Enteroscopy in diagnosis and treatment of small bowel bleeding: A Delphi expert consensus

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A B S T R A C T

Background: Enteroscopy plays an important role in the management of small bowel bleeding. However, current guidelines are not specifically designed for small bowel bleeding and recommendations from different international societies do not always align. Consequently, there is heterogeneity in the definitions of clinical entities, clinical practice policies, and adherence to guidelines among clinicians. This represents an obstacle to providing the best patient care and to obtain homogeneous data for clinical research.
Aims: The aims of the study were to establish a consensus on the definitions of bleeding entities and on the role of enteroscopy in the management of small bowel bleeding using a Delphi process.
Methods: A core group of eight experts in enteroscopy identified five main topics of small bowel bleeding management and drafted statements on each topic. An expert panel of nine gastroenterologists participated in three rounds of the Delphi process, together with the core group.
Results: A total of 33 statements were approved after three rounds of Delphi voting.
Conclusion: This Delphi consensus proposes clear definitions and a unifying strategy to standardize the management of small bowel bleeding. Furthermore, it provides a useful guide in daily practice for both clinical and technical issues of enteroscopy.

1. Introduction

Small bowel bleeding (SBB) is defined as bleeding originating between the ligament of Treitz and the ileocecal valve and accounts for 5–10% of gastrointestinal bleeding events [1]. Enteroscopy is central to the diagnosis and management of patients with SBB. The latest European and American guidelines [2–4] are

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designed for diagnosis and treatment of all small bowel disorders and are largely based on retrospective cohorts and studies with a small sample size, which provide recommendations based on a moderate to low quality of evidence. Furthermore, the management strategies for patients with midgut bleeding promoted by current national and international societies are heterogeneous and might be challenging to adopt in real-life clinical practice, as recently showed by an ESGE international survey [5]. A report published in 2021 showed a wide variability in quality performance measures for small bowel capsule endoscopy (SBCE), with only 40% of procedural minimum standards met by a relevant proportion of the centers analyzed (≥ 80%) [6].

Agreement on technical issues and indications for enteroscopy based on standardized terminology would lead to improved, reproducible clinical management resulting in better quality of care and progress in clinical research. This consensus would provide a comprehensive and updated guide to optimize the clinical and endoscopic management of patients with SBB, from diagnostic workup to therapy and follow up, focusing on terminology and technical issues relating to small bowel endoscopy.

2. Methods

2.1. Design

The consensus process used a Delphi methodology – a validated technique to reach consensus on topics in which the scientific literature may not be solid enough to draw definitive conclusions and develop agreement [7]. Statement drafts were voted on using an online application (https://docs.google.com/forms/u/0/) by 17 gastroenterologists from the RAVE (*Riunione Annuale Videocapsula Endoscopica* - Capsule Endoscopy Annual Meeting) Study Group.

2.2. Participants

Two members of the RAVE Study Group (LE and GET) and a third researcher (AS) presented the project at the annual RAVE meeting on June 30th, 2021. A core group of nine enteroscopy experts (C.C., L.E., R.M., S.O., M.P., M.E.R., E.R., C.S., G.E.T.) identified five main topics of SBB management (i.e., role of SBCE and device-assisted enteroscopy (DAE), patient preparation and technical issues of SBCE, patient preparation and technical issues of DAE, classification of small bowel findings, and obscure GI bleeding), and formed five working groups responsible for elaboration of statements on each topic. Each working group provided also the supporting evidence for the approved statements. A total of 34 statements were drafted for the first round of the Delphi process. Eight members of the RAVE study group (S.C., R.C., R.dF., C.M.G., C.M., G.S., M.S., M.V.) formed the expert panel invited to participate in the rounds of the Delphi process. Core group and expert panel experience on enteroscopy is outlined in Appendix A.

2.3. Setting the delphi rounds

For each round, the core group (9) and the expert panel (8) members were invited to rate the 34 statements made, using a numerical Likert scale with 5 possible answers (strongly disagree, 1 point; disagree, 2 points; neither agree nor disagree, 3 points; agree, 4 points; strongly agree, 5 points). When a statement received a score other than 5, participants were asked to leave a comment to improve the statement in the next round. Two measures were used to define the consensus reached: the agreement score (i.e., average of the score (from 1 to 5)), and the degree of consensus, (i.e., percentage of agree and strongly agree out of the total number of scores). The statement was accepted if the agreement score was ≥4 points and the degree of consensus was ≥80% within three rounds. Statements with insufficient consensus were rewritten by the responsible working group, incorporating the anonymous comments of the participants and submitted for vote in the following round. The Delphi process was stopped when a consensus was established or after the third round, even if consent had not been reached (Fig. 1).

3. Results

Among the statements examined, 33 out of 34 reached the predetermined consensus threshold after three rounds of voting. Four statements were related to definitions of bleeding entities and thirty statements were focused on the management of SBB. The results of the rounds of the Delphi process are summarized in Fig. 1.

