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Review Article

Device-assisted enteroscopy: An update on techniques, clinical indications and safety

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ABSTRACT

After more than 15 years since its introduction into clinical practice, indications for device-assisted enteroscopy have greatly expanded. Alongside the consolidated indications such as the diagnosis and treatment of small bowel bleeding, Crohn's disease, hereditary polyposis, small-bowel tumors and complicated celiac disease, device-assisted enteroscopy is nowadays largely used to perform endoscopic retrograde cholangiopancreatography in patients with altered anatomy, stent placement, retrieval of foreign bodies, direct insertion of jejunal feeding tubes, and in selected cases of incomplete colonoscopy. This has been made possible by the technical improvements of the enteroscopes and accessories and by the widespread use of the method. Device-assisted enteroscopy endotherapy currently offers a safe and effective alternative to major surgery and often represents the preferred option for treatment of small-bowel pathology. Its safety profile is favourable even in the elderly patient, provided that it is performed in high-volume and experienced centers. The evolution of the enteroscopy technique is a challenge for the future and could be facilitated by the new enteroscopes models. These prototypes need a thorough clinical and safety assessment especially for the complex therapeutic procedures. Large prospective, multicenter studies should be performed to assess whether the use of device-assisted enteroscopy leads to improved patients' long-term outcomes.

1. Introduction

Enteroscopy is a generic term, which means endoscopic evaluation of the small bowel (SB). Since a limited SB evaluation is undertaken during oesophagogastroduodenoscopy (EGD) and colonoscopy, the enteroscopy usually refers to an extensive endoscopic examination of the small intestine, extending beyond the duodenum or the terminal ileum. The direct inspection of SB mucosa can be performed wirelessly, by means of SB video capsule endoscopy (VCE), or achieved through dedicated endoscopes (enteroscopes). If on one hand VCE allows a complete, non-invasive and detailed evaluation of the SB mucosa, on the other hand it is a purely diagnostic technique without therapeutic capabilities. Therefore, VCE represents in several clinical conditions the first diagnostic tool, which guide and direct endoscopic therapy delivered through enteroscopes.

The current review is focused on enteroscope-based SB evaluation: in the following paragraphs we will review different enteroscopy techniques, current clinical indications as well as the enteroscopy safety profile.

2. Enteroscopy techniques

With the exception of intraoperative enteroscopy (IOE), the SB is usually accessed through the upper (per-oral or anterograde approach) or lower (per-anal or retrograde approach) gastrointestinal tract. In everyday clinical practice, the choice between antegrade and retrograde approach depends on clinical indication and on results of previous examinations (including VCE and imaging tests). Combining antegrade and retrograde approach, when clinically indicated, recently developed enteroscopy techniques may allow to visualize the entire SB.

Enteroscopy techniques include push enteroscopy (PE), device-assisted enteroscopy (DAE) and intraoperative enteroscopy (IOE). PE can be performed by means of dedicated enteroscope or standard colonoscope, with or without an overtube. The endoscope is generally inserted through the mouth or the anus and advanced

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Fig. 1. Motorized Spiral Enteroscope (courtesy of Olympus Europe, Hamburg, Germany).

into the SB: torque and withdrawal maneuvers as well as regulation of the stiffness of the instrument are used with the aim of reducing loop formation. PE SB inspection is however generally limited to the proximal jejunum, approximately 50–100 cm beyond the ligament of Treitz [1], or to the distal ileum. In recent years, DAE has largely replaced push-enteroscopy, enabling diagnostic and therapeutic procedures throughout the entire length of the SB.

DAE is a generic term for endoluminal examination of the SB by any endoscopic technique that includes assisted progression, i.e. with a balloon, overtubes, or other stiffening devices. DAE includes double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), spiral enteroscopy (SE) and balloon-guided endoscopy (BGE). Table 1 shows the main characteristics of the currently available DAE systems.

DBE and SBE procedures are based on the presence of an overtube, placed onto the endoscope, with a balloon attached at the tip of it; the endoscopes used for DBE (Fujinon Inc., Saitama, Japan) are equipped with a second balloon on their distal end. The rationale of the DBE technique combines the inflation-deflation of the balloon(s) with insertion-retraction of the scope ("push-and-pull" technique) gradually pleating and shortening the SB on the overtube, thus allowing deep progression in the intestinal lumen [2]. The "push-and-pull" technique is also used in SBE (Olympus Optical Co., Tokyo, Japan) in which there is no balloon at the endoscope tip, but a stable position of the endoscope is mainly maintained with scope tip angulation and suction of the bowel wall ("hook-and-suck" technique) [3].

