factors associated with a higher bleeding risk in patients under oral anticoagulants therapy are: (1) Age: In patients older than 70 years annual bleeding risk is 3%; (2) A previous episode of GI bleeding or peptic ulcer increases the risk in up to 2.1% to 6.5%; (3) Co-

morbidities: Chronic kidney failure, diabetes, cardiac disease, alcohol abuse; and (4) Association with antiplatelet drugs.

Recently, some new anticoagulants have been developed with lower rates of intracranial bleedings[25] but with a likely increase in GI bleeding[26].

DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN THE PATIENT WITH AN OVERT OGIB

For the evaluation of OGIB, particularly mid GI bleeding, angiography, gamma praphy and intraoperative enteroscopy have been classically performed. But the technological improvements with capsule endoscopy, CT-angiography and balloon assisted enteroscopy (BAE) have relegated the classical techniques to a second step and are nowadays used only in selected patients. Moreover, the diagnostic procedure selected in each case depends largely on different factors, as patient's symptoms, bleeding severity, as well as local expertise and availability, or the need of therapeutic procedures.

Repeated upper and lower endoscopy

Bleeding lesions within reach of upper endoscopy have been indentified in 10%-64% of patients who underwent push enteroscopy and in 24%-25% of patients who underwent BAE because of a suspected OGIB. Nevertheless, few missing lesions are found in lower enteroscopy, with about 7% of findings within the reach of a conventional colonoscope, usually in patients with a previous poor bowel cleansing or with profuse bleeding. In the previously mentioned study, repeated endoscopy (upper or lower) revealed overlooked lesions in 15% of patients[27-32]. However, in another Australian paper, only 4% of 50 patients submitted for enteroscopy had overlooked lesions by upper or lower endoscopy, concluding that repeated endoscopy is not cost-effective[33].

Therefore, despite lesions within the reach of conventional endoscopy might be overlooked, it is not recommended to repeat these procedures in all cases, because this would raise the costs, delaying the definitive diagnosis and overloading endoscopy units. So, it is only recommended to repeat these procedures in selected cases, as in those with previous suboptimal results due to a bad bowel cleansing or with a recurrent GI bleeding with a high suspicion of an upper GI tract origin. If hemobilia or hemosuccus are suspected, upper endoscopy with a duodenoscope is mandatory.

Some authors recommend that, if needed, the second conventional endoscopy should be performed with a push enteroscope, which would allow a deeper exploration in case no other lesions are found in the upper GI tract[34,35].

Small bowel series

Neither small bowel series nor enteroclysis have a diagnostic accuracy of more than 5% (22) and 21% respectively[36], with a particular lack of accuracy in flat mucosal lesions, as angiodysplasia, a frequent cause of bleeding cause in the small bowel. The development of capsule endoscopy and enteroscopy has limited its use to a few situations[25,37,38].

The development of other radiologic methods as CT or MRI enteroclysis with new multidetector equipment, offers higher diagnostic capabilities, even for flat vascular lesions[39].

CT angiography

It has been recently added to the diagnostic armamentarium for OGIB, with a reported sensibility and specificity of 79%-90% and 95%-99% respectively[40,41]. It detects bleedings of 0.3-0.5 mL/min with a diagnostic accuracy near 100%, having the advantages of its availability and non-invasiveness. Nevertheless it lacks therapeutic capabilities, requires radiation exposure and need intravenous contrast with a known association with nephropathy and allergic reactions.

For all those reasons, CT angiography should be considered as the first diagnostic procedure in patients with active bleeding and hemodynamic impairment, instead of other procedures with a longer duration as gammagraphy, or more invasive as arteriography, which should be reserved for therapeutic purposes in patients with an active bleeding in CT angiography.

Furthermore, CT angiography has shown its usefulness in patients with an intermittent OGIB and a normal endoscopic study, leading to the detection of unusual cases of OGIB, like stromal tumors up to 1-2 cm. It is also the first option in diverticular disease with an excellent accuracy when studying vascular abnormalities causing GI bleeding, like aortoenteric fistulae.