3.1. Definitions of small bowel bleeding

Statements

- Suspected small bowel bleeding refers to patients with unknown bleeding origin after upper and lower endoscopic examinations performed for overt gastrointestinal bleeding or persistent iron deficiency anemia. *Approved in the first round (Agreement score 4.3, Degree of consensus 94%)*
- Overt small bowel bleeding refers to patients presenting with melena or hematochezia with a source of bleeding identified in the small intestine. *Approved in the first round (Agreement score 4.35, Degree of consensus 82%)*
- Occult small bowel bleeding refers to patients presenting with persistent iron-deficiency anemia and a small bowel source of bleeding, without overt hemorrhage. *Approved in the third round (Agreement score 4.05, Degree of consensus 82%)*
- Obscure gastrointestinal bleeding refers to patients presenting for GI bleeding with unknown origin after upper, lower, and small bowel endoscopic examinations (with small bowel capsule endoscopy and/or end-to-end enteroscopy). *Approved in the second round (Agreement score 4, Degree of consensus 88%)*

3.2. Role of small bowel capsule endoscopy in the management of small bowel bleeding

Statements

- Small bowel capsule endoscopy is a first-line examination when small bowel evaluation is indicated for suspected small bowel bleeding, unless contraindications are present. *Approved in the first round (Agreement score 4.7, Degree of consensus 100%)*
- In patients with overt gastrointestinal bleeding, small bowel capsule endoscopy should be performed as soon as possible after negative upper and lower endoscopic examinations, ideally within 48–72 h from bleeding onset. *Approved in the third round (Agreement score 4.6, Degree of consensus 94%)*
- There is not sufficient evidence to recommend early small bowel or panenteric capsule endoscopy as a triage tool after a negative esophagogastroduodenoscopy (EGD) and before colonoscopy in patients with ongoing melena. *Approved in the third round (Agreement score 4.4, Degree of consensus 100%)*

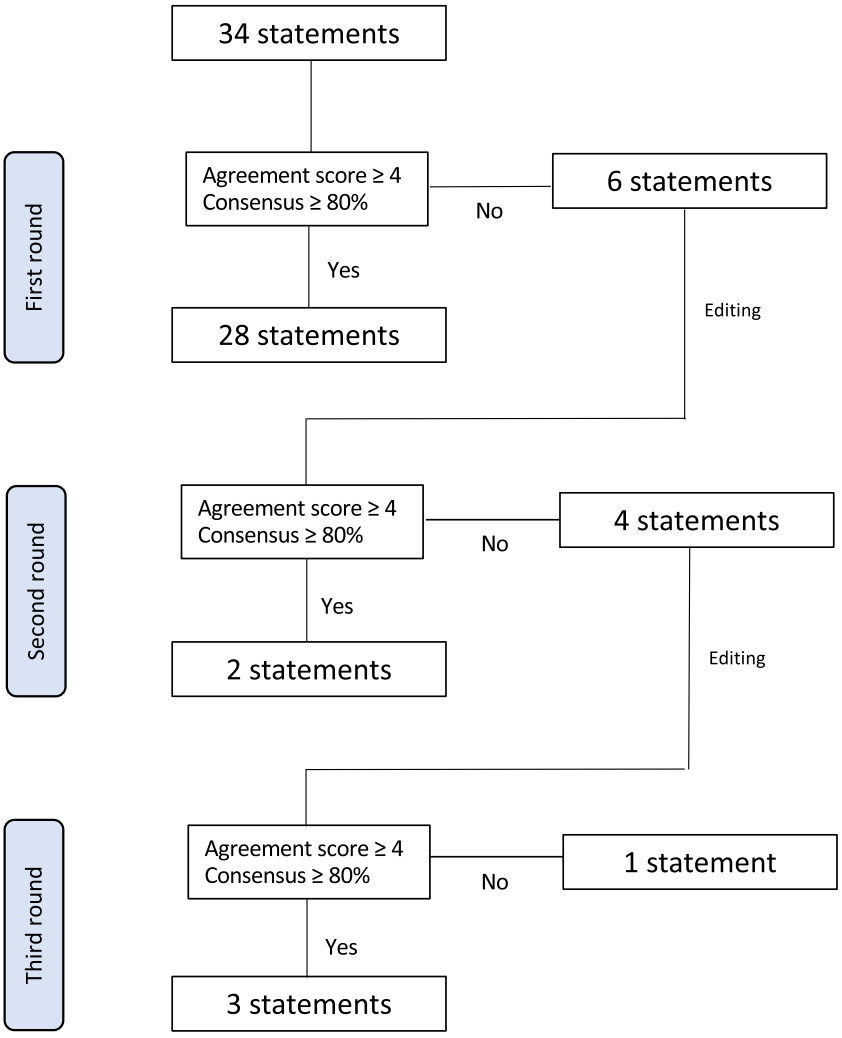

Fig. 1. Flowchart of the Delphi process.

SBCE is a non-invasive procedure that allows visualization of the entire small bowel in 80–90% of patients [8]. It increases diagnostic yield (DY) of DAE and guides the optimal approach (anterograde vs retrograde) [9]. Three randomized control trials (RCTs) in patients with suspected SBB demonstrated the superiority of SBCE in terms of DY compared with catheter angiography, dedicated small bowel contrast radiography and push enteroscopy [10–12]. Compared to push enteroscopy, SBCE has a superior DY (56% and 26%, respectively) for clinically significant findings in patients with SBB [13]. Therefore, current international guidelines recommend SBCE as a first-line examination in patients with suspected SBB [2,4,14].

