Small bowel capsule endoscopy in obscure gastrointestinal bleeding: normalcy is not reassuring

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Background/Aim **Small bowel capsule endoscopy (SBCE) is currently a fundamental tool in the etiological study of obscure gastrointestinal bleeding (OGIB). However, the impact of a negative exam and the risk of rebleeding are not entirely known. The aim of this study was to evaluate the outcomes of patients with OGIB and a negative SBCE examination in terms of follow-up duration, additional diagnostic studies, and achievement of a diagnosis as well as to assess the incidence of rebleeding and possible associated factors.**

Materials and methods **We retrospectively analyzed 256 patients who consecutively underwent an SBCE examination for the study of OGIB between April 2006 and December 2011, and then selected the 79 whose results excluded potentially bleeding lesions. Eleven patients were lost to follow-up and the remaining 68 were eligible for a nested case–control analysis. Pre-SBCE and post-SBCE information was collected, including follow-up interval and incidence of rebleeding, defined as admission to the hospital for symptomatic anemia, need for blood transfusion, decrease in hemoglobin value of greater than 2 g/dl, or evidence of melena or hematochezia. Univariate analysis included age, sex, OGIB presentation (occult or visible), hemoglobin levels at presentation, and comorbidities.**

Results **In the 68 patients analyzed, the mean age was 52 ± 18 years and 61.8% were women. The OGIB was occult in 54 patients (79.4%) and overt in 14 patients (20.6%). Patients were followed up for an average of 32 months. Thirty-nine patients (57.4%) underwent further diagnostic investigations during the period of follow-up and a cause for the gastrointestinal bleeding was found in five of them. Rebleeding was documented in 16 (23.5%) patients, occurring on average 15 ± 13.8 months after the SBCE. Male sex was associated significantly with higher incidence of rebleeding ($P = 0.004$).**

Conclusion **Approximately one quarter of patients with OGIB and negative SBCE examination will experience rebleeding, with higher incidence among men; thus, a negative SBCE in this setting is not reassuring. As the vast majority of rebleeding episodes seem to occur within the following 2 years after SBCE, the maintenance of regular medical surveillance during the above-mentioned period of time after a negative SBCE seems advisable.** ***Eur J Gastroenterol Hepatol*** **00:000–000 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Obscure gastrointestinal bleeding (OGIB), which represents almost 5% of all gastrointestinal (GI) hemorrhage and 30% of all cases of iron-deficiency anemia, remains a diagnostic and therapeutic challenge for gastroenterologists [1,2]. It is defined as bleeding from the GI tract that persists or recurs without an obvious etiology after esophagogastroduodenoscopy and colonoscopy [3]. OGIB may present in the form of occult OGIB (positive fecal occult blood test or iron-deficiency anemia) or overt OGIB (passage of visible blood) [3].

When the origin of bleeding is located in the small bowel, which occurs in 75% of cases of OGIB [4], patients tend to undergo more diagnostic procedures, have longer hospital stays, require more blood transfusions, and have associated higher healthcare costs when compared with patients with colonic or upper GI bleeding [5].

Small bowel capsule endoscopy (SBCE) is currently recommended as a first-line diagnostic study for the etiological investigation of OGIB [6], which remains the most common indication for this procedure [4,7]. In addition to being safe, noninvasive, and well tolerated, several studies have confirmed that SBCE has a higher diagnostic yield in identifying the cause of OGIB than other procedures such as push enteroscopy, small bowel barium radiography, computer tomography enteroclysis, mesenteric angiography, intraoperative enteroscopy, or magnetic resonance enteroclysis [8].

Despite its high diagnostic yield [9,10], in about 20–40% of patients with clinical OGIB subjected to SBCE, no

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lesions are identified [11]. As guidelines for this specific situation are lacking and most studies include not only a small number of patients but also short-term follow-up, the long-term outcomes of these patients remain unclear.

The primary aim of this study was to evaluate the outcomes of patients with OGIB and a nondiagnostic SBCE examination, namely, duration of follow-up, performance of additional diagnostic studies, and achievement of a diagnosis. We also aimed to report the rate of rebleeding in this subset of patients and to identify possible associated risk factors.