Gammagraphy

Gammagraphy consists in the injection of patient's red cells tagged with Tc99 that survive in the bloodstream up to 24 h, leading to the detection of GI bleedings even of a very low rate (> 0.1 mL/min)[42]. Both properties make the procedure highly sensitive but with poor specificity, finding positive results in around 45% of patients in different published series[43]. The use of colloidal-sulphur Tc99 determines a quicker exploration because there is no need to tag red cells, but it has a lower accuracy because of the quicker dilution of the isotope in the bloodstream.

The main drawback of gammagraphy is its low precision when locating the bleeding source in the bowel, which can be mistaken in up to 25% of patients[44]. For these reasons, as well as for the high rate of false positive and negative results and the lack of therapeutic abilities, this procedure has a very limited role in OGIB, sometimes only as a previous step to angiography[45].

Angiography

It has diagnostic and therapeutic capabilities. It needs higher bleeding rate than angiography (> 0.5 mL/min),

with a better performance in severe cases. However, it allows the diagnosis of non-bleeding lesions as angiodysplasia or tumors and, for this reason, its sensibility shifts between 30% and 47%[38,46], while its specificity is usually near 100%. Nevertheless, angiography is an invasive procedure with associated risks and complications in up to 9.3% of patients[47]. Therefore, it is considered a second line procedure, limited to clinical pictures in which a lesion is likely.

A provocative test, giving to the patient hypo coagulants drugs, fibrinolytic agents or vasodilators, has not shown an improvement on angiography accuracy[48].

As a therapeutic method, it allows the administration of vasoactive agents inside the responsible vessel or to perform an embolization with different substances, leading to bleeding resolution in up to 70%-100% of patients[49,50].

Wireless capsule endoscopy

Wireless capsule endoscopy (WCE) has been a great progress in small bowel examination, representing a safe and minimally invasive method for the diagnosis of OGIB.

In a 2010 systematic review, 66% of WCE indications were OGIB, with a diagnostic yield of 60.5%, being angiodysplasia the most frequent finding (50%), followed by ulcers (26.8%) and neoplasms (8.8%)[51]. Different studies have shown that WCE is more useful in overt OGIB than in occult OGIB[51-55]. Other factors related to an increase in WCE yield are[56]: (1) Performance within two weeks after the bleeding episode; (2) Hemoglobin< 10 g/dL; (3) Persistence of GI bleeding for more than 6 mo; and (4) More than one overt bleeding episode.

But WCE has other potential roles, as the detection of overlooked lesions on conventional procedures like upper endoscopy[56] or colonoscopy[57], assessing number, size and location of lesions for a better planning of the therapeutic procedure. Indeed, in a 2008 study[58] from our group, 30 patients with angiodysplasia found on CE were followed for one year, observing that patients with bigger angiodysplasia (> 1 cm) have a higher clinical impact (lower hemoglobin rates, higher transfusion requirements) and therefore higher needs of therapeutic interventions after WCE (75% *vs* 18.2%), which lead to lower rates of rebleeding. In conclusion, this paper found that angiodysplasia size (> 1 cm) and number (> 10) is related with a higher mortality (20% *vs* 4% and 25% *vs* 0% respectively).

When compared with push enteroscopy or small bowel series, WCE has proved to be superior in OGIB: In a metaanalysis published by Triester in 2005, diagnostic yield of WCE was 63% compared to 28% and 6% of push enteroscopy and small bowel series respectively. Another meta-analysis of the same year showed similar results[59-61].

Regarding other procedures, CE has shown a higher yield than angiography or CT-angiography but very similar to BAE, with the differences of its invasiveness and its ability to explore the whole small bowel in a single procedure[62-64].

This higher yield has shown to have a direct impact on management of two thirds patients with OGIB[65,66], as well as a high negative predictive value, with a rebleeding rate after a normal CE in the following 19 mo of 5.6%[67].

Therefore, CE is a first line procedure for OGIB management, although it is far from the ideal. Important disadvantages, like biopsy sampling, lack of therapeutic abilities, lack of a remote motion control, battery limitations etc. imply the need of other methods to manage those patients[68,69].

