Review

Obscure Gastrointestinal Bleeding – A Multimodal Imaging Approach

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Abstract
Gastrointestinal (GI) bleeding represents one of the most frequently encountered clinical case scenarios in the emergency department. *In the United States, the annual rate of hospitalization for any type of GI hemorrhage accounts for 300/100,000 population, with more than 1,000,000 hospitalizations each year and an approximately mortality rate of 5%. Upper GI bleeding (UGIB) is more common than lower GI bleeding (LGIB), yet there are many sites and multiple lesions from which bleeding could occur and the source could remain unidentified after upper endoscopy or colonoscopy evaluation. The uncertain etiology of GI hemorrhage is traditionally defined as obscure GI bleeding (OGIB) and constitutes a diagnostic challenge, so accurate investigations are crucial. Even if the mainstay of initial evaluation consists of upper endoscopy, colonoscopy or contrast X-ray studies, current guidelines suggest that video capsule endoscopy, push enteroscopy, angiography and radionuclide imaging are best suited, allowing an appropriate examination of the entire small bowel, which represents the most common source of OGIB. Hence, the aim of this review is to provide a multimodal investigation approach and to highlight the most adequate imaging technique according to the leading cause of OGIB.*

Keywords: gastrointestinal bleeding, obscure, imaging, endoscopy, video capsule

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INTRODUCTION

Definitions and Epidemiology

Obscure gastrointestinal bleeding (OGIB) is defined as a gastrointestinal (GI) bleeding of uncertain etiology after upper endoscopy, colonoscopy, or barium small bowel follow-through, with a recurrent pattern. It accounts for approximately 5% of all cases of clinical GI hemorrhage and the small intestine represents the most common source (around 75% cases) [1]. Depending on the clinical presentation and the rate of blood loss, OGIB can be classified as overt and occult. Thus, overt OGIB refers to a visible acute GI bleeding, manifested as hematemesis - vomitus of red blood or "coffee-grounds" material, melena - black, tarry, foul-smelling stool, or hematochezia - passage of bright red or maroon blood from the rectum. OGIB has a chronic character because of microscopic hemorrhage, usually being associated with an initial presentation of a positive fecal occult blood test (FOBT) or fecal immunochemical test (FIT – which detects only human hemoglobin from the lower GI tract), without

any visible blood in the stool, with or without unexplained iron deficiency anemia, according to American Gastroenterological Association [2][3].

Regarding the localization, upper GI bleeding (UGIB) includes hemorrhage originating from the esophagus to the ligament of Treitz, at the duodenojejunal flexure, while lower GI bleeding (LGIB) originates from a site distal to the ligament of Treitz - small bowel, colon, or rectum. Nevertheless, recent literature describes UGIB above the ampulla of Vater within reach of an upper endoscopy and lower GI bleeding has been further subdivided into mid GI bleeding, coming from the small bowel between the ampulla of Vater to the terminal ileum, and lower GI bleeding, sourcing from the colon.

Overt GI bleeding is a major cause of hospitalization, being more common in elderly men. In the United States, although the mortality rate is similar (almost 5-10%), the annual incidence of UGIB is considerably higher than that of LGIB (40-150 episodes/100,000 population vs. 20-27 episodes/100,000 population) [4][5]. Occult GI bleeding may occur anywhere from the oral cavity to the anorectum, usually being detected with a routine FOBT (considering that normal fecal blood loss is 0.5-1.5 mL/day), with or without iron deficiency anemia secondary to chronic blood loss. Of all referrals for outpatient gastroenterology consultation, iron deficiency anemia reaches 4% to 13%, especially in developed countries, with a frequency of 5% in postmenopausal women and 2% in adult men [4][6][7].

