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Article:

Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline

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Introduction

The field of gastrointestinal endoscopy has made great strides over the past several decades, and endoscopists have gained mastery over the art of advancing flexible video endoscopes in the upper and lower part of the gastrointestinal tract. Endoscopic evaluation of the entire length of the small-bowel (SB) (i.e. enteroscopy), on the other hand, poses unique challenges which have plagued physicians for decades. With the development of newer enteroscopic modalities, a more thorough evaluation is now possible. These new techniques comprise SB videocapsule endoscopy (VCE) and device-assisted enteroscopy (DAE); the latter includes double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), spiral enteroscopy (SE) and balloon-guided endoscopy (see **Box**). VCE has revolutionized SB imaging by providing a reliable and noninvasive method for complete visualization and assessment of the mucosal surface. Given the increased detection rate of small bowel pathology by the capsule, innovations in DAE have been crucial for confirmation of pathology (histologic diagnosis), enabling endoscopic therapy in select cases without necessitating surgery. With these recent advances in technology, enteroscopy currently has a pivotal role in the evaluation of patients with suspected SB diseases, including obscure gastrointestinal bleeding (OGIB), iron-deficiency anaemia (IDA), suspected and known Crohn's disease (CD), tumours, polyposis syndromes and celiac disease. The aim of this evidence-based and consensus based Guideline commissioned by the European Society of Gastrointestinal Endoscopy (ESGE) is to provide caregivers with a comprehensive review to guide the clinical application of enteroscopy.

Methods

The ESGE commissioned this Guideline and appointed a guideline leader (M.P.) who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (M.P. and C.S.) and then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, and divided the key topics among these task forces. Each task force performed a systematic literature search to prepare evidence-based and well-balanced statements on their assigned key questions (see **Appendix e1**, available online). The coordinating team independently performed systematic literature searches with the assistance of a librarian. The Medline, EMBASE and Trip databases were searched including at minimum the following key words: VCE, DBE, SBE, SE, SB, and enteroscopy. All articles studying the use of VCE and DAE in patients with OGIB, IDA,

CD, SB tumours, polyposis syndromes and celiac disease were selected by title or abstract. All selected articles were graded by the level of evidence and strength of recommendation according to the GRADE system [1,2]. The literature searches were updated through September 2014. Each task force proposed statements on their assigned key questions which were discussed and voted on during the plenary meeting held in November 2013. In September 2014, a draft prepared by the coordinating team was sent to all group members. After agreement on a final version, the manuscript was submitted to *Endoscopy* for publication. The journal subjected the manuscript to peer review and the manuscript was amended to take into account the reviewers' comments. All authors agreed on the final revised manuscript. This Guideline was issued in 2014 and will be considered for review and update in 2019 or sooner if new and relevant evidence becomes available. Any updates to the Guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Recommendations and statements

Evidence statements and recommendations are stated in italics and bold.

Obscure Gastrointestinal Bleeding

Statement: The ESGE recommends VCE as the first line test in patients with OGIB (strong recommendation, moderate quality evidence).

OGIB accounts for approximately 5% of all cases of gastrointestinal bleeding and is usually due to a lesion in the SB. Studies evaluating accuracy parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios) of VCE in OGIB (occult and overt) patients are scarce. However, the present evidence on diagnostic usefulness of VCE is enough to support the use of VCE for OGIB [3,4].

Accuracy parameters for VCE are not truly known because there is no standard comparative method. The main reason for this is related to the lack of a reliable criterion standard to compare with. In this setting the ideal criterion standard would be intra-operative

enteroscopy (IOE). Nevertheless, IOE carries significant mortality and morbidity (5 and 17% respectively) and it cannot be routinely recommended for patients with OGIB for diagnostic purposes [5]. In the setting of OGIB, there is only one trial reporting accuracy parameters comparing VCE and IOE (VCE sensitivity of 95% and a specificity of 75%) [6], a few studies comparing VCE with the complete SB exploration performed by DAE, and one trial in which there is a combined criterion standard (including results of other procedures and/or outcomes during follow-up) [7-9]. For all these reasons, a diagnostic yield (DY) (i.e. rate in which the procedure detects what are thought to be significant findings) is typically reported in SB studies, as a proxy estimate of the diagnostic capability of VCE. There are limited data regarding differentiating OGIB as occult vs. overt subtype and thus the DY for VCE in OGIB is generally reported as an overall composite DY. In a recently published "updated" meta-analysis [10], the reported "pooled DY" for VCE was 61.7% (95% CI: 47.3-76.1). Similarly, in a large systematic review, Liao et al. reported a "detection rate" for VCE in OGIB of 60.5% (95% CI: 57.2-63.9) [11]. Other earlier reported meta-analyses reported similar overall DYs for VCE in OGIB patients [12-14].

There have been a number clinical factors reported to be associated with a higher DY at VCE in patients with OGIB. Pennazio et al. reported that the highest yield at VCE was in those patients with active bleeding or occult bleeding (92.3% and 44.2%, respectively), whereas those patients with previous overt bleeding had the lowest yield (12.9%) [8]. A larger and more recent study confirmed that overt bleeding is the factor most strongly associated with a definitive diagnosis in OGIB by VCE [15]. Increased age, use of warfarin and liver co-morbidity seem also to be correlated with a higher VCE yield [16,17]. It was also shown in a multivariate analysis that an increasing number of oesophagogastroduodenoscopies (EGDs) performed prior to VCE examination (odds ratio [OR], 1.17; 95% CI: 1.00 –1.37), increasing transfusion requirements (3–9 units: OR, 1.70; 95% CI: 1.08–2.66, and ≥10 units: OR, 2.72; 95% CI: 1.69 – 4.37), and connective tissue disease (OR, 2.24; 95% CI: 1.14 – 4.41) were all significantly associated with identification of positive findings by using VCE (all p-values p<0.045) [18]. In patients with OGIB, VCE showed an excellent safety profile [11], thus routine SB imaging or the use of the PillCam® patency capsule (Covidien Plc, Dublin, Ireland) prior to VCE in these patients is not essential.

Statement: The ESGE recommends performing VCE as close as possible to the bleeding episode, optimally within 14 days, in order to maximize a higher diagnostic yield (strong recommendation, moderate quality evidence).

Timing of VCE appears to be an important factor associated with significantly higher DY compared with delayed VCE. There are no prospective studies addressing the relationship between timing of VCE and DY. However, several retrospective studies, evaluating clinical outcome of patients with OGIB, have shown that earlier VCE contributes to an increased DY as compared with delayed VCE. Two studies [8,16] addressing the higher yield of VCE with overt versus occult OGIB, also demonstrated that shorter intervals between the performance of VCE and the bleeding episode increased the DY. Katsinelos et al. [19] evaluated, whether timing of VCE, influences DY. In their study, the DY was 87.5% (14/16) in patients with overt bleeding who had VCE performed during the first 10 days following the bleeding episode, while it was only 1/9 (11.1%) for overt bleeders who underwent VCE more than 10 days after the bleeding episode. Similar results were obtained by Bresci et al. [20] who demonstrated a positive yield of 92% when VCE was performed within 15 days after diagnosing OGIB, compared to only 34% when VCE was conducted more than 15 days after diagnosis. This hypothesis has recently been confirmed in a group of 144 patients with overt OGIB, in whom early use of VCE within 3 days of hospital admission resulted in a significantly higher DY [21].

Statement: The ESGE recommends against PE as the first line test in OGIB patients, because of its lower diagnostic yield, when compared to VCE (strong recommendation, moderate quality evidence).
Due to VCE's excellent safety profile, patient tolerability, and potential to evaluate the entire small bowel, the ESGE recommends performing VCE first, prior to DAE, when small bowel evaluation is indicated for OGIB (strong recommendation, moderate quality evidence).

When comparing VCE with alternative modalities, VCE has been shown to be significantly superior to push enteroscopy (PE), conventional radiology, cross-sectional radiology and as good as DAE in evaluating and finding the lesion(s) causing the bleeding. When comparing VCE and PE in the evaluation of OGIB, the DY of VCE for "clinically significant findings" was 56% for VCE vs. 26% for PE, p<0.001, 95% CI: 21-38% [12,22]. However, studies used to populate the meta-analyses have several limitations, such as the absence of a gold standard

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modality and subjective criteria for positive findings of VCE. There is only a single cross-over RCT on this topic [23]. In that study, a definitive source of bleeding was identified in more patients in the VCE group than in the PE group, 50% vs. 24% overall, 43% vs. 11% SB only. Fewer lesions were missed by VCE than by PE. VCE missed no lesions in the SB, whereas all missed lesions with PE were located in the SB. Patients who started with VCE were less likely to require the second test than were patients who initially underwent PE.

There has been no randomized controlled trial comparing the efficacy of VCE and DBE in OGIB, however four meta-analyses comparing VCE and DBE have been published, all finding similar results with respect to the overall DYs between the two modalities [10,13,14,24]. In detail, when comparing the DY of VCE to that of DAE in OGIB, the pooled DY for VCE was 61.7% (95% CI: 47.3–76.1) and for DBE was 55.5% (95% CI: 48.9–62.1) [10].