Anyway, significant research is being conducted in this field, with devices that will likely allow biopsy sampling, therapeutic interventions, real time motion control from outside the patient by means of magnetic fields control or articulated arms (Spider Pill), improvements in batteries durability etc. Some of those advances have already been incorporated, as bleeding lesions detection improvements by pattern differences in color wavelength (FICE-CE, Given Imagin)[70].

Enteroscopy

Enteroscopy allows the endoscopic observation of the small bowel beyond the angle of Treitz by means of an enteroscope.

Push enteroscopy: Until recently, push enteroscopy (PE) has been the standard of care in patients with OGIB, after a normal upper endoscopy and colonoscopy. It consists in the passage of an enteroscope by mouth, which makes possible the exploration of a variable length of the small bowel, ranging from 30-160 cm beyond the angle of Treitz[71]. PE permits only a partial vision of the small bowel, but its main indication is still OGIB, with a global diagnostic yield of 12%-80% and better results in overt OGIB.

In conclusion, PE has the advantage of its therapeutic capabilities but also the important drawbacks of a partial exploration of the GI tract and its invasiveness. Thus, it should be carefully used for previously identified lesions which are likely within the reach of this enteroscope[25,71-75].

Double balloon enteroscopy: Double balloon enteroscopy (DBE) has been a great improvement in small bowel exploration, because it provides a complete examination of the bowel lumen, as well as biopsy sampling and therapeutic abilities[76].

First described in 2001, it was widely available in 2004, consisting in an enteroscope with a balloon attached to its tip, as well as another balloon over an overtube. The alternative inflation and progression with the overtube and the balloon-enteroscope system provides a deeper progression through the small bowel, with a significantly increased mean bowel length explored as compared to PE[77,78].

The combination of lower and upper DBE grants

a visualization of the whole length of the small bowel, which is not always needed[79].

Diagnostic yield of DBE in OGIB ranges between 47%-80%[5], similar to that of WCE[58]. Its yield is increased when the procedure is performed within one month after the bleeding event.

Keeping in sight the similar diagnostic yield of WCE and DBE, they are actually considered complementary procedures[80], being WCE the first tool to be used, because of its lower cost, less invasiveness and higher availability. Information from WCE examination is helpful to decide between an upper or lower enteroscopy. In case we don't have a previous WCE, or if an upper and lower enteroscopy is needed, it is usually recommended to begin the endoscopic examination with the upper enteroscopy, because it is technically easier and has an increased likelihood of finding the causative lesion[81,82].

The main drawback of DBE is that a complete small bowel examination is not feasible in up to 29%[5], it needs sedation (usually under general anesthesia), its availability is limited to referral centers, and it has a prolonged examination time and other difficulties usually found in the lower approach due to poor bowel preparation, abdominal adhesions etc.

Nevertheless, DBE is a safe procedure, with less than 1% complications, being the most usual perforation (0.4%), pancreatitis (0.3%), and ileus[83,84]. Complications are not related to age, but with therapeutic maneuvers or anatomical abnormalities of the bowel (*i.e.,* previous surgeries, abdominal radiotherapy or intestinal lymphoma treated with chemotherapy)[6].

Other enteroscopies: Other enteroscopes used with overtube and balloons are: (1) Single balloon enteroscopy (Olympus Inc.): Exploration times and depth of insertion in small bowel enteroscopy are similar to these of DBE. In a 2010 paper[85] 100 patients were studied (50 patients with DBE and 50 with SBE) achieving DBE a higher number of complete enteroscopies when compared with SBE (66% *vs* 22%) and a higher number of findings. However, in this study, a system different from the original SBE (Olympus®) was used (Fujifilm®), having a different flexibility and balloon pressure. Later, Takano *et al*[86] had to stop prematurely a study comparing DBE with SBE, because of the differences in complete enteroscopies between both systems (57.1% *vs* 0%), finding no differences with regards to findings or complications[86]. Finally, in 2011 and 2012 two studies with 130 and 107 patients respectively[87,88] showed no differences between both systems regarding depth of insertion, complete bowel examination, complications and findings; (2) Spiral enteroscopy (Endo-Ease Discovery SB, Spirus Medical Inc.): The device includes an overtube with a helical portion which grasps the bowel folds, reaching as far as 200 cm beyond the angle of Treitz; and (3) Shapelock (USGI Medical Inc.): It consists in an overtube with multiple titanium rings, joined by four titanium wires and covered by a detachable sheath. When tension is applied on the wires, the overtube is fixed, allowing the passage of the enteroscope. Today, it has more applicability in patients with altered anatomy due to previous surgeries, in incomplete colonoscopy and in NOTES[89-92].

