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Review

Navigating celiac disease with small bowel capsule endoscopy: current state and future horizons

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***Abstract*:** Celiac disease (CeD) is a widely diffused chronic autoimmune disorder triggered by the ingestion of gluten, in genetically predisposed individuals. Small bowel capsule endoscopy (SBCE) plays a pivotal role as a noninvasive tool for diagnosing and monitoring CeD. This review aims to summarize the current and potential future role of SBCE in the field of CeD. SBCE offers the advantage of visualizing the entire small bowel, allowing the extent of disease involvement to be described. According to international guidelines, SBCE has a defined role in cases of inconclusive histopathology or when clinical suspicion persists despite negative duodenal biopsies. To date, more and more interest is shown toward its role in monitoring CeD, specifically in terms of mucosal healing, early detection of complications such as ulcerative jejunitis, or performing differential diagnosis among other small bowel diseases that mimic CeD. With the rise of artificial intelligence systems being applied in this field, the future role of SBCE in CeD is expected to improve diagnostic accuracy and streamline the evaluation process, allowing its use as a routine tool for monitoring and early diagnosis of CeD-related complications. The environmental impact of SBCE is still under debate, but increasing evidence is suggesting ways to apply circular economy to the capsule lifecycle, turning it into a more sustainable device. In conclusion, SBCE is increasingly recognized as a critical tool in the diagnosis and monitoring of CeD.

Keywords: celiac disease, celiac disease diagnosis, celiac disease monitoring, novel technologies, SBCE sustainability, small bowel capsule endoscopy

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Introduction

Celiac disease (CeD) is a chronic autoimmune disorder of the small bowel (SB) that affects genetically predisposed individuals, carrying the HLA DQ2 and or DQ8 haplotypes, in response to the ingestion of gluten.[1,2]

CeD stands as one of the most common autoimmune diseases, with an estimated prevalence of 1% of the global population.[3]

The clinical presentation of CeD can vary widely among individuals, ranging from typical gastrointestinal symptoms (e.g., chronic diarrhea, abdominal bloating, and weight loss) to extraintestinal symptoms (e.g., headaches, skin rashes, anemia, osteoporosis, and depression).[4] The diagnosis of CeD entails specific antibodies, the presence of macroscopic signs of duodenal atrophy (smooth or scalloped appearance of the SB mucosa, mosaicism, and granular mucosa, flattened or absent folds, and visible transparency of underlying blood vessels due to mucosal thinning), and the hallmark of the disease represented by villous atrophy and crypt hyperplasia in the SB mucosa.[1,5–7]

In a small percentage of patients, CeD can be present without antibody positivity (named seronegative CeD), whose diagnostic workup is complex,

being mandatory to rule out other causes of villous atrophy.[8]

Furthermore, in a subset of individuals, CeD may manifest as refractory CeD (RCeD), which represents a challenging and often severe variant of the disease. RCeD is defined by persistent or recurrent symptoms and intestinal villous atrophy despite strict adherence to a gluten-free diet (GFD).[2] It is further categorized into two subtypes: type 1 RCeD and type 2 RCeD according to the presence of an aberrant, clonal intraepithelial lymphocyte population.[9] To distinguish between subtypes of RCeD and to rule out the presence of enteropathy-associated T-cell lymphoma (EATL), a comprehensive diagnostic approach is imperative.[10]

The initial diagnostic workup of type 2 RCeD should also incorporate SB imaging using SB capsule endoscopy (SBCE), along with computed tomography or magnetic resonance enterography. SBCE enables clinicians to visualize the SB and detect any suspicious lesions or abnormalities that may be indicative of malignancy or severe inflammatory processes.[11]

Since EATL is a rare but aggressive form of non-Hodgkin lymphoma, several diagnostic modalities, including flow cytometry, immunohistochemistry, and T-cell receptor rearrangement studies, play pivotal roles in this diagnostic process.[10] It is worth emphasizing that the accurate interpretation of these studies necessitates collaborative efforts between gastroenterologists and expert hematopathologists. In summary, RCeD represents a rare yet more severe manifestation of CeD, often requiring immunosuppressive treatments, primarily involving agents such as budesonide.[9]

