

## Small bowel enteroscopy – A joint clinical guideline by the Spanish and Portuguese small-bowel study groups

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### ABSTRACT

The present evidence-based guidelines are focused on the use of device-assisted enteroscopy in the management of small-bowel diseases. A panel of experts selected by the Spanish and Portuguese small-bowel study groups reviewed the available evidence focusing on the main indications of this technique, its role in the management algorithm of each indication, and its diagnostic and therapeutic yield. A set of recommendations was issued accordingly.

Enrique Pérez-Cuadrado-Robles and Rolando Pinho contributed equally to the present guidelines and are the first co-authors.

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## INTRODUCTION

Device-assisted enteroscopy (DAE) has shown high diagnostic yields for small-bowel (SB) diseases (1). Furthermore, this technique is the first-line therapeutic procedure for several SB pathologies. However, its role, place in the management algorithm, and yields are dependent on numerous factors, namely the indication and previous examinations such as capsule endoscopy (CE). The aim of the present guidelines is to provide evidence-based recommendations on the clinical indications and on the diagnostic and therapeutic yields of DAE in SB diseases.

## METHODS

The present guidelines were promoted and supported by the Capsule Endoscopy and Enteroscopy Group of the Spanish Society of Gastrointestinal Endoscopy (SEED) and the Portuguese Small-Bowel Study Group (GEPID) – a section of the Portuguese Gastroenterology Society (SPG). Two guideline coordinators (EPCR, RP) were designated, who invited members from both societies and selected experts in the field from Spain and Portugal.

Seven task force groups comprising 3-5 persons coordinated by a group leader were created for the following subjects: overt SB bleeding, occult SB bleeding, Crohn's disease (CD), tumors, polyposis syndromes, celiac disease, and miscellaneous indications. Each group contained members from both societies, with variable levels of expertise and from different institutions (Table 1).

The key questions to be addressed were decided by each group coordinator but included indications, diagnostic yield, and therapeutic yield or impact on the patient's clinical course. Technical aspects and the use of DAE in specific settings outside the SB, such as difficult colonoscopy and enteroscopy-assisted endoscopic retrograde cholangiopancreatography, were not included in these guidelines.

A systematic review of the literature was performed. The literature search was carried out in PubMed, the Cochrane Library, and Scopus until November 2019, combining the following common and specific terms:

- *Common terms for all task forces:* enteroscopy OR double-balloon OR DBE OR single-balloon OR SBE.

- *Specific terms depending on the topic:* obscure gastrointestinal bleeding OR OGIB OR small-bowel bleeding OR anemia OR anaemia; Crohn OR inflammatory bowel disease OR IBD; tumor OR tumors OR tumour OR tumours OR neoplasia OR cancer; polyp OR polyps OR polyposis OR Peutz-Jeghers OR Familial adenomatous polyposis; celiac disease OR coeliac disease.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used for assessing evidence levels and recommendation strengths (Table 2). The guideline development process included online discussions and one meeting during the Iberian Meeting of Enteroscopy in January 2020 to discuss draft proposals and the main recommendations for all topics. Finally, a panel of experts was selected by the Editorial Committee of *The Spanish Journal of Gastroenterology -Revista Española de Enfermedades Digestivas (REED)*- to perform an external review of the manuscript.

The present document is intended to be an evidence-based, state-of-the-art guide for endoscopists dedicated to SB diseases. These guidelines will be considered for review in 2025, but an update will be added sooner if relevant evidence becomes available meanwhile.

## SMALL-BOWEL BLEEDING

Obscure gastrointestinal bleeding (OGIB) accounts for approximately 5 % of all cases of gastrointestinal bleeding and is usually due to a SB lesion presenting with SB bleeding (SBB) (1). Several meta-analyses have shown comparable diagnostic yields for CE and DAE (2). CE is recommended as the first-line examination due to its non-invasiveness and favorable safety profile. DAE should be performed after the detection of the bleeding source or in the emergency setting in patients with massive bleeding (1,3). The diagnostic yield of DAE ranges from 47 % to 75 % (2,4-8), depending on the type of lesion and indication (9,10). Xin et al. showed a pooled overall diagnostic yield for double-balloon enteroscopy (DBE) of 68 % in a meta-analysis (11). In addition, this rate is significantly higher when DAE is performed following a positive CE (75 % vs 27.5 %) (2).