SE (Spirus Medical LLC, West Bridgewater, Massachusetts, USA) involves the presence of an overtube with a raised spiral ridge: the small bowel is actively pulled and pleated onto the overtube by continuous rotation of the spiral and progression into the SB is allowed by clockwise rotation of the overtube during insertion and counterclockwise during withdrawal. Antegrade and retrograde examinations require different types of overtubes [4]. SE overtubes are no longer available in the market, but they have been replaced by a new enteroscopy system produced by Olympus (Fig.1). In the new motorized spiral enteroscopy (NMSE) system, a reusable endoscope with an integrated electric motor is used for rotating a disposable short spiral overtube mounted on the insertion tube portion; the rotation of the spiral allows to "pleat"or "unpleat" the bowel, either on or off the insertion tube as the spiral thread rotates in a clockwise or counter-clockwise direction. In a preliminary report, NMSE appeared to offer advantages over traditional methods, in particular concerning the duration of the procedure, the depth of maximum insertion and a substantial rate (10%) of complete anterograde examinations of the small bowel from mouth to cecum [5]. Although very promising, these data will need to be confirmed in larger studies.

Balloon guided endoscopy (BGE) is performed by using an on-demand through-the-scope (TTS) balloon (NaviAid, SMART Medical Systems Ltd., Ra'anana, Israel) inserted in the working channel of the endoscope. The balloon is then inflated, allowing anchoring in the SB, and progression is obtained with repeated push-and-pull maneuvers by sliding the endoscope over the catheter. The balloon catheter can be removed for therapeutic interventions, if needed, and then reinserted for further progression of the scope [6]. In the few published studies in which BGE using a standard adult colonoscope with the aid of a TTS balloon was used for both for antegrade and retrograde procedures the diagnostic yield and depth of insertion were reported as similar to those of other forms of deep enteroscopy [7,8].

Several studies have compared the different DAE techniques with regards to the diagnostic yield, the extent of the evaluated SB and the complication rate [9,10]. Unfortunately, these studies mostly involve DBE and SBE, are retrospective, non-randomized, single-center, and performed by expert endoscopists only. Despite these methodological limitations, the recently published ESGE guidelines suggest that, although DBE seems to be associated with a deeper SB insertion, the diagnostic yield as well as the safety profile of DBE, SBE and SE are comparable and all these techniques appear similarly suitable for routine clinical practice [11] (Table 2). For all these reasons and also for the need for synthesis, in the rest of the manuscript we have considered DAE as a whole even though we are aware that the supporting literature is numerically and qualitatively in favor of DBE. The limited data available for BGE and NMSE do not allow drawing firm conclusions or comparisons with other DAE techniques.

In selected cases, exploration of the SB can also be performed in an intraoperative setting, by inserting the endoscope through the mouth of the patient or through an enterotomy. During IOE, the progression through the intestinal loops is manually assisted by the surgeon. Compared with DAE techniques, IOE is invasive and carry significantly higher morbidity and morbidity. In addition, IOE is applied to a very limited number of patients in whom it has not been possible to reach a diagnosis using other DAE methods, or when a surgical treatment is necessary [12]. For all these reasons, in the following paragraphs we will exclusively focus on DAE techniques.

DAE is a complex procedure that should only be performed by advanced endoscopists having enough experience in both diagnostic and therapeutic endoscopy. Thus, important issues are how and where appropriate training should be provided and how to achieve and maintain competence. Although there is little evidence regarding the number of procedures required for training for individual certification of DAE competence, the recent ESGE Quality Improvement Initiative on Performance Measures for Small Bowel Endoscopy [13] suggests that training should only be provided by experienced enteroscopists in units with a sufficient volume of work (50–100/year) to ensure an appropriate case mix. Trainee proficiency should be assessed by direct observation of procedures prior to being signed off by their supervisor. Although performance will vary according to the individual's endoscopic skillset, at least 10–15 cases performed under expert supervision are necessary to achieve appreciable small bowel insertion depth for anterograde DAE procedures. The retrograde insertion route is usually found to be more challenging and at least 30–35 cases are needed to achieve an appreciable, effective insertion depth.

3. DAE clinical indications

DAE is currently used for diagnosing SB disorders but especially for its therapeutic capabilities. In everyday clinical practice the main clinical indication for DAE is diagnosing and treating patients with suspected SB bleeding, whereas in patients with suspected SB tumors allows to take biopsy samples and place tattoo or clips for marking it. In patients with Crohn's disease (CD) and inherited

Table 1
Device-assisted enteroscopy systems: endoscope types and characteristics.