In addition to RCeD, untreated or undiagnosed CeD carries a spectrum of potential complications (e.g., osteoporosis and anemia).[10] One notable concern is the heightened risk of malignancies (in addition to the aforementioned EATL), such as SB adenocarcinoma, and an increased risk of certain extraintestinal cancers, including thyroid cancer and esophageal cancer, has been observed.[10,12]

The advent of SBCE has provided insights into mucosal damage that was previously challenging to attain with traditional diagnostic tools, supporting the diagnosis and monitoring of diseases affecting the SB. In the field of gastroenterology, SBCE represents a significant technological advancement, offering a noninvasive means of visualizing the gastrointestinal tract.[13,14] SBCE made its debut in the early 21st century, marking a notable milestone in medical imaging. The first-generation video capsules were developed in the early 2000s, and subsequent iterations have incorporated increasingly sophisticated technologies.[15]

The driving force behind the creation of capsule endoscopy stemmed from the need for a less invasive and patient-friendly alternative to traditional endoscopic procedures. Conventional enteroscopy often entails uncomfortable insertion of a long, flexible tube through the mouth or anus, causing discomfort for patients and limitations in thoroughly examining the SB.

On the contrary, in SBCE patients, the capsule is ingested, which then travels through the digestive system, capturing high-quality, real-time images along the way. These images are wirelessly transmitted to an external data recorder worn by the patient or recorded in the capsule itself, enabling healthcare providers to review and analyze the footage at their convenience.[16]

Video capsule endoscopy has found diverse applications in clinical practice.[13] As previously mentioned, it is particularly useful for evaluating the SB, an area that was historically challenging to access using conventional endoscopy. This capability has proven invaluable in diagnosing and monitoring conditions such as obscure gastrointestinal bleeding, Crohn's disease, SB tumors, and—of course—CeD.[13,17,18]

The main complication associated with SBCE is retention, which occurs when it remains in the SB for more than 15 days. Overall, the SBCE retention rate is low, approximately 2.1%. Limited data are available regarding the retention rate in SBCE performed for CeD, but it appears to be comparable to the general rate.[19]

In the present review, we discuss the actual and future uses of SBCE in CeD.

Celiac disease diagnosis

As aforementioned, SBCE permits direct visualization of the entire SB, providing an opportunity to assess mucosal surfaces inaccessible to traditional diagnostic methods such as upper endoscopy. CeD can affect the SB mucosa in a

discontinuous manner, leading in some cases to biopsies that do not accurately reflect the actual presence of the disease.[20] Furthermore, the technique's ability to detect subtle mucosal changes could allow for the identification of early stage CeD and aid in the differentiation from other gastrointestinal disorders presenting similar clinical features. Adherence to dedicated Delphi consensus statements can enhance differential diagnosis accuracy.[7,21] For example, in the case of Crohn's disease typical findings are those reflecting severe mucosal inflammation with ulcerative and erosive lesions, rather than atrophy.

To date, SBCE is not recommended to diagnose CeD,[13] due to the fact that SBCE is still inferior to histology, with 89% (95% CI (82%–94%)) sensitivity, 95% (95% CI (89–98%)) specificity, 12.90 (95% CI (2.89–57.58)) LR(+) and 0.16 (95% CI (0.1–0.25)) LR(–) as shown in a metanalysis conducted by Rokka and Niv.[22] Moreover, studies that deal with this topic might overestimate SBCE performance due to the high pre-test probability of CeD in the participants with antiendomysial antibody (EmA) or high-titered antitransglutaminase antibodies (tTG).[22–24]

Nevertheless, the most recent European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend using SBCE for CeD in cases of diagnostic uncertainty (e.g., seronegative CeD) or in nonresponsive or refractory CeD, both for disease diagnosis and monitoring.[13]

Regarding equivocal diagnoses, the most frequent cases include seronegative CeD, positive CeD serology without villous atrophy, contraindications to undergoing esophagogastroduodenoscopy, and clinical signs and symptoms of malabsorption without villous atrophy. In these situations, SBCE may play a role in identifying distal atrophy, detecting alternative underlying diseases (e.g., Crohn's disease and autoimmune enteropathy), and monitoring uncertain cases to assess their progression. Table 1 presents the SBCE diagnostic yields for these specific cases. The literature still lacks a proper classification of the specific mucosal appearances at SBCE for the main atrophic enteropathies.[24–28]

Table 1. Reported diagnostic yield of SBCE in equivocal CeD cases.