Although the clinical presentation may indicate the preferential endoscopic insertion route for DAE, VCE is also an effective tool for guiding the selection of the correct approach (oral vs anal approach). Even if different thresholds have been proposed, the point in time when VCE identifies the lesion should guide the choice of the insertion route [25,26].

Statement: *The ESGE recommends performing VCE first, prior to small bowel radiographic studies and mesenteric angiography, when small bowel evaluation is indicated for OGIB (strong recommendation, high quality evidence). CTE may be a complementary examination to VCE in selected patients (weak recommendation, low quality evidence).*

VCE has been consistently demonstrated to be superior to SB barium radiography in patients with OGIB. In what appears to be the only RCT evaluating VCE vs. SB radiography in OGIB patients, the DY was 30% with VCE vs. 7% with dedicated SB radiography (difference 23%; 95% CI: 11%–36%)[27]. However, the primary study endpoint of further bleeding was not statistically different between groups, being 30% with VCE and 24% with radiology (difference, 6%; 95% CI: -9% to 21%). Previously, Triester et al. [12] performed a meta-analysis comparing VCE vs. SB barium radiography (follow-through (SBFT) or enteroclysis) and reported a yield of "clinically significant findings" of 42% for VCE versus 6% for SB barium radiography (p<0.001; 95% CI: 25%–48%).

VCE is superior to mesenteric angiography/computed tomography angiography (CTA) in determining the cause of bleeding in patients with OGIB. In a randomized controlled trial comparing VCE vs. angiography, Leung et al. [28] evaluated the DY and long-term outcomes in

60 patients with overt OGIB. The DY for immediate VCE was significantly higher than angiography 53.3 % vs. 20.0 % (difference = 33.3 % , 95 % CI: 8.9 – 52.8 %). The cumulative risk of re-bleeding in the angiography and VCE group was 33.3 % and 16.7 %, respectively (p = 0.10, log-rank test). There was no significant difference in the long-term outcomes between the two groups including further transfusion, hospitalization for re-bleeding, and mortality. Furthermore, Saperas et al. [29] reported on a prospective cohort study whereby 28 consecutive patients admitted for OGIB underwent both CTA and standard mesenteric angiography, followed by VCE. A source of bleeding was detected by VCE in a greater proportion of patients, DY 72% (95% CI: 50.6–87.9%), than CTA, 24% (95% CI: 9.4-45.1%, p = 0.005 *vs* VCE), or angiography, 56% (95% CI: 34.9–75.6%, p = NS).

The DYs of VCE and CT-enterography (CTE) may be dependent upon the underlying causes of OGIB, thus CTE may be a complementary examination to VCE and could be helpful in determining the cause of OGIB in selected patients. In a study by Agrawal et al. [30], 52 patients with OGIB were prospectively enrolled to undergo VCE. CTE was then performed in 25 patients who had no definitive source of bleeding identified at VCE. In none of the 11 patients with occult bleeding CTE was able to identify the source of bleeding while the DY was 50% (7/14) in patients with obscure overt bleeding (p < 0.01), suggesting that in case of non-diagnostic VCE examination, CTE may be useful for detecting a source of gastrointestinal bleeding in patients with overt, but not occult OGIB. The supremacy of VCE when compared to CTE in OGIB patients was confirmed also in other studies with a DY ranging between 57-63% and 21-30%, respectively [31,32]. Conversely, Huprich et al. [33], prospectively comparing multiphase CTE and VCE in 58 OGIB patients, reported that the sensitivity of CTE was significantly greater than that of VCE (88% vs 38%, respectively; p = 0.008), largely because CTE found more SB masses (100% vs 33%), respectively; p = 0.03). There have been a few other small studies (prospective and retrospective case series) that have failed to demonstrate any significant difference between VCE and CTE [34-36].

Finally, in a comparative study of 38 OGIB patients, VCE was significantly superior to magnetic resonance enterography/enteroclysis (MRE) for detecting abnormalities [37].

Statement: *When VCE is unavailable or contraindicated, the ESGE suggests to consider DAE as the first diagnostic test in OGIB patients (weak recommendation, low quality evidence). When performed as a diagnostic test, the ESGE suggests to perform DAE as close as possible to the bleeding episode (weak recommendation, low quality evidence).*

Studies evaluating accuracy parameters of PE/DAE in patients with OGIB (occult and overt) are scarce. One trial used a combined criterion standard (including results of other procedures and/or outcomes during follow-up) to calculate sensitivity, specificity, PPV and NPV of DBE in the diagnoses of small-intestinal lesions in patients with OGIB, 92.7%, 96.4%, 98.1%, and 87.1%, respectively [38]; these figures are similar to those already known for VCE [8]. As with VCE, the outcome that is most frequently reported is DY. The DY of PE and DAE in OGIB patients (including both occult- and overt-OGIB patients) is approximately 25-35% [39-41] and 55%, respectively [10], being generally higher in those with overt bleeding. As far as DAE is concerned, although the majority of published studies were performed with DBE and significant differences among DAE devices have been reported (i.e. depth of SB intubation, rate of complete enteroscopy), clinical outcomes (namely DY) seem to be consistently similar across studies, regardless of the device used [42-46]. When prospectively comparing PE and DAE, the overall DY is significantly higher for DAE [47]. Conversely, when lesions located in the proximal SB are considered, the DY appears to be comparable between the two techniques [48-50]. Nevertheless, sedation, examination time and X-ray exposure are lower with PE. Therefore, PE could represent a reliable diagnostic tool when a lesion is known to be located in the proximal SB. When comparing CTE with DBE in OGIB patients, the DY of DBE is significantly higher [51-53]. The DY of CTE increases significantly when a SB tumor is suspected [33]; in this subset of patients CTE should precede DAE. The available studies evaluating the performance of CTA in patients with OGIB (including both occult- and overt-OGIB) showed diagnostic performances inferior to DAE [29]. However, when overt-GI bleeders are selected, both techniques yielded similar results [54,55]. Adequately powered studies, comparing head-to-head DAE with CTA in patients with occult- and overt-OGIB, are lacking, as well as studies comparing MRE and DAE.

Optimal timing of DAE has not yet been clearly defined, however, proximity to the bleeding episode seems to confer higher DYs. For patients with overt-OGIB the DY of DAE significantly increases if the procedure is performed early (within 1 month) after clinical presentation [56].

Statement: The ESGE recommends consideration of the performance of emergency VCE in patients with ongoing overt OGIB (strong recommendation, moderate quality evidence).

In such patients, the ESGE suggests to consider also DAE as a possible first-line test given its ability to make a diagnosis and to perform therapy at the same time (weak recommendation, low quality evidence).

The prospect of utilizing VCE for severe ongoing overt-OGIB is appealing due to the relative safety, ease and feasibility of the procedure in this setting. In addition, it has already been established, that early performance of VCE confers superior DY that translates to better patient management and outcomes [8,15,16,20,24,57]. Specifically, with regard to urgent VCE, only two retrospective studies [58,59] and one RCT [28], comprising less than one hundred patients overall, have been reported so far. Based on limited data, emergency VCE, performed within 24–72 h from admission, during severe ongoing overt-OGIB, appears to be an effective modality, with a DY up to 70% and a significant impact on patient management.

Limited data on the role of emergent DAE for the diagnosis and treatment of severe overt-OGIB is reported. In a small study of 10 patients with ongoing overt-OGIB, emergency DBE was performed within 24 hours of clinical presentation and showed a diagnostic and therapeutic yield of 90% [54]. In a separate retrospective report of 120 patients with overt OGIB, urgent DBE was defined as DBE performed within 72h from the last visible gastrointestinal bleeding; in this study the DY in urgent DBE was significantly higher than that in non-urgent DBE, 70% (52/74) versus 30% (14/46), p<0,05 [60]. It also appears that DAE may be more cost effective than VCE when a high probability of a positive finding and need for therapy exists [61]. Thus, in patients with ongoing overt-OGIB, DAE should also be considered as first-line endoscopy, given its ability to make a diagnosis and to perform therapy at the same time, and especially in centers where it is readily available and expertise in therapeutic enteroscopy exists. The absolute best strategy for the evaluation of these patients remains however unanswered and should be clarified with prospective studies.