Clinical Presentation

It is of great importance a careful attention focused on clinical presentation, considering the complexity and the wide range of underlying pathology. Clinical history (GI symptoms such as obstructive symptoms or weight loss) together with an appropriate physical examination and initial laboratory findings could provide essential information for determining the etiology of GI bleeding or at least could offer additionally paths for further investigations. Furthermore, family history (malignancies or inflammatory bowel disease), comorbidities such as hemodialysis, portal hypertension, cardiovascular or haematological diseases, prior interventions (abdominal surgeries) and medication history (especially NSAIDs or anticoagulants) could give valuable clues for an accurate diagnostic approach.

For instance, UGIB commonly presents with hematemesis, “coffee-ground” emesis, melena or nasogastric (NG) lavage with return of a large amount of blood. Moreover, even if generally hematochezia implies LGIB (with colonic or anorectal source), occasionally it could indicate a brisk UGIB with rapid and severe transit of blood, especially when the patient is hypotensive. On the other hand, LGIB classically manifests as hematochezia or melena (if the bleeding comes from the small intestine or the proximal colon) and it is to be noticed that while bleeding from the right colon usually tends to be darker and maroon-colored, mixed with the stool, bleeding from the left colon shows red-colored. Nevertheless, there are other clinical presentations, such as abdominal pain, distension, diarrhea, hemodynamic instability, or symptoms of anemia like fatigability, syncope or angina which might be associated with both UGIB and LGIB, yet patients with iron deficiency anemia could be asymptomatic. Hence, literature suggests a targeted initial investigation towards the specific location of symptomatology, when possible, otherwise, it is recommended that the colon should be firstly evaluated, followed by the upper GI tract if it is negative.

Etiology

The complex etiology of OGIB consists of wide range of causes which vary particularly by age, according to the American College of Gastroenterology clinical guideline 2015. Thus, in patients younger than 40 years, the

most common causes include neoplasia, inflammatory bowel disease, Dieulafoy's lesion, Meckel's diverticulum, or polyposis syndromes, whereas patients older than 40 years are more likely to bleed from vascular causes such as angiodysplasias and non-steroidal anti-inflammatory drugs (NSAIDs) ulcers [3][8]. Patients with iron deficiency anemia, with no GI symptoms, might have GI diseases which cause iron malabsorption, such as coeliac disease, Helicobacter pylori gastritis or atrophic gastritis [9][4]. Among rare causes there are Henoch-Schönlein purpura, small bowel varices and/or portal hypertensive enteropathy, Von Willebrand disease, amyloidosis, blue rubber bleb nevus syndrome, pseudoxanthoma elasticum, Osler-Weber-Rendu syndrome, Kaposi's sarcoma with acquired immunodeficiency syndrome (AIDS), Plummer-Vinson syndrome, Ehlers-Danlos syndrome, inherited polyposis syndromes (familial adenomatous polyposis, Peutz-Jeghers syndrome), malignant atrophic papulosis, haemobilia, aorto-enteric fistula, hemosuccus entericus [2].

DIAGNOSTIC TESTS

OGIB is a diagnostic challenge and current investigations include both radiological and endoscopic techniques. Yet, due to their poor efficiency in determining the cause of GI bleeding, the role of imaging and radiological evaluation has declined significantly, several factors accounting for the limited visualization of the small intestine, such as the length, its free intraperitoneal location, its overlying loops and vigorous contractility. With the advent of video capsule endoscopy and push enteroscopy, unless the clinical findings suggest a prior use of NSAIDs, an inflammatory disease or malignancy, there is no use for either small bowel series or enteroclysis in the evaluation of OGIB.

Imaging

The radiographic examination of the small bowel consists of barium studies (small bowel follow-through and enteroclysis), computed tomography (CT) and magnetic resonance imaging (MRI) with enteroclysis, nuclear studies such as Meckel's scan (^{99m}Tc-pertechnetate scintigraphy for Meckel's diverticulum, especially in young patients) or ^{99m}Tc-labeled red blood cell scintigraphy and angiography [1]. Because of its limited ability to distend the bowel and visualize mucosal lesions, barium small bowel follow-through is no longer utilized, also not recommended for patients with an acute bleeding since residual barium contrast could make it harder to perform urgent endoscopy or angiography.