### Overt small-bowel bleeding

Data on the diagnostic yield of DAE focused on overt OGIB are restricted to small case series. In this setting, DAE

**Table 1.** Group member distribution among the different areas of expertise

<b>Overt OGIB</b>	Cristina Carretero*, Eduardo Valdivielso, Ana Ponte, Sandra Lopes, Noemí Caballero
<b>Occult OGIB</b>	Cristina Chagas*, Pilar Borque Barrera, Pedro Alonso, Carlos Bernardes, Consuelo Gálvez
<b>Crohn's disease</b>	Begoña González*, Federico Argüelles-Arias, Bruno Rosa, Juan Egea-Valenzuela
<b>Tumors</b>	Susana Mão de Ferro*, Nuno Almeida, Mileidis San Juan-Acosta, Óscar Nogales
<b>Polyposis</b>	Pilar Esteban Delgado*, Miguel Mascarenhas Saraiva, Javier García Lledó, Francisco Sánchez Ceballos
<b>Celiac disease</b>	Pedro Figueiredo*, Patrícia Andrade, José Francisco Juanmartiñena-Fernández, Blas José Gómez-Rodríguez
<b>Miscellanea</b>	Enrique Pérez-Cuadrado Martínez*, Helder Cardoso, César Prieto-Frías

\*Group leader.

OGIB: obscure gastrointestinal bleeding.

**Table 2.** GRADE score according to benefits and risks

GRADE	Benefit vs. risk	Quality of evidence
1 A	Benefits clearly outweigh risks, or <i>vice versa</i>	RCTs with no important limitations or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of the effect.
1 B	Recommendation may apply to most patients in most circumstances	RCTs with important limitations or strong evidence from observational studies. Further higher-quality research may have an important impact.
1 C		At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research is likely to have an important impact
2 A	Benefits balanced with risks; best action may differ depending on circumstances	RCTs with no important limitations or exceptionally strong evidence from observational studies. Further research is unlikely to change our confidence in the estimate of the effect.
2 B	or patient/society values	RCTs with important limitations or strong evidence from observational studies. Further higher-quality research may have an important impact
2 C	Benefits balanced with risks; other alternatives may be equally reasonable	At least one critical outcome from RCTs with serious flaws, observational studies, case series, or indirect evidence. Further higher-quality research is likely to have an important impact

RCT: randomized controlled trial.

proved to have a higher diagnostic yield when performed in the urgent setting (< 72 h), averaging 70-90 % (12). This compares favorably with the diagnostic yield of DAE in the non-urgent setting, which averages 30-50 % (13-15).

The therapeutic yield of DAE performed in the overt OGIB setting ranges from 41.4 % to 88.9 % (14,16-21). Therapeutic procedures vary according to etiology and include clipping, argon plasma coagulation, epinephrine injection, heater probe coagulation, and polypectomy (14,18,21-24). Additionally, endoscopic tattooing may be performed for a subsequent surgical approach (20). The timing in which DAE is performed may also influence therapeutic yields. Recent studies reported that emergent DAE (< 24-72 h) resulted in endoscopic therapy in 28.6-57.5 % of cases, while non-emergent DAE resulted in endoscopic therapy in 13-50 % of cases (14,24-26). Concerning rebleeding, repeating DAE therapy after an initial therapeutic DAE may decrease the number of overt rebleeding episodes in patients with recurrent OGIB (27). Moreover, Aniwani et al. concluded that rebleeding rate was lower after emergent DBE when compared to non-emergent DBE, although not significantly so (10 % vs 29 %,  $p = 0.08$ ) (26).

The oral route is usually selected first (12,14,16,28,29). Previous findings from imaging studies or CE have a major role guiding a further approach (5,12,14,28,30-33). If a lesion detected on CE is within the initial 75 % of SB transit time, an antegrade approach should be chosen (14,17,20,22,24,25,34). Pérez-Cuadrado Robles et al. concluded that real-time CE findings may also be useful to decide the initial route on emergent SBB (17). When a prior study failed to reveal a potential bleeding source, the oral approach should be chosen, or the insertion route should be selected according to the type of bleeding (5,12,16,19,22,25-28,30,31,33-37). The presence of melena prompts to antegrade DAE and hematochezia to retrograde DAE (16,26,36). In fact, Zhu et al. showed that the presence of melena doubles the odds of finding a bleeding site within the proximal SB (OR 1.97, 95 % CI: 1.17-3.33,  $p = 0.01$ ), prompting for oral DAE in these patients (38). If clinical suspicion is high for

bleeding despite negative findings on the initial insertion route, the limit of insertion should be marked by clipping or tattooing, and DAE should be performed using the opposite route of insertion (12,14,19-22,25,26,28,33,35-37). When a bleeding source has been identified, total enteroscopy is not required (27,30,35).