Materials and methods

Patients and study design

This study was a single-center retrospective nested case–control investigation. All patients referred to our center for the etiologic study of OGIB with SBCE between April 2006 and December 2011 were included. Following the definition of OGIB [3], all patients underwent nondiagnostic esophagogastroduodenoscopy and colonoscopy before referral for SBCE. Furthermore, women were evaluated to exclude abnormal gynecological bleeding. Patients' clinical information was collected from medical records, including sex, age, type of presentation of OGIB, hemoglobin levels, clinical history, and medical therapy. Patients whose SBCE examination was incomplete (capsule not reaching the cecum within reading time) were not included.

SBCE procedure

SBCE was performed using PillCam SB or PillCam SB2 capsules from GIVEN Imaging (Yoqneam, Israel). Patients received a clear liquid diet the day before capsule ingestion and an overnight 12 h fast. Patients were allowed to drink fluids after 2 h and to have a light meal after 4 h of capsule ingestion. Informed consent was obtained from every patient before SBCE. Consensual contraindications for the SBCE procedure were respected and have been described elsewhere [12].

Analysis of SBCE findings

The complete video obtained in each SBCE was reviewed by two gastroenterologists experienced with the use of capsule endoscopy. In case of no interobserver agreement, the findings were reviewed by both gastroenterologists and a consensus was reached. Lesions were classified according to their bleeding potential using the system reported by Saurin *et al.* [13]. Three categories of lesions were considered: P0 lesions, such as visible submucosal veins, nodules without mucosal break, or diverticula without the presence of blood, were assumed to have no bleeding potential. P1 lesions, namely, mucosal erosions or mucosal red spots were considered to have uncertain bleeding potential. P2 lesions, including typical angiomata, tumors, large ulcerations, or varices, were considered to have high bleeding potential. In our study, SBCE examination was considered positive when P2 lesions were found, whereas P1 or P0 lesions and normal recordings were classified as negative SBCE examination. The diagnostic yield of SBCE was defined as the ratio of the number of cases with small bowel findings responsible for OGIB (namely P2 lesions) to the total number of cases of OGIB subjected to SBCE.

Patients' follow-up

Follow-up data were obtained by reviewing the medical records. Rebleeding was defined as evidence of symptomatic anemia, need for blood transfusion, decrease in hemoglobin value of greater than 2 g/dl, or evidence of melena, or hematochezia with nondiagnostic upper and lower GI endoscopy when performed. We assessed the interval of follow-up after SBCE for each patient, the occurrence, and timing of rebleeding episodes; additional studies were carried out for the investigation of OGIB and definite diagnosis.

Data analysis

Statistical analysis was carried out using the statistical packages for social sciences software, version 17.0 (IBM, Armonk, New York, USA). Quantitative data, namely age and hemoglobin value, were expressed as mean ± SD. Univariate analysis between cases (patients with rebleeding during the follow-up) and controls (patients without new rebleeding episodes) was carried out. As age had a normal distribution, a parametric statistic (Student's *t*-test) was used. Hemoglobin values did not have a normal distribution and a nonparametric statistic (Mann–Whitney test) was applied. For nominal variables, the χ^2-test or Fisher's exact test was used as appropriate. Statistical significance was considered when the P value was less than 0.05.

Results

Patients' description

Between April 2006 and December 2011, a total of 256 patients underwent SBCE in our center for etiologic investigation of OGIB. No complications related to the procedure occurred. In 177 of these patients (69.1%), SBCE examination identified the lesions responsible for the GI bleeding. However, in the remaining 79 patients (30.9%), SBCE examination was negative. From the 79 patients selected to enter this study, 11 had been sent from other hospitals or primary care centers and as additional clinical data were unavailable, they were excluded from the study analysis (Fig. 1). Among the remaining 68 patients, five had P1 lesions on SBCE (small bowel erosions), one had P0 lesions (visible submucosal veins), and the remaining 62 patients had normal SBCE. From the analyzed patients, 42 (61.8%) were women, and the mean age was 52 ± 18 years, ranging between 21 and 85 years. The indication for SBCE examination was occult OGIB in 54 patients (79.4%),