Current ESGE and ASGE guidelines do not recommend a routine second-look endoscopy (upper and/or lower) before small bowel evaluation [2,4] as SBCE may also identify lesions missed during the previous gastroscopy and/or colonoscopy[15,16]. A second-look endoscopy before capsule examination should be considered only on a case-by-case basis, especially in cases of incomplete or low quality first-line examinations (e.g., presence of blood, food debris, or stools). When upper endoscopy is repeated, push enteroscopy might be useful to visualize distal duodenum and proximal jejunum, small bowel portions not always seen with SBCE. Push enteroscopy may be performed with a dedicated device or with a pediatric colonoscope and allows examination of about 50–70 cm of the midgut beyond the ligament of Treitz [17]

There is compelling evidence that shorter intervals between the bleeding episode and SBCE are associated with significantly higher DY and positively influences patient management and outcome [18]. Therefore, the latest ESGE guidelines recommend SBCE as soon as possible after the bleeding episode, ideally within 14 days [2]. Bresci et al. reported a DY of 91% in patients submitted to SBCE within 15 days from bleeding onset, compared with only 34% for examinations performed after [19]. Singh et al. reported higher DY, rate of therapeutic intervention, and reduction in length of stay when SBCE was performed within 72 h of admission [20]. Studies have also demonstrated that the yield of SBCE and DAE in overt SBB is greater than in occult hemorrhage [18,21–23]. Evidence from a recent meta-analysis report a DY of 65.2% (95% CI 58.9–71.2%) for SBCE and 74.0% (95% CI 62.3–84.3%) for DAE, and a therapeutic yield of 55.9% (95% CI 44.3–67.1%) for SBCE and 35.8% (95% CI 30.6–41.2%) for DAE in overt midgut bleeding [24]. Despite this study reporting a lower therapeutic yield of DAE compared to SBCE, the former has indirect therapeutic implications – the performance of biopsy, clip placement and tattooing of small bowel lesions often leads to medical, radiological or surgical treatment of lesions unsuitable for endoscopic therapy. The study reports that the optimal timing for SBCE and DAE in terms of therapeutic yield is within 48 h from bleeding onset. Consistently, a large single-center retrospective study has recently shown that agreement between SBCE and DAE significantly increased (k = 00.59

to 0.323) when both procedures were done within 1–5 days of the other [23]. Future research in this field is needed as the evidence to date mostly comes from retrospective and heterogeneous studies.

Despite supported by evidence, performance of SBCE in the acute setting has well-known limitations that hamper its diffusion and availability. SBCE is a time-consuming and operator-dependent procedure, while acute intestinal hemorrhage often requires rapid management within the emergency room. The future implementation of an out-of-hours SBCE-reader service and the use of artificial intelligence for rapid and semi-automated capsule reading could overcome this limitation in tertiary referral centers [25].

Patients with brisk suspected SBB and hemodynamic instability might not be suitable for endoscopy. In this setting, or in case of overt midgut bleeding [26] and failed endoscopic hemostasis, the multiphasic CT-scan (CT angiography) should be promptly considered because is rapid, broadly available and allows detection and characterization of the site and etiology of the active hemorrhage with high accuracy (sensitivity 89%, specificity 85%) [27,28]. After the radiological identification of the site of active hemorrhage, angiography and subsequent embolization represent the optimal treatment option in most cases of massive midgut bleeding. Notably, a remarkable rate of adverse events (about 10%) may occur during angiography. The most relevant are renal insufficiency, infections and bowel ischemia [29].

A new approach with panenteric capsule endoscopy (PCE) has been investigated in patients with melena and a negative upper GI endoscopy [30]. In a recent proof-of-concept study, PCE was found to be feasible and safe, leading to identification of the bleeding site in 83% of patients and therapeutic interventions in 50% of patients [30]. More evidence supporting the usefulness of PCE comes from a recent retrospective study [31]. Definitive conclusions cannot be drawn from studies with small sample size and retrospective design, but PCE is promising, and further research is needed to clarify its role as a triage tool in patients with melena and negative EGD. Furthermore, bowel preparation administered for capsule endoscopy would help the patient to be cleaned for an eventual subsequent colonoscopy.

3.3. Role of device-assisted enteroscopy in the management of small bowel bleeding

Statements

- Device-assisted enteroscopy (DAE) or push enteroscopy, according to lesion location, should be performed as soon as possible to confirm and possibly treat bleeding sources identified by capsule endoscopy or small bowel imaging. *Approved in the first round (Agreement score 4.3, Degree of consensus 88%)*
- Device-assisted enteroscopy is a first-line diagnostic and therapeutic option in selected cases, including known hemorrhagic small bowel lesion, brisk hemorrhage without hemodynamic instability, contraindications to SBCE, and surgically altered anatomy (e.g., Roux-en-Y gastrojejunostomy). *Approved in the first round (Agreement score 4, Degree of consensus 82%)*
- Patients with overt small bowel bleeding failing to achieve endoscopic hemostasis should be promptly considered for on-call interventional radiology and surgical consulting. *Approved in the first round (Agreement score 4.3, Degree of consensus 88%)*
- Intraoperative enteroscopy should be available during the surgical procedure to localize the source of bleeding and possibly perform combined endoscopic-surgical therapy. *Approved in the first round (Agreement score 4.2, Degree of consensus 94%)*

DAE encompasses balloon-assisted (i.e., single-balloon and double-balloon) or spiral enteroscopy and represents both a diagnostic and therapeutic examination [32,33]. Moderate sedation/analgesia, deep sedation/analgesia, and general anesthesia are all acceptable alternatives for DAE and should be tailored to patients according to the complexity of the procedure, patient's risk factors for sedation-related complications, and local protocols [34,35].

