The predictive value of negative capsule endoscopy for the indication of Obscure Gastrointestinal Bleeding: no reassurance in the long term.

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Abstract

Background and aims : **Capsule Endoscopy (CE) has become the first-line tool to identify an underlying etiology for Obscure Gastrointestinal Bleeding (OGIB) in the small bowel (SB). This study aims to investigate the long-term outcome of patients with a negative CE.**

Patients and methods : **Retrospective review of standardized application forms of all patients who underwent CE for OGIB at the Ghent University Hospital between 2002 and 2013. Follow-up data on patients with a negative CE result (n=263) were collected by contacting the referring physician.**

Results : **Follow-up was available for 211 patients (Male, n=107 ; Female, n=104 ; Overt bleeding, n=76 ; Occult bleeding, n=135). Median follow-up time was 51.7 months (range 1.4-139.6 months). Ninety-six patients underwent further diagnostics, showing a cause for OGIB in 57 (59.4%). Final outcome for the complete cohort of negative CEs was : 139 (65.9%) true negative (i.e. non-SB cause of bleeding/ resolved OGIB), 19 (9%) false negative (i.e. SB cause of OGIB) and 53 (25.1%) ongoing bleeding without cause. Missed SB lesions were : angiodysplasia (n=11), Meckel's diverticulum (n=3), SB malignancy (n=3), jejunal erosions (n=1) and NSAID-induced SB ulcerations (n=1). Bleeding resolved in 138/209 patients (66%) of which 79 underwent non-specific therapy.**

Conclusions : **Negative CEs in patients with OGIB do not reassure the treating physician, but warrant close monitoring. In suspicious cases, alternative diagnostic modalities are recommended, showing a high diagnostic yield.** (Acta gastroenterol. belg., **2016**, 79, **405-413**).

Key words : negative capsule endoscopy, small bowel, OGIB, CE, outcome

Introduction

Obscure Gastrointestinal Bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs following negative endoscopic evaluation of the gastrointestinal tract, including EGD and colonoscopy. (1) OGIB is a common problem encountered by gastroenterologists and accounts for approximately 5% of all GI bleedings.(1) OGIB can be overt (melena, hematochezia, hematemesis) or occult (iron-deficiency anemia with or without occult fecal blood loss). OGIB is mostly caused by a lesion located in the small bowel (SB). It can however originate from lesions in other parts of the GI tract, which were missed on routine endoscopy. (2) Capsule Endoscopy (CE) has revolutionized the diagnosis of patients with OGIB, being able to visualize the entire SB in a non-invasive, well-tolerated way, showing an overall diagnostic yield (DY) of around 60%, equal to double-balloon enteroscopy (DBE) and superior to all other diagnostic modalities. (3-6) Few studies have investigated the long term follow-up of negative CEs in OGIB, regarding further diagnostics, therapy and patient outcome. We present the longest and largest series in negative CE for OGIB so far. Our aim was to investigate the long-term outcome in these patients and to define the incidence, cause of and predictive factors for continuation of OGIB during follow-up.

Materials and methods

Patient Inclusion and Capsule Endoscopy procedure

Between August 2002 and August 2013, 458 patients underwent a CE for the indication of OGIB at the Ghent University Hospital, a tertiary-care center in Belgium. All patients undergoing a CE had at least undergone EGD and colonoscopy to rule out upper and lower GI causes of OGIB and did not have contraindications for CE examination. (7) Before CE, the referring gastroenterologists were asked to complete a form with data on indication, relevant patient comorbidities (i.e. Diabetes Mellitus (DM), Liver Cirrhosis (LC), Renal Insufficiency (RI) and Aortic Stenosis (AS)), lowest hemoglobin value, latest medication regimen (including antiplatelet or anticoagulation medication and NSAID use) and transfusion requirements. The PillCam® (Given Imaging, Ltd, Yoqneam, Israel) was used in this study. During the study period, the versions of PillCam® have changed, which might have led to a higher diagnostic yield and therefore a lower number of false negative CEs. (8) A standardized CE procedure was followed. (9) Capsule data were first read by a fellow (BVD, CS, DD, PH), followed by second reading by a senior gastroenterologist (DDL). Positive CEs were defined as CE procedures visualizing SB lesions held responsible for

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OGIB. Capsule Endoscopies were considered negative if no lesions were visualized in the SB or if the visualized SB lesions on CE were not held responsible for OGIB. The latter were irrelevant SB mucosal erosions, red spots or angiomas, classified according to previous criteria. (10) Patients with negative CEs were included in this study. The study protocol was approved by the ethical committee of the Ghent University Hospital, according to the Helsinki Declaration.