DAE system types	Single-balloon enteroscopy	Short-single balloon	Double-balloon enteroscopy	Double-balloon enteroscopy	Short-double balloon	Balloon-guided enteroscopy	Spiral enteroscopy	Spiral enteroscopy
Company	Olympus, Tokyo, Japan	Olympus, Tokyo, Japan	Fujifilm Corporation, Tokyo, Japan	Fujifilm Corporation, Tokyo, Japan	Fujifilm Corporation, Tokyo, Japan	Smart Medical Systems Ra'anana, Isreal	Spirus Medical, Stoughton, Massachusetts, USA	Olympus, Tokyo, Japan
Endoscope model	SIF-Q180	SIF-H290S	EN-580T	EN-580XP	EI-580BT	No specific scope	No specific scope; Compatible scopes: SIF-Q180, EN-450TS; EN-450T5/W; EN-450P5/20; EC-450BI5	SIF-YOO19 Motorized spiral overtube
Optical system: field of view	140°	140°	140°	140°	140°			140°
Optical system: depth of field	3–100 mm	3–100 mm	2–100 mm	2–100 mm	2–100 mm			2–100 mm
Outer diameter, distal end of endoscope	9.2 mm	9.2	9.4 mm	7.5 mm	9.4 mm			11.3 mm
Working length	2000 mm	1520	2000 mm	2000 mm	1560 mm			1680 mm
Instrument channel inner diameter	2.8 mm	3.2	3.2 mm	2.2 mm	3.2 mm			3.2 mm
Catheter length						NaviAid AB device 350 cm		
Overtube required	Yes	Yes	Yes	Yes	Yes		Yes	Yes
Outer diameter of overtube	13.2 mm	13.2 mm	13.2 mm	11.6 mm	13.2 mm		14.5 mm	POWER SPIRAL TUBE Fin: max outer diameter 31.1 mm Tube: outer diametrer 18.1 mm

Table 2
DAE Techniques: Pro and Cons.

Technique	PROS	CONS
Double-balloon enteroscopy (DBE)	Highest rate of complete enteroscopy	Long preparation time
Single-balloon enteroscopy (SBE)	Technically easier than DBE	Rate of complete enteroscopy lower than DBE
Balloon guided endoscopy (BGE)	No need of a spedific scope	Limited data available
Spiral Enteroscopy (SE/NMSE)	Fast examination method. Reliable controlled withdrawal	SE: overtube no longer available in the market NMSE: limited data available

Table 3
Indications for device-assisted enteroscopy.

INDICATIONS
Diagnostic
Anterograde and/or retrograde enteroscopy
Afferent limb/excluded stomach
Incomplete colonoscopy
Therapeutic
Hemostasis
Endoscopic resection
Stricture dilatation
Foreign body retrieval
Jejunal tube placement
PEJ
PEG in gastric bypass
Intestinal SEMS placement
ERCP in altered anatomy

ERCP, endoscopic retrograde cholangiopancreatography; PEG, percutaneous endoscopic gastrostomy.
PEJ, percutaneous endoscopic jejunostomy; SEMS,self-expandable metal stent.

polyposis syndromes, DAE allows to dilate fibrotic stenosis and to remove polyps. More recently DAE has also be proved to be useful in other clinical conditions: retrieving foreign bodies entrapped in the SB, direct percutaneous jejunal tube placement, intestinal stenting, cecal intubation in patients with previous incomplete colonoscopy or reaching the ampulla of Vater in subjects with altered anatomy needing endoscopic retrograde cholangiopancreatography (ERCP) (Table 3).

3.1. Suspected small bowel bleeding

Approximately 5% of all gastrointestinal bleedings can origin from SB lesions. In this subset of patients, VCE is the first diagnostic technique to be used because of its higher diagnostic yield [14] and its higher rate of complete examination of the SB. In addition, VCE can estimate the location of mucosal lesions all along the SB allowing to select the optimal DAE approach [15]. In fact, most guidelines advise the use of DAE in patients with suspected SB bleeding, especially when other tests for the study of the SB (e.g. VCE or dedicated cross sectional imaging techniques) are positive [16,17]. The most common findings in patients undergoing DAE for suspected SB bleeding is a vascular lesion. In order to distinguish between venous/capillary and arterial lesions detected during DAE, Yano et al. [18] developed a simple classification that considers the size, pulsation, presence of active bleeding and surrounding venous dilatation. This classification is useful because it allows stratifying patients for choosing the optimal endoscopic treatment.

As already demonstrated for VCE, in the setting of patients with suspected SB bleeding and particularly in those with overt bleeding, the timing of DAE is a key issue. The diagnostic yield of enteroscopy in this setting is higher if the procedure is performed close to the last bleeding episode. Shinozaki et al. [19] documented a decrease in the diagnostic yield from 84% before to 57% when DAE was performed later than 1 month after the last bleeding episodes. Thus, Japanese clinical guidelines indicate a cut-off timing of 2 weeks in order to maximize the efficacy of the procedure [20].

In selected cases, DAE may be used as first-line investigation when there is an overt massive suspected SB bleeding. In fact, one of the advantages of DAE, is that diagnosis and therapy can be carried out in the same session. In this setting, the timing is still an issue. In a retrospective report of 120 patients with overt suspected SB bleeding, urgent DBE was defined when the examination was performed within 72 h after the last visible gastrointestinal bleeding; in this study the diagnostic yield in urgent DBE (70%, 52/74) was significantly higher than that in non-urgent DBE (30%, 14/46; $P < 0.05$) [21]. Recently Rodrigues et al. [22] evaluated the role of urgent DAE in overt suspected SB bleeding, highlighting how the diagnostic yield in procedures undertaken <24, <48 or <72 h from the onset of the bleeding was similar whereas the therapeutic yield was significantly decreasing over time.