Group	SBCE diagnostic yield*
Seronegative villous atrophy	28%[28] – 31.6%[26] – 73.7%[29]
Marsh 1-2 with positive serology (potential CeD)	7%[28] – 55%[27] – 69.2%[29]
Contraindications to esophagogastroduodenoscopy	50%[29]
Malabsorption without atrophy	44.4%[29]

*Defined as signs of atrophy (e.g., scalloping, mosaic mucosal pattern, reduction or absence of Kerckring's folds); from the lowest to the highest value reported in literature.
CeD, celiac disease; SBCE, small bowel capsule endoscopy.

Celiac disease monitoring and treatment evaluation

The long-term management of CeD necessitates lifelong adherence to a strict GFD, which currently constitutes the sole effective therapy. SBCE might serve as a valuable tool for assessing treatment response by visualizing mucosal healing and determining the degree of villous restoration.

This is particularly relevant in circumstances such as seronegative CeD, where clinical and mucosal response to GFD is crucial to confirm the diagnosis. To date, the only accepted method is a rebiopsy approach with histopathologic confirmation of mucosal improvement.[8] SBCE could play a complemental role to evaluate and monitoring these patients, as highlighted in the recent work of Chetcuti et al.[25] where it has been shown that patients with seronegative CeD with a positive SBCE for atrophy or active disease are at higher risk of developing adverse events and complications compared to the ones with a negative capsule. Furthermore, a positive association was identified between mortality and the extent of atrophy, emphasizing the prognostic significance of SBCE in such cases and its utility as a monitoring instrument to gauge the response to therapeutic interventions and management decisions. This particular aspect has been highlighted in a recent study, where SBCE has shown promise in quantifying the extent of villous atrophy, and a CeD score has been proposed to provide a more objective way of quantifying mucosal features of CeD and a comparison of the severity of CeD between different SBCEs.[29]

We propose an algorithm for the role of SBCE in the management of CeD patients (Figure 1) where the use of SBCE in patient monitoring could be extended to selected CeD patients (e.g., with persistent symptoms), helping to customize

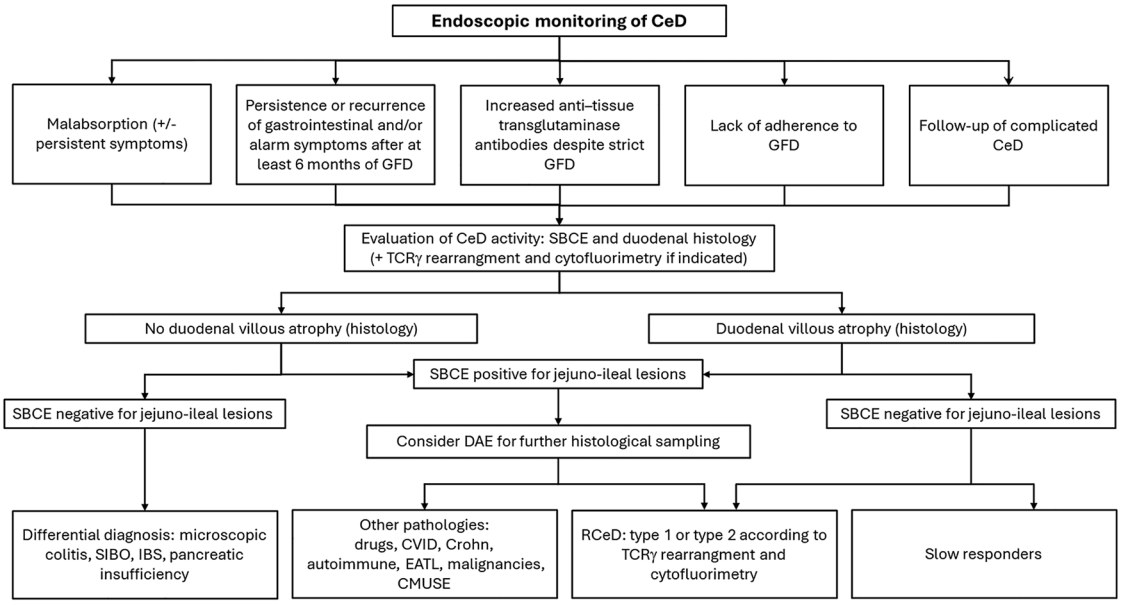

Figure 1. Algorithm for the role of endoscopy in CeD monitoring.
CeD, celiac disease; CMUSE, cryptogenic multifocal ulcerous stenosing enteritis; CVID, common variable immune deficiency; DAE, device-assisted enteroscopy; EATL, enteropathy-associated T-cell lymphoma; GFD, gluten-free diet; IBS, irritable bowel syndrome; RCeD, refractory celiac disease; SBCE, small bowel capsule endoscopy; SIBO, small intestine bacterial overgrowth; TCRγ, T-cell receptor γ