Data collection

Retrospective data collection started in April 2014 and ended in August 2014. A standardized form was sent to the patient's GP, with questions on general wellbeing, further diagnostic procedures, established diagnosis, further treatment, transfusion needs during follow-up and the latest hemoglobin value. Non-responding GPs were contacted by telephone within two months to ensure high response rates. True negative (TN) CEs were defined as CEs with a cause of bleeding outside the SB, identified during follow-up or as bleeding of unknown origin, which spontaneously resolved during follow-up. False negative (FN) CEs were defined as bleeding sources located in the SB, held accountable for OGIB, but not diagnosed during the initial CE. These FN CE studies were revised by a fellow (LV). Resolution of OGIB was defined as resolution of visible bleeding during follow-up with a recent hemoglobin value above 13 g/dL in males and above 12 g/dL in females or identification of a non-GI diagnosis for anemia during follow-up. Non-resolution of OGIB was defined as persistent visible bleeding during follow-up or a recent hemoglobin value of <13 g/dL in males and <12 g/dL in females after exclusion of other non-GI causes for anemia during follow-up. Specific therapy during follow-up was defined as all therapeutic procedures targeting a presumed cause of OGIB (i.e. pharmacological, endoscopic, surgical or a combination). Non-specific therapy was defined as watchful waiting, transfusions or iron suppletion.

Statistical analysis

Data were analyzed using SPSS 22 (SPSS Inc., Chicago, Illinois). All continuous variables followed a parametric distribution. Data were expressed by mean (SD) or median (range) and statistically compared using the independent student t-test. Categorical variables were expressed as frequencies and analyzed using the $\chi 2$-test or the Fisher's Exact test, when the required conditions for using the $\chi 2$-test were not fulfilled. All tests were two-tailed. Significant findings found in univariate analyses were subsequently included in multivariate analyses with correction for age and gender. A P-value below 0.05 was considered as statistically significant (95% confidence intervals) and missing values were excluded from the analysis.

Results

Patient Characteristics

Between August 2002 and August 2013, 458 patients (Female, n=193 ; Male, n=265) underwent a CE for the indication of OGIB. In 263 patients (57.4%), CE investigations turned out negative and they were subsequently included in this study. Follow-up was eventually retrieved for 211 patients (Table 1) with a mean age of 60.05 years (SD, 15.75 ; range 8-88). At the time of the initial CE, mean Hb value was 8.54 g/dL (SD ± 1.83) and blood transfusion was administered in 64,5% of patients, indicating the severity of OGIB in this cohort. Small bowel findings on the initial CE procedure, which were not held accountable for OGIB in these patients,

Table 1. — **Characteristics of the included patient population after initial negative CE.**

Study population	**n=211**
Age (years), mean ± SD (range)	60.05 ± 15.750 (8-88)
Gender, total (%)	Male: 107 (50.7%) Female: 104 (49.3%)
Indication for initial CE, total (%)	Obscure-overt bleeding: 76 (36%) Obscure-occult bleeding: 135 (64%)
Hemoglobin level at the moment of CE (g/dL), mean ± SD	8.54 ± 1.83
Transfusion need before CE procedure, total (%)	136 (64.5%)
Comorbidities, total (%) DM LC RI AS	 56 (26.5%) 13 (6.2%) 40 (19.0%) 15 (7.1%)
Anticoagulants, antiaggregants use, total (%)	85 (40.3%)
Irrelevant SB findings on initial CE, total (%)	65 (30.8%)
Follow-up period (months), median (range)	51.7 (1.4-139.6)
>12 months follow-up, total (%)	199 (94.3%)

CE, Capsule Endoscopy; DM, Diabetes Mellitus; LC, Liver Cirrhosis; RI, Renal Insufficiency; AS, Aortic Stenosis; SB, small bowel.