Various endoscopic techniques can be applied for hemostasis during enteroscopy: thermal (argon plasma coagulation (APC), bipolar or heater probe coagulation), mechanical (hemoclip) or combination therapy [20,23]. ESGE guidelines recommend performing endoscopic therapy during the withdrawal phase of the procedure, cautiously due to the thin wall of the SB, at higher risk of perforation than other sections of the gastrointestinal tract [11]. To reduce the risk of perforation, it is suggested to inject saline solution into the submucosa before application of APC, particularly for large (>5–7 mm) vascular lesions and to choose low wattage. In treating angioectasias, the most frequent bleeding vascular lesion, APC is safe, successful and is the most used (easy to use, low cost, limited depth of coagulation) method [23]. Dieulafoy's lesions of the SB can be treated with electrocautery, multipolar electrocoagulation, APC and clip placement when electrocoagulation is unsuccessful, with low rates of rebleeding and no adverse events [10]. A prospective multicenter study showed that despite long-term remission in most patients with SB vascular lesions who underwent endotherapy during DAE, about one-third of them had rebleeding at 1 year [24]. The presence of multiple SB vascular lesions, of comorbidities such as chronic renal failure, cirrhosis, use of antithrombotic drugs, is frequently associated with rebleeding. However, in rebleeding patients repeating DAE endotherapy may result in an improved long-term outcome in patients with refractory bleeding [25]. Moreover, long-acting somatostatin analogues may provide significant beneficial effect in patients with refractory SB angioectasia [26]. Recent studies are evaluating whether combining DAE and somatostatin analogues may improve long-term outcomes in patients bleeding from SB vascular lesions [26,27].

3.2. Small bowel tumors

A relatively small but definite rate of patients evaluated for suspected SB bleeding is finally diagnosed with a SB tumor. Although studies based on SB evaluation with VCE showed that this figure is around 5–10%, a recent systematic analysis of the literature reported that SB tumors accounted for 18.5% of patients investigated for suspected SB bleeding [28]. Similarly, in a large meta-analysis, Sulbaran et al. [29] found a higher overall prevalence of SB neoplasias ($26.36\% \pm 22.68$) in enteroscopies performed to diagnose SB disease in patients with high-risk for polyps or tumours presenting with suspected SB bleeding.

In this clinical setting VCE plays a pivotal role for the detection of a suspected SB tumor. However, a retrospective study showed a suboptimal VCE sensitivity (83.3%), with missed lesions especially in the proximal SB due to capsule rapid passage in this segment [30]. Similarly, it is known that SB tumors can also be missed by radiological techniques as well. Therefore, when the clinical suspicion of SB tumor is high, despite a negative VCE and a negative dedicated SB cross-sectional imaging study, the use of DBE as diagnostic tool seems to be justified. Nevertheless, in patients with suspected SB tumors, DAE's usefulness mostly rely in confirming the diagnostic suspicion, precisely identifying the tumor location, taking biopsy samples and marking the lesion to guide further surgical treatment, when needed. In a recent study, DBE showed a positive detection rate of 85.9%, when a SB tumor was suspected, even higher than CT scan (72.9%) [31]. In the same paper, positive biopsy rate for adenocarcinoma and lymphoma were, respectively, 71.4 and 60%; biopsy on lesions suspected for gastrointestinal stromal tumors (GISTs) are taken less frequently, due to the higher bleeding risk related to biopsy and to the lower positive biopsy rate (46.7% in a recent Japanese study) [32].

3.3. Crohn's Disease

In patients with CD, SB involvement is frequently limited to the terminal ileum, however 10% of CD patients present with lesions in more proximal tracts [33]. Magnetic resonance enterography (MRE) and VCE are the first line diagnostic examinations in this setting, allowing assessment of intra- and extra-luminal extension and severity of the disease. However, enteroscopy is a useful tool in CD patients, given the possibility of providing biopsy sampling hence a histological confirmation of the diagnosis, when the disease is suspected with other imaging modalities and when affected areas are inaccessible to conventional endoscopy [16]. The diagnostic yield of DAE in patients with suspected CD may range from 22% to 79% [34,35], being lower in patients with no previous SB imaging examinations [36].