Statement: *The ESGE does not recommend the routine performance of second-look endoscopy prior to VCE, however the decision to perform second-look endoscopy before VCE in OGIB and IDA should be undertaken on a case by case basis (strong recommendation, low quality evidence).*

Although several studies reported a significant rate of lesions detected by VCE in stomach/duodenum or colon in patients with OGIB, the limited available data suggest that the yield of repeat systematically EGD and/or ileocolonoscopy prior to VCE (i.e. second-look

endoscopy) in these patients is low. Selby et al. reported on 92 patients with OGIB and showed that at VCE, lesions were found as often in patients who had only one preceding endoscopic evaluation as in those who had multiple endoscopic procedures [62]. Subsequently, from this same group, Gilbert et al. performed repeat endoscopies (EGD + ileocolonoscopy) prior to VCE on 50 patients referred for the investigation of OGIB [63]. A probable cause of bleeding was found on repeat EGD in only 2/50 (4%) and repeat colonoscopy revealed no additional sources of bleeding. The authors concluded that the yield of repeat EGD and colonoscopy immediately prior to VCE (after a negative preliminary endoscopic evaluation) is low when these procedures have previously been non-diagnostic. They also concluded that this approach was not cost-effective. Similarly, Vlachogiannakos et al. [64] in a retrospective analysis of 317 patients who underwent VCE for OGIB (after previous negative EGD and colonoscopy) reported that in 3.5% of cases, the source of bleeding was found in the stomach or the cecum. Routine repetition of conventional endoscopy before VCE was not a cost-effective approach. To date, there are no time- or referral-based criteria for selecting patients where second-look endoscopy before VCE may be worthwhile to perform. At the present time the decision to perform second-look endoscopy before VCE in OGIB and IDA (see below) patients should be taken only on a case by case basis.

Statement: *The ESGE recommends to manage conservatively those patients with OGIB and a negative VCE who do not have ongoing bleeding manifested as overt bleeding or continued need for blood transfusions since their prognosis is excellent and the risk of re-bleeding low. The ESGE recommends further investigation using repeat VCE, DAE or CTE for patients with OGIB and a negative VCE who have ongoing bleeding manifested as overt bleeding or continued need for blood transfusions (strong recommendation, moderate quality evidence) .*

Up to one third of patients undergoing VCE for OGIB will have a negative VCE. Several studies have shown that in most cases of a normal VCE, re-bleeding rates and the need for transfusions are low. Forty-nine patients who underwent VCE for OGIB were followed up for a mean of 19 months; the overall long-term re-bleeding rate was 32.7%. The cumulative re-bleeding rate was significantly lower in patients with negative VCE (5.6%) than in patients with positive VCE (48.4%) [65]. In another study [66], 42 patients with OGIB were followed up for a mean of 17 months after VCE. The overall re-bleeding rate was 28%, and there was a statistically significant difference in re-bleeding rates between patients with a positive study

(42%) and those with a negative study (11%); both in this last study and in another more recent [67], anticoagulant use was associated with an increased risk of re-bleeding.

Although other studies on this topic came to different conclusions [68] several reviews and consensus recommendations [69,70] concluded that patients with OGIB and a normal VCE should be managed conservatively without further investigation. Such conservative management may include a "wait and see" policy, iron supplementation or blood transfusions. Nevertheless, in cases of ongoing overt bleeding or continuous need for blood transfusions an alternative approach is warranted. In such patients, repeat VCE can yield a positive finding, and especially in patients with a drop in Hb of at least 4 g/dL or in those with a change in clinical presentation from occult to overt bleeding [71]. Alternatively, DAE [72,73] or CTE [30] can be performed after an initial negative VCE, and can yield a positive finding. Randomized controlled trials comparing these modalities in the subgroup of patients with a non-diagnostic initial capsule study are still needed to clarify the most appropriate management.

Statement: *In patients with positive VCE, the ESGE recommends DAE as a possible therapeutic intervention to confirm and treat lesions identified by VCE (strong recommendation, high quality evidence) .*

Teshima et al. [10] found that the pooled DY of DBE performed after a previously positive VCE was 75.0% (95% CI: 60.1–90) and the odds ratio for the yield of DBE performed after a previously positive VCE, compared with that of DBE performed in all patients, was 1.79 (95% CI: 1.09–2.96; p = 0.02). In that same study, a subgroup analysis revealed that the pooled DY of DBE performed after a previously negative VCE was 27.5% (95% CI: 16.7–37.8).

Although studies have assessed the DY of VCE, PE, and DAE in OGIB, the exact significance of lesions identified and their impact on clinical outcome has not consistently been evaluated for the aforementioned modalities. When we consider outcome in clinical practice, the emphasis should be on meaningful results. In the case of OGIB, a positive patient outcome should either be cessation of bleeding or resolution of anemia. In addition, other important clinical outcomes to be evaluated may include mortality, hemoglobin levels as well as reduction in endoscopic procedures, hospitalizations, and blood transfusions. Several studies demonstrate change in patient management and improved outcomes following VCE [8,16,17]

and DAE [56,74-78]. However, prospective comparative trials have not consistently confirmed these results [23,27,28].

Iron-deficiency anemia

Statement: In patients with IDA, the ESGE recommends that prior to VCE, all the following are performed: a complete medical history (including medication use, co-morbidities, and gynecological history in premenopausal females), esophagogastroduodenoscopy with duodenal and gastric biopsies, and ileocolonoscopy (strong recommendation, low quality evidence).

IDA occurs in 2-5% of adult men and post-menopausal women in developed countries and is a common reason for referral to gastroenterologists [79]. According to the most recently published practice guidelines, upper and lower gastrointestinal endoscopy are the cornerstone for the investigation of IDA (particularly in postmenopausal females and all male patients). Bidirectional endoscopy identifies the cause of IDA in 70-80% of patients. When negative, the SB is often targeted for further investigation [79].

Although there are no data comparing the effect of different selection criteria on diagnostic performance of VCE, the studies applying strict criteria tend to have a higher DY [80-82]. Therefore, it is advisable that in patients with IDA referred for SB evaluation, a complete work-up should be performed including: bidirectional endoscopy (with ileoscopy whenever possible); exclusion of celiac disease (through serology and/or histopathology); complete past medical history (paying particular attention to medications and comorbidities); gynaecological evaluation (for pre-menopausal women) and haematological evaluation.

In IDA patients, some authors [83-86] reported an increased incidence, higher than that reported in OGIB studies, of lesions detected by VCE within the reach of conventional endoscopy; they also reported that after positive VCE, up to 30% of patients with lesions identified by VCE have been managed by repeating EGD or colonoscopy. Unfortunately, studies evaluating the cost-effectiveness of a systematic second-look endoscopy before SB exploration in IDA patients are lacking. Therefore, at the present time, the decision to perform a second-look endoscopy before SB exploration should be taken on a case by case basis.

Statement: The ESGE can not advise regarding the optimal timing of small bowel evaluation in patients with IDA since there are no data on this issue. Nevertheless, the ESGE recommends, in

the setting of IDA, an adequate empiric trial of iron supplementation before small bowel evaluation (strong recommendation, low quality evidence).

Although published guidelines recommend an empiric trial of iron supplementation [79] before referring patients for SB evaluation, studies focused on IDA do not provide any details about that policy in their patients. Whether the systematic application of guidelines can impact the referral rate or DY of VCE is therefore unknown. Since we do not have these data, at the present time, after a complete diagnostic work-up, it seems reasonable, taking into account the chronic nature of IDA and the length of an empiric trial of iron supplementation (1-3 months), to institute this before SB evaluation.

Statement: *In patients with IDA, the ESGE recommends VCE prior to other diagnostic modalities, when upper and lower GI endoscopies are inconclusive and small bowel evaluation is indicated (strong recommendation, moderate quality evidence).*

In a systematic review, Koulaouzidis et al. [87] reported that, pooling data from four studies focused on IDA [80-82,88], the DY of VCE was 66% (95% CI: 61.0%-72.3%), which is comparable to that reported in other studies on the same topic [9,83,86]. Nevertheless, other recent studies [17, 85, 89-91] reported a lower DY, ranging between 25% and 48%. Pooling together all studies focused on IDA [80-83,85,86,88-90] the cumulative DY of VCE in IDA patients is 53% (95%CI: 41%-65%). There are no studies specifically designed to evaluate the DY of PE and DAE in IDA patients. Nevertheless, several studies focused on OGIB patients had IDA as part of their inclusion criteria. Thus the DY of PE/DAE in IDA patients should be similar to that reported in occult-OGIB patients. In those studies, the DY of PE varies widely (range 30-70%; mean approximately 40%) [39,92-96] whereas the DY of DAE appears comparable to that of VCE. In a prospective randomized trial, comparing VCE with PE, De Leusse et al. [23] found that VCE has a higher DY (50% *vs* 24%; p<0.05). Although this study was to evaluate OGIB patients (half of those referred for SB exploration was for IDA), they reported that the yield of the diagnostic procedures was not significantly influenced by the nature of the OGIB, therefore we can assume that VCE is superior to PE even when only IDA patients are concerned. Retrospective observational studies [91,93,97,98] reporting the DY of PE in IDA, which is about 30-60%, appear to support this hypothesis. The success of VCE over radiological techniques in IDA patients is mostly related to the nature of findings that, in 50-

60% of cases, are small, flat vascular lesions [99]. There are no head-to-head studies comparing DAE and VCE in IDA patients. Studies reporting the DY of DAE, when used as a primary diagnostic tool in IDA, are scarce and include only a small number of patients [100]. Once again, looking at DY of DAE in OGIB patients only (particularly those with obscure-occult bleeding), the DY of DAE appears to be comparable [10,13], especially when a complete enteroscopy is achieved [9] with that of VCE. Similar DYs might be reasonably expected in IDA patients, also. In the setting of IDA there are two prospective studies comparing head-to-head VCE and radiological examination. Once again, this comparison is based on DY rather than accuracy. VCE has been found to be significantly superior to SB enteroclysis (DY: 56.9% *vs* 11.8%, p<0.001) [88] and to CTE (DY: 77.8% *vs* 22.2%, p<0.01) [81]. There are no studies comparing MRE and VCE in IDA patients.