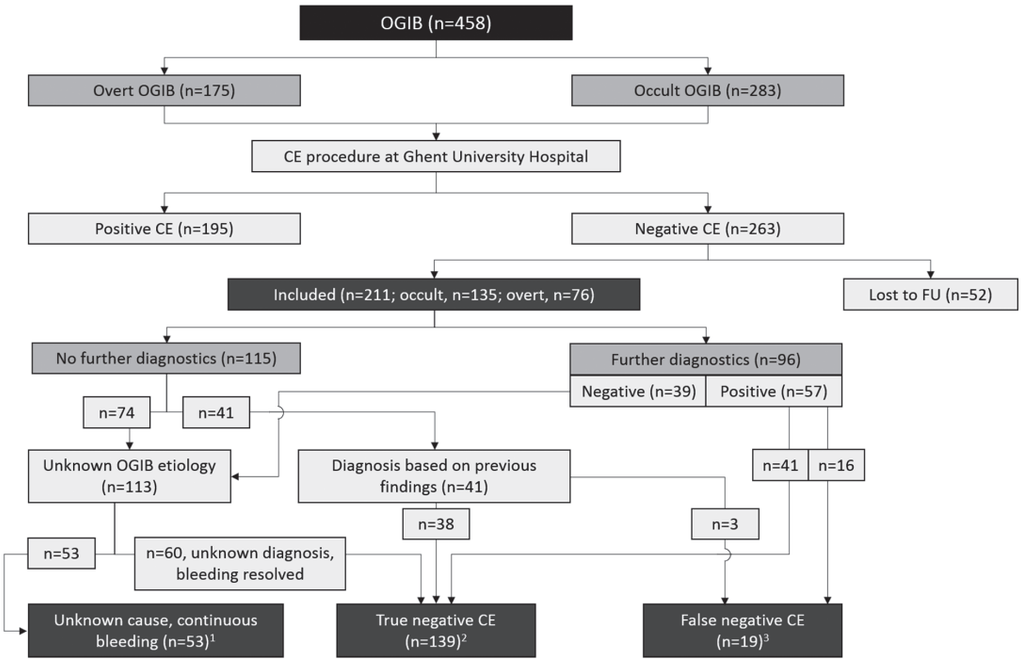

Fig. 1 — Patient cohort and diagnostic follow-up. OGIB, Obscure Gastrointestinal Bleeding ; CE, Capsule Endoscopy ; FU, Follow-up ; SB, Small Bowel. [1]Unknown etiology and OGIB not resolved, [2]Etiology outside the SB (n=79) or etiology unknown, but resolved OGIB (n=60), [3]Etiology inside the SB and missed on CE.

were found in 30.8% of all negative CEs. They were not associated with the identification of SB diagnoses for OGIB or a lower OGIB resolution rate during follow-up ($p>0.05$). At median follow up of 4.4 years, the global outcome of the complete cohort of negative CEs was : 139 TN CEs (65.9%), 19 FN CEs (9%) and 53 patients with undiagnosed ongoing bleeding (25.1%) (Figure 1). In 79/139 TN CEs, a cause of OGIB was found outside the SB and in 60/139 TN CEs, bleeding of unknown origin spontaneously resolved during follow-up. After the initial negative CE, further diagnostics, single or in combination, were performed in 96/211 patients because of ongoing bleeding/anemia. These included endoscopy (n=78, 81.3%, i.e. gastroduodenoscopy, colonoscopy, Double-balloon enteroscopy or repeat CE), imaging (n=18, 18.6%, i.e. CT scan, CT Enterography (CTE), SB transit, Meckel scintigraphy, ultrasound or angiography), surgical exploration (n=11, 11.5%) and gynaecological/proctological examinations (n=4, 4.2%). In 57/96 patients, further diagnostics after CE had proven useful in the identification of the cause of bleeding, resulting in an overall DY of 59.4%. In 41 of the remainder 115 patients without further diagnostics, a cause of anemia/OGIB was presumed at index CE and the CE procedure was done to exclude or confirm with certainty SB involvement. No further diagnostics were therefore required. Altogether, during follow-up, a final diagnosis for OGIB was withheld in 98 patients (46.4%).