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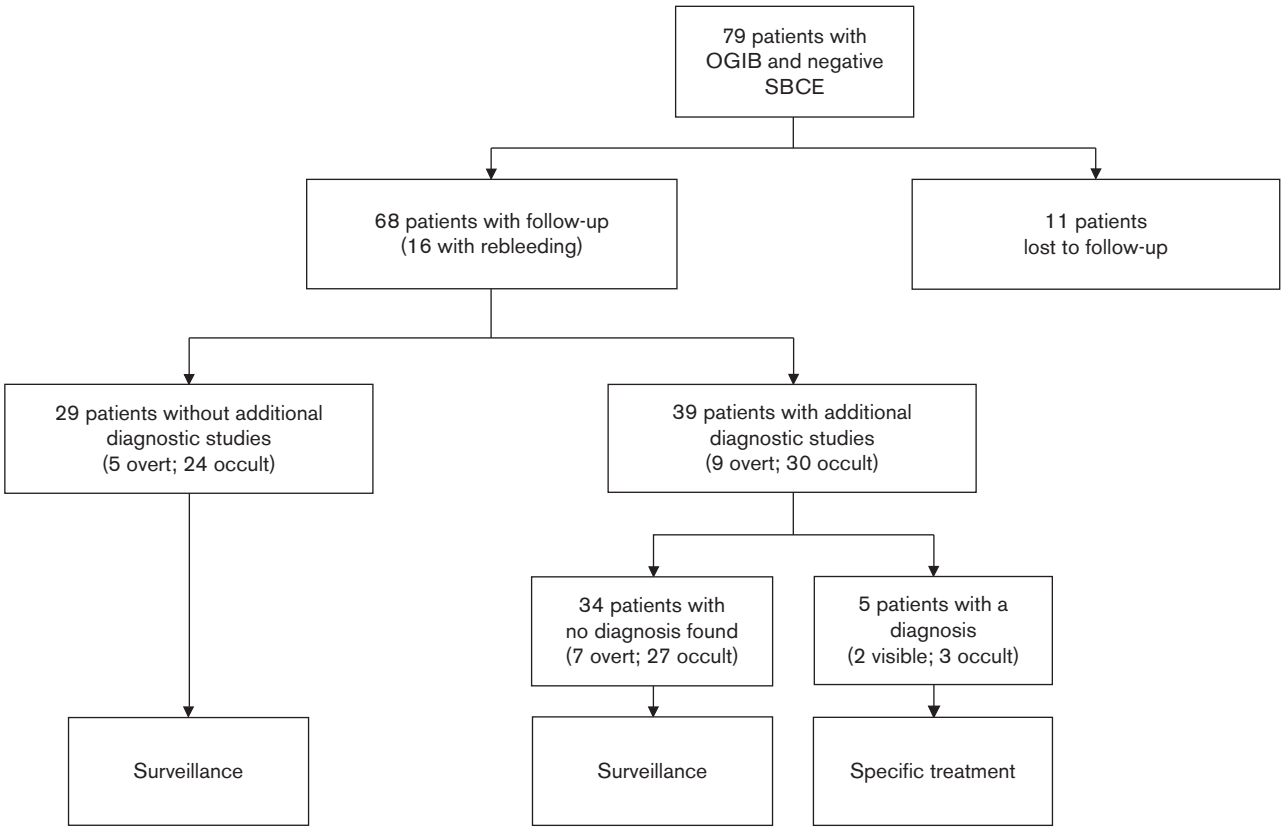
Fig. 1



Patients' follow-up. OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy.

whereas only 14 patients (20.6%) had overt OGIB. Baseline characteristics are summarized in Table 1.

Patients' follow-up

Medical records of the follow-up were available for 68 patients (Fig. 1). The follow-up interval was largely variable between patients, with a mean of 32 ± 21 months, ranging from 1 to 83.

During follow-up, a total of 39 patients (57.4%) were subjected to further GI investigations to find a definitive diagnosis to explain the OGIB. These investigations included 44 second-look esophagogastroduodenoscopies, 36 colonoscopies, six SBCEs, seven nuclear scans, and one small bowel series. According to the policy at our center, deep enteroscopy was not used in any patient with negative capsule endoscopy.

In five patients (7.4%), a cause for the OGIB was found on subsequent examinations after SBCE, including two patients with angioectasias in the ascending colon, two patients with celiac disease, and one patient with colon cancer. All these patients received specific treatment for their condition, namely, argon plasma coagulation for angioectasias, a gluten-free diet for celiac disease, and right hemicolectomy for colon cancer.

Rebleeding

Episodes of rebleeding, as defined above, were monitored during the follow-up. Sixteen patients (23.5%) had at least one rebleeding episode and the mean time interval between the SBCE and rebleeding was 15 ± 13.8 months, ranging from 1 to 51 months. Remarkably, rebleeding occurred in the first year after SBCE in 10 patients (62.5%), and in 13 patients (81.3%) it occurred within the first 2 years after SBCE.