treatment strategies and identify nonresponsive cases that may require further intervention as suggested in the recently published work of Elli et al.[30]

In cases where patients exhibit persistent symptoms and/or elevated antibody titers, nonadherence to the GFD should first be ruled out through nutritional assessment and testing for gluten peptides in stool or urine.[30] If strict adherence to the GFD is confirmed, SBCE and, if necessary, esophagogastroduodenoscopy should be performed. The available literature does not provide a standardized timeframe for when persistent antibody levels in asymptomatic patients should be considered pathological. As a result, a waiting period of at least 24 months is commonly observed. For additional details, refer to Figure 1.

That being said, to date, while it has been shown a correlation between atrophy and clinical parameters such as bone mineral density,[31] SBCE it is not recommended for routine use due to the lack of therapeutic options other than a GFD. Maybe this could change once pharmacological treatments for CeD become available.

Detection of complications

Complications of CeD, such as RCeD, ulcerative jejunitis, and SB malignancies, are often challenging to diagnose using conventional techniques because of their common localization in the distal SB. SBCE enables the identification of such complications, allowing for early intervention and improved patient outcomes.[32] In particular, SBCE can be more accurate than SB radiology in detecting premalignant lesions, such as ulcerative jejunoileitis and EATL, as well as the less common SB adenocarcinoma.[30] In Figure 2, we present examples of varying degrees of SB atrophy, different morphologies of ulcerative jejunoileitis, and the possible appearances of T-cell lymphoma and SB adenocarcinoma on SBCE.

A comprehensive evaluation of the SB, particularly during the initial years post-diagnosis, is imperative for older and symptomatic patients with suspected complicated CeD (CCD).[33] Assessing the extent of the disease is crucial in these patients because it has been shown that patients with a CCD tend to have a large portion of the SB involved and a corresponding worse prognosis (RCeD type 2 vs type 1 vs uncomplicated CeD).[34]