Gastrointestinal sources of bleeding (n=74) were located in the upper GI tract (n=30, e.g. hiatal hernia, hypertensive gastropathy, esophagitis, angiodysplasia, and neoplasia), the lower GI tract (n=25, e.g. angiodysplasia, diverticulosis, polyposis, neoplasia, and hemorrhoids) or in the SB (n=19). A non-GI cause of bleeding was identified in 24 patients (i.e. gynaecological, renal, urological or hematological). Patient characteristics (i.e. age, gender, overt/occult bleeding, comorbidities, medication use, transfusion need before CE, irrelevant SB findings on the initial CE) did not impact the identification of a final diagnosis, whereas further diagnostics did (yes vs. no, $p<0.05$, OR=2.707, (1.546-4.742)). However, only further endoscopy after negative CE yielded a significant number of final diagnoses (endoscopy vs. no endoscopy, $p<0.05$, OR=2.033, (1.152-3.588)). However, although impacting therapeutic follow-up (diagnosis vs. no diagnosis, $p<0.001$, OR=11.588, (5.884-22.823)), a final diagnosis did not lead to significantly higher OGIB resolution rates or lower persistence of anemia during follow-up. Moreover, a final diagnosis was associated with higher transfusion needs in the long term, following univariate analysis. (Table 2).

False negative Capsule Endoscopy

Missed SB lesions accounted for 9% (19/211) of all negative CEs and included angiodysplasia (n=11), Meckel's diverticulum (n=3), SB malignancy (n=3), jejunal erosions (n=1) and NSAID-induced SB ulcerations (n=1) (Table 3). All patients with FN CEs had been extensively examined before CE procedure. After retrospective analysis of the missed SB lesions, no relevant lesions could be detected, nor was the quality of the CE procedure insufficient. The second reviewer was not blinded for the eventual outcome of the patient

Table 2. — **Influence of patient characteristics on follow-up, univariate and multivariate analysis.**

	Resolution of OGIB during follow-up			**Anemic Hb value after follow-up**			**Transfusion need during follow-up**		
	P value	**OR**	**CI (95%)**	**P value**	**OR**	**CI (95%)**	**P value**	**OR**	**CI (95%)**
Age category (50≤)	0.251	/	/	0.043	2.088	1.014-4.292	0.004	10.870	1.439-83.333
DM	0.018	0.469	0.249-0.884	0.020	2.154	1.119-4.147	0.101	/	/
LC	0.065	0.301	0.095-0.956	0.389	/	/	0.015	4.014	1.220-13.213
RI	0.112	/	/	<0.001 <u><0.001*</u>	7.250 <u>5.933</u>	3.093-16.994 <u>2.456-14.332</u>	0.011	2.888	1.247-6.685
AS	0.029	0.318	0.108-0.933	0.081	/	/	0.191	/	/
Use of Anticoagulants	0.331	/	/	0.015	2.073	1.149-3.740	0.758	/	/
Transfusion need before CE	0.642	/	/	0.495	/	/	<0.001 <u>0.02*</u>	16.748 <u>11.440</u>	2.225-126.067 <u>1.477-88.589</u>
Diagnosis	0.773	/	/	0.418	/	/	0.014	2.700	1.201-6.068

OGIB, Obscure Gastrointestinal Bleeding; DM, Diabetes Mellitus; LC, Liver Cirrhosis; RI, Renal Insufficiency; AS, Aortic Stenosis. Significant p-values after univariate analysis are given. <u>*</u> Significant p-values following multivariate analysis with correction for age and gender (underlined).

to ensure a profound examination of the actual bleeding location. The SB cause of bleeding was identified by subsequent diagnostic testing (n=16) or based on previous diagnostic work-up (n=3, i.e. although CE was negative, SB origin was presumed based on previous findings). FN CEs could not be predicted by patient characteristics before CE. Furthermore, the Hb value at the moment of CE was not significantly different between TN and FN CEs (8.51 vs 8.69 g/dL ; p=0.688). The lesions missed on CE were significantly more detected by imaging and subsequent surgical exploration (imaging vs. no imaging, p=0.014 ; surgical exploration vs. no surgical exploration, p=0.007). Further endoscopy (i.e. EGD, DBE, repeat CE) or gynaecological/proctological examinations were not associated with a higher diagnosis rate for SB origin of bleeding.