DAE is often performed soon after SBCE to confirm or clarify the diagnosis and mostly to provide treatment [36,37]. However, DAE can also represent the optimal first-line diagnostic and therapeutic option in selected cases, such as known hemorrhagic small bowel lesion, brisk hemorrhage without hemodynamic instability, surgically altered anatomy or contraindications to SBCE [4,38,39].

Push enteroscopy may be performed after SBCE, in highly selected cases, for lesions located in the distal duodenum and proximal jejunum. Despite the relatively low overall DY of push enteroscopy compared to DAE, the DY of the two techniques appears to be comparable in the setting of proximal lesions [40,41]. To date, DAE has largely replaced push enteroscopy for the management of proximal bleeding lesions because finding locations with SBCE and/or radiology may be inaccurate.

Hemostatic enteroscopic procedures vary according to the type of culprit lesion and include mechanical therapy, electric cauterization, drug injection or spray, and polypectomy [14].

The DY of balloon-assisted enteroscopy for suspected SBB is reported to be 55–78% [22,23,42–44]. DAE showed a higher DY when it was performed after a positive SBCE (75%; 95% CI 60.1–90.0) compared with a previous negative result (27.5%; 95% CI 16.7–37.8) [45]. In a recent metaanalysis, the therapeutic yield of DAE varied between 73.5%, when enteroscopy was performed within 24 h from bleeding onset, and 68.5% for enteroscopy done within 72 h [46]. To date, high-quality prospective data assessing the optimal timing of DAE in SBB are lacking. However, there is increasing evidence supporting the performance of DAE early after the onset of hemorrhage to maximize its diagnostic and therapeutic impact and reduce the rebleeding rate [46–48].

In cases of failure of endoscopic hemostasis in patients overt bleeding, a rapid multidisciplinary consultation between the gastrointestinal endoscopist, interventional radiologist, and surgeon is key for achieving the fastest and most effective management, according to local availability and expertise. Surgical treatment for midgut bleeding is generally performed when interventional radiology is unavailable or unfeasible. When indicated, surgery is usually guided by a combination of SBCE, tattooing performed during previous DAE, and/or angiographic techniques [49,50]. In these cases, intraoperative enteroscopy (IOE) should be available to allow identification of the source of bleeding and possibly perform combined endoscopic-surgical hemostasis [38]. IOE may be also indicated on a case-by-case basis when DAE is impractical due to intestinal adhesions, or cannot reach the bleeding lesion, or in cases of persistent obscure GI bleeding with suspected small bowel source [4]. IOE is performed during laparotomy or laparoscopy through an enterotomy or via peroral or rectal route, and should be carefully selected because it is associated with a considerable risk of complications (e.g., prolonged ileus, wound infections, and adhesive intestinal obstruction) and mortality [51,52].

3.4. Patient preparation and technical issues of small bowel capsule endoscopy

Statements

- A reliable patency test (i.e., patency capsule or CT/MRI-enterography) should be performed first in patients with potential risk of capsule retention. *Approved in the first round (Agreement score 4.4, Degree of consensus 82%)*
- Small bowel capsule endoscopy can be safely used in patients with a cardiac pacemaker or defibrillator. *Approved in the first round (Agreement score 4.2, Degree of consensus 94%)*
- Patients undergoing SBCE should receive a modified diet (i.e., low-fiber diet or clear liquid) and a purgative solution before the examination for better visualization of the small bowel. *Approved in the first round (Agreement score 4.2, Degree of consensus 82%)*
- Antifoaming agents (e.g., simethicone) could be administered before capsule ingestion to improve the quality of mucosal visualization. *Approved in the second round (Agreement score 4, Degree of consensus 81%)*
- Prokinetic agents could be reserved for patients with known or expected delayed gastric outflow. *Approved in the first round (Agreement score 4, Degree of consensus 96%)*
- Real-time view should be routinely used to exclude delayed gastric outflow, particularly in patients at risk of prolonged gastric transit time and who have experienced gastric capsule retention. *Not approved (Agreement score 3.8, Degree of consensus 70%)*
- After capsule ingestion, patients should fast for at least 2 h. Patients may be allowed to drink clear liquids after 2 h, and to eat solid food after 4 h. *Approved in the first round (Agreement score 4.2, Degree of consensus 82%)*

The risk of capsule retention increases in patients with small bowel stenosis or predisposing conditions (e.g., previous abdominal surgery, symptoms of obstruction, or Crohn's disease with stenosis). Capsule retention rate is approximately 2% for patients undergoing evaluation for suspected SBB [53]. A thorough evaluation of past medical history should always precede capsule administration to identify the need for a patency test (i.e., patency capsule or CT/MRI-enterography). The PillCam™ patency capsule helps to avoid the risk of retention in most patients [54,55]. Its accurate localization is essential for cases without excretion [54], and can be assessed through the identification of the barium radiofrequency tag with a two-view abdominal X-ray or noncontrast CT scan. The excretion of the PillCam™ patency capsule should be checked 32–33 h after ingestion, but a recent study suggests that 24 h might be enough [56].