With regard to factors potentially associated with a positive diagnosis in IDA patients, a favourable association between increased VCE DY and age and severity of anaemia has been found [80,89,90]; nevertheless, because of the incidence of relevant findings in young patients, age alone cannot be recommended as a reliable criterion for patient selection [90,101]. A potential positive association between VCE DY and concomitant anticoagulation therapy as well as the presence of comorbidities has been suggested and needs to be verified by further studies [80,89,90,102]. There are no data about factors affecting the DY of DAE as the primary diagnostic tool in IDA patients.

At the present time, there are few studies evaluating the long-term outcome of IDA patients undergoing SB evaluation. In addition, the studies that do exist, are retrospective and heterogeneous in terms of patient characteristics, follow up length/modalities, and work-up performed after the SB examinations. Two studies [83,89], evaluating the impact of VCE in IDA patients, reported that overall VCE results led to changes in management, regardless of the result of VCE, in 44-60% of patients. This is more evident when the analysis is restricted to patients with positive VCE; taking into account both specific therapeutic interventions and iron supplementation, change in management occurs in the large majority (up to 100%). When specific interventions only (i.e. specific medical therapy - such as steroids, lanreotide, thalidomide, gluten free diet- or surgical/endoscopic therapy) are included, changes in management are observed in 30-50% of patients with positive VCE. Some studies [83,86,88] reported that the rate of resolution of anaemia at the end of follow-up is high (range 57-86%), but yielded conflicting results when comparing patients with positive and negative VCE. If Apostolopoulos et al. [88] reported a significant difference in the rate of anaemia resolution between patients with positive and negative VCE (100% vs 68%; p<0,05), both Sheibani et al.

[86] and Holleran et al. [83] did not disclose any difference between these two groups. There are no studies evaluating the clinical outcome of other diagnostic tools for SB evaluation, as primary diagnostic method in IDA patients.

As far as safety concerns in IDA patients, VCE showed an excellent safety profile (similar to that observed in OGIB; capsule retention range 0-4% [81]), whereas there are no specific data about DAE safety in IDA patients. Nevertheless it can be expected, a DAE complication rate comparable with that observed in OGIB. As far as costs, there are no data about cost-effectiveness of different diagnostic approaches for the evaluation of the SB in IDA patients. This is the main target for further studies taking into account not only efficacy but also local costs and reimbursement policies, which differ widely among countries and health care systems.

Crohn's Disease

Statement: *The ESGE recommends ileocolonoscopy as the first endoscopic examination to investigate patients with suspected CD (strong recommendation, high quality evidence). In patients with suspected CD and negative ileocolonoscopy, the ESGE recommends VCE as the initial diagnostic modality to investigate the small bowel, in absence of obstructive symptoms or known stenosis (strong recommendation, moderate quality evidence). The ESGE does not recommend routine small bowel imaging or the use of the PillCam patency capsule prior to VCE in these patients (strong recommendation, low quality evidence). In the presence of obstructive symptoms or known stenosis, the ESGE recommends that dedicated SB cross-sectional imaging modalities such as MRE or CTE should be used first (strong recommendation, low quality evidence).*

Up to 66% of patients with CD have SB involvement at diagnosis [103]and in approximately 90% of patients with SB CD, the disease involves the terminal ileum [104]. Thus, ileocolonoscopy is considered to be the first line investigation for CD and is sufficient to establish the diagnosis in the vast majority of patients [103]. However, skip lesions of the terminal ileum may result in false negative results at ileocolonoscopy [105] and VCE should therefore be considered when retrograde ileoscopy is not achieved or when lesions in the proximal SB need to be excluded. VCE has been shown to have a consistently high sensitivity and high negative predictive value which ranges from 96% to 100% [106-110]. However, the lack of a gold standard for the diagnosis of CD hinders precise definition of VCE accuracy for this condition and 'DY' for findings consistent with CD has often been adopted as a 'surrogate' in the appropriate clinical context. Furthermore, the mucosal inflammatory changes which are found in active SB CD, are not specific to this disease and this has fuelled debate about where VCE should fit within the diagnostic algorithm for CD [111,112]. The high DY of VCE versus other imaging modalities may therefore not directly translate into a higher diagnostic accuracy since lesions detected by VCE may also be induced by other aetiologies [113] such as non-steroidal anti-inflammatory drugs (NSAIDs) in particular [114-118]. Moreover, VCE may detect minor mucosal breaks and erosions in up to one fifth of healthy individuals [107,119]. Nonetheless, VCE has been shown to compare favourably with SB cross-sectional imaging for the detection of mucosal lesions consistent with CD [113,120].

In a meta-analysis conducted by Dionisio et al. [120] VCE was found to be superior to SBFT/SB enteroclysis and CTE, with a significant incremental yield (IY) in patients with

suspected CD (VCE *vs.* SBFT/SB enteroclysis: 52% *vs.* 16% (IY=32%, p<0.0001, 95% CI:16-48%), VCE *vs.* CTE: 68% *vs.* 21% (IY=47%, p<0.00001, 95% CI:31-63%). A recent prospective study confirmed that VCE was better than SBFT and equivalent to ileocolonoscopy in detecting SB inflammation in patients with suspected CD; this study also suggested that VCE can establish the diagnosis of CD in patients with proximal SB inflammation, when ileocolonoscopy is negative [121]. Some recent studies have shown that VCE may be superior to MRE, particularly for the detection of early disease and proximal SB lesions [122-124]. Although MRE and CTE have been shown to have a similar accuracy for the detection of inflammation in CD [125-129]. 'MRE has the advantage of being free from ionising radiation, a factor of increasing concern in the medical community (136) and awareness amongst patients (137), but is limited by higher cost, longer examination time and slightly inferior spatial resolution [125]. In a previous prospective, blinded randomised controlled trial by Solem et al. [130] which compared VCE, CTE, SBFT and ileocolonoscopy in patients with known or suspected CD (using a consensus clinical diagnosis as the reference 'gold standard'), the sensitivity of VCE and CTE was similar (83% for VCE, 67% for CTE and ileocolonoscopy, and 50% for SBFT) but the specificity of VCE was lower (53%) than that of all other tests (100%, p < 0.05). The results of this key study highlight the importance of interpreting VCE findings within an appropriate and well set clinical context.

The risk of capsule retention in patients with suspected CD without obstructive symptoms or known stenosis and no history of SB resection is low ($\sim$ 1.6%) and similar to that of patients who are being investigated for OGIB [11,131-134]. In patients with suspected CD and a negative ileocolonoscopy, SB stricturing disease is infrequent and in the absence of suspicious clinical symptoms, routine SB imaging or use of the PillCam® patency capsule   prior to VCE is not essential. A careful clinical history may be the most useful way to determine the risk of capsule retention in this setting[132,135]. If patients with suspected CD present with obstructive symptoms or suspected/known stenosis, dedicated SB cross-sectional imaging in the form of CTE or MRE (which may also provide additional evaluation of mural and extra-mural pathology) should be the method of choice. VCE may still be used in this setting if functional patency of the SB is confimed with the use of the PillCam® patency capsule [136-138].

Statement: *In the setting of suspected CD, the ESGE recommends careful patient selection (using the clinical history and serological/faecal inflammatory markers) prior to VCE, in order*

to improve VCE diagnostic accuracy for lesions consistent with active small bowel CD (strong recommendation, low quality evidence).   The ESGE recommends discontinuation of NSAIDs for at least 1 month before VCE since these drugs may induce small bowel mucosal lesions indistinguishable from those caused by CD (strong recommendation, low quality evidence).

Careful patient selection remains critical to increasing the specificity and PPV of VCE findings. At present, no specific index for the diagnosis of CD exists and although the presence of clinical symptoms remain an important trigger of the diagnostic process, abdominal pain or chronic diarrhoea alone rarely result in the detection of clinically significant SB lesions at VCE [139,140]. Some more objective predictive clinical markers of SB CD include the presence of weight loss [141], perianal disease [142] raised inflammatory markers [143-146] and faecal calprotectin (FC) levels [147-149]. The International Conference on Capsule Endoscopy (ICCE) [69] recommended that patients with suspected CD may be appropriate candidates for VCE if they present with typical symptoms *in addition to* either extra-intestinal manifestations of CD, raised serological/haematological inflammatory markers and/or iron deficiency, and/or abnormal SB imaging (e.g. SBFT and/or CTE/MRE).

FC has recently been shown to be a sensitive marker of intestinal inflammation [150] and has the potential to be used as a cost-effective measure for the selection of patients with suspected or known CD being considered for VCE [147-149,151,152].