Continuation of OGIB

Data regarding therapeutic follow-up and resolution of OGIB were obtained for 198 and 209 patients respectively. Eighty-three patients received specific therapy, of which 52 guided by further diagnostics. One hundred fifteen patients received non-specific therapy. Bleeding resolved in 138/209 patients (66.0%) and was achieved in 59/83 patients following specific therapy (71.1%) and in 79/115 patients following non-specific therapy (68.7%). Continuation of OGIB during follow-up was as high as 34.0% (71/209). Re-bleeding during follow-up, which resolved spontaneously or following specific diagnostics and treatment, was not included in this percentage. A recent Hb value was available in 191 patients. One hundred eleven patients (58.1%) had a normal, recent, non-anemic Hb value, while 80 patients (41.9%) were still anemic. In 32/80 patients, OGIB resolved during follow-up, but anemic Hb values, not related to OGIB (i.e. concomitant DM or RI), were found during follow-up, while in 16/111 patients OGIB did not resolve, although Hb levels could be stabilized at a non-anemic level. Follow-up of patients was influenced by patient characteristics (Table 2). Following multivariate analysis with correction for age and gender, anemia was significantly higher patients with RI. Furthermore, transfusion needs during follow-up were significantly higher in patients needing transfusions before the initial CE. During follow-up, 5 patients died as a result of gastrointestinal bleeding. In two patients, the etiology of OGIB was found in the SB (Table 4). They died as a result of progressive deterioration of their general condition. In one patient, death followed active diverticular bleeding in the colon. The remainder two patients died from massive bleeding originating from the GI tract, without definite established diagnosis. All five patients had a fragile clinical condition and none of these deaths could be prevented : all necessary diagnostics were done and/or maximal supportive therapy was given.

Discussion

Capsule endoscopy is a useful tool in the evaluation of OGIB, yet the approach of negative procedures remains vague. In our study, we found that in 68.7% (79/115) of CE-negative patients undergoing non-specific therapy, OGIB spontaneously resolved during follow-up, which strengthens the idea that further investigations can initially be deferred (11-15). When OGIB does not resolve or anemia persists, further diagnostics give a yield of 59.4% in defining the cause of OGIB/anemia. This diagnostic yield was not impacted by patient characteristics. Consistent with our findings, other authors report diagnostic yields in these patients of 14.29-72.5% (16-24). In this study, only further endoscopy significantly led to more diagnoses for OGIB outside the SB, yet not to the identification of more SB etiologies. Therefore, an etiology outside the SB should be ruled out first, which is in line with previous authors (22,24). Repeating EGD or colonoscopy is a suitable initial approach, if clinical

symptoms or laboratory data do not indicate otherwise. When diagnostics remain inconclusive and OGIB does not resolve or anemia persists during follow-up, the exclusion of a SB etiology by further imaging (e.g. CTE, Meckel Scan) can be the next step, since imaging was associated with significantly more SB diagnoses. According to our results, malignancy in older patients should be considered as etiology for OGIB, whereas in younger patients Meckel's diverticulum should be excluded (Table 3). Angiodysplasia (n=11) was the most common etiology for OGIB in patients with a FN CE and diagnosis was established using EGD (duodenal or proximal jejunal origin, n=4), DBE (jejunal or ileal origin, n=4) or was based on previous findings (n=3). Further imaging and surgical exploration both led to the identification of significantly more FN CEs. This was

Table 3. — **False negative CE procedures: indication, work-up before and after negative CE, final diagnosis.**