Novel cross-sectional imaging techniques include helical CT enteroclysis, helical CT angiography and MRI enteroclysis. CT enteroclysis using a multidetector scanner is a non-invasive, operator independent method which provides better views of the small intestine than standard CT and detects extraluminal structures, as well as mucosal and intramural lesions. Unlike barium solutions, CT enteroclysis could provide a better evaluation of the small bowel wall by distending it with the ingestion of a neutral contrast agent. However, in an emergency case, dynamic or enhanced helical CT without enteroclysis may offer valuable information regarding massive lesions such as tumors, including gastro-intestinal stromal tumor (GIST), lymphoma, cancer and metastasis, inflammation (Crohn's disease), vascular diseases (ischemic enteritis). MRI with enteroclysis have also been described as a serial imaging alternative with the advantage of not exposing the patient to radiation. Notwithstanding, studies suggested inferior results when comparing to CT enteroclysis in detecting pathological signs of small intestine, such as wall thickening or bowel wall enhancement. CT angiography involves catheterization of the abdominal aorta followed by helical CT angiography before and after intra-arterial injections of a contrast medium. In such manner, the site of bleeding may be recognized as a hyperdense area by way of the extravasation of contrast medium

in the intestinal lumen – it requires at least 0,5 mL/min rate of ongoing arterial bleeding to reliably show extravasation of contrast [10]. Besides, this procedure provides evidence of recent bleeding and could also evidence neoplasms or vascular malformations and provide evidence of recent bleeding. By indicating the precise source of hemorrhage and the possible etiology, CT angiography could offer additional help in managing the treatment. Literature focused on diagnostic accuracy of helical CT angiography revealed higher sensitivity, specificity, and positive predictive value by contrast with a gold standard of colonoscopy and mesenteric angiography [11]. For instance, a prospective study of 18 patients with bleeding colonic angiectasias, helical CT angiography showed a sensitivity of 70% and a specificity of 100% [12] and a systematic review demonstrated a sensitivity and a specificity of 86% and 95% respectively, in the evaluation of patients with acute GI bleeding [10].

Nuclear studies including Meckel scan (^{99m}Tc-pertechnetate) and ^{99m}Tc-labeled red blood cell scan could also be used to investigate an OGIB and they might be positive in a significant proportion of patients presenting with vivid bleeding, especially in delayed images captured 3-4 hours after injection of the radioactive material. A positive result requires a bleeding rate of 0,1-0,4 mL/min and the sensitivity of the scan could be raised by increasing the uptake of pertechnetate [2][13]. Meckel's scan with ^{99m}Tc-pertechnetate is a relatively less invasive technique used particularly in children and young patients, but a positive scan result only suggests the presence of gastric mucosa in the small bowel. ^{99m}Tc-labeled red blood cell scan is more commonly used for the investigation of OGIB, allowing for frequent abdominal images up to 24 h, if necessary [3][8]. Even if this technique is beneficial as a guide for surgical resection, a positive nuclear scan is not sufficient for surgical planning.

Furthermore, angiography represents another imaging method as part of the OGIB evaluation. Although the data on its clinical utility is quite limited, angiography might detect both acute bleeding and nonbleeding lesions, especially angiectasias, also offering the possibility of therapeutic embolization if needed. Literature described provocative angiography, in which heparin or another anticoagulant is administered to provoke GI bleeding that has been intermittent, but despite of its performance, this technique could associate severe complications and the overall yield is quite low [9][14].