Although DAE allows reaching areas unreachable by other techniques (in 40–50% of cases) and defining the length of bowel involvement and the presence of strictures, its main contribution is related to stricture dilatation in patients with established Crohn's disease [37]. The endoscopic examination allows direct visualization of the strictures, selective imaging through injection of contrast medium, biopsy sampling and dilatation [20]. Indeed, endoscopic dilatation is minimally invasive and may preserve intestinal length [20,38] preventing or delaying surgical interventions. A recent systematic review assessed the role of DAE in 581 SB dilatations (310 patients included), showing an 80% long-term success rate without the need for surgery during follow-up (2.5 years per patient). In this case series, DAE dilatations resulted to be relatively safe with a complication rate of 4.8% per patient and 2.6% per dilatation [39]. ESGE's recent technical guideline suggests to carefully evaluate number, location, characteristics and length of the strictures before undertaking dilatations, since those shorter than 5 cm, without deep ulcers and without significant angulation, are more likely to have a favorable long-term response [11,40]. Moreover, dilatation performed in stenoses with one or more of these features carries an increased risk of complications (namely perforation) [39–41].

3.4. Inherited polyposis syndromes

The SB is affected in 96% of patients with Peutz-Jeghers syndrome (PJS) [42]. Although VCE and MRE are currently recommended for surveillance, one study showed that MRE and DBE have a comparable diagnostic yield of polyps ≥15 mm [43]. Moreover, DAE seems to be more accurate than VCE in sizing and locating

Fig. 2. Polypectomy of a ileal polyp in PJS.

polyps [44]. The main symptoms in PJS patients arise by local complications such as bleeding, intestinal obstruction and, overall, intussusception; in addition, adenoma and cancer may occur in PJS polyps (up to 30% of polyps >20 mm in diameter [20]). Enteroscopy is therefore fundamental in PJS patients since polyp resection is currently recommended in polyps larger than 15 mm; in these patients DAE allows to spare multiple surgical resections [11] significantly decreasing the risk of developing short bowel syndrome. In high-risk patients or when dealing with large polyps that are difficult to resect endoscopically, IOE still represents a viable alternative to DAE. During DAE, polyps can be removed with hot or cold snare or biopsy forceps. En-bloc or piecemeal resection can be performed, depending on the size and the type of the polyp (sessile or stalked, with thick or thin stalk) [45] (Fig.2). Due to their low risk of degeneration, hamartomatous polyps can be resected close to the polyp head in order to reduce the risk of bleeding (easier clip placement) and perforation [11]. Sessile and large lesions should be resected piecemeal after submucosal injection with saline and diluted epinephrine. Although it is generally considered an easy procedure, submucosal injection can represent a critical issue in the SB. In fact, it should be done step-by-step and the overall amount of injected solution should be large enough to ensure a safe resection, but, at the same time, it should be minimized to avoid narrowing the SB lumen otherwise it could significantly reduce the visibility of the mucosa and the maneuverability of the endoscope, precluding the possibility of performing an endoscopic resection [11]. In order to overcome these issues, to improve the polyp visualization and to safely and effectively lift the polyp head, underwater endoscopic mucosal resection has been recently tested [46].

DAE has also been proposed for patients with familial adenomatous polyposis (FAP). Although in these patients the majority of polyps arise in the colon, with an extremely high incidence of colorectal carcinoma, adenomatous polyps can also be found in the SB and especially in the proximal SB. Thus, periodical surveillance focused on the proximal SB with both forward- and lateral-viewing endoscopes in the same session is suggested [16,47]. However, if VCE or cross-sectional imaging techniques identify jejunal or ileal polyps larger than 1 cm (found especially in Spigelman stages III/IV), DAE is usually performed to obtain targeted biopsies and accomplish local endoscopic therapy [47,48]. Interestingly, the feasibility of endoscopic submucosal dissection (ESD) in the jejunum via pocket-creation method with DBE has recently been demonstrated in a patient with FAP: in this setting, the overtube ensures stability of the technique without paradoxical movements [49].

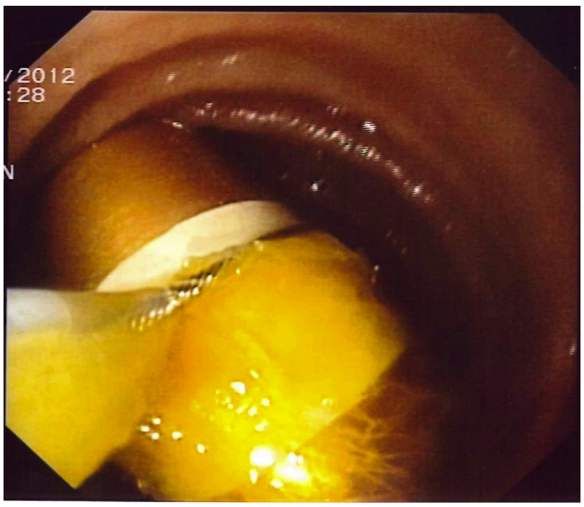

Fig. 3. Capsule retrieval.

4. Other indications

4.1. Coeliac disease

The role of enteroscopy in coeliac disease is mainly related to the assessment of possible complications. Coeliac disease can be complicated by premalignant (i.e. ulcerative jejuno-ileitis) or malignant lesions such as enteropathy-associated T-cell lymphoma and SB adenocarcinoma [50]: the possibility of biopsy by DAE is an extremely important resource in the management of these patients, even because these complications often affect the distal part of the SB [51,52].