	Age (y)	Gender	Indication[1]	TFNB CE	Work-up before CE	Work-up after CE	Diagnosis
1	60	female	occult	yes	2 EGDs + colonoscopy + DBE + CT	DBE	Bleeding from jejunal angiodysplasia
2	71*	male	occult	yes	EGD + colonoscopy + DBE + Meckel Scan	CT + surgical exploration	Metastatic SB invasion of undifferentiated spinocellular epithelioma due to radiotherapy
3	59	female	occult	yes	EGD + colonoscopy + DBE	second CE	SB angiodysplasia
4	61	male	overt	yes	4 EGDs + colonoscopy + CT angiography + SBFT	none	Bleeding from duodenal angiodysplasia
5	66	male	overt	yes	2 EGDs + colonoscopy	CT + SBFT	Bleeding from SB diverticulum perforation caused by SB Non-Hodgkin Lymphoma
6	53	female	overt	yes	2 EGDs + 2 colonoscopies + abdominal CT + 2 abdominal ultrasounds	EGD + colonoscopy	NSAID-induced SB ulcera
7	58	male	occult	no	2 EGDs + 2 colonoscopies	CT + surgical exploration	GIST tumor located in the ileum
8	21	male	overt	no	EGD + colonoscopy + Meckel Scan	Surgical exploration	Meckel Diverticulum accepted as bleeding cause
9	74	female	overt	yes	multiple EGDs + DBE + SB transit	EGD	Duodenal angiodysplasia + Ulcera
10	84	male	overt	yes	2 EGDs + 1 colonoscopy + CT enteroclysis	DBE + EGD	Bleeding from several jejunal Erosions
11	23	male	overt	no	Plain abdominal radiography + SBFT + EGD + colonoscopy	Meckel scan	Meckel Diverticulum accepted as bleeding cause
12	77	male	occult	yes	8 EGDs + 4 colonoscopies + 3 abdominal CTs	EGD + aortic angiography	Small bowel angioma + Stomach erosion
13	8	male	overt	no	EGD + Meckel Scan	Surgical exploration	Meckel Diverticulum accepted as bleeding cause
14	72	female	occult	yes	EGD + colonoscopy + 2 abdominal ultrasounds	EGD + colonoscopy	SB angiodysplasia
15	70	male	occult	yes	2 EGDs + 2 colonoscopies + DBE + CT enterography	DBE	Bleeding from proximal jejunal angioma
16	82*	female	overt	yes	EGD + colonoscopy + CT enterography	none	Angiodysplasia in SB and colon + anticoagulants use
17	58	male	overt	yes	6 EGDs + DBE	EGD + colonoscopy	Angiodysplasia + Acquired Von Willebrand Factor deficiency
18	71	female	occult	yes	EGD + colonoscopy + 4 DBEs + CE	DBE	Bleeding from proximal jejunal angiodysplasia
19	71	male	occult	yes	2 EGDs + 2 colonoscopies + 2 DBEs + CT enterography	none	Recurrent bleeding from proximal jejunal angioma

DBE, Double-balloon Enteroscopy; SBFT, Small bowel follow-through; SB, Small Bowel; TFNB CE, transfusion need before CE; vWF, von Willebrand Factor; NHL, Non-Hodgkin Lymphoma; GIST, Gastrointestinal Stromal Tumor. [1]Indication is defined as overt or occult bleeding. *OGIB-related death of patient.

Table 4. — **Previous CE negative studies and re-bleeding rates.**

Author, year	Country	Number of CE-negative patients, n	Follow-up period, n (months)	Re-bleeding rates, n (%)
Delvaux M, 2004 [31]	France	17	12	52.9
Neu B, 2005 [32]	Germany	18	13	22.0
Lai LH, 2006 [10]	China	18	19	5.6
Macdonald J, 2008 [12]	UK	18	17	11.0
Viazis N, 2009 [20]	Greece	161	24.8	64.6
Esaki M, 2010 [21]	Japan	32	20	28.1
Lorenceau-Savale C, 2010 [23]	France	35	15.9	22.9
Park JJ, 2010 [15]	Korea	28	31.7	35.7
Riccioni ME, 2013 [11]	Italy	207	24	16.4
Kim JB, 2013 [16]	Korea	63	23.5	27.0
Koh SJ, 2013 [17]	Korea	57	23.7	22.8
Magalhães-Costa P, 2015 [33]	Portugal	117	48	27.4
Van de Bruaene C, 2016[1]	Belgium	211	51.7	34.0

[1]Current study, re-bleeding is defined as continuation of OGIB duringfollow-up.

in line with previous studies, which emphasized on the importance of CTE or MRE in the detection of missed SB lesions.(16, 25-27) A possible explanation for FN CEs was given by previous authors (25,28), stating that poor visual quality, incomplete transit, quick transit through the duodenum, inability to inflate the SB or the capsule's angle of view could lead to missed SB lesions. DBE can overcome these limitations, given its flexibility and ability to smoothen the wall during retraction. This confirms the fact that after a negative CE, DBE can be preferred over repeating CE, when bleeding persists and if SB pathology is suspected. Also, it gives the opportunity to treat angiodysplastic lesions locally. A recent meta-analysis confirmed the DY of subsequent DBE after negative CE.(29) Another possibility can be repeating the CE procedure with a reported overall DY of 35-75% and a subsequent management change in 39-62.5% of cases. (19,30) Viazis N et al. concluded that repeating the CE procedure should only be considered if the bleeding presentation switches from occult to overt bleeding or if the hemoglobin level drops with more than 4g/dl. (21)