Endoscopy

Video Capsule Endoscopy (VCE)

The diagnostic approach of OGIB was revolutionized with the advent of video capsule endoscopy (VCE). By using a swallowed disposable capsule which transmits images wirelessly to a data recorder worn by the patient, VCE represents a noninvasive tool with a superior potential to push enteroscopy, barium contrast radiology, CT, and MRI for the evaluation of the entire small bowel in almost 80-90% of patients [15]. Considering its accuracy, its excellent safety profile and patients' tolerability, current guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend VCE as the first-line diagnostic modality for suspected small-bowel bleeding (strong recommendation, moderate quality evidence) [16]. The literature data reported a diagnostic yield of VCE which ranges from 30% to 87%, a higher capacity of direct visualization of the small bowel mucosa, with a higher sensitivity for detecting vascular or inflammatory lesions when comparing with other radiological modalities [6][16][17]. For instance, VCE has been significantly proved to be superior to small bowel barium studies in patients with OGIB and small bowel lesions; one randomized controlled trial showed a diagnostic yield of 30% with VCE versus 7% with dedicated small-bowel

radiography (difference 23%) [18]. Moreover, a meta-analysis comparing the two methods reported a diagnostic yield of 42% for VCE versus 6% for small-bowel barium radiography (incremental yield 36%) [19]. Capsule endoscopy also improved considerably the detection rates for small bowel lesions (67%) in contrast to small bowel barium studies (8%) and findings which influence clinical management (42% vs. 6%) [20]. Besides, VCE compared favorably to CTE due to its ability to identify angioectasias - a report of 22 patients with OGIB revealed the inferiority of CTE in the detection of potential bleeding lesions, such as angioectasias in the small bowel [4][6]. Either if CTE proved to be effective for detecting small bowel tumors (with a sensitivity over 90%) and in young patients this is the most common leading cause of OGIB, the overall sensitivity of CTE remains low (around 50%) [6][21]. The diagnostic yield of VCE following negative CTE is high, thus, ESGE suggests that CTE might be a complementary examination to capsule endoscopy in selected patients, depending on the underlying cause of OGIB [16]. In one study, 52 patients with OGIB were prospectively enrolled to undergo VCE [22]. CTE was then performed in 25 patients in whom VCE could not identify a definitive source of bleeding. CTE did not identify the source of bleeding in any of the 11 patients with occult bleeding (0/11, diagnostic yield 0%), while in 7/14 patients with obscure overt bleeding the diagnostic yield was 50%, suggesting that when VCE is nondiagnostic, CTE might be helpful for detecting the etiology in patients with overt, but not occult OGIB [16]. Other studies had also enforced the superiority of VCE compared with CTE in OGIB patients, reporting diagnostic yields of 57% and 63% for VCE, and 30% and 21% for CTE [23][24]. VCE is even superior to mesenteric angiography/CT-angiography in determining the source of bleeding. A randomized controlled trial which assessed the diagnostic yield and long-term outcomes in 60 patients with overt OGIB reported that the diagnostic yield for immediate VCE was significantly higher (53,3%) than for angiography (20,0%), with a difference of 33,3 % and the cumulative risk of re-bleeding in the VCE group was 16,7% vs. 33,3% in the angiography group, with no significant difference between the two groups regarding the long-term outcomes [25]. Additionally, a prospective cohort study in which 28 consecutive patients admitted for OGIB underwent both CT-angiography and standard mesenteric angiography, followed by VCE showed that a source of bleeding was detected by VCE in a greater proportion of patients (diagnostic yield 72%) than by CT-angiography (diagnostic yield 24%) or by angiography (diagnostic yield 56%) [26]. Nevertheless, a comparative study of 38 OGIB patients highlighted the higher potential of VCE by contrast to MRI enteroclysis for detecting abnormalities [27].

To maximize its efficacy, another strong recommendation with moderate quality evidence of ESGE is to perform small bowel capsule endoscopy as soon as possible after the bleeding episode, optimally within 14 days, particularly in patients with overt OGIB [16][28]. Pennazio et al. reported that the highest VCE yield was in patients with active bleeding (92,3%) or occult bleeding (44,2%), whereas the lowest diagnostic yield was in patients with previous overt OGIB (12.9%) [16]. In the overt OGIB group, the diagnostic yield was inversely proportional to the length of time since the last bleeding episode, as delay in the use of CE allows for healing of the bleeding site. Hence, there are several important issues to consider with a considerable influence on the success rate of VCE. The most powerful factors associated with an appropriate and definitive diagnosis by VCE in OGIB patients include the overt bleeding (>1 episode), a low hemoglobin value (<10 g/dL), iron deficiency anemia and ongoing transfusion requirements [1][5].