Major adverse events associated with DAE procedures in overt OGIB (such as perforation or pancreatitis) are very rare and occur in about 0.5 % of cases (8,16,20,29,31,37,39). Minor complications occur in about 11 % of patients, and include abdominal discomfort, abdominal pain for < 48 hours, sore throat, and minimal SB mucosal trauma. Patients may usually be discharged on the same day of the procedure (19,31,34,37,40). Mortality related to DAE or endoscopic therapy is extremely rare (41).

### Occult small-bowel bleeding and iron-deficiency anemia

DAE has a high diagnostic yield in the setting of occult-OGIB or iron deficiency anemia (IDA) ranging from 52.4 % to 75.6 % (2,25,36,40,42-46), which increases when DAE is performed after a positive CE (20). The most frequently identified lesions are angiodysplasias, erosions, ulcers and tumors (1,2,44). The yields and findings appear to be similar to those achieved with CE, especially when a complete DAE is achieved (47-49). CE prior DAE is useful to identify potential lesions and to select the most convenient route for the procedure, as described above for overt-OGIB (2,47).

There are no randomized controlled trials evaluating the efficacy of DAE in patients with occult-OGIB/IDA. Moreover, most cohorts don't divide their therapeutic results between patients with overt and occult-OGIB/IDA. However, several retrospective and prospective observational studies reported a high therapeutic yield -usually defined as the ability to successfully perform therapeutic endoscopic procedures or improvement in hemoglobin levels/decrease in transfusion requirements (19,20,39,50-55). In spite of achieving a high endoscopic therapeutic success and a reduction in the need

for transfusion support, two systematic reviews concluded that the rate of recurrence/rebleeding is substantial (56,57). Given the fact that the major cause of occult-OGIB/IDA are SB angiodysplasias, which tend to be multiple, additional studies to verify the role of periodic enteroscopic interventions and/or its association with medical treatment in the prevention of rebleeding are needed.

The outcomes of occult-OGIB/IDA after DAE therapy evaluated in different publications are numerous: resolution of anemia (or improvement in hemoglobin levels), need for endoscopic procedures, number of hospital admissions, hospitalization time, transfusion requirements, mortality etc. Most retrospective studies and case series report high diagnostic and therapeutic yields, resulting in reduced transfusion requirements, iron supplementation or the need for subsequent endoscopic treatment (58). Rebleeding after an initial DAE hemostasis ranges from 20 % to 52.6 % (18,19,21,23,27,55,59-61). Female sex (OR: 1.96, 95 % CI: 1.1-3.3), Osler-Weber syndrome (OR: 4.35, 95 % CI: 1.2-15.4) and cardiac disease (OR: 1.89, 95 % CI: 1.1-2.9) were associated with rebleeding in a recent meta-analysis (62). Williamson et al. demonstrated a significant decrease in blood transfusion requirements, need for iron supplementation and additional procedures after a first therapeutic DAE (55). Repeating therapeutic DAE has proven to be useful in rebleeding patients (53).

Furthermore, patients with treatable lesions have better clinical outcomes (26,35,63). When multiple SB vascular lesions are identified, treatment efficacy can be limited, but a reduction in the number of transfusions may be achieved. In the case of erosions or ulcers, patients with potentially treatable lesions, such as NSAIDs use, or inflammatory bowel disease (IBD), have better long-term outcomes than those in which the cause remains unknown (35).

## CROHN'S DISEASE

DAE has a limited role in the initial evaluation of patients with suspected IBD. However, when SB lesions are identified by cross-sectional imaging modalities or CE, histologic evaluation may be necessary to rule out other diseases (64,65). If the location of these lesions lies outside the reach of standard endoscopy, DAE is the preferred technique. In this setting, it has a higher diagnostic yield than radiologic techniques (SB barium contrast, CT enterography and magnetic resonance enterography, MRE) (66).