According to our results, an OGIB diagnosis should be intensively sought if bleeding does not resolve or anemia persists, since it impacted therapeutic follow-up in a significant way. However, finding a diagnosis was not associated with higher OGIB resolution rates, less anemic patients or lower transfusion needs during FU. Previous authors came to a similar conclusion regarding the DY of CE in OGIB, stating that an established diagnosis paradoxically did not cause an improvement in patient outcome and specific therapy was not predictive for lower re-bleeding or resolution of anemia in the long term.(18, 20) Irrelevant SB findings on the initial CE were correctly interpreted by the treating physician, since irrelevant SB findings were not associated with more diagnoses in the total GI tract or a higher OGIB resolution rate during follow-up, which strengthens the diagnostic value of CE in determining the cause of OGIB.

Nineteen SB origins for OGIB were missed (9%). Angiodysplasia was most frequently missed on CE, followed by Meckel's diverticulum and SB malignancy. These FN CEs could not be predicted by patient characteristics. In our study, all false negative CEs were revised. No relevant lesions could be detected, nor was the quality of the CE considered inadequate, confirming the interpretation of the initial CE. Also, the Hb value at the moment of CE was not significantly different between TN and FN CEs, which is consistent with Esaki M et al. (22) False negative CEs, when compared to TN CEs did not significantly differ in further follow-up of lesions causing OGIB. In accordance with our study, other studies reported tumors or polyposis potentially missed on CE because of their unifocality and capsule velocity in proximal parts of the SB. (25,28) In a pooled analysis (31), 5.9% of the vascular SB lesions and 18.9% of the neoplastic SB lesions were found to be missed on CE, resulting in an equal number of missed lesions in the SB (1.5% of all SB lesions) due to the high prevalence of vascular lesions. This might explain the high number of missed angiodysplasia in our study. Similar lesions were missed in previous studies. (16,18,21)

In our study, OGIB continued in 34% of cases (71/209). Reported re-bleeding rates vary (Table 4). Reason for the heterogeneity might be the variation in follow-up period and sample size, since a long follow-up increases the possibility of re-bleeding. Furthermore, the number of patients with continuation of OGIB might be an underestimation of the actual re-bleeding rate after negative CE, since re-bleeding after the initial CE, which resolved during follow-up was not included

in this percentage. Moreover, previous authors (16-18) found that re-bleeding in CE positive groups did not significantly differ from bleeding in CE negative groups, emphasizing the importance of negative CEs in OGIB. In 16/111 non-anemic patients, OGIB did not resolve, but Hb levels could be stabilized. This supports the idea that in patients with stabilized hemoglobin values and without a diagnosis for unresolved OGIB, further diagnostics may be deferred and non-specific therapy is acceptable, in the absence of alarm symptoms.(15) Obscure Gastrointestinal Bleeding resolved in 66% of all patients. Specific therapy had a success rate of 71.1%, which did not significantly differ from non-specific therapy (68.7%) and was similar to the success rate of specific therapy in CE positive patients. (9)

Renal insufficiency and transfusion need before CE were found to be significant independent risk factors for an impaired outcome, since they presented with higher transfusion needs and/or anemia during follow-up. Patients presenting with one of these characteristics should be followed more closely. Although re-bleeding was reported to be higher in patients using anticoagulants (13,18), we did not find a significant association between the use of these drugs and OGIB resolution. This can probably be explained by the fact that we did not make a distinction between anticoagulants, antiplatelet therapy and NSAID use. Also, in accordance with previous studies (13,17), we found no significant difference in resolution rates between overt and occult bleeding, in contrast to Riccioni ME et al., who found that the indication of melena was an independent risk factor for re-bleeding during follow-up. (12)

The current study has some limitations. First of all, it is a retrospective, single-center study. This shortcoming was minimized using standardized questionnaires and checklist forms to overcome potential bias in our data. Secondly, no comparison between an equal number FN and TN CEs could be made. Although the number of patients included in this study is the largest CE negative population in literature so far (n=211), the number of FN CEs remained relatively small (n=19). This was taken into account when doing statistical analyses on these data. Since all patients with negative CEs between 2002 and 2013 were included in this study, heterogeneity in our patient population could not be avoided. Also, no data on the period between CE and re-bleeding was