Enteroscopy

As well as VCE, enteroscopy represents another significant breakthrough for the diagnosis of OGIB and small bowel diseases. In the Japanese literature, the success rate of total enteroscopy varies between 60-85% in attempted cases [8]. Push enteroscopy (PE) could investigate the GI tract to 60-80 cm of the proximal jejunum, being readily available and relatively safe, allowing tissue sampling and endoscopic treatments. PE has been reported to identify the source in 24-75% of patients with OGIB, but most often in about 30% of cases the source of bleeding is detected [4][29]. The diagnostic yield of push enteroscopy in patients with obscure bleeding ranges from 3% to 70%, the most common lesions identified being represented by angioectasias (7–60% of examinations) (Table 3 of [2] and references herein). However, recently its usage has diminished and has been replaced by device-assisted enteroscopy (DAE), which could reach to the distal small bowel, performed via the antegrade (oral) or retrograde (anal) route. DAE includes the double balloon enteroscopy (DBE), the single balloon enteroscopy (SBE), the spiral enteroscopy and the balloon-guided endoscopy.

The DBE system (Fujinon Inc., Saitama, Japan) allows deep intubation of the small bowel by pleating the bowel onto a long, flexible enteroscope fitted with a specialized overtube. The enteroscope and the accompanying overtube have latex balloons at their distal end, which can be inflated and deflated with air from a pressure-controlled pump system. DBE facilitates complete visualization of the entire small intestine with a diagnostic yield which varies from 40-80% and a treatment success ranging between 15-55% in OGIB (see Table 5 of [2]) [30][31]. It is worth mentioning that like VCE, DBE evidenced a higher diagnostic yield in overt OGIB rather than occult OGIB, indicating that the period between the last bleeding episode and the DBE examination is a key point in diagnosing the causative lesion. Focusing on a comparison of VCE and enteroscopy, it seems that among the variety of methods considered, only DAE proved similar performances to that of VCE [2][5]. Even though DAE's therapeutic potential covers the wide range of upper endoscopy and colonoscopy interventions and that provides real-time controlled observation, allowing tissue sampling and endoscopic treatment, DAE is highly invasive and has a lower rate of complete examination of the small bowel, in contrast to VCE. When comparing CE with PE in patients with OGIB, CE identified more lesions, but failed to provide a meaningful improvement in outcome [4][13]. On the other hand, after the evaluation of several studies and meta-analysis, it is to be noticed that the average rate of positive findings was significantly higher for VCE than for PE (around 25% vs. around 65% diagnostic yield) [19]. A systematic review of 14 trials comparing PE to VCE evidenced clinically significant findings in 26% and 56% of patients, respectively [32]. Moreover, comparative studies of VCE and DBE have revealed similar diagnostic yields in small bowel diseases and OGIB. For instance, one study reported diagnostic yields of 54% and 64% respectively when directly comparing VCE with DBE [33] and a meta-analysis of more relevant studies also concluded comparable diagnostic yields (60% for VCE vs. 57% for DBE) [34][35]. Interestingly, literature reported some results which are not entirely concordant, meaning that miss rates for VCE and DBE have been around 20-30% for each method compared with the other ([2] and references herein). There are studies suggesting that VCE might identify more potentially bleeding lesions than DBE, probably due to the false positive results found by VCE or to its capacity to investigate more of the small bowel [36][37]. Considering the non-invasive nature of VCE, but also the major advantage of performing treatment of enteroscopy, the choice between these two techniques should be individualized for each patient. It is strongly suggested that

these two investigations to be considered as complementary and that VCE to be the initial screening modality in OGIB. One approach consisting of prior VCE followed by a targeted DBE has been shown to improve both diagnostic and therapeutic yields of enteroscopy (73-93% and 53-73% respectively) [28][38][39]. One study revealed that after a previously positive VCE, the pooled diagnostic yield of DBE was 75%, whereas following a previously negative VCE, the pooled diagnostic yield of DBE was 27,5% [40].