The optimal patency test before SBCE administration is still to be determined. A small, comparative, prospective study suggested that capsule retention in high-risk patients is not accurately predicted by negative small bowel cross-sectional imaging [57]. Given the small amount of available evidence, it is still unclear whether patency capsule, albeit preferred in many centers, should be chosen over small bowel cross-sectional imaging.

As recommended by the latest ESGE technical review [58] on small bowel endoscopy, SBCE is safe in patients with a cardiac pacemaker or defibrillator as numerous studies did not find interferences during capsule endoscopy in patients with implantable cardiac devices [59–61].

Ideal patient preparation for SBCE is yet to be established. The presence of bile, food debris, or bubbles on the small bowel lumen may hamper the quality of SBCE. The benefit of a purgative solution on visualization quality is supported by metanalytic studies and therefore current guidelines recommend the use of 2 liters of polyethylene glycol (PEG) solution before SBCE [62–67]. Low-volume PEG is a valid choice for SBCE, but the best timing for administration of bowel preparation is still under investigation [68–70]. The use of a split-dose PEG regimen, as supported by a RCT, is well tolerated and may help to improve small bowel cleanliness [71]. However, a recent metanalysis by Gkolfakis et al. showed that neither the SBCE visualization quality (RR 1.14 [95%CI 0.96 to 1.35]; $P = 0.15$) nor completion rate (RR 0.99 [95%CI 0.95 to 1.04]; $P = 0.76$) significantly improved after purgative preparation compared to fasting [72]. A systematic review and metanalysis by Yung et al. reported improved visibility without advantages in DY or completion rate [73].

The use of antifoaming agents before SBCE is supported by two metanalysis [65,74] and recommended by European guidelines but is still overlooked in clinical practice [58]. A recently conducted RCT evaluating different dosages of simethicone administered 30 minutes before SBCE showed that, compared to the standard dose (300 mg simethicone in 200 ml water), a higher dose (1125 mg simethicone in 750 ml water) does not improve visualization quality [75].

A metanalysis by Koulaouzidis et al. evaluated the role of prokinetics in SBCE; the use of prokinetic alone reduced gastric transit time and small bowel transit time of the capsule, but did not increase completion rates [76]. Therefore, the use of prokinetics (e.g., metoclopramide or domperidone) is not routinely recommended, but could be useful in patients with known or expected delayed gastric outflow (e.g., previous abdominal surgery, prolonged gastric transit time at a previous examination, gastroparesis, diabetic neuropathy, or opioid use).

Consensus was not reached on the routine use of the real-time view (RTV) for evaluation of gastric outflow of the capsule. In fact, studies supporting the use of a RTV were conducted with old generation devices that recorded for a maximum of 8 h [77,78]. Hence, patients with a prolonged gastric transit time had an elevated risk of incomplete small bowel examination. Instead, modern capsule devices record for at least 10–12 h, which is sufficient to evaluate the entire small bowel even in most cases of prolonged gastric transit time. Considering this technological advancement, the usefulness of systematic RTV may be limited. In a recent ESGE survey evaluating the adherence to guidelines, 73.2% of respondents used the RTV; 38.4% used the RTV in all patients, and 34.8% used it only if prolonged gastric transit time was suspected [5]. In conclusion, the role of RTV is controversial, but it is probably useful in selected patients at risk of prolonged gastric transit time in order to administrate prokinetics and favor gastric outflow.

Fasting for 2 h after SBCE ingestion is a practice recommended by manufacturers and guidelines [6], but supported by a scant amount of evidence. Consequently, research evaluating the possibility of administering clear liquid or bowel preparation promptly after SBCE ingestion is increasing and encouraging [67,68,79]. Therefore, current recommendations about post-SBCE ingestion regimen might change in the near future.

3.5. Patient preparation and technical issues of device-assisted enteroscopy

Statements

- Standard preparation for anterograde device-assisted enteroscopy consists of 8–12 hours' fasting from solid food and 4–6 hours' fasting from liquids before the procedure.

Approved in the first round (Agreement score 4.2, Degree of consensus 88%)

- Bowel preparation is needed if the DAE is performed via a retrograde route. *Approved in the first round (Agreement score 4.7, Degree of consensus 100%)*
- The insertion route of DAE should be guided by the results of previous diagnostic investigations (e.g., SBCE or dedicated cross-sectional imaging techniques). *Approved in the first round (Agreement score 4.4, Degree of consensus 94%)*
- If the location of the small bowel lesion is unknown or uncertain, or in the setting of massive overt bleeding, the initial anterograde route is generally preferred. *Approved in the first round (Agreement score 4.5, Degree of consensus 100%)*

Bowel cleansing is particularly important in DAE as food residue or fecal debris may impair mucosal visualization and prevent adequate sliding between the enteroscope and the overtube. Current ESGE guidelines recommend 8–12 hours' fasting from solid food and 4–6 hours' fasting from liquids for patients undergoing antegrade DAE [58]. In urgent settings, peroral DAE could be performed safely even with a shorter fasting period. Precautions for airway protection (i.e., endotracheal intubation) should be considered in cases with a high risk of aspiration (e.g., short fasting period, altered mental status, hematemesis, large volume of blood in the upper GI tract) or hemodynamic instability..