Intraoperative enteroscopy: It has been considered the gold standard for small bowel examination for long time[4], and although balloon assisted enteroscopy (BAE) is preferred because it is less invasive and have similar results in the diagnosis and management of small bowel disorders, the IE is an important reserve tool. It consists in the insertion of the endoscope through an enterotomy, exploring the mucosa while the surgeon facilitates the advance of the endoscope and observes the serosal surface. Palpation and transilumination play an important role in this procedure, which allows the whole bowel examination in more than 90% of patients.

Intraoperative enteroscopy (IE) has a diagnostic yield of 50%-100%[4,93], with therapeutic possibilities, but it is invasive. 12%-33%[77,78] of complications and 8%[94-96] of mortality limit its use to cases in which the other diagnostic methods are contraindicated or impossible, and always in patients with clinically significant OGIB[93-98].

PROPOSAL OF A DIAGNOSTIC ALGORITHM

In a patient with OGIB, after conventional upper endoscopy and colonoscopy, we should consider to repeat colonoscopy when a poor bowel cleansing is reported, or when we suspect an incomplete colonic evaluation. Upper endoscopy should be repeated if a strong suspicion of an upper GI tract bleeding lesion is still a concern despite a previous normal upper endoscopy.

Once a bleeding cause within reach to conventional endoscopy has been ruled out, depending on patient' s situation, an evaluation of the small bowel by WCE and BAE (balloon assisted enteroscopy, DBE or SBE) should be the next step, beginning with the less invasive one, which is WCE[5,67,75,99].

After normal WCE, if the bleeding stops spontaneously, a conservative attitude is recommended, with a clinical follow-up of the patient. If there is a strong suspicion of small bowel disease, even with a previous normal WCE, BAE should be performed[100].

Nevertheless, some authors think that if pretest likelihood of a correct diagnosis and treatment with BAE is higher than 25%-30%, we should proceed directly with BAE, because it is the most cost-effective option[101,102]. Moreover, in centers with a high number of patients and experienced endoscopists, DBE can be considered as a first step procedure in some clinical settings[102].

After rebleeding, repeated WCE finds lesions in up to 20%-35% of patients. Those lesions can be found and treated afterwards with BAE, which can also detect up to 30% of lesions previously overlooked by WCE[103-105].

If a patient presents hemodynamic instability and an active bleeding, angiography and IE should be the first