Additionally, to its therapeutic possibilities, DBE proved to offer valuable help in clarifying the origin of bleeding when VCE shows only blood in the lumen or doubtful findings. In this manner of speaking, ESGE forcefully recommends DAE that in patients with positive findings at small bowel capsule endoscopy, to confirm and possibly treat lesions identified by CE [16][28].

The SBE system (Olympus Optical Co, Tokyo, Japan) was introduced after DBE and consists of only one latex-free balloon attached to the distal end of the overtube. Unlike the DBE, there is no balloon attached to the enteroscope, thus, a stable position of the device must be maintained by a combination of endoscope tip angulation and suctioning into the small-bowel wall. Although instrument preparation time is faster, the complete enteroscopy rate was reported to be lower with SBE than with DBE, with a lower diagnostic yield [6][41].

Spiral enteroscopy (Spirus Medical LLC, West Bridgewater, Massachusetts, USA), consists of an enteroscope passed through a disposable specialized overtube that has a spiral raised element at its distal end, which aids in the advancement of the enteroscope through the small bowel by a gentle push and manual clockwise rotation. Motorized spiral enteroscopy (PowerSpiral; Olympus Corp., Tokyo, Japan) is a new technology with an incorporated user-controlled motor contained in the handle of the endoscope, which facilitates insertion, accelerates the procedure and simplifies the technique with a single operator. Though, this method needs further assessment concerning its accessibility in the adhesive intestine, adverse events, and interventional ability.

Balloon-guided endoscopy - the NaviAid AB device (SMART Medical Systems Ltd., Ra'anana, Israel) is an on-demand balloon catheter that is inserted through the 3.7-mm working channel of a standard colonoscope and enables it to advance deep into the small bowel, in either an antegrade or retrograde approach. It consists of a balloon inflation-deflation system and a single-use latex-free balloon catheter, designed for anchoring in the small bowel.

Finally, intraoperative enteroscopy (IOE) is an exploration of the small bowel with a flexible endoscope during a surgical procedure, which could be introduced orally or via an enterotomy. Either if previously considered the gold standard of small intestine imaging, with the highest sensitivity in detecting bleeding small bowel lesions (diagnostic yield of 80-100%) [42], the expense of extreme invasiveness turns this technique into a last resort in the investigation OGIB, recommended when small bowel lesions cannot be managed by angiographic embolization or endoscopic treatment or when surgery is required.

MAIN LIMITATIONS

The overall diagnostic approach of OGIB is based on a wide range of investigations, each presenting several limitations and disadvantages. For instance, radiographic imaging studies fail to detect many mucosal lesions and usually are inadequate for evaluation the small bowel. The main limitations of CT angiography include the lack of therapeutic capability, contrast allergy and the risk of contrast induced nephropathy, being recommended only in stable patients [6][43]. The role of nuclear scans is also limited, due to their capacity of providing only functional data, need for active bleeding

at the time of investigation, their poor capacity to identify the bleeding source, especially in the foregut and poor capacity to predict subsequent angiogram results [1][44].

As far as VCE is concerned, although its beneficial potential has been widely accepted, there are several limitations that need to be mentioned. First, the patency capsule is not entirely safe particularly in patients with Crohn's disease, small bowel tumors, medical history of abdominal surgery, radiation therapy or with NSAIDs because it could induce small bowel obstruction and retention of the coating membrane after dissolution, leading to VCE retention [45]. Furthermore, other disadvantages of VCE include inaccessibility to a reconstructed intestine such as Roux-en-Y jejunal loop, overlooking diverticula because of the impossibility of air insufflation, missing small bowel tumors through the duodenum and proximal jejunum due to the rapid passage and, finally, the lack of therapeutic capacity.