NSAID use may be complicated by a drug-induced enteropathy with SB mucosal erosion and ulceration which may lead to the formation of short, diaphragm-like strictures [153,154]. Several VCE studies have shown that NSAIDs (both non-selective and selective Cox-2 inhibitors) use may be associated with a high incidence of SB erosion and ulceration (of the order of 55% to 75%) [115-118,155-157]; chronic low dose aspirin has also been shown to be associated with the presence of similar SB lesions [158,159]. Since the endoscopic appearances of SB lesions induced by NSAIDs are endoscopically indistinguishable from lesions caused by other aetiologies such as CD, their presence may be confounding and potentially lead to misdiagnosis. In view of this, NSAIDs should be stopped before VCE, particularly if the patient is being investigated for the presence of active SB CD. Although recommendations in the current literature are heterogeneous, arbitrarily stopping these agents for at least 1 month before VCE appears to be an acceptably prudent strategy [117].

Statement: *In patients with established CD based on ileocolonoscopy findings, the ESGE recommends dedicated cross-sectional imaging for small bowel evaluation since this has the*

potential to assess extent and location of any CD lesions, to identify strictures and assess for extra-luminal disease (strong recommendation, low quality evidence). In patients with unremarkable or non-diagnostic cross-sectional imaging of the small bowel, the ESGE recommends VCE as a subsequent investigation, if deemed to influence patient management (strong recommendation, low quality evidence). When VCE is indicated, the ESGE recommends PillCam patency capsule use to confirm functional patency of the small bowel (strong recommendation, low quality evidence).

In patients with known CD, irrespective of the findings at ileocolonoscopy, further investigation is recommended to assess the extent and location of any CD lesions in the more proximal SB, since any positive findings may have prognostic and therapeutic implications [103]. Dedicated SB cross-sectional imaging with CTE or MRE generally takes precedence over VCE for the evaluation of the SB in patients with established CD, since these modalities may also identify strictures and have the ability to assess the transmural and extra-luminal nature of the disease and its anatomical distribution [111].

Dionisio et al. [120] showed that VCE was superior to SBFT/SB enteroclysis and CTE in the evaluation of patients with known CD, with a significant higher DY (VCE *vs.* SBFT/SB enteroclysis: 71% *vs.* 36 %, IY = 38 % , p < 0.00001, 95 % CI: 22% – 54 %; VCE *vs.* CTE: 71% *vs.* 39 %, IY = 32 % , p = < 0.0001, 95 % CI: 16% – 47 %). Conversely, the DY of VCE was found to be inferior to that of MRE: 70% *vs.* 79 %, IY = − 6 %, p = 0.65, 95 % CI: − 30% to 19 %. Nonetheless, VCE has been shown to improve the detection of lesions in the proximal SB when compared to both CTE and MRE [122,160] and may detect proximal SB lesions in up to 50% of patients with previously diagnosed ileal CD [161]. Despite the suggestion from a recent study that CTE or MRE may be sufficient for the investigation of most patients with known SB CD [162], VCE may still be of value if a CD flare-up is still suspected despite negative SB cross-sectional imaging. In this context, VCE may be used as a further investigation if the presence of SB mucosal lesions may influence patient management. Although prospective controlled trial data are lacking, a few retrospective studies have highlighted the potential impact of VCE on the management of patients with established CD [163-170].

The risk of capsule retention is increased and can be of the order of 13% in patients with known CD [11,132-134,171,172]. Although findings of SB stenosis at CTE or MRE may preclude subsequent VCE in 27 to 40% of patients with known CD [125], not all strictures actually result in significant mechanical obstruction and the use of the PillCam® patency

capsule may help to identify patients who are at increased risk of capsule retention [136]. One retrospective study compared the performance of the patency capsule and radiological examinations to detect clinically significant SB strictures [137]. In this study, both methods were equivalent, suggesting that if cross sectional imaging show no stricture or the patency capsule is excreted intact, the patient will most likely pass the actual capsule safely.

Statement: *The ESGE recommends an initial conservative treatment in case of a retained capsule. The ESGE recommends DAE if medical therapy has not been able to promote spontaneous passage (strong recommendation, low quality evidence).*

Cases of capsule retention can often be managed conservatively with anti-inflammatory agents and/or immunomodulators [173], resulting in spontaneous passage of the capsule [174]. If the capsule does not pass spontaneously after a trial of medical therapy, it may be retrieved by DAE [175,176]. If attempts at endoscopic capsule retrieval are unsuccessful and the patient is clinically well and without obstructive symptoms, an observant, conservative approach may be appropriate in this setting and only a minority of patients will need to undergo surgery to retrieve a retained capsule. In a large retrospective study of 2300 patients [177], including 301 with known CD, of whom 196 (65.1%) had definite SB involvement; capsule retention occurred in only 5 patients (1.66%). In 3 of these patients, the capsule passed spontaneously after a course of glucocorticoid therapy, while in the other 2, surgery was required for capsule retrieval.

Statement: *The ESGE suggests the use of activity scores (such as the Lewis score and the Capsule Endoscopy Crohn's Disease Activity Index) to facilitate prospective VCE follow up of patients for longitudinal assessment of the course small bowel CD and its response to medical therapy (using mucosal healing as an endpoint) (weak recommendation, low quality evidence).*

Efforts are being made to introduce standardised quantitative scoring systems to describe the type, location and severity of SB lesions [178]. The original threshold of ≥3 ulcers proposed by Mow et al. [108] although widely used, does not assess the distribution or the severity of inflammatory activity, does not consider other inflammatory features such as oedema or

stenosis, and has a modest positive predictive value of 50-69% for the diagnosis of CD [107,163,179]. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) score evaluates three parameters of SB pathology in CD: inflammation, extent of disease and presence of strictures, both for the proximal and distal segments of the SB, based on SB transit time of the capsule. This score has been recently validated in a multi-centre prospective study [180,181]. The Lewis score [182,183] is a cumulative scoring system which is based on the presence and distribution of villous oedema, ulceration and stenosis. It should be emphasised that although these scoring systems can quantitatively describe the type, distribution and severity of mucosal lesions, they cannot be used as a diagnostic tool per se [184]. In view of the non-specific nature of SB inflammatory lesions, the results of these scoring systems must be interpreted in the appropriate clinical context, in corroboration with other findings; it should be borne in mind that a diagnosis of active SB CD cannot be based upon the appearances seen at VCE alone.

Mucosal healing is recognised as an increasingly important endpoint for assessment of therapeutic efficacy in patients with inflammatory bowel disease (IBD) and recent clinical trials have begun to evaluate the potential role of VCE for its assessment in the SB [185-187] using quantitative scores such as the Lewis score [183] or CECDAI [181] for this purpose in research trials and clinical practice, analogous to the application of the CDEIS or SES-CD to ileocolonoscopy [188].

The potential role of VCE in the assessment of patients with IBD unclassified (IBDU) has also been investigated. Although current data is scant, there is a suggestion that the findings at VCE may help to establish a definite diagnosis and SB lesions compatible with CD may be seen in up 17% -70% of patients with this condition [163,189-191]. However, it must be borne in mind that a negative VCE only rules out *current* disease activity and cannot definitely exclude a future diagnosis of CD in these patients [192,193].

In the natural history of CD, intestinal resection is unavoidable in a significant proportion of patients. A majority of patients develop disease recurrence at or above the anastomosis and endoscopic recurrence precedes the development of clinical symptoms. Although VCE has been shown to detect superficial proximal SB lesions (undiagnosed by other modalities) in patients with CD early after surgery, the clinical significance of these findings and how they may impact on patient management remains a matter of debate [194]. VCE currently should not replace ileocolonoscopy in the routine management of patients after surgery; it should be considered in the assessment of postoperative recurrence when ileocolonoscopy is unsuccessful or contraindicated [195-198].

Statement: *The ESGE recommends DAE with small bowel biopsy in patients with non-contributory ileocolonoscopy and suspicion of CD on small-bowel cross-sectional imaging modalities or VCE. DAE with small bowel biopsy is more likely to provide definitive evidence of CD than cross sectional imaging tests, although these latters offer a useful less invasive alternative which better defines transmural complication (strong recommendation, high quality evidence).*

Although there is no gold standard for the diagnosis of CD and a corroboration of clinical and investigation findings are required [103], its presence can be supported by the findings at ileocolonoscopy in the majority of patients with suspected CD [113]. Dedicated SB cross-sectional imaging (CTE or MRE) should be considered if symptoms raise suspicion for the presence of stricturing or perforating disease and is complementary to VCE which in turn is more sensitive in detecting mucosal inflammation [110,120,199]. PE may provide direct endoscopic assessment and biopsies for histopathology especially in patients whose prior radiological or VCE findings suggest a lesion within the proximal SB [93,200,201]. Lesions which lie deeper in the SB, beyond the reach of ileocolonoscopy and PE, may be accessed by DAE which should be considered if histological assessment is needed to confirm a diagnosis of CD or exclude other conditions which mimic the appearance of CD, such as infections or malignancy [202-207].

In the setting of suspected SB CD, the DY of DAE ranges between 22% and 70% [202,203,208], being higher if the indication for DAE is based on previous SB investigations (which may identify suspected lesions and guide the route of insertion) [203]. Two meta-analyses [13,14] showed that VCE and DBE have similar DYs. The authors concluded that in view of its non-invasive nature, VCE should be considered first.