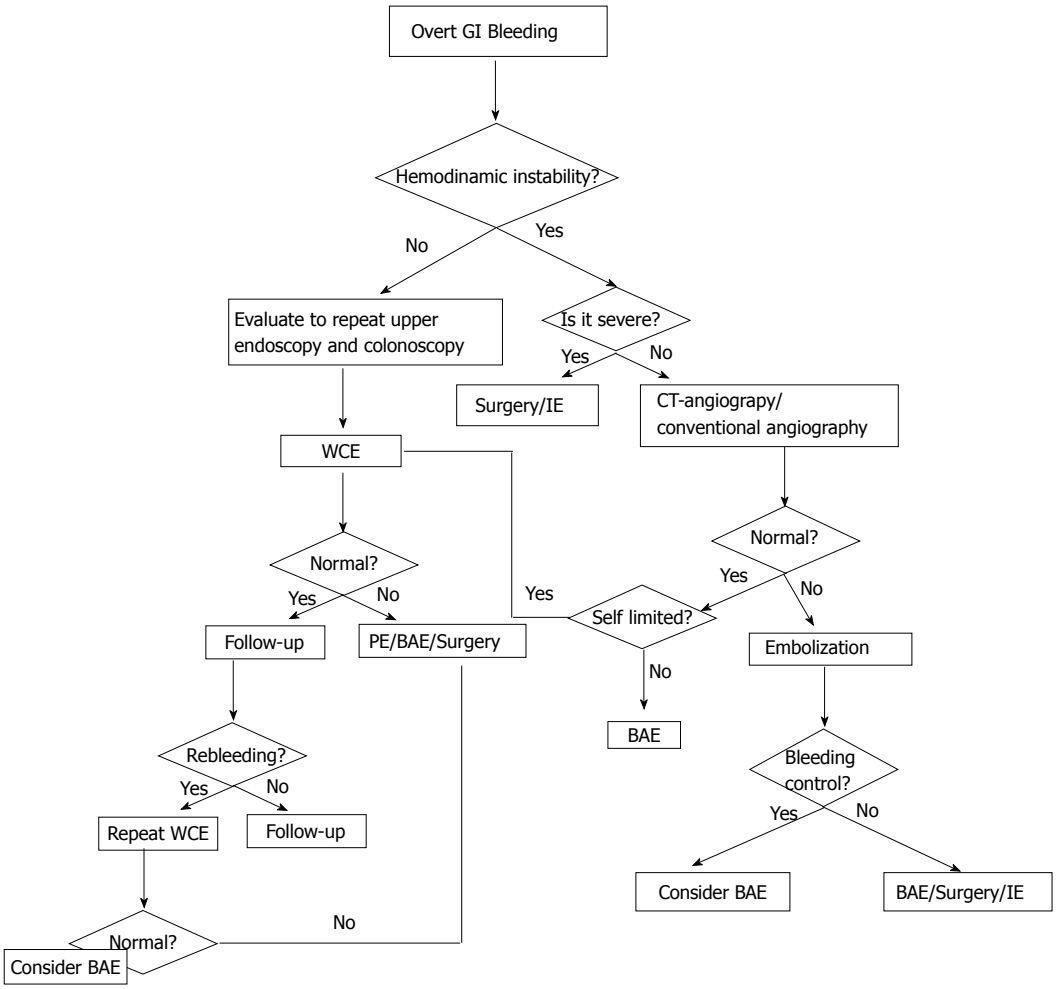

Figure 1 Proposal of a diagnostic algorithm. OGIB: Obscure gastrointestinal bleeding; WCE: Wireless capsule endoscopy; DBE: Double balloon enteroscopy; PE: Push enteroscopy; IE: Intraoperative enteroscopy.

diagnostic procedures. CT angiography is increasingly being used in this setting, because it offers an accurate diagnosis in many patients, it is less invasive, widely available and quick. Anatomical location of the lesion is usually accurate with few complications. After detecting a lesion by CT-angiography, conventional angiography or surgery can be used to apply the specific therapy[106] (Figure 1).

OGIB THERAPY

Therapy is directed by the type of lesion and its location. There are three major types of available therapies.

Pharmacological therapy[107]

Hormonal therapy (estrogens and progesterone) was initially explored by Koch et al in 1952 after observing that a patients with hereditary hemorrhagic theleangiectasia (HHT) whose bleeding varied depending on her menstrual cycle. The mechanism of action is not well understood, but there are several theories: (1) Estrogen and progesterone receptors have been detected in nasal and epidermal telangiectatic lesions in patients with HHT, and the hormone-receptor binding improved endothelial integrity in patients with HHT; (2) In animals this treatment improved vascular stasis within the mesenteric microcirculation and decreased the mucosal blood flow; (3) In patients on dialysis, estrogens shorten bleeding time by the reduction of endothelial prostacyclin production; and (4) Finally hormones may also decrease vascular endothelial growth factor.

Estrogens and progesterone therapy has been widely used in OGIB, with contradictory results, although some reports have observed a significant reduction in transfusion requirements, and even a complete resolution of bleeding.