Despite of facilitating the evaluation and allowing specific treatment in patients with OGIB, deep enteroscopy has limited availability, is more costly (including the prolonged procedural time, as well as the anesthesia support needed) and relatively invasive when comparing to VCE [46]. Moreover, this procedure does not allow the visualization of the entire small bowel because of the inability to reach lesions beyond the middle jejunum and associates complications such as mucosal injuries, pancreatitis, ileus, intestinal perforation, or those related to sedation [47].

Most studies are focused on short-term endoscopic results so far, thus, the long-term outcomes such as re-bleeding risk, the effectiveness in prediction or the necessity for ongoing treatment of this investigation are still unclear and under assessment.

DIAGNOSTIC ALGORITHM

With regards to the diagnostic algorithm of OGIB, literature exposed different perspectives between Japan and other countries, mainly concerning what procedure should be caried out as the first line and the concept of DAE as the core method. There are factors such as an atypical location, a small size, a compromised visualization or an inadequate equipment which might lead to missing the bleeding source. Hence, an endoscopic or colonoscopic re-evaluation might be more appropriate as the first step, as the American Gastroenterological Association recommends [2][6].

The approach of ESGE (2015) consists of: 1) in patients with overt OGIB, small-bowel VCE should be performed after the bleeding episode, optimally as soon as possible (within 14 days); 2) if VCE is unavailable or contraindicated, DAE should be preferred as initial test for investigating the small-bowel – if results of VCE are negative, clinical follow-up with a "wait and see" policy is advocated (in case of recurrence consider repeat VCE, DAE or CTE) and if results of VCE are positive, depending on findings, DAE or further tests might also be considered; 3) in patients with significant active bleeding and unsuitable for flexible endoscopy, CT-angiography or angiography might be considered; 4) upper or lower GI endoscopy might be considered to identify overlooked lesions at the initial endoscopic evaluation [16]. CTE might be a complementary examination to SBCE in selected patients with overt, but not occult OGIB when SBCE is nondiagnostic.

The 2017 Japanese Clinical Practice Guideline advocates for the deep enteroscopy as the baseline modality for diagnosis due to its capacity of tissue sampling, endoscopic ultrasonography with a miniature probe and a detailed investigation [28]. Yet, this procedure requires a skilled and experienced endoscopist, also is time consuming and associated with complications such as infection, perforation, pancreatitis, or aspiration pneumonia, so that SBCE and contrast-enhanced CT are indicated. In patients with both overt and occult OGIB,

without contraindications (renal failure or allergy to contrast agents), contrast-enhanced helical CT should be performed and if possible, dynamic contrast-enhanced multiphase imaging should be carried out to offer a better enhancement of small-bowel lesions [48] [49]. In addition, plain CT might be carried out for an abdominal scanning and, considering the probability of pulmonary etiology of OGIB, a chest scanning should be performed simultaneously.

CONCLUSION

OGIB requires an accurate evaluation and an appropriate diagnostic algorithm and the availability of procedures, patient preferences, physician expertise, costs and risks have a major impact on investigation and management. There is various imaging, endoscopic and surgical techniques, each with their own advantages and limitations, but current literature and guidelines suggest that video capsule endoscopy and device-assisted enteroscopy have the pivot role in the diagnostic approach.

Most studies focused on short-term outcomes of these modalities, so the re-bleeding risk, the effectiveness in prediction or the necessity for ongoing treatment are still unclear and under assessment. Thereby, further investigations regarding the long-term outcomes of the diagnostic methods are required.

Author Contributions:

R.I.D. conceived the original draft preparation. R.I.D., A.G.P., L.B.G. and C.C.D. were responsible for conception and design of the review. R.I.D., A.G.P., L.B.G. and C.C.D. were responsible for the data acquisition. R.I.D, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. R.I.D., A.G.P., L.B.G. and C.C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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