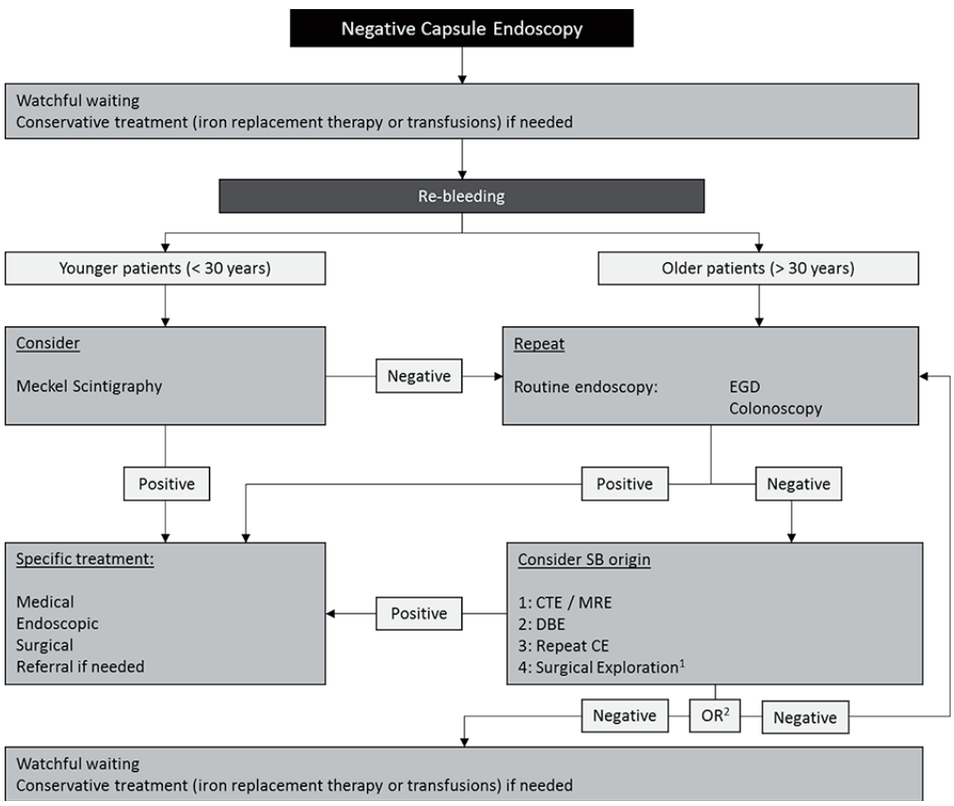

Fig. 2. — Recommended approach for diagnosis and treatment of Obscure Gastrointestinal Bleeding (OGIB) in patients with a negative CE. DBE, Double-balloon Enteroscopy; PE, Push Enteroscopy; 1Surgical exploration is indicated when patient characteristics, clinical symptoms, laboratory data or previous imaging (CTE/MRE) do not reassure the physician to exclude SB malignancy in patients with persisting anemia and non-resolving OGIB,2If clinical outcome of OGIB can be stabilized and clinical data is reassuring, no further diagnostic steps should be taken except close follow-up and conservative treatment. If not, further diagnostics are recommended.

available, since this was outside the scope of our study. Our OGIB continuation rate of 34% might therefore be an underestimation of the actual OGIB problem. However, we believe that our data show the natural course of OGIB and is representative for all patients with a negative CE for the indication of OGIB.

Conclusions

Our long-term follow-up study gives an interesting insight in the course of patients with OGIB and a negative CE. Capsule endoscopy remains a useful tool in the evaluation of OGIB. When initial CE is negative, further diagnostics can initially be deferred. Persisting anemia should be investigated by repeating routine endoscopy, if no other approach is indicated. If negative, re-investigation of the SB with imaging as first-choice diagnostic tool might be necessary. If anemia can be stabilized in patients with undiagnosed OGIB, no further diagnostic procedures are needed and non-specific therapy should be continued, in the absence of alarm symptoms. Relevant SB lesions account for 9% of all negative CEs and could not be predicted by patient characteristics at the moment of CE. Continuation of OGIB was high (34%) and might be underestimated. In conclusion, negative CEs in patients with OGIB do not reassure the treating physician, but warrant close monitoring and alternative diagnostic modalities in suspicious cases. We present a flowchart for the approach of patients with OGIB with a negative CE, based on our new findings in this study (Figure 2).

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