A study of 43 patients, 38 of which were treated with hormonal therapy and followed for a mean time of 535 d (range 25-1551 d), reported benefits in patients with bleeding from sporadic angiodysplasia[108]. However, this has not been confirmed in other studies. The best data come from a multicenter, placebo-controlled trial involving 72 noncirrhotic patients which had bleedings from documented angiodysplasia; there was no benefit from hormonal therapy[109]. Based on these findings, hormonal therapy seems to have poor therapeutic advantages in

patients with sporadic angiodysplasia.

Some other papers do not recommend their use because of their lack of beneficial effects on OGIB and their adverse events (thrombosis, gynecomastia, loss of libido in males, metrorragia…). In general, their efficacy has not been proved, except for the treatment of hereditary hemorrhagic telangiectasia, von Willebrand disease, chronic kidney failure and gastric antral vascular ectasia (GAVE), in which hormonal therapy reduces transfusion requirements but not the size or number of lesions[98-100].

Somatostatin analogs: Octeotride reduces splacnic arterial flow by inhibiting angiogenesis and endothelial related growth factors[101-103]. Also, octeotride can inhibit angiogenesis by inhibiting endothelial cell proliferation. It has shown efficacy in acute and chronic GI bleeding, and can be used in patients with contraindications or a poor response to hormonal therapy. In Rossini et al study[110], treatment with octreotide in 3 patients decreased the need for blood transfusions during the follow-up period (8 to 17 mo). Other authors have published similar results[111], and have observed comparable side effects including diarrhea, steatorrhea, or changes in glucose metabolism.

A 2010 meta-analysis[112] analyzed 3 studies with a total of 62 patients, observing that 76% of patients responded to this therapy, achieving a significant reduction in transfusion requirements.

Depot formulations like LAR-Octeotride, which allow intramuscular administration once a month, have gained acceptance in selected cases[113,114]. In a study with 15 patients[115] treated with LAR-Octeotride for a recurrent bleeding from gastrointestinal angiodysplasia, the proportion of patients who experienced a bleeding event was lower during treatment than prior to treatment (20 *vs* 73), median transfusion requirements were reduced (2 *vs* 10 units), and median hemoglobin levels were higher during therapy (10 *vs* 7 g/dL).

Non-selective beta-blockers: They reduce splacnic flow, pulse and cardiac output. They are usually used in portal hypertension related OGIB and monotherapy or in association with LAR-Octeotride.

Thalidomide: It was retired in the 60s because of its teratogenic effect. However, thalidomide has recently shown to be an effective anti-inflammatory treatment in Crohn's disease. In addition to its anti-inflammatory effects, it also displays antiangiogenic activity, which may be useful for the treatment of GI bleeding. It can be taken orally and it could be used in patients with contraindications to other therapies. Obviously it is forbidden in childbearing aged women and in patients with peripheral neuropathy. It must be used cautiously in patients with cardiovascular or neurologic diseases, chronic kidney or liver failure and in immunosuppressed patients.

Some reports show promising outcomes in bleeding control[112]. In a randomized trial in 2011[116] patients treated with thalidomide were more likely than those treated with iron supplements to experience a positive clinical outcome (71% *vs* 4%).

Other drugs: (1) Antifibrinolitics: Tranexamic acid is an antifibrinolytic agent whose haemostatic effect is due to the inhibition of plasminogen activation in body fluids and tissues. Epsilon-aminocaproic acid has controlled chronic bleeding in patients suffering from HHT. These drugs have a prothrombotic activity and, for this reason, coagulation abnormalities or thrombophilia have to be ruled out before initiating the therapy; (2) Danazol: There are two single reports with positive results after hormonal therapy failure in patients with hereditary hemorrhagic teleangiectasia; (3) Desmopresin; and (4) Recombinant factor Ⅶ: Reserved to cases of massive overt OGIB.

Endoscopic therapy

There are different methods, injection therapies, thermal methods or mechanical devices which can be used with different endoscopes, depending on the location of the bleeding cause.