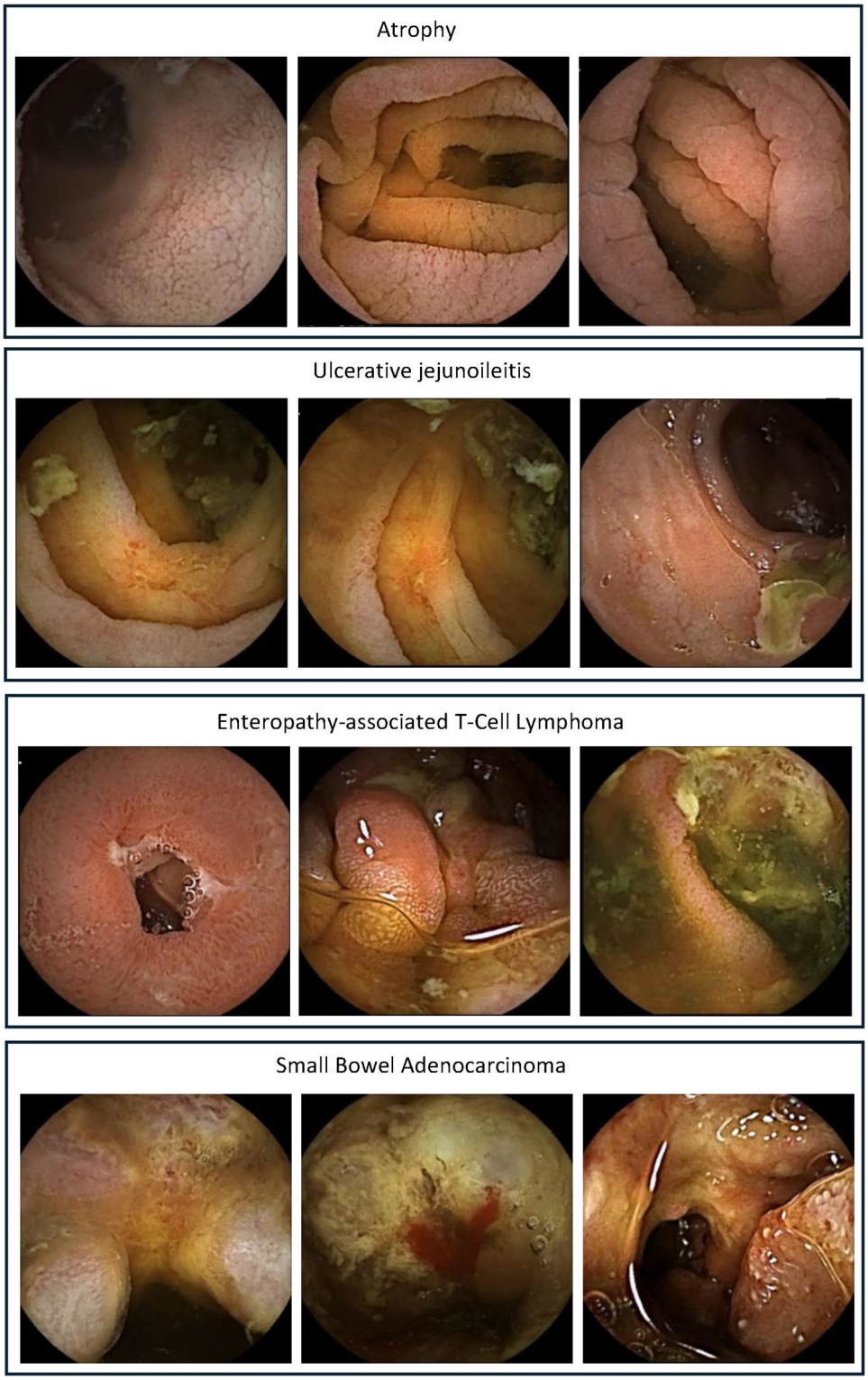

Figure 2. SBCE frames showing some examples of CeD-related small bowel atrophy and complications (i.e., ulcerative jejunoileitis, enteropathy-associated T-cell lymphoma, and small bowel adenocarcinoma).
CeD, celiac disease; SBCE, small bowel capsule endoscopy.

In addition, in situations involving CCD, it is suggested that SBCE should be prioritized as the initial approach for detecting complications and identifying patients in need of device-assisted enteroscopy, necessary for a histologically definitive diagnosis.[32]

Patients with RCeD require close clinical and histological monitoring to assess their response to treatment (corticosteroids and immune-modulating medications) and rule out further complications such as EATL. Repeated SBCE can play a pivotal role in this periodic monitoring, given its low invasiveness, high safety, and complete SB visualization, but the appropriate surveillance interval is still uncertain and may be different based on the type of ReCD.[30,34] A worsening or only a slight improvement in the severity of the disease (e.g., extent and severity of atrophy) can be considered an indication of escalation therapy.[30]

The application of enteroscopy for the identification of malignant and premalignant lesions within the SB in individuals afflicted with CCD is crucial, and it is evident that contemporary research endeavors are converging in this particular investigative trajectory, as highlighted in a recent metanalysis.[32]

Small bowel capsule endoscopy limitations

Despite its advantages, SBCE has certain limitations. The first significant drawback of SBCE lies in its limited maneuverability. In fact, currently available SBCE systems rely on bowel movement for transportation. However, even in individuals with normal motility, bowel transit time can vary significantly, potentially causing relevant sections to pass by too quickly, or others to be missed because of battery exhaustion, therefore affecting the thoroughness of examination.

Specifically, some bowel segments are particularly difficult to explore because of the sharply angulated tracts where capsule propulsion is faster, such as the proximal SB, where a higher miss lesion ratio has been reported.[18] In addition, without the capability for maneuverability, a comprehensive examination of the extensive inner surface of the stomach remains a challenge.[35]

The development of effective locomotion systems in capsule endoscopy is a critical focus area, aiming to enhance the performance and capabilities of these miniature devices. Key criteria and mechanisms are under exploration to optimize capsule movement within the gastrointestinal tract.