In the setting of patients with established CD, the presence of SB strictures may limit safe use of VCE and as a result, DAE may be considered earlier in the evaluation of such patients [209]. DAE may allow complete SB examination and has a higher yield in patients where a high clinical index of suspicion for active CD persists. In such a setting, when compared to radiological test, DAE seems to be more accurate than SB barium contrast studies [210] and MRE [211,212]. As for other settings, positive findings at DAE were more likely if these were guided by the findings of prior diagnostic imaging; which may also identify optimal route for insertion [26,203,213]. DAE, however, is technically challenging, may require a bidirectional

approach, deep sedation or general anaesthesia and has a major complication rate of around 0.72% (which may be higher in patients with CD) [214] and therefore should only be performed if it alters therapeutic strategy. In a small prospective trial, positive findings at DAE led to a step-up of medical therapy in 26 of 35 patients (74%), leading to clinical remission in 23 (88%) [209].

Statement: *The ESGE recommends DAE if small bowel endotherapy (including dilation of CD small bowel strictures, retrieval of foreign bodies and treatment of small bowel bleeding) is indicated (strong recommendation, low quality evidence).*

Reported indications for DAE in the setting of known or suspected CD include diagnosis and therapeutic endoscopy in patients with bleeding [203,210], dilatation of strictures (EBD) in symptomatic patients and retrieval of retained capsules [203,215]. Technical success in dilating strictures which are accessible, less than 5cm in length without severe inflammatory activity is reported in between 60 and 80% of patients and repeat EBD may be undertaken [216-218], but long-term outcomes are less well known. Perforation rates following EBD of CD related strictures at DAE may be as high as 9% [216,219-222].

Statement:
The ESGE recognises VCE/DAE and MRE/CTE as complementary strategies (weak recommendation, low quality evidence). Cost-effectiveness data regarding optimal investigation strategies for diagnosis of SB CD are lacking.

Cost-effectiveness analyses are intended to support resource-allocation decisions and are therefore dependent on local/regional socio-economic perspectives [223]. Diagnostic techniques may affect patient outcomes indirectly by their influence on subsequent management strategies, implying that benefits from a specific diagnostic test depends on performance characteristics (e.g. sensitivity and specificity) as well as other factors, such as prevalence of the disease and effectiveness of available treatments [224]. In Europe alone CD directly results in a healthcare expenditure of between 4.6 to 5.6 billion Euros per year. In addition to this the indirect costs are estimated to be twice as high as the direct costs [225] and any delay in establishing the diagnosis may augment this burden further [226]. Mitigation

of this by cost-effective diagnostic and therapeutic strategies is therefore paramount. The use of high pre-test probability indicators in suspected SB CD (such as the application of the ICCE criteria [69] +/- appropriate use of faecal inflammatory markers [147-149,227] may improve allocation of limited resources and reduce the need for more invasive and expensive diagnostic investigations in patients with a low pre-test probability. In patients with strongly suspected CD, ileocolonoscopy is the diagnostic method of choice to detect colonic CD and/or disease activity in the terminal ileum. In order to establish disease extent at first presentation, further SB imaging should be included in the diagnostic work-up, however the preferred, most cost-effective method for this remains unknown [228]. In about 10% of patients, CD only affects the SB proximal to the terminal ileum and disease activity in these patients may not be detected by ileocolonoscopy. The most cost effective diagnostic algorithm vis-à-vis SB endoscopy *vs.* dedicated cross-sectional imaging in patients with a negative ileocolonoscopy is still under debate. Cost-effectiveness analysis of performing VCE immediately after ileocolonoscopy or only after dedicated SB cross-sectional imaging in patients with suspected CD has produced conflicting results [229]. Although meta-analysis suggest a higher sensitivity and optimal negative predictive value for endoscopic methods as compared with radiology, transmural and extramural lesions are only detected by dedicated SB cross-sectional imaging [120] and these two types of technology are therefore best considered complementary [230]. Cost-effectiveness comparisons of currently available SB radiological investigations have also yielded conflicting results. Sensitivity analysis in one study suggested that in patients with a high prevalence of complications, MRE becomes as cost-effective as SBFT/SB enteroclysis which although cheaper, is less accurate and may miss extramural disease while exposing patients to ionising radiation [231]. A comparison of MRE and CTE showed that although MRE has the advantage of being radiation free and allows dynamic evaluations of SB peristalsis, it is a more expensive and longer examination with slightly inferior spatial resolution. In younger patients (≤50 years-of-age), MRE is likely to reach cost-effectiveness (when compared to CTE), however low-dose CTE may become an alternative cost-effective choice in the future [232]. Although cost-effectiveness comparisons of algorithms involving VCE and DAE in the setting of SB bleeding have shown that a capsule-directed DAE appears to be the most cost-effective strategy [61,233], similar data for VCE *vs.* DAE in the workup of CD are lacking. DAE also offers the potential to apply endotherapy (such as EBD of strictures) in patients with SB CD and this may considered as a beneficial and effective alternative to surgery in selected patients [216,221]; however, cost-effectiveness or comparative studies of endoscopic vs. surgical treatment of SB strictures are not available.

Small bowel tumours

Statement: *The ESGE recommends early application of VCE for the search of a small bowel tumour when OGIB and IDA are not explained otherwise   (strong recommendation, moderate quality evidence).*

Most of SB tumours (SBT) are detected during work-up of OGIB or IDA, but represent only about 3.5-5% of these patients [87], making this symptom a weak predictor. The clinical manifestations of SBT, unfortunately, tend to be very unspecific; which can delay the diagnosis, especially in the early stages. Associated with a higher risk of SBT are non-Hodgkin´s lymphomas as follicular lymphoma, hepatic metastasis of previously undiagnosed primary neuroendocrine tumor [234-236], and malignant melanoma in stage IV or in stage III with positive fecal occult blood test [237]. Complicated celiac disease with anemia, persistent complaints in spite of gluten-free diet, refractory celiac disease may be associated with T-cell lymphoma or adenocarcinoma [238,239] and might represent an indication for VCE.

Data on SB endoscopy in SBT are often retrieved as small part from larger mixed series, the small percentage of SBT compared to other findings in OGIB makes prospective trials almost impossible. A meta-analysis showed that VCE has a significantly higher DY compared to PE in patients with OGIB [12]: for the small number of included tumors, VCE only showed a non-significant trend towards higher DY than PE. In a highly selected group of 30/112 patients with SBT detected by VCE, PE had a DY of 70% [240]. Thus,, PE could represent a reliable tool for further work-up of SBT clearly localized to the proximal jejunum. In OGIB patients, VCE DY is similar to that of DBE [10,13] and of IOE [6]. Translating these results also to the small subgroups of patients with SBT included in these studies, VCE appears to be sufficiently accurate in detecting SBT. Of note, compared to DBE, concordance of findings was less good in patients with SBT than in patients with inflammatory and vascular lesions [241]. Factors associated with diagnosis of SBT by DBE were suspected tumour at radiology or VCE, evaluation or therapy of disease as lymphoma, but not presence of stenotic symptoms, sex and age. Indication of OGIB was significantly lower in patients with SBT diagnosed at DBE [242]. Thus, DBE is rather applied in a highly selected group, while VCE may serve as a filter for patients with SBT in the large group with OGIB. Positive findings at VCE, including tumors,

can direct the insertion route for DAE in case of [25,26], and previous VCE increases the DY of subsequent DAE [10].

The risk of false negative results in VCE should be always considered, being more frequent in large SBT and polyps, in duodenum and proximal jejunum, and in submucosal masses with missing mucosal component like neuroendocrine tumors or gastrointestinal stromal tumors (GIST) [73, 235, 243-246]. VCE seems to be superior to SB barium radiography [12,240,247]. Data concerning CTE and MRE are sparse and contradictory. MRE was demonstrated having high sensitivity (86%) and specificity (98%) for SBT [248]. In a retrospective analysis of 77 patients, specificity of MRE was higher than that of VCE (0.97 vs. 0.84, p = 0.047), whereas sensitivity was similar (0.79 vs. 0.74, p = 0.591) [249]. In a prospective blinded comparison, the overall DY for VCE and multiphase CTE was similar in 58 patients with OGIB: 28 (48%) for CTE and 25 (43%) for VCE. However, CTE diagnosed 9/9 SBT, while VCE found only 3 (33%) [33]. On the other hand, VCE was superior to CTE in detecting SBT in patients with Lynch syndrome by detecting one carcinoma and two adenomas while CTE only raised suspicion of one carcinoma [250].

SBT diagnosis by VCE can be challenging. A retrospective analysis demonstrated that a proposed tumor score composed of bleeding, mucosal disruption, an irregular surface, color, and white villi was helpful to identify SB mass lesions [251]. A score (SPICE for smooth protruding lesions (with the criteria: unsharp edge with the surrounding mucosa, diameter larger than height, non-visible lumen in the frames in which it appears, and an image lasting less than 10 minutes) had a sensitivity of 83 % and a specificity of 89% in a small prospective study. However, 2 false positive and 1 false negative diagnosis of SBT were still encountered [252]. Further larger prospective studies are needed to validate such scoring systems.