Argon plasma coagulation: It is safe and the most common and successful method used to treat angiodysplasia because of its easy application (especially for large superficial lesions), low cost, and reported limited depth of coagulation. Argon plasma coagulation (APC) has been used for a variety of bleeding lesions, including angiodysplasia, in these lesions submucosal saline injection prior to treatment with APC may protect against deep wall injury.

In a study of 50 patients with small bowel lesions, 44 patients were treated with APC for angiodysplasia[117]. After a mean follow-up of 55 mo, hemoglobin levels increased from a mean of 7.6 g/dL prior to treatment to 11.0 g/dL following it, and there was a significant decrease in the number of patients requiring blood transfusions. However, small bowel bleeding recurred in 21 of the patients treated with APC. A later study with 98 patients[118] reported similar results. The risk factors associated with rebleeding were the number of lesions and the presence of valvular and or arrhythmic cardiac disease.

Electrocoagulation: Bipolar or heater probe coagulation is effective for treatment of angiodysplasia in the colon or upper gastrointestinal tract. The risk of perforation with heater probe coagulation may be increased in the colon and small bowel, beyond the duodenum. Monopolar coagulation may be less effective and is associated with an increased rate of complications.

Mechanical hemostasis: Mechanical hemostatic methods such as endoscopic clips have the advantage of avoiding tissue injury, which may be particularly desirable in patients taking anticoagulants and/or antiplatelet agents, or in patients with coagulation defects.

Another mechanical method that has been described in some case reports is band ligation[119], that is safe and

effective for the treatment of acutely bleeding small bowel vascular lesions with similar results to APC (recurrent bleeding in 43%) and which can be a definitive treatment for Dieulafoy's lesion.

Angiography

Angiography is indicated in patients with GI bleeding who fail to respond to medical and/or endoscopic therapy, as an alternative to surgery in hemodynamically unstable patients with severe bleeding or for patients with ongoing or recurrent bleeding following attempts to control the bleeding endoscopically. Angiographic therapies include the infusion of vasoactive drugs (vasopressin) or the delivery of agents to mechanically occlude the vascular supply of the bleeding lesion (embolization).

Vasopressin causes generalized vasoconstriction via a direct action upon vessel walls, especially the arterioles, capillaries, and venules. It should be used with caution in patients with coronary artery disease, congestive cardiomyopathy, severe hypertension, or severe peripheral vascular disease. Other side effects are arrhythmias and water retention leading to hyponatremia.

Agents used for embolization include biodegradable gelatin sponge, polyvinyl alcohol particles, liquid agents, and metallic coils. Microcoils have become the preferred agent for embolizing bleeding vessels and can be deployed by means of a microcatheter to the site of bleeding. The complications of embolization include those associated with arteriography itself (*e.g.*, hematomas, arterial thrombosis, dissection, embolism, and pseudoaneurysm formation), and bowel infarction.

The choice between vasopressin and embolization should be individualized for each patient, taking into account angiography experience. Embolization with microcoils may be more successful than vasopressin infusion (95% *vs* 80%-90%)[120,121]) but it is associated with a higher rate of complications.

Initial hemostasis may be achieved in up to 80%-95% of patients in whom angiographic therapy is technically feasible, but rebleeding is a common problem (9%-56% in embolization and 5%-50% in intra-arterial vasopressin infusion).

Surgery

Surgical therapy is reserved for patients with a known bleeding cause, found with other methods, patients with increasing transfusion requirements or life-threatening bleedings from clearly identified origins, or for cases in which haemodinamic instability does not allow the clinicians to complete the diagnostic algorithm and an IE is mandatory. In this last situation, rebleeding is usual[86,87].

CONCLUSION

Despite technological advances, OGIB is still a diagnostic challenge for gastroenterologists, with important hospital resources consumption and delayed diagnoses. WCE is the most cost-effective diagnostic procedure to identify the bleeding source and its location. In selected cases, with an outstanding severity, CT-angiography is an alternative.

Although therapy depends on the bleeding cause, BAE plays an important role in the management of lesions found in WCE. It is less aggressive than intraoperative enteroscopy and has a high index of success. A pharmacological alternative to surgery or endoscopy are depot formulations of somatostatin analogs.

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