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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Obscure Gastrointestinal Bleeding in Cirrhosis: Work-up and Management

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Abstract

Purpose of Review Obscure gastrointestinal bleeding (OGIB) in patients with cirrhosis can be a diagnostic and therapeutic challenge. Recent advances in the approach and management of this group of patients can help to identify the source of bleeding. While the work-up of patients with cirrhosis and OGIB is the same as with patients without cirrhosis, clinicians must be aware that there are conditions exclusive for patients with portal hypertension that can potentially cause OGIB.

Recent Findings New endoscopic and imaging techniques are capable to identify sources of OGIB. Balloon-assisted enteroscopy (BAE) allows direct examination of the small-bowel mucosa and deliver specific endoscopic therapy. Conditions such as ectopic varices and portal hypertensive enteropathy are better characterized with the improvement in visualization by these techniques. New algorithms in the approach and management of these patients have been proposed.

Summary There are new strategies for the approach and management of patients with cirrhosis and OGIB due to new developments in endoscopic techniques for direct visualization of the small bowel along with the capability of endoscopic treatment for different types of lesions. Patients with cirrhosis may present with OGIB secondary to conditions associated with portal hypertension.

Keywords Obscure gastrointestinal bleeding · Cirrhosis · Portal hypertension · Ectopic varices · Portal hypertensive enteropathy

Introduction

Obscure gastrointestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs after initial negative endoscopic (gastroscopy, colonoscopy) investigations [1]. This term has been proposed to be replaced by "suspected small-bowel bleeding" because most bleeding sources outside the upper and lower gastrointestinal (GI) tracts are found within the small bowel on further investigations [2••]. OGIB accounts for approximately 5% of all causes of GI bleeding and patients may present with overt (melena, hematochezia) or occult (iron-deficiency anemia) GI bleed. In about 80% of patients with OGIB, the etiology will be found in the small bowel. In patients with cirrhosis, the etiology of GI bleeding can be divided as related or independent from portal hypertension. Mortality from GI bleeding in patients with cirrhosis is around 25% with the most common cause being bleeding from esophageal varices. Table 1 shows the most frequent causes of GI bleed in patients with cirrhosis [3]. There is very scarce data regarding the incidence and prevalence of non-variceal bleeding in patients with cirrhosis; however, the diagnostic approach to OGIB in patients with cirrhosis will be the same as patients without this condition [4]. Furthermore, there are other potential causes of OGIB in patients with cirrhosis that are more specific for patients with portal hypertension; these include portal hypertensive enteropathy, ectopic varices, and vascular lesions in the small bowel.

Evaluation of Patients with OGIB

Clinicians need to consider a repeat gastroscopy and colonoscopy examination in patients that have been diagnosed with OGIB; this depends mainly in the timing and quality of the last endoscopic examinations. Adequate visualization on previous examinations could have been compromised by the

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Table 1 Most frequent causes of GI bleeding in patients with cirrhosis

Independent of portal hypertension	Related to portal hypertension
Peptic ulcer disease	Esophageal varices
Mallory-Weiss syndrome	Gastric varices
Esophagitis	Ectopic varices[a]
Gastric antral vascular ectasia (GAVE)	Portal hypertensive gastropathy
Vascular lesions	Portal hypertensive enteropathy (PHE)[a]
Malignancy	Portal hypertensive colopathy
Meckel's diverticulum	Vascular lesions in small bowel?[a]

[a] Potential cause for OGIB

presence of blood or a poor bowel preparation. A repeat endoscopic examination is associated with a diagnostic yield ranging from 20 to 60% [5–7]. Among the most common causes of OGIB found on a repeat gastroscopy in patients with cirrhosis is the presence of gastric antral vascular ectasia (GAVE), which does not appear to be directly related with the presence of portal hypertension and can be treated endoscopically [8, 9].

After initial negative endoscopic examinations, the next step in the evaluation would be to perform a video capsule endoscopy (VCE). This is generally acceptable except in patients with signs or symptoms of intestinal obstruction. This group should first undergo evaluation with cross-sectional imaging, ideally computed tomography enterography (CTE) or magnetic resonance enterography (MRE). The same approach is recommended for patients with history of abdominal radiation, chronic use of non-steroidal anti-inflammatory drugs (NSAIDs), or Crohn's disease [2••].