Regarding established CD, DAE may be useful in patients with unclear symptoms and for therapy of SB strictures or bleeding lesions (67-70). This technique can confirm suspected CD with a diagnostic yield of 22-80 % (65,71-73), and can also change the initial diagnosis in up to 12 % of cases when the lesions that are observed or the histological findings are different from those reported by CE or radiology (73-75).

Therapeutic DAE in CD is mainly indicated to perform balloon dilation of SB strictures to prevent or delay surgical interventions. In experienced hands the technical feasibility is over 90 %, which is equivalent to conventional endoscopic balloon dilation for colon and ileocolonic anastomoses (69). Dilation of anastomotic or primary strictures, shorter

than 5cm, non-angulated and without significant inflammatory activity namely deep ulcers or fistulae, proved to be safe and associated with better long-term outcomes (69,70,76-78). Data on adjunctive therapies for refractory strictures, such as triamcinolone or infliximab injection, stent placement or cutting techniques are scarce and mixed, currently not supporting their routine use. Approximately 80 % of CD patients submitted to DAE balloon dilation remain symptom-free after 3 years, although nearly half of these cases will require at least one re-dilation procedure. The mean diameter of dilation reported is 12-15 mm, with an overall complication rate of 4.8 % per patient and 2.6 % per dilation (76,77). The presence of large and deep ulcers, fistulas and/or abdominal or pelvic abscesses are contraindications for balloon dilation.

## SMALL BOWEL TUMORS

SB tumors (SBT) comprise less than 5 % of gastrointestinal cancers. The incidence of primary SBT is increasing, mainly due to the rise of neuroendocrine tumors (NETs). The most common SBTs are gastrointestinal stromal tumor (GIST), adenocarcinoma, NET, and lymphoma (79). Overall, SBTs are more frequent in the jejunum, followed by the duodenum and ileum, and most present with SBB (80-83).

CE and DAE are complementary, with high diagnostic concordance for the detection of SBT and polyps (84). However, DAE may have a higher diagnostic yield than CE (85). Both endoscopic techniques performed better in SBT detection than contrast-enhanced computed tomography (85-87). DBE is an useful procedure to determine the extent, location and endoscopic characteristics of SBT, allowing biopsy examination and tattoo injection to guide a possible surgery. It also provides additional information to other procedures, that may be decisive in the clinical course of these patients (81-83,87-90).

If there are no doubts about the diagnosis of SBT at CE, direct surgery is acceptable if cross-sectional imaging excludes inoperability (1). In all other cases, histological confirmation is crucial to make treatment decisions (83,90,91). Biopsies have a high diagnostic value, especially for adenocarcinoma and lymphoma (71.4 % and 60 %, respectively) (87). The need for histology of GISTs must be thoroughly balanced, since the rate of a positive histological diagnosis by DAE does not exceed 46.7 % and the risk of bleeding is not negligible (92,93).

Concerning NETs, a retrospective study demonstrated that bidirectional DAE performed in patients with previously known tumors, to exclude multifocality, revealed additional neuroendocrine tumors in 51.1 % (94).

DAE can modify the clinical course in 25-65 % of patients by delaying or avoiding emergent surgery or by modifying the surgical approach (83,86).

DAE allows therapeutic interventions, primarily hemostasis of bleeding SBT (using argon plasma coagulation, haemostatic powder, clipping, and epinephrine or sclerosant injections). Some case series proposed DAE for stenting in SB obstruction secondary to SBT (as emergency treatment and in palliative patients) (95-98). The evidence is scarce



given the limited working channel of the enteroscope and the high degree of technical skills required.

After surgical resection of SBT in patients without polyposis or other inherited syndromes there are no clear recommendations for follow-up. However, some authors recommend DAE (99).

## SMALL BOWEL POLYPOSIS

Small bowel polyps occur in 90 % of Peutz-Jeghers syndrome (PJS) patients and in more than 75 % of those with familial adenomatous polyposis, being distal small bowel polyps more frequent in patients who also have duodenal polyps (100). A retrospective study showed that CE identified the number, location and size of polyps and could indicate the route (oral or anal) for DAE and predict the difficulty of polypectomy during deep enteroscopy (101). However, DAE was better than CE to define the size and location of polyps.