A recent meta-analysis investigated the role of enteroscopy for the detection of SB lesions in the "complicated coeliac disease": enteroscopy resulted in a diagnostic yield of about 20% for malignancies and premalignant lesions originating from the SB mucosal layer. In patients uncompliant or unresponsive to gluten-free diet, with alarm symptoms or iron deficiency anemia, the risk of developing SB malignancies is high; in this scenario, VCE, upper endoscopy and imaging tests can be the first steps, followed by enteroscopy in order to obtain mucosal samples of focal damages or suspected lesion for histologic and molecular analysis [53].

4.2. Foreign body retrieval

Several case reports and some case series have underlined the role of DAE in retrieving foreign bodies accidentally or voluntary swallowed. Although the enteroscopic retrieval of coins, bones, dentures or migrated stents has been described, the most common foreign body retrieved from the SB is videocapsule (Fig. 3). As demonstrated in various studies, DAE is an effective (90–100 % of cases) and minimally invasive method for retrieval of retained videocapsules, avoiding unnecessary surgery [54–56]. Although surgical intervention remains the first choice in all cases in which a neoplastic disease is unequivocally suspected, endoscopic retrievals of retained capsule might allow to better clarify the cause of retention, to take biopsies, to place a tattoo and to plan the further patient management [11]. Either a polypectomy snare, a Roth net or a nitinol Dormia basket can be used to safely retrieve and remove foreign bodies [45].

4.3. Incomplete Colonoscopy

Total colonoscopy can be unsuccessful in 5–10% of patients for a number of reasons such as loop formation, post-surgical colonic adhesions, long and tortuous colon and patient's discomfort [57]. Other factors that have been found to be associated with incomplete colonoscopy are: female gender, elderly, diverticular disease and low body mass index [58]. DAE could be helpful in completing incomplete colonoscopies, by straightening the redundant colon or in case of loop formation, with a high cecal intubation rate [57–59]. A recent meta-analysis demonstrated a pooled cecal intubation rate of 97% and a mean time to cecum of 21 min, using balloon overtube assisted colonoscopy (without differences between SBE and DBE), in 667 patients with previous incomplete colonoscopy. The procedure with DAE appears to be well tolerated and safe, enabling conventional endoscopic interventions such as biopsies sampling, hemostasis, polypectomy and endoscopic mucosal resections [60]. The high rates of cecal intubation with DAE-assisted colonoscopy have been also confirmed by a small prospective randomized study in patients who were predicted to have difficult colonoscopies by using a novel scoring system, emphasizing additional benefits such as improvement in patient comfort and lower sedation requirements [61]. The stable position maintained by the overtube in the colon and in the rectum may also facilitate ESD and allows retrieval of multiple resected polyps, retracting and reinserting the endoscope from the colon [57,59].

An evolution of this first BGE is the NaviAid G-EYE system, that comprises a standard colonoscope with a permanently integrated (reprocessable and reusable), inflatable balloon at the colonoscope bending section. The balloon straightens the folds and the flexures of the colon, improving the visualization of the mucosa and leads to a high cecal intubation rate [62]. In one study, the NaviAid G-EYE system, allowed high rates of cecal intubation and the use of standard colonoscopes [62]. In another one, time to cecal intubation was similar using the balloon colonoscopy or the standard colonoscope, but withdrawal time was longer for balloon colonoscopy (8.3 ± 3.4 vs. 6.3 ± 2.6 min; $p < 0.0001$) [63]. Feasibility and safety of a motorized spiral-assisted endoscope examination of the colon (MSC) has recently been assessed in a proof-of-concept single-center trial including 30 patients with an indication for diagnostic colonoscopy [64]. MSC was shown to be feasible and safe with a cecal intubation rate of about 97%. If these preliminary data will be confirmed by larger randomized studies, in future this new instrument could become part of the available armamentarium useful in case of incomplete colonoscopies.

4.4. Endoscopic Retrograde Cholangio-pancreatography

In patients with altered anatomy, such as Whipple's pancreatoduodenectomy, Billroth II partial gastrectomy and Roux-en-Y gastric bypass, some intestinal segments are out of reach of standard endoscopes. The possibility of accessing these segments makes DAE useful in performing ERCP in post-surgical settings [59,65–68]. In these patients, ERCP with standard side-viewing endoscopes is often difficult or impossible, due to the length and the tortuosity of the surgical limbs [69,70]. DAE assisted ERCP markedly improves the success rate of reaching the papilla or the biliary anastomosis, although cannulation of naïve papilla with a forward-viewing instrument is still challenging [71]. The overall ERCP success rate in patients with altered anatomy ranges from 70% to 90%, as reported by Skinner et al. [72] in a large study of 945 procedures. Roux-en-Y gastric bypass anatomy has the lower success rate, compared to Billroth II anatomy, probably due to the different length of the surgical limbs [68,72]. The same study reports an overall major adverse event rate of 3.4% [72]. Interestingly, direct cholangioscopy using DAE has also been described, after balloon dilatation of the papilla or the bilioenteric anastomosis [73].