The ingestion of bowel preparation for a routine anterograde DAE is not recommended, but it might be considered, as well as a prolonged fasting period, in selected patients with small bowel stenosis or obstructive symptoms. A randomized, multicenter study confirmed that 2L-PEG preparation, compared to "fasting only" (12 h for solid food and at least 2 to 4 h for clear liquids before the examination), did not significantly improve the visualization of the mucosa during peroral single-balloon enteroscopy. However, the oral intubation depth was significantly higher in the PEG versus the fasting group (261 $\pm$ 87 vs. 203 $\pm$ 66 cm; $P = 0.019$; mean $\pm$ SD) [80]. Consequently, PEG preparation might be favored for patients where deep intubation of the small bowel is needed.

For patients undergoing retrograde DAE, bowel preparation is mandatory to allow cecal intubation and scope progression, both in elective and in urgent settings. There are no studies comparing high, low, or very low volume PEG regimens and their impact on transanal DAE. International guidelines recommend the use of the bowel preparation regimens adopted for elective colonoscopy [14,58], with the last dose started within 5 h and completed at least 2 h before the beginning of the procedure [81].

An accurate evaluation of the DAE insertion route is key to prompt appropriate treatment and achieve clinical success. In addition, the correct choice of DAE route of insertion optimizes patient's compliance and avoids unnecessary invasive procedures. The choice of anatomical route should be guided by lesion location in previous diagnostic examinations (i.e., SBCE or dedicated cross-sectional imaging techniques) [14,58]. Transit time-based indexes and reader estimated location of lesions detected can help in the choice of insertion route and should be indicated in the SBCE report. In the future, artificial intelligence, 3-D localization, and tracking systems will be essential to localize small bowel lesions detected at SBCE. Computed tomography (CT) may represent a valid alternative to SBCE in suspected small bowel bleeding for route selection, as recommended by the Japanese guidelines [14]. If previous investigations are unable to suggest the insertion route, or in the setting of massive, overt bleeding, the antegrade approach is preferred, as it can be performed without bowel preparation and vascular pathology is more frequent in the proximal tract [4,58]. Furthermore, the retrograde approach may be limited by clots and blood in cases of massive bleeding. On the contrary, if Crohn's disease or neuroendocrine tumor are suspected, the retrograde approach should be considered first, given the propensity of these conditions to involve the distal small bowel. If no abnormalities are detected using one approach, the other should be performed as soon as possible. Irrespective of the initial route of insertion and patient setting, if a deep enteroscopy is needed, the point of maximal insertion should be marked with a submucosal tattoo of sterile carbon particles. Similarly, if a suspected neoplastic lesion is found, it should be tattooed to permit a subsequent therapeutic approach, either endoscopic or surgical [58,82].

3.6. Classification of small bowel findings

Statements

Clinical relevance of findings-SBCE

- The SBCE report must distinguish between clinically relevant and clinically nonrelevant findings (according to e.g., endoscopic appearance, medical history, clinical indication, comorbidities, medications, and setting). *Approved in the first round (Agreement score 4.4, Degree of consensus 94%)*
- For lesions with bleeding potential, clinical relevance should be reported according to the Saurin classification. *Approved in the first round (Agreement score 4.4, Degree of consensus 100%)*
- For protruding lesions, dedicated scores (e.g., SPICE score and/or Shyung score, and/or protrusion angle score) for differentiation between submucosal masses and innocent bulging should be reported. *Approved in the first round (Agreement score 4.4, Degree of consensus 94%)*
- For inflammatory findings, the report should include dedicated scores; either Lewis's score or CECDAI score should be used in the setting of inflammatory bowel diseases. *Approved in the first round (Agreement score 4.2, Degree of consensus 88%)*

Finding description/reporting-SBCE

- Clinically relevant findings detected at SBCE should be reported with description, estimated location, and extensive photo documentation. *Approved in the first round (Agreement score 4.5, Degree of consensus 100%)*
- Clinically relevant findings detected at SBCE should be described according to standardized terminology. *Approved in the first round (Agreement score 4.6, Degree of consensus 94%)*
- The location of small bowel clinically relevant findings at SBCE should be reported according to time-based transit indexes, and endoscopist anatomical estimation. *Approved in the first round (Agreement score 4.4, Degree of consensus 100%)*

Finding description/reporting-DAE

- Findings detected at DAE should be reported according to estimated location and minimal standard terminology for upper and lower endoscopy. All the lesions should be photo and/or video documented. *Approved in the first round (Agreement score 4.4, Degree of consensus 94%)*
- Vascular lesions detected at DAE should be described according to location, size and endoscopic appearance (e.g., Yano-Yamamoto classification). *Approved in the first round (Agreement score 4.2, Degree of consensus 100%)*

3.6.1. Clinical relevance of findings-SBCE

Adequate finding description and reporting is central to any endoscopy practice and facilitates the exchange of information about findings, therapy, clinical recommendations, adverse events, and performance [83]. SBCE often highlights multiple findings, many of which are not clinically relevant, according to medical history, clinical indication, comorbidities, medications and setting. The SBCE reader must clearly distinguish clinically relevant findings from those without clinical significance, as this is fundamental to planning the following diagnostic/therapeutic workup [2,4,58]. For this purpose, a few scores have been developed to concisely highlight whether an individual finding is clinically relevant.

For lesions with bleeding potential, according to the Saurin classification, SBCE findings are classified as P0, P1, and P2 if they have a low, intermediate, or high potential of bleeding, respectively [84].