A prospective study showed that MRE and DAE have similar diagnostic yield for detecting clinically relevant SB polyps ( $\geq 15$  mm in diameter) in patients with PJS (102), but the most important advantage of DAE compared with MRE is its ability for immediate polypectomy, tattooing and biopsy.

An initial CE/MRE may be preferred to select for enteroscopy only those patients needing therapy (1) although the diagnostic rate is similar to DAE (103). Polyp size is the most important risk factor for SB intussusception, being intussusception generally due to polyps  $\geq 15$  mm in diameter. Consequently, large polyps (10-15 mm) or symptomatic or rapidly growing polyps should be removed in PJS (104,105). DAE proved to be useful in the resection of SB polyps resulting in a decrease in the average number and size of lesions in periodic enteroscopies (106-108). Additionally, absence of intussusception or complications requiring surgery after a follow-up of up to 56.5 months (107) and an adequate safety profile was also verified. There are series in which complications are not reported (109), but other studies report complications between 4-6 % including bleeding, pancreatitis, perforation and post-polypectomy abscesses, treated with conservative management in most cases (106-108,110). The effect on cancer reduction after enteroscopy resections remains unknown.

There is little evidence in determining the indication for DAE in familial adenomatous polyposis patients. Screening and surveillance with DAE of SB adenomas could be useful in patients with Spigelman scores III or IV (111), even though the malignant potential of these lesions is unknown (112-114).

## CELIAC DISEASE

There is a little role for DAE in the diagnosis of celiac disease (CeD) as most patients are diagnosed based on endoscopic and histologic findings of upper GI endoscopy. Some studies reported a patchy distribution of histologic abnormalities (115), thus DAE may be indicated in cases of strong clinical suspicion with positive specific serology and negative duodenal biopsies at upper-GI endoscopy.

The role of DAE is mainly for the diagnosis of CeD complications (116). Patients uncompliant or unresponsive to a gluten-free diet, with alarm symptoms or iron deficiency anemia, have an increased risk of developing SB malignancies (117); in this case, SB evaluation by CE, upper endoscopy and imaging tests followed by DAE in order to obtain mucosal samples for histological and/or molecular analysis is recommended. Currently, it is difficult to know the diagnostic yield of DAE as only a few retrospective papers and a single meta-analysis (117) can be found. Among these studies, the overall diagnostic yield approaches up to 20 %, although this value decreases when evaluating SB malignant and premalignant lesions separately. The diagnostic yield for malignant lesions ranges between 16.7-24 %, whereas for premalignant lesions it ranges from 9 to 16 % (118,119).

## MISCELLANEOUS

There are other clinical conditions in which DAE is useful. Due to its ability to perform biopsies of the entire SB, DAE has been reported in the diagnosis of malabsorption syndromes and SB chronic infections, mainly tuberculosis and Whipple's disease (120,121). It also enables the characterization of other diseases such as NSAID enteropathy (122), ischemic enteritis and radiation-induced enteritis, graft versus host disease with SB involvement, and other lesions such as inflammatory fibroid polyps and SB diverticula, including Meckel's diverticulum (123). In altered anatomy, such as *Roux-en-Y* anastomosis and gastrojejunostomy, DAE enables the study of intestinal segments that are inaccessible to regular endoscopes, including CE (124). Endoscopic enteroclysis can be useful in selected cases such as stenosis. DAE has also been used for therapy: retrieval of potentially harmful foreign bodies, especially retained CE (125), but also bezoars (126), needles (127), coins (128), gastric bands (129), dentures (130) and migrated stents (131). Many SB strictures secondaries to NSAIDs, radiation, surgical anastomosis, or malignancy have been treated with balloon dilation (76,132,133) or stenting, using both over-the-wire or through-the-scope techniques (134-136). DAE can also be used for percutaneous endoscopic jejunostomy (137) and SB intussusception (138).

## CONCLUSIONS

Since its introduction in routine clinical practice almost two decades ago, the diagnostic and therapeutic capabilities of DAE have continuously evolved (139). The evidence published in the last few years helped better define the role of DAE in its various indications, as well as its advantages and disadvantages over other endoscopic and radiologic procedures. As the technology continues to evolve and mature, further refinements in its capabilities and use are anticipated.