Video Capsule Endoscopy

VCE has emerged as an important tool in the evaluation of patients with OGIB as it can capture multiple images of the small bowel while advancing by peristalsis. Patients can swallow the video capsule or it can be released in the duodenum with a special device during gastroscopy (VCE drop). The VCE drop is particularly indicated in hospitalized patients or in those whom there is suspicion of delay in gastric emptying. The high-definition images are transmitted at different rates ranging from 2 to 6 per second. If a small-bowel lesion is identified, the VCE can provide an accurate estimation of its location as the reader can calculate the total small bowel transit time (TSBT) and its relation with the time the lesion was located. The TSBT is the time from the first duodenal image to the time of the first cecal image. This provides valuable information to decide the route of balloon-assisted enteroscopy (BAE) if indicated afterwards. If a lesion that is suspected to be the culprit of OGIB is less than half of the TSBT in a complete VCE examination or at less than 75% from ingestion to arrival into the cecum, then an oral route approach for BAE is recommended [10]. The diagnostic yield of VCE in OGIB increases with the presence of active overt GI bleed or within 2 weeks of an episode of overt GI bleed (inactive overt). The yield of VCE for clinically significant findings has been reported to be around 56% in a meta-analysis of 20 prospective studies [11]. Negative findings on VCE in patients with OGIB are associated with low re-bleeding rates and good prognosis, especially in patients without overt GI bleed and absence of concerning signs or symptoms [12–14]. Patients with negative findings on an initial VCE may undergo a repeat VCE; this is especially useful in patients with recurrence of overt bleeding or anemia after iron replacement. The yield of a repeat VCE increases considerably in patients with a new drop in hemoglobin levels or a recent episode (within 2 weeks) of overt GI bleed [15].

Balloon-Assisted Enteroscopy

BAE allows to directly visualize and perform therapeutic maneuvers in the small bowel. Double balloon enteroscopy (DBE) and single balloon enteroscopy (SBE) are the main available systems for deep enteroscopy. BAE is usually the next step in the evaluation of patients with OGIB after a positive finding in VCE or imaging study. The diagnostic yield of BAE ranges from 40 to 80%; however, it is higher in patients with recent (within 2 weeks) or active overt GI bleed with diagnostic yields near 100% [16–18]. These groups of patients can also be considered to undergo direct BAE without previous VCE. During BAE, therapeutic procedures can be performed such as polypectomy, argon plasma coagulation (APC), hemoclips placement, epinephrine or glue injection, and placement of endoscopic endoloops among others. The complication rate of BAE ranges between 1 and 2%; the most commonly reported are bleeding, perforation, and pancreatitis [19].

Patients with active overt GI bleeding who are hemodynamically unstable should undergo urgent CT angiography and likely subsequent angiography with embolization by interventional radiology [20].

Causes of OGIB Directly Related to Portal Hypertension

Ectopic Varices

Ectopic varices may account for 1–5% of all cause of GI bleeding in patients with cirrhosis. Rectal varices are the most prevalent with rates between 28 and 56%; however, bleeding is rare but can be massive. Duodenal varices are responsible for 17% of bleeding from ectopic varices; their prevalence has been reported around 0.2 to 0.4% of all patients undergoing upper endoscopy [21–24]. Duodenal and rectal varices usually look prominent and tortuous at endoscopic examination; however, in patients with recent bleeding, they may be flattened and difficult to identify. Clinicians must be aware for subtle features of recent bleeding in ectopic varices (e.g., nipple sign) that may be helpful for making the correct diagnosis. The treatment of a duodenal or rectal varix that is suspected to be the OGIB culprit is mainly endoscopic. Injection of glue (cyanoacrylate) has been reported to be successful in the majority of series [23, 25–27]. Other treatment options for these patients include transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO). Case series and reports have shown good initial response and low re-bleeding rate in most patients [28–33]. Endoscopic band ligation of rectal varices is another endoscopic option that has been reported to be successful for initial hemostasis and with low re-bleeding rates [34]. Jejunal varices including the ones located at anastomotic sites (e.g., choledochojejunostomy) represent a diagnostic and therapeutic challenge; however, there are reports of successful endoscopic treatment with cyanoacrylate glue, BRTO, TIPS, and embolization with coils via the portal vein [35–39]. Small-bowel varices can be identified at VCE or BAE by the presence of multiple blue prominent venous lakes; this can be followed by an angiography for confirmation and treatment if indicated [40].

Portal Hypertensive Enteropathy

Portal hypertensive enteropathy (PHE) is a common condition associated with portal hypertension characterized by edematous and congestive mucosa in the small bowel, frequently associated with diffuse vascular and inflammatory lesions [41, 42•]. The prevalence in cirrhotic patients varies from 15 to 25% when traditional endoscopic methods have been used,