Statement: In the setting of suspicion of a small bowel tumour, the ESGE does not recommend specific investigations before VCE in patients without evidence for stenosis or previous small-bowel resection (strong recommendation, low quality evidence). The ESGE recommends to consider DAE over VCE if there is already a suspicion of SBT at imaging tests (strong recommendation, low quality evidence).

Most patients with SBT detected at VCE had the indication of OGIB or IDA [253]. Considering that only a minority of such patients have a neoplasm [240], that retention rate in SBT is only slightly higher than in other bleeding disorders [134,247],   that retention is in general

asymptomatic [240], and that most patients with SBT will undergo surgical resection of the tumour (with the possibility to retrieve the capsule easily) it does not seem justified to perform tests routinely to exclude a stenosis before VCE in bleeding patients without clinical evidence for obstruction. Conversely, if there is already a suspicion of SBT at imaging tests, DAE should be considered over VCE, in order to avoid capsule retention and to obtain histology.

Statement: The ESGE recommends cross-sectional imaging to ascertain operability when a VCE finding of SBT with a high diagnostic certainty is identified. In case of uncertain diagnosis of SBT at VCE, biopsy sampling by DAE is required (strong recommendation, low quality evidence). When a submucosal mass is detected by VCE, the ESGE recommends to confirm the diagnosis by DAE (strong recommendation, low quality evidence). In case of high suspicion of submucosal mass at VCE and a negative but incomplete DAE, the ESGE suggests cross-sectional imaging tests to confirm the diagnosis (weak recommendation, low quality evidence).

In case of a clear diagnosis of SBT at VCE (ulcerated, bleeding mass lesion, stenosis) surgery without previous histology seems justified. Cross sectional imaging techniques should be requested to exclude inoperability. Uncertain protruding SB lesions detected by VCE require DAE or imaging techniques, since innocent bulges may be confused with submucosal tumours (false positive VCE findings). A tattoo placed during DAE may facilitate recognition of small mass lesion at subsequent (laparoscopic) surgery [240].

Most studies on DAE in SBT are related to DBE. Small series on SBE and SE suggesting similar results need further confirmation. When compared to VCE, DAE seems to have comparable sensitivity. A lower specificity of VCE seems to be related to the high rate of false positive (mainly submucosal) masses . In a Chinese series, all 32 tumors detected by VCE and confirmed by DBE were further confirmed by surgery [26]. Six further submucosal tumors suspected at VCE were considered as false positive findings, as they were not confirmed by DBE. DBE was superior to CT scan in diagnosis of SBT, including submucosal masses [254,255]. In a series of 12 GIST, the detection rates of DBE, VCE and CT were 92%, 60% and 67%, respectively. All cases, except for one incomplete study, were identified using DBE. One case was not diagnosed as a tumor because of the presence of extramural growth [245]. In a

study of 159 patients with SBT, VCE and DBE had significantly higher DYs than contrast enhanced computed tomography (CECT), and DBE had significantly higher DYs than VCE, but a combination of CECT and VCE had a DY similar to that of DBE [256].

Statement: The ESGE recommends against VCE in the follow up of treated SBT because of lack of data (strong recommendation, low quality evidence).

VCE detected lesions similarly as DBE in treated follicular lymphoma. However, as identification of residual lymphoma required biopsy, the authors recommend DBE for follow-up [257]. Only one of 11 patients with VCE diagnosis of malignant SBT who underwent surgery had recurrent bleeding due to metastasis of gastric and papillary cancer in familial adenomatous polyposis (FAP) [258]. There are no studies to support regular follow-up of asymptomatic patients after resection of SBT in the absence of inherited polyposis syndromes.

Inherited polyposis syndromes

- **Familial adenomatous polyposis**

  Statement: The ESGE recommends that surveillance of the proximal small bowel in FAP is best performed using conventional forward and side-viewing endoscopes (strong recommendation, moderate quality evidence).
  When small bowel investigation is clinically indicated in FAP, the ESGE suggests that VCE and/or cross-sectional imaging techniques may be considered for identifying polyps in the rest of the small bowel, but the clinical relevance of such findings remains to be demonstrated (weak recommendation, moderate quality evidence)

In FAP, the reference examination for the proximal SB, according to the high cumulative risk of severe duodenal polyposis and high relative risk of duodenal cancer is axial and lateral viewing endoscopy in the same time [259-262]. Jejunal and ileal polyps can be found in 40-70% of FAP patients; a correlation between the severity of duodenal polyposis and the presence of more distal SB polyps has also been demonstrated [261,263-265]. It is known that

adenomas in the duodenum and the periampullary region are poorly identified with VCE, at least with an accuracy that is inferior to that of axial viewing endoscopy [265,266]; exact polyp size estimation is another limitation of VCE [267].

Studies comparing PE to VCE in FAP patients showed conflicting results [264,268], whereas systematic comparison of VCE with DAE in these patients is still warranted. VCE demonstrated higher sensitivity for polyps than radiological investigations such as SB barium studies and MRE [240,264,265,269]. The location of bigger polyps and determination of their exact sizes has shown to be more accurate by MRE than VCE [269]. The clinical relevance of detecting "distal" SB polyps in FAP patients is highly uncertain being the majority lymphoid hyperplasia, without evidence for advanced adenomas [270] and considering the low frequency of jejunal and ileal carcinomas in these patients [271].

FAP patients present with desmoid tumors in 10 % of cases. Asymptomatic extensive mesenteric desmoid tumors represent a risk in this situation. Cases of acute occlusion related to VCE retention have been reported including a case of desmoid in a FAP patient [272,273]. Exclusion of intraabdominal desmoid tumors by imaging techniques seems reasonable in FAP patients if VCE is considered.

Limited evidence exists concerning the use of DAE in FAP patients [274-277]. If polyps larger than 1 cm are identified at VCE or with cross-sectional imaging techniques, DAE is usually performed in order to obtain targeted biopsies and accomplish local endoscopic therapy [265,278]. Although technically feasible, the value of such an approach in these patients has yet to be demonstrated. In FAP patients with reconstruction with a Roux-en-Y anastomosis after a Whipple procedure, DAE may be useful for investigation of such anatomically altered bowel segments [279].

- **Peutz-Jeghers syndrome (PJS)**

  Statement: *The ESGE recommends small bowel surveillance in PJS patients. VCE and/or MRE appear adequate methods for this purpose, depending on local availability and expertise, or patients´ preference (strong recommendation, moderate quality evidence).*

The initial main purpose of SB surveillance in Peutz-Jeghers syndrome (PJS) patients is to reduce the polyp burden and the likelihood of polyp related complications, particularly intussusception. With advancing age, this focus may shift to the early detection of SB cancer or

precancerous lesions; however, the preventive effect of surveillance on development of such neoplasia remains to be proven [280,281]. VCE has a greater sensitivity than SBFT in detecting SB polyps [282-284].   When compared to MRE, VCE was superior at detecting small polyps. Polyps >1 cm were detected equally with both modalities and location of polyps and determination of their exact sizes was more accurate with MRE [269,285,286]. MRE was also shown to be less prone to missing large polyps than VCE [285]. A small study reported a 93% concordance between MRE and enteroscopy (i.e. DBE, laparoscopic endoscopy or surgery) for larger (>15 mm) and more risky polyps [287]. Compared to DAE, VCE has the advantage to allow a more complete examinations of the SB in PJS patients, however false-negative results may occur with VCE [288,289]. In a retrospective multicenter study, 25 patients underwent VCE followed by consecutive DBE when treatment was indicated. Authors found a strong agreement for polyp location and size, but not for number of polyps for which DAE was more accurate [290]. The PillCam® patency capsule test may be considered before VCE in PJS patients with history of prior SB resection, as it has been shown to be useful in detection of relevant stenosis [136,291].

> **Statement:** *The ESGE recommends DAE with timely polypectomy when large polyps (> 10-15 mm) are discovered by radiological examination or VCE in PJS patients (strong recommendation, moderate quality evidence).*

 It is now well acknowledged that polyp size is the most important risk factor for SB intussusception with intestinal obstruction and that intussusception is generally due to polyps ≥ 15 mm in diameter [292-294]. Consequently, large polyps (10-15 mm) or symptomatic or rapidly growing polyps should be removed.   DAE is clinically useful for diagnosis and relatively safe for therapy of SB polyps in PJS patients, both in adults and in children [277,292,295-299].

A study described 29 diagnostic and therapeutic DBE procedures in 13 patients with PJS, with removal of multiple polyps > 1 cm [295] without complications. However, two other studies, report a complication rate of up to 6.8%, including acute pancreatitis (2.7%) [297] and post-polypectomy syndrome (5%) [296].