Recently, shorter DBE and SBE enteroscopes have been introduced for greater maneuverability in this setting, also allowing the use of all conventional ERCP accessories and catheters [74]; the

Table 4
Complication rates of DAE.

Study	Design (Country)	Centres (n)	Period of study	Number of procedures (% therapeutic)	Major complication rate (% perforation; bleeding; pancreatitis)	Major complication rate for diagnostic DBE	Major complication rate for therapeutic DBE
[98]	R (International)	10	NR	2362 (73%)	0.9% (0.3; 0.8; 0.3)	0.8%	4.3%
[86]	R (USA)	9	2004-2008	2478 (35%)	0.9% (0.4; 0.2; 0.2)	0.6%	0.5%
[87]	P (Germany)	62	2004-2007	2245 (NR)	1.2% (0.1; 0.3; 0.2)	NR	NR
[99]	R (UK)	6	2005-2010	950 (37%)	0.8% (0.3; 0.3; 0.1)	0%	2.3%
[85]	SR (International)	NR	2001-2011	9047 (NR)	0.7% (0.2; 0.2; 0.06)	NR	NR

DBE: double balloon enteroscopy; NR: not reported; P, prospective; R: retrospective; SR: systematic review.
Gerson et al. included 65 (3%) DBE- endoscopic retrograde cholangiopancreatography.
Modified from Rondonotti E, et al. [100]. Data from studies specifically designed to assess complication rates of DBE.

3.2 mm working channel of these new instruments also allows the insertion of biliary self-expanding metal stents [75,76]. SE have also been applied in ERCP setting: in a recent study by Ali et al. [77] the overall success rate was 86% despite a long time procedure (3 h median time).

4.5. Intestinal stenting and direct percutaneous endoscopic jejunal tube insertion

Self-expandable metallic stent (SEMS) placement deep in the SB or in surgically reconstructed intestine is challenging because of the long length of the organ and the angulated bifurcation of surgically reconstructed intestine. Additionally, SEMS placement is impossible through the working channel of balloon enteroscopes, because it is too small and too long for the stent device. A trick proposed to overcome this issue is the over-the-wire technique: after reaching the malignant intestinal obstruction with the help of DAE, the overtube and a guidewire are left in place while the enteroscope is removed, eventually the metal stent is inserted over the guidewire through the overtube, under fluoroscopic control. This technique allows enteral insertion of SEMS in intestinal segments previously excluded from endoscopic access [78].

The newly developed shorter enteroscopes and the through-the-scope (TTS) balloon-assisted enteroscopy using standard endoscopes with a large working channel also allow the deployment of SEMS in the biliary tree and deep SB in patients with surgically altered anatomies [79,80]. However, in one of the few studies of TTS balloon-assisted enteroscopy, the target was successfully reached in 23 (60.5%) out of 38 procedures, with 22 (95.7%) technical success and 21 (91.3%) clinical success achieved [81]. Given the lower overall success rate, TTS BAE is, at present, an affordable alternative to DAE, particularly in centers where DAE is not available.

Enteral nutrition has an important role in reducing morbidity and mortality in debilitated and critically ill patients. Percutaneous endoscopic feeding tube placement (PEG) provides safe enteral access, without the need for surgical gastrostomy. Since its inception in the late 1970s, PEG has become a standard procedure. However, not all patients requiring enteral support are suitable candidates for gastrostomy tube placement. Specifically, patients with gastric motility disorders, gastric outlet obstruction, and/or chronic, recurrent aspiration may benefit from more distal placement of the tube. The available options for these patients are limited: nasojejunal tube, jejunal enteral tube placed though a PEG surgical jejunostomy, and direct radiologic endoscopic and/or jejunal feeding tube placement (DPEJ) [82]. Although DPEJ can be performed by combining PE and fluoroscopy, it remains a technically challenging procedure with significant failure rates. DAE, with its ability to provide controlled SB intubation may facilitate DPEJ. In a prospective series of 10 cases the DBE-assisted DPEJ was successful in all the 9 cases in which the transillumination was obtained [83]. The authors also provided some technical tips and tricks to make the procedure effective and easier, such as the use of a 21 Gauge needle as 'seeker' needle and snaring of it in order to anchor jejunal loop position during insertion of the DPEJ trocar. Although these data appear promising, larger comparative studies are required to clearly establish any advantages over the originally described push enteroscopy method.