## STATEMENTS

### SMALL-BOWEL BLEEDING

- In OGIB, the route of insertion for DAE should be based on pre-DAE investigations, such as CE. GRADE 2B (weak recommendation, moderate-quality evidence).

- DAE should be the first-line therapeutic procedure following CE in both patients with overt and occult OGIB. GRADE 2A (weak recommendation, high-quality evidence).
- There are no serious complications associated with the examination or endoscopic treatment. The procedure is generally well tolerated. GRADE 2B (weak recommendation, moderate-quality evidence).

### 1. Overt OGIB

- DAE has a high therapeutic yield in overt OGIB. The therapeutic technique should be selected according to the bleeding source. GRADE 1B (strong recommendation, moderate-quality evidence).
- In patients with recurrent overt OGIB a second therapeutic DAE is recommended. GRADE 2C (weak recommendation, low-quality evidence).
- In overt OGIB, DAE should be performed whenever possible within the first 72 h, as this leads to higher diagnostic and therapeutic yields, and lower rebleeding rates. GRADE 2C (weak recommendation, low-quality evidence).

### 2. Occult OGIB

- DAE has a high therapeutic yield in occult OGIB. Recommended treatment options include: argon plasma treatment for angiectasia coagulation; hemostatic clipping for Dieulafoy lesions or bleeding ulcers; polypectomy for bleeding small-bowel polyps; and/or lesion tattooing for further surveillance or treatment. GRADE 2B (weak recommendation, moderate-quality evidence).
- Follow-up of patients with vascular lesions is recommended because of a high rebleeding rate. Repeated treatment with DAE may improve the management of refractory OGIB. Grade 1C (strong recommendation, low-quality evidence).

## CROHN'S DISEASE

- DAE is indicated for suspected CD in patients with SB lesions identified by other non-invasive techniques (CE or CT/MR enterography) and non-accessible to conventional endoscopy. In these cases a histological diagnosis is recommended. GRADE 1B (strong recommendation, moderate-quality evidence).
- In established CD DAE may be useful for diagnosis and therapy in selected cases (dilatation of strictures and retrieval of impacted capsules). GRADE 1B (strong recommendation, moderate-quality evidence).
- DAE dilatation of primary or anastomotic strictures shorter than 5 cm, non-angulated, and without significant inflammatory activity represents a safe, effective intervention with a low rate of complications. GRADE 1B (strong recommendation, moderate-quality evidence).

## TUMORS

- DAE should be used in a combined approach with CE and radiological examinations for the diagnosis

of SB tumors. GRADE 1C (strong recommendation, low-quality evidence).

- DAE should be considered in patients with a high clinical suspicion of SB tumors despite negative CE and cross-sectional studies. GRADE 2C (weak recommendation, low-quality evidence).
- In patients with suspected SB tumors, if there is no undeniable indication for surgery, DAE should be performed to confirm the diagnosis, obtain biopsies for histological documentation, establish the precise location of the lesion, and mark it for further surgical treatment. GRADE 1C (strong recommendation, low-quality evidence).

## POLYPOSIS

- DAE therapy is recommended for polyps > 10-15 mm to prevent polyp-related complications. GRADE 1B (strong recommendation, moderate-quality evidence).
- DAE may also be used in symptomatic patients with polyps causing intussusception symptoms and hemorrhage/anemia in intestinal polyposis syndromes (FAP and PJS). GRADE 1C (strong recommendation, low-quality evidence).
- DAE may be used in FAP patients with Spigelman stages III/IV for screening and surveillance of intestinal adenomas and endoscopic treatment. GRADE 2C (weak recommendation, low-quality evidence).

## CELIAC DISEASE

- There is a little role for enteroscopy in the diagnosis of celiac disease. Enteroscopy may be indicated in cases of strong clinical suspicion with positive specific serology and negative duodenal biopsies at upper GI endoscopy. GRADE 2C (weak recommendation, low-quality evidence).
- The role of enteroscopy is mainly for the diagnosis of celiac disease complications. In patients noncompliant with or unresponsive to gluten-free diet, with alarm symptoms or iron-deficiency anemia, enteroscopy is recommended after SB evaluation by CE, upper-GI endoscopy, and imaging tests in order to obtain mucosal samples for histologic and/or molecular analysis. GRADE 2B (weak recommendation, moderate-quality evidence).

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