We investigated factors that could possibly be associated with a higher risk of rebleeding, namely, sex, patients' age, indication for SBCE, antithrombotic drugs, as well as some common comorbidities such as hypertension, hypercholesterolemia, diabetes mellitus, chronic liver disease, or chronic kidney disease. Rebleeding was significantly more common in men (68.8 vs. 31.2%; $P = 0.004$). Anticoagulant drug users also seemed at a higher risk of developing rebleeding, but this was not statistically significant in our series. The other variables

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Table 1 Baseline characteristics of negative SBCE patients, with and without rebleeding

Factors	Without rebleeding	With rebleeding	Total [*n* (%)]	*P*
Mean age (years)	50.3±17.8	56.7±19.9	–	0.217
Sex				
Male	15	11	26 (38.2)	0.004*
Female	37	5	42 (61.8)	
Indication for SBCE				
Occult OGIB	40	14	54 (79.4)	0.492
Overt OGIB	12	2	14 (20.6)	
Hypertension				
No	31	9	40 (58.8)	0.811
Yes	21	7	28 (41.2)	
Dyslipidemia				
No	34	10	44 (64.7)	0.833
Yes	18	6	24 (35.3)	
Diabetes mellitus type 2				
No	40	13	53 (77.9)	1.000
Yes	12	3	15 (22.1)	
Chronic liver disease				
No	50	14	64 (94.1)	0.233
Yes	2	2	4 (5.9)	
Chronic kidney disease				
No	45	14	59 (86.8)	1.000
Yes	7	2	9 (13.2)	
Mean hemoglobin value (g/dl)	10.6±1.9	10.9±2.1	–	0.303
Antiplatelet drug use				
No	35	9	44 (64.7)	0.418
Yes	17	7	24 (35.3)	
Anticoagulant drug use				
No	48	12	60 (88.2)	0.081
Yes	4	4	8 (11.8)	

OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy.
*Statistically significant.

were not statistically different between patients with and without rebleeding and are summarized in Table 1.

Discussion

Since its appearance in 2000, SBCE has become an essential tool for the investigation of the small bowel [14]. For OGIB, which remains the most common indication for SBCE, the examination has a considerably high diagnostic yield, varying between 45 and 75% [15]. However, a significant proportion of patients presenting with occult or overt OGIB have nondiagnostic SBCE examinations, making the management of this topic even more challenging. The impact of negative small bowel examinations on the patients' outcome, namely risk of rebleeding, is currently under debate and the optimal approach in these situations is far from well defined. What is the rebleeding rate in these patients? What is the acceptable follow-up interval? Which patients are at an increased risk of rebleeding? These are some of the questions whose answers remain controversial.

In this study, although 16 patients (23.5%) were monitored for less than 1 year, the remaining 52 (76.5%) had long-term follow-up intervals, varying from 12 to 83 months. The mean interval of follow-up was 32 months, which is one of the longest described in the literature. Some studies have shown the results of patients monitored during 1 year [2], whereas others showed results of longer intervals, [11,16–19] but the appropriate follow-up interval of patients with OGIB after negative SBCE remains unclear.

During the follow-up interval, either because there was a lack of a definitive diagnosis or because rebleeding occurred, some patients were subjected to additional examinations. According to the literature, it is not rare to find possible causative lesions when further investigations are performed and several different lesions have been described. Such lesions include Dieulafoy's, diverticula, small bowel ulcers, lymphomas, angioectasias (gastric, intestinal, or colonic), hiatus hernia ulcerations (Cameron's lesions), Meckel's diverticula, GI stromal tumors, small bowel adenocarcinomas, carcinoid tumors, arteriovenous malformations, or aorto-enteric fistulas [2,9, 11,17,18,20]. One study reported that patients with OGIB and a lesion seen on SBCE still could have an undiscovered lesion within the reach of conventional scopes in up to 15% of patients [21]. Although there is no consensus on the number of upper endoscopies and colonoscopies before patients undergo SBCE, some authors consider SBCE after two negative investigations [22,23]. In our study, patients underwent SBCE after one negative upper endoscopy and colonoscopy and the results showed that all of the five patients with OGIB and negative SBCE, who received a final diagnosis at follow-up, had lesions that were in the reach of upper endoscopy and colonoscopy. These findings may indicate that second-look upper endoscopies and colonoscopies could be considered after negative SBCE.