5. DAE safety profile

DAE is generally considered a safe procedure provided that some precautions are taken such as, for example, adequate, safe sedation with anesthetist support, the use of fluoroscopy during the learning curve, in patients with altered anatomy, or in those with small-bowel strictures, and the constant use of carbon dioxide (CO_2) for insufflation. Moreover, when therapeutic interventions are performed, additional specific safety measures are needed to prevent complications [11]. As reported by ESGE guideline for SB flexible enteroscopy published in 2008, contraindications of DAE are similar to those for conventional upper GI endoscopy or colonoscopy [84]. The rate of adverse events reported in literature is low and commonly associated with therapeutic procedures being bleeding and perforation the most frequent [11,45,85–88]. (Table 4) Post-procedure abdominal pain is significantly reduced with the use of CO_2 insufflation [89]. A meticulous evaluation of the patient history is mandatory with particular attention to medications (i.e. antiplatelets and anticoagulants), comorbidities, previous abdominal surgery, previous radiation therapy, radiological imaging [11,20,90]. Risk factors associated with perforation are: altered surgical anatomy [86,87], resection of large (e.g. > 30 mm) [45] polyps, inflammatory bowel disease [85], active inflammation or sharp angulation of strictures [11].

Procedure-related adverse events are similar to those for upper and lower gastrointestinal endoscopy (e.g. perforation, bleeding, aspiration pneumonia, infection, and mucosal damage) while acute pancreatitis is unique to DAE. Acute pancreatitis (usually from mild to moderate) is a particular adverse event mostly related to antegrade enteroscopy with a reported rate of 0.3% [11]. Interestingly, although post-DAE acute pancreatitis is relatively uncommon, asymptomatic hyperamylasemia is frequently observed (up to 50–60% of patients undergoing anterograde DAE) and it appears to be associated with longer procedures and interval time between the first and the second inflation [11,91,92]. Although the cause of acute pancreatitis is still uncertain, two main mechanisms have been postulated: (1) the reflux of duodenal fluids into the pancreatic duct due to the increased duodenal intraluminal pressure during DAE and (2) mechanical straining of scope, overtube, or balloon during push-and-pull-maneuvers exerting some torsion on parts of the mesentery and resulting in traumatic injury to the

pancreas [11]. Therefore, the risk of pancreatitis may be reduced by a careful, atraumatic technique, minimizing mechanical stress to the papilla and the pancreas, and avoiding inflation of balloons within the proximal duodenum, together with a slow retraction of the scope [11,93].

Enteroscopy is considered a safe procedure even in the elderly. Published studies from Europe, USA and China confirmed a low complications rate either procedure- or sedation-related), regardless of patient age [94–97]. The use of DAE in the elderly is justified by the increased diagnostic yield in this population which leads to an improvement in the management of this group of patients. The study by Sidhu et al., comparing patients older than 70 years and younger, demonstrated a higher yield ($p = 0.008$) with DBE in the elderly group [97]. In agreement with these findings, Hegde et al. found that the elderly patients more frequently require endoscopic therapy and present with angioectasias [95].

As underlined by ESGE guideline [11], DAE procedures are lengthy and require adequate SB distension for effective lesion visualization and treatment. Furthermore, both the enteroscope and overtube need to be advanced and withdrawn repeatedly over the course of the procedure; this manipulation of the SB, its mesentery, and adjacent viscera may cause discomfort/pain. This may impact on the patient's compliance and the overall effectiveness of the procedure. In addition, patient movement during DAE can make the procedure more technically challenging. Adequate safe sedation during DAE is therefore highly advantageous being conscious sedation, deep sedation, and general anesthesia all acceptable alternatives. The complexity of the procedure, clinical factors and local organizational protocols contribute to the choice of the type of sedation. Currently available data suggest that the sedation regimen does not appear to generate differences in SB insertion depth and overall DAE procedure success rates. Not enough data currently exist that relate to different DAE techniques or to different insertion routes according to the sedation regimen [11]. Together with procedure-related events, even sedation-related complications should be kept in mind: aspiration pneumonia and infections, hypotension, oxygen desaturation/hypoxia, hypoventilation, bradycardia, hypertension, arrhythmia, and allergic reactions [11,90]. Sedation-related complications may occur in about 0.5% of cases [87].

6. Conclusions and future directions

DAE represents a major milestone in the evolution of SB endoscopy, both diagnostic and therapeutic. DAE complements the limitations of capsule endoscopy; however, it is invasive and, since it requires a significant investment in terms of time and other resources, DAE should mainly be a technique with therapeutic purposes. Appropriate training as well as high procedure volume are relevant factors for mastering DAE and for ensuring technical success and clinical effectiveness.

The evolution of the enteroscopy technique is a challenge for the future and could be facilitated by new enteroscopes models. These prototypes need a correct clinical and safety assessment especially for the more complex procedures of enteroscopy. Large prospective, multicenter studies are needed to assess whether the use of DAE leads to improved patients' long-term outcomes and affects the natural history of SB disorders.

Conflict of interest

All authors have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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