In PJS, completeness of SB investigation by DAE may be jeopardized by previous laparotomies [296]. If there is no information on polyp burden an initial VCE/MRE from the age of 8-10 years [280,281,293,300] may be preferred to select only those patients for DAE with a need

for therapy. In case of high polyp burden, incomplete polypectomy during preceding DAE, next surveillance may be preferably done by DAE as this is more cost-effective in a setting with high percentage of therapy. Indeed, repeated DBE examinations have been reported to reduce SB polyp burden and to prevent polyp-related complications as intussusception [295-297]. In case a polyp is too large for safe removal with DAE or when a polyp cannot be reached with DAE, IOE could be considered for polypectomy or enterotomy.

Celiac Disease

Statement: *The ESGE strongly recommends against the use of VCE for suspected celiac disease but suggests that VCE could be used in patients unwilling or unable to undergo conventional endoscopy* (*strong recommendation, low quality evidence).*

Celiac disease is a common autoimmune condition characterised by a heightened immunological response to ingested gluten, with prevalence rates in the United States and European populations estimated to range between 0.2-1% [301,302]. The current gold standard diagnostic test for celiac disease is EGD with duodenal biopsies and SB histology demonstrating the presence of villous atrophy (VA) (Marsh 3a to 3c) [303]. Corroborative evidence used to support the diagnosis of celiac disease comes from positive serological tests (tissue transglutaminase (tTG) and endomysial (EMA) antibodies) and a clinical response to a gluten-free diet (GFD). Occasionally when diagnostic uncertainty exists, human leucocyte antigen (HLA) typing is undertaken which may help to exclude celiac disease, given the high negative predictive value of this test.

There are several potential limitations of EGD as part of this diagnostic pathway. These include its invasive nature and its inability to evaluate SB mucosa beyond the duodenum. Changes of celiac disease are well recognised to be patchy [304] and occasionally in some patients the SB distal to the reach of a standard gastroscope may be more affected than the proximal bowel where biopsies are taken [305-307]. There has been increasing interest in the role VCE may have in celiac disease. With an 8-fold magnification power comparable to a dissecting microscope, VCE has the potential to detect VA and other SB complications seen in celiac disease.

In the studies assessing the utility of VCE in diagnosing celiac disease, sensitivity, specificity, PPV and NPV of VCE were 70-100%, 64-100%, 96-100% and 71-93%, respectively [305,308-

311]. A consistent finding in all of these studies is that the PPV and specificity in the presence of EMA or significantly elevated tTG for the recognition of endoscopic markers of celiac disease is 100%. However, the high pre-test probability of celiac disease in all of these studies may again be a potential limitation leading to an overestimation of VCE performance. However they accurately reflect real life clinical practice where patients are likely to be selected for VCE of the basis of positive serology and suggest that VCE may be an appropriate tool for patients who are unable to undergo EGD.

Statement: *The ESGE recommends that there is no role for VCE to assess the extent of disease or response to a gluten-free diet* (*strong recommendation, low quality evidence*).

One area where VCE may confer an advantage over standard endoscopy is that VCE has the potential to image the entire SB. It would seem intuitive that the more of the bowel that is affected the more severe symptoms and the higher the chance of potential complications. However this has not been proven mainly because it is difficult to assess the extent of disease. In a study of 38 untreated celiac patients and 38 controls [305], the authors were unable to show a relationship between either qualitative or quantitative measurements of extent of disease and severity of clinical presentation, however a positive EMA was associated with more extensive disease. In the 30 celiac patients who agreed to repeat VCE after GFD, the mean time with abnormality reduced from 60 minutes to 12 minutes. A second more recent study of 12 patients with celiac disease who had repeat VCE after 12 months on a GFD has also demonstrated this improvement [310]. Although there was no initial correlation between extent of disease and clinical severity they did demonstrate a significant reduction in the mean time with VA. These two studies have so far failed to demonstrate any relationship between extent of SB involvement and clinical severity of disease. As experience with VCE in celiac disease increases however this may become possible.

Statement: *The ESGE suggests the use of VCE in equivocal cases of celiac disease (weak recommendation, low quality evidence).*

Another area where VCE may play a role is in the investigation of equivocal cases of celiac disease. The changes of celiac disease can be patchy and a duodenal biopsy in patients with positive serology may not demonstrate VA. Lesser degrees of histology that can be associated with celiac disease are non-specific and are seen in a variety of other conditions. This can

leave some patients without a definitive diagnosis. In a study of 8 patients with positive serology (EMA or tTG) and a normal duodenal biopsy, VCE did not reveal any endoscopic features of celiac disease [310]. Thus the investigators concluded that there was no benefit in performing VCE for this sub-group of patients; another similar study came to the same conclusions [312]. There is however conflicting evidence. In a further study of 30 patients with Marsh 1 or 2 changes, only 6 of whom had positive EMA or tTG, one patient was diagnosed with celiac disease and another with SB CD on the basis of VCE appearances [313]. It is clear that further work is required to assess the cost effectiveness of the use of VCE in these equivocal cases if the yield is as low as in this final study. VCE use may be justified however, in EMA or tTG positive patients with Marsh 1 or 2 changes or gastrointestinal symptoms particularly if they are unwilling to undergo further EGD and repeat biopsies.

Patients with antibody-negative VA represent another diagnostic challenge since there is a wide range of differential diagnoses for VA. In the study of equivocal cases by Kurien et al.[313] they also included a group of patients with antibody-negative VA to see if this increased the DY. Patients were extensively investigated for celiac disease including HLA phenotyping, by monitoring response to GFD and in some cases repeat duodenal biopsies. On the basis of VCE appearances and other ancillary tests 7 patients could be diagnosed with celiac disease and 2 further patients were diagnosed with SB CD as a cause for VA. Again this is a single small study and further work needs to be done to clarify the role of VCE in antibody-negative VA cases. This is particularly important as VCE alone is probably insufficient to confirm a diagnosis of celiac disease as endoscopic markers are not specific to celiac disease rather they are predictors of mucosal disease [314].

Statement: *The ESGE recommends initial assessment by VCE followed by DAE in non-responsive or refractory celiac disease* (*strong recommendation, low quality evidence).*

The distribution of serious complications of celiac disease such as refractory celiac disease (RCD) and enteropathy associated T-cell lymphomas (EATL) is particularly important as these appear to be more commonly seen in the distal SB [315-319]. Ulcerative jejunitis is usually associated with RCD type II and with a high risk of developing EATL. Early identification of RCD type II may allow effective treatment with immunosuppression and prevent progression to EATL. VCE could therefore play a role in the investigation of these patients . In two studies of patients with celiac disease and persisting symptoms, a few

serious complications were identified by VCE including cases of EATL, ulcerative jejunitis, RCD type I and II, some of which were confirmed by DBE and biopsy [313, 316]. The use of VCE to assess the extent and severity of disease in patients with known RCD may also be helpful as shown in a recent study of 29 patients with RCD and 9 patients with symptomatic celiac disease [239]. Three cases of EATL were identified and 5 cases of ulcerative jejunitis requiring specific treatment in the RCD cohort. The majority of the RCD patients also underwent DAE and the authors concluded that 17 patients could have avoided this invasive investigation based on VCE findings. Apart from this final study, where there was an unusually high proportion of patients with RCD, the apparent DY for complications such as EATL and ulcerative jejunitis appears low. However these diagnoses carry significant rates of morbidity and mortality which may be reduced by prompt diagnosis. The use of capsule followed by DAE [320.321] in non-responsive patients may therefore be justified. Patients with ulcerative jejunitis and EATL can have a significant risk of SB stricturing. VCE should be used with caution therefore and a patency capsule should always be employed to reduce the incidence of capsule retention. MRE has also been suggested to detect celiac related malignancies [322].

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

M.Pennazio, speaker (Covidien, formally Given Imaging)

Abbreviations	
CD	Crohn's disease
CECDAI	Capsule endoscopy Crohn's disease activity index
CI	Confidence interval
CECT	Contrast enhanced computed tomography
CTE	Computed tomography enterography/enteroclysis
CT	Computed tomography
CTA	Computed tomography angiography
DAE	Device assisted enteroscopy
DBE	Double-balloon enteroscopy
DY	Diagnostic yield
EATL	Enteropathy associated T-cell lymphomas
EBD	Endoscopic balloon dilatation
EGD	Oesophagogastroduodenoscopy
EMA	Endomysial antibodies
FAP	Familial adenomatous polyposis
FC	Fecal calprotectin
GFD	Gluten free diet
GIST	Gastrointestinal stromal tumours
HLA	Human leucocyte antigen
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
ICCE	International conference on capsule endoscopy
IDA	Iron deficiency anaemia
IOE	Intra-operative enteroscopy
IY	Incremental yield

MRE	Magnetic resonance enterography/enteroclysis
MRI	Magnetic resonance imaging
NPV	Negative predictive value
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OGIB	Obscure gastrointestinal bleeding
PE	Push enteroscopy
PJS	Peutz-Jeghers syndrome
PPV	Positive predictive value
RCD	Refractory celiac disease
RCT	Randomized controlled trial
SB	Small bowel
SBFT	Small-bowel follow-through
SBT	Small-bowel tumours
SE	Spiral enteroscopy
VCE	Small bowel capsule endoscopy
SBE	Single-balloon enteroscopy
tTG	Tissue transglutaminase antibodies
VA	Villous atrophy

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