Regarding the distinction between innocent bulging (not clinically relevant) and submucosal masses (clinically relevant) detected at SBCE, three different scores (known as smooth, protruding lesions index on capsule endoscopy [SPICE- score], Shyung score, and protruding angle score) have been proposed [85–87]. The SPICE score is the only one for which a clinical validation has been performed [88] and some studies are available. However, the evidence supporting the use of these scores is very limited, and there are no head-to-head comparative studies. The combination of scores has recently been reported as potentially increasing their reliability [89].

When inflammatory changes are detected, mainly in the setting of Crohn's disease, objective reporting of any visualized inflammatory change should be made according to the Lewis score or Capsule Endoscopy Crohn's Disease Activity Index – CEC-DAI score [90,91]. Both of them have been clinically validated [91,92] and even if some differences in the correlation with clinical/biochemical markers have been observed [93,94], head-to-head comparative studies [95–97] suggest that they perform similarly for quantitative assessment of mucosal inflammation, at least in the setting of Crohn's disease. However, the use of these scores is particularly relevant when there is a need for repeated evaluation of inflammatory changes over time (e.g., to assess response to therapy) [98]. An international group of experts has recently reviewed all scores used to assess the clinical relevance of SBCE results and proposed a comprehensive guide [99] for several clinical scenarios.

3.6.2. Finding description/reporting-SBCE

Although relevant small bowel findings must be described in detail, free text reporting is strongly discouraged, because it might lead to incomplete data and low-quality reporting [83,100–102]. Endoscopy reporting systems should be populated with standard terminology, whenever possible, limiting the use of free text data entry. Indeed, the use of standard terminology has recently been included among quality performance measures in SBCE [82].

Unfortunately, the attempt to create a comprehensive SBCE standard terminology platform has generated a complex and cumbersome system, which does not reduce variation among readers and is not widely applied in clinical practice [103,104]. Therefore, more recently, an international expert panel established a new consensus-based, standard nomenclature for vascular and inflammatory findings [105,106]. The panel also provided a semantic description of each finding to reduce the ambiguity in describing and categorizing small bowel findings. However, the impact of these definitions on the overall quality of SBCE reports in clinical practice remains to be determined.

An estimate of finding location should always be included for every small bowel abnormality. This facilitates further diagnostic workup and the selection of the appropriate approach for a subsequent DAE [9,58,107]. The estimate of finding location is generally based on transit time indexes. Since different transit time-based indexes with different decisional thresholds exist [108], it is crucial to specify which one has been used for calculation. Although transit time-based indexes have many obvious limitations (i.e., they cannot be calculated for incomplete examinations, they do not take into account SBCE retrograde movements, they are influenced by individual variables and by the presence of lesions slowing down or accelerating SBCE transit, etc.), high quality evidence [108] demonstrated that they can provide a reliable finding location estimate. However, keeping in mind the limitations listed above, the endoscopist still plays a crucial role in estimating the location of findings by integrating the transit time-based index with other variables. Therefore, the transit time-based indexes should always be combined with the reader's anatomical estimation of the finding location.

Although general ESGE guidelines concerning endoscopic reports [83] have been issued, there are currently only limited data [58] about what kind of photo/video documentation is needed to implement proper reporting and image sharing in SBCE setting. While it is relatively easy to provide the full SBCE video, not all endoscopy centers are equipped with the reading software and not all endoscopists are familiar with the SBCE video-reading process. Therefore, adequate photo documentation is the minimum standard to produce a high-quality report and has important clinical (e.g., comparison of the SBCE images with DAE findings is essential) and legal consequences.

3.6.3. Finding description/reporting-DAE

Findings identified at DAE should be reported according to reporting guidelines and minimal standard terminology for upper and lower endoscopy [83,109–112]. For vascular lesions, a dedicated DAE classification (the Yano-Yamamoto classification) [113], that works for selection of treatment options has been developed. Therefore, DAE vascular findings should be classified into six categories according to the Yano-Yamamoto classification: types 1a and 1b are angioectasias; types 2a and 2b are Dieulafoy's lesions of arterial origin; type 3 are arteriovenous malformations; and type 4 are not classified into any of the above categories.

3.7. Management of obscure gastrointestinal bleeding

Statements

- In patients with obscure gastrointestinal bleeding, second-look endoscopy (upper and/or lower) should be considered on a case-by-case basis before second-look small bowel reevaluation. *Approved in the first round (Agreement score 4, Degree of consensus 82%)*
- Second-look SBCE could be performed in patients with obscure GI bleeding and incomplete small bowel visualization, ongoing bleeding, a drop of Hb >4 gr/dl, persistent iron deficiency anemia after iron supplementation or history of previous GI bleeding. *Approved in the first round (Agreement score 4.2, Degree of consensus 94%)*
- Regular medical and laboratory follow-up with complete blood count is advisable in patients with obscure gastrointestinal bleeding for early detection of rebleeding for at least two years after the episode, especially for those with high rebleeding risk (assessed by dedicated scores, e.g., Rehmitt, ORBIT, Ohmiya). *Approved in the first round (Agreement score 4.1, Degree of consensus 82%)*

Table 1
Questions for future research on small bowel bleeding.