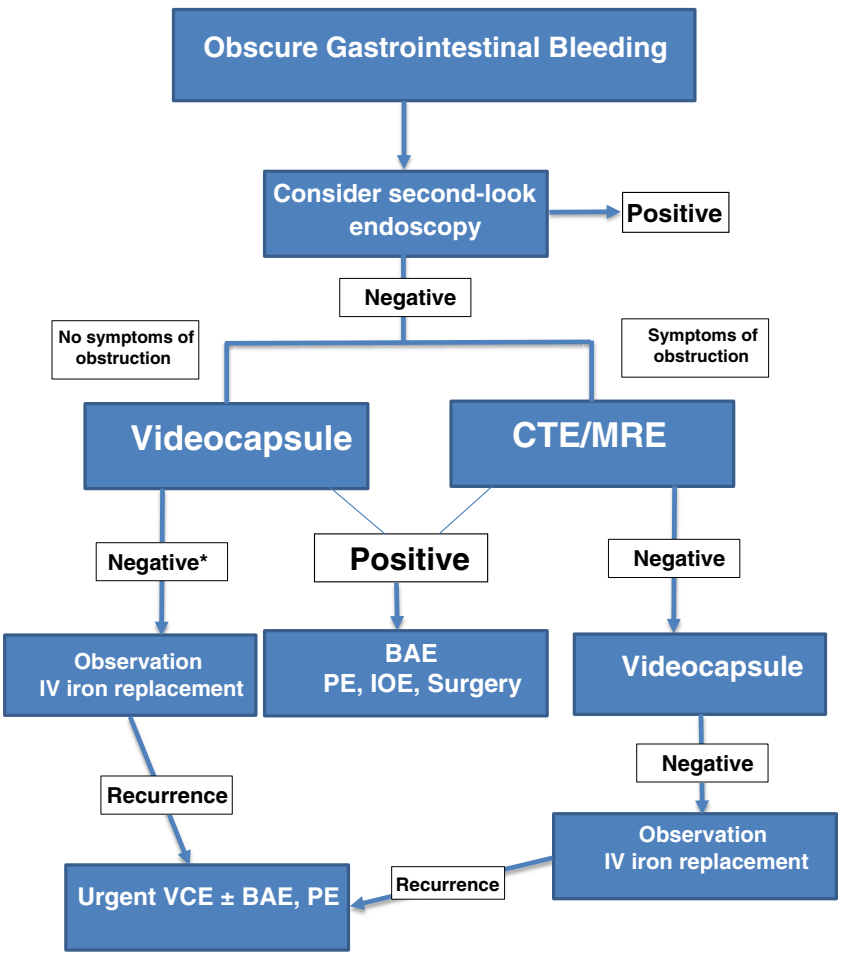

Fig. 1 Proposed algorithm for the evaluation and management of OGIB in patients with cirrhosis. Asterisk indicates consideration of CTE, especially in high suspicion of Meckel's diverticulum or neoplasia. CTE computed tomography enterography, MRI magnetic resonance enterography, BAE balloon-assisted enteroscopy, PE push enteroscopy, IOE intraoperative enteroscopy, VCE videocapsule endoscopy

to 40–80% when VCE or BAE are utilized [43, 44, 45•, 46•]. The clinical presentation of PHE ranges from occult GI bleeding to active overt bleeding and its commonly associated with large esophageal varices, history of endoscopic treatment for varices, portal hypertensive gastropathy/colopathy, thrombocytopenia, splenomegaly, and advanced hepatic dysfunction (Child-Pugh C classification) [47, 48]. The appearance of PHE at endoscopic examination when evaluated by DBE is mainly characterized by the presence of erythema, angiodysplasia, and edema with swelling of villi (herring-roe like) [49]. Endoscopic treatment for PHE is directed to lesions that may be actively bleeding (angiodysplasia), traditionally with argon plasma coagulation (APC). Unfortunately, PHE has a diffuse distribution with areas that can be oozing intermittently, thus limiting the ability to have a significant impact with endoscopic treatment in decreasing the rate of bleeding. Patients with PHE should be on beta-blocker therapy to decrease the risk of bleeding by reducing portal pressure. There have been reports of beneficial effects and decrease in the number of vascular lesions in PHE with thalidomide treatment as well as improvement of histopathological changes in a rat model of portal hypertensive enteropathy after treatment with long-acting octreotide [50, 51].

Small-Bowel Vascular Lesions

Small bowel angiodysplasia is frequently found in patients with cirrhosis. In a prospective study focusing in the assessment and identification of mucosal abnormalities in the small bowel by VCE, angiodysplasias were found in 24% of patients and red spots in 62% in patients with occult GI bleeding and cirrhosis [44]. It is believed that patients with cirrhosis and portal hypertension have a higher prevalence of vascular lesions secondary to changes in the intestinal circulation; however, there is a lack of large epidemiological studies to confirm these assumptions. There are only isolated reports as well as retrospective studies that have shown cirrhosis and portal hypertension as a risk factor for the presence of small-bowel vascular lesions, particularly angiodysplasias [52, 53•]. Other types of vascular lesions such as Dieulafoy's lesions may also be identified as a cause of OGIB in patients with cirrhosis [54]. Most vascular lesions in the small bowel can be treated endoscopically; however, when these are multiple or patients have recurrent episodes of bleeding, medical treatment with long-acting octreotide or thalidomide may be effective [55, 56].

Conclusions

OGIB in patients with cirrhosis represent a clinical challenge; the diagnostic approach is the same as patients without cirrhosis. A proposed algorithm is shown in Fig. 1. Clinicians must be aware of other potential causes of bleeding in patients with cirrhosis such as PHE and ectopic varices. The treatment of most lesions is mainly endoscopic but there are also medical treatment options for patients with recurrent bleeding or extensive lesions. There is a better understanding and characterization of these lesions due to recent progress in endoscopic visualization and cross-sectional imaging; however, there is a need for more clinical research regarding the prevalence of PHE, ectopic varices, and vascular lesions in patients with cirrhosis and other treatment options for this group of patients.

Compliance with Ethical Standards

Conflict of Interest Sergio Zepeda-Gomez and Brendan Halloran each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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