The techniques that can be used to further assess these patients include device-assisted enteroscopy, radiologic studies, or intraoperative enteroscopy [24]. Some authors have suggested that a subgroup of patients (especially those who changed presentation from occult to overt OGIB and those with a decrease in hemoglobin of 4 g/dl or more) could benefit from a second-look SBCE [15]. In our study, however, only six patients were subjected to a second-look SBCE examination, which was again nondiagnostic in all of those cases. These results were slightly disappointing, considering the increased costs of repeating SBCE.

Independent of the presence or absence of further investigation after a negative SBCE, patients with OGIB are at risk of having rebleeding episodes. However, the rate of rebleeding during the follow-up is highly variable, ranging from 0% [2] up to 50% [25], as summarized in Table 2. In our study, we found an intermediate rebleeding rate of 23.5%, which is comparable with several other studies [18,27,28]. The discrepancies found on rebleeding rates in the literature might be explained by differences in patients' selection and subsequent management as well as by different follow-up intervals. The timing of the rebleeding episodes after a negative SBCE

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Table 2 Follow-up duration and rebleeding rates in patients with OGIB and negative SBCE

References	Patients with OGIB and negative SBCE	Mean follow-up duration (months)	Rebleeding rate after negative SBCE (%)	Mean time to rebleeding (months)
Delvaux *et al.* [26]	17	12	0	NA
Saurin *et al.* [27]	16	12	25	NA
Neu *et al.* [28]	18	13	22.2	NA
Lai *et al.* [11]	18	19	5.6	1
Endo *et al.* [25]	32	11.6	50	NA
Macdonald *et al.* [19]	49	17	11.1	NA
Park *et al.* [16]	28	31.7	35.7	13.8
Lorenceau-Savale *et al.* [2]	35	15.9	0	NA
Iwamoto *et al.* [29]	25	20.1	4	8
Riccioni *et al.* [17]	207	24	16.4	NA
Koh *et al.* [18]	57	23.7	22.8	NA
This study	68	32	23.5	15

NA, not applicable; OGIB, obscure gastrointestinal bleeding; SBCE, small bowel capsule endoscopy.

examination has not been investigated extensively in the literature, but intervals ranging from 1 to 13.8 months have been reported [11,16], whereas in our series, we found a longer mean time interval of 15 months between the SCBE procedure and the rebleeding episode.

A secondary outcome of our study was to evaluate possible factors associated with the risk of rebleeding in patients with OGIB and nondiagnostic SBCE examination. This topic has scarcely been explored in previous studies. We found the male sex to be significantly associated with rebleeding episodes after a negative SBCE. Moreover, similar to what has been reported before [18, 19], anticoagulant drug use was also marginally associated with rebleeding episodes in these patients, although not reaching statistical significance. Unlike what has been reported previously [17], we found no association between age or the indication for the SBCE (overt or occult OGIB) and the occurrence of rebleeding episodes during follow-up.

Conclusion

Our study represents one of the largest series in the literature of patients having OGIB and negative SBCE examinations (Table 2). We have shown that although some patients may benefit from a more exhaustive attempt to clarify the etiology of OGIB, in approximately three quarters of cases, patients with OGIB and negative SBCE do not seem to be at an increased risk of adverse outcomes and may be safely followed with no need for further investigations or interventions. Nonetheless, even when SBCE shows no potentially bleeding lesions, almost one quarter of patients, particularly men, are likely to experience an episode of rebleeding when followed up for longer periods. In the absence of stringent guidelines for patients with OGIB and nondiagnostic SBCE, and taking into account the present results, it seems reasonable to assume that these patients are still at risk of rebleeding and a close monitoring for recurrence of bleeding episodes is required. The appropriate duration of follow-up is unclear, but in view of our results, patients may benefit from close follow-up for at least 2 years, which, in our experience, will cover about 80% of the episodes of rebleeding.

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Cúrdia Gonçalves T. carried out the study, data analysis, performed literature search, and drafted the manuscript; Dias de Castro F. participated in the design of the study and data collection and reviewed the videos of capsule endoscopies; Moreira M.J. participated in the design of the study and reviewed the videos of capsule endoscopies; Rosa B. revised the manuscript and reviewed the videos of capsule endoscopies; and Cotter J. approved the study design, critically revised the manuscript, and approved the final version to be submitted.

Conflicts of interest

There are no conflicts of interest.

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