- *Small bowel endoscopy indications-*
  Can early SBCE be performed before colonoscopy in patients with melena and normal upper GI endoscopy?-
  Can early panenteric capsule be performed before colonoscopy in patients with melena and normal upper GI endoscopy?
- *Bowel preparation for enteroscopy-*
  What is the optimal bowel preparation regimen for SBCE?-
  What is the optimal bowel preparation timing for SBCE?-
  What is the optimal bowel preparation regimen for retrograde DAE?-
  Which is the ideal fasting time for solid food and liquids after SBCE administration?
- *SBCE technical issues-*
  In which patients should the real-time view be routinely used to reduce the risk of incomplete SBCE?-
  Can artificial intelligence be routinely applied for semi-automated reading and reporting of SBCE?
- *Obscure GI bleeding-*
  What is the role of second-look SBCE in OGIB?-
  What are the predictors of rebleeding in OGIB and SBB patients?-
  What is the optimal follow-up time for patients with OGIB?

In cases of bleeding with unknown origin after upper, lower, and small bowel endoscopic examinations (i.e., obscure GI bleeding, OGIB), a careful, noninvasive watch-and-wait strategy with scheduled clinical reevaluation is advisable as rebleeding episodes are possible, often within 2 years after small bowel evaluation [23,114]. A negative SBCE performed during the previous bleeding workup correlates with lower rebleeding rates. A metanalysis by Yung et al. concluded that pooled rebleeding rates were higher in positive SBCE compared to negative SBCE patients (29% versus 19%, $P < 0.0001$) [115]. However, the possibility of rebleeding is still noteworthy despite the negative result of a SBCE [115]. Studies providing long-term follow-up of patients with SBB are scant. Furthermore, data on rebleeding are inconsistent among patient populations with different bleeding lesions. The independent predictors associated with rebleeding were cirrhosis, incomplete small bowel visualization and previous GI bleeding [116]. Therefore, scores that can help to stratify the individual rebleeding risk of the patient had been described recently. Among these, the RHEMITT score encompasses 7 variables independently associated with higher rebleeding rates (renal disease; heart failure; endoscopic capsule lesions; major bleeding; incomplete SBCE; tobacco use; treatment by endoscopy) [117]. Patients with a high-risk RHEMITT score ($\geq$11) had a 63.8% rebleeding probability during a minimum follow-up of 12 months while no rebleeding event was detected in patients with a low risk (score 0–3). The ORBIT score, to evaluate the bleeding risk in patients on chronic anticoagulation, and the Ohmiya score, based on comorbidities and age at the onset of midgut bleeding, are other promising tools to identify patients with a higher risk of rebleeding, in whom a closer follow-up and a more rapid diagnostic and therapeutic strategy are advisable [118,119]. Considering this evidence, the duration of follow-up might be tailored to the patient's risk of rebleeding. In patients with GI bleeding from an unknown etiology or with a high risk of rebleeding, a two-year clinical follow-up with complete blood count is reasonable, even if there is little evidence to support this practice [114].

Non-small bowel lesions may be responsible for obscure GI bleeding (OGIB). In these cases, culprit lesions can be detected through second-look endoscopy (upper and/or lower) performed after a complete small bowel evaluation. Therefore, especially in patients with poor quality of first-level examinations (e.g., poor intestinal preparation, patient intolerance, or incomplete exams), and persistent bleeding, second-look endoscopy should be carefully considered before performing a second-look small bowel reevaluation with SBCE, CTE or DAE.

In patients with OGIB, midgut bleeding is frequently detected on second-look SBCE. The DY of the repeated SBCE is highest in those with bleeding on their initial SBCE (83.3%) and lower in those with initially normal examinations (45.8%) or when an alternative cause, such as angioectasia is seen (14.2%) [120]. Moreover, the rate of positive findings in second-look SBCE is higher when the bleeding presentation changes from occult to overt or when the hemoglobin drop is $\geq$4 g/dL [116].

4. Discussion

In the first decades of the 21st century, the advent of small bowel endoscopy determined exciting improvements in the endoscopic management of midgut hemorrhage, often avoiding the need for more invasive approaches such as surgery or interventional radiology. Despite these achievements, there is still scant uniformity on terminology of clinical entities, enteroscopy indications and reporting, patients' preparation and treatment strategies. Disagreement on the management of midgut bleeding hampers the adoption of timely interventions, which are crucial in the setting of acute bleeding, and represents an obstacle for high-quality patient care and cost saving policies.

Thus, we performed an evidence-based Delphi expert consensus that, merging the latest evidence and international guidelines, proposes clear definitions and a unifying strategy to standardize the management of SBB in real life, from diagnosis to treatment. The strength of this consensus is its focus on patients with SBB that provides physicians with a useful guide in daily practice and a comprehensive perspective for both clinical and technical issues of enteroscopy. The present consensus also outlines emerging trends and future research directions for the management of patients with SBB, such as early panenteric capsule for patients with melena and normal upper GI endoscopy, usefulness of real time viewer, optimal timing, and regimen for enteroscopy preparation, and repeated-SBCE in OGIB with high rebleeding potential (Table 1).

Source(s) of support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

Dr. Spada is consultant for Medtronic and Norgine and received grant from AlfaSigma, Pentax, Olympus. Dr.Pennazio received speaker's honoraria from Medtronic and Olympus. Dr. Rondonotti is member of the expert group of Fujifilm, received speaker's honoraria from Fujifilm and consultancy agreement from Medtronic. Dr. Tontini is a consultant for NTC Pharma and F. Hoffmann-La Roche Ltd and received speaker's honoraria from Pentax, Medtronic and NTC Pharma.

Acknowledgment

None.

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