The most advanced approaches in addressing these limitations involve the development of magnetic fields to guide a videocapsule containing magnetic components. This method harnesses an external magnetic field generated by either electromagnetic coils or permanent magnets to propel the capsule within the gastrointestinal tract.[36,37]

Another issue is represented by the inaccurate localization of lesions visualized at SBCE. In fact, it is time dependent as it relies on the capsule gastric and SB transit times, which are far from precise. Considering that SBCE often guides the insertion route of the following exam, usually a device-assisted enteroscopy, it appears self-explanatory that the more specific the lesion localization is, the easier and faster the definitive diagnosis could be made.[18] According to scientific literature, anterograde device-assisted enteroscopy is the preferred method with a higher diagnostic yield; however, available studies suggest following a SBCE transit time-based according to which a retrograde approach should be used if the lesion was detected after more than 2/3 of the capsule transit time from ingestion to cecal visualization (positive and negative predictive values were 94.7% and 96.7%, respectively).[38]

Lastly, in the realm of cutting-edge academic exploration, ongoing research is dedicated to addressing even more complex medical challenges, which include noninvasive biopsy methods through SBCE and the use of "tattoos" to mark suspicious lesions for future surgical guidance. These developments promise to enhance minimally invasive diagnostic and treatment approaches. In this setting, a group of Chinese researchers is currently pioneering a groundbreaking design for a magnetically actuated biopsy capsule robot, which is based on rectangular coils and would enable precise control of both locomotion and biopsy procedures.[39,40]

Future challenges

Ongoing advancements in video capsule technology, including improvements in image resolution, battery life, artificial intelligence (AI)-enhanced video analysis, and maneuverability, hold promise for enhancing the utility of enteroscopy in CeD management.

Further research is needed to establish standardized protocols for utilizing SBCE in different clinical scenarios, optimizing its diagnostic accuracy and clinical impact.

AI-enhanced video analysis, for example, could be a potential solution to the prevailing issue of poor inter- and intra-observer agreement in the context of SBCE.[41]

AI is undergoing rapid advancement across various medical domains, with a notable surge in research activities within the area of gastrointestinal endoscopy.[42] It presents an opportunity for standardized, observer-independent evaluation of images and videos, thereby alleviating the workload on human operators.

Numerous algorithms boasting high levels of accuracy have been proposed for the analysis of SBCE; among these, convolutional neural networks (CNNs) have emerged as the predominant deep learning algorithm for image analysis in the field of endoscopy, demonstrating outstanding performance in the detection of esophageal, gastric, and colonic lesions.[43–45] Ding et al.[46] also confirmed these notable results in the field of SB endoscopy. They trained and subsequently validated a deep CNN-based algorithm model to recognize common SB pathologies, achieving a sensitivity and specificity of 99.9%. This performance surpassed that of human reviewers, who identified abnormalities with a 74.6% sensitivity, and significantly reduced the reading time from 96.6 min to 5.9 min.

It is worth noting that there is an ongoing debate regarding the potential role of AI as a secondary reader when addressing uncertainties posed by human readers. However, it is imperative to underscore that this dimension remains relatively uncharted territory within the current landscape of AI research, primarily due to the prevalent focus on AI as a primary or "first reader" in the majority of existing studies.[47]

In the field of enteropathies, research on AI applications has focused on systems enhancing textural features of SB mucosa in capsule endoscopy, capsule motility, automata-based polling, and the use of CNN algorithms to identify CeD features on SBCE videos.[48] Notably, a recent study by Zhou et al.[49] demonstrated that a deep CNN architecture (GoogLeNet) could distinguish SBCE videos of CeD patients from those of healthy individuals based on villous atrophy, while also providing a quantitative assessment of the pathology and its severity. This specific feature, integrated as an auxiliary reading system, could be beneficial for gastroenterologists in monitoring CeD patients, especially RCeD, as previously mentioned, as it allows for a standardized and faster evaluation of their trend. Nevertheless, there exist several noteworthy shortcomings that must be addressed before CNNs can be seamlessly integrated into clinical practice.

Sustainability considerations

Cost-effectiveness of SBCE in diagnosing CeD is a critical factor in its adoption as a standard diagnostic tool. While the initial costs associated with SBCE may appear higher compared to traditional upper endoscopy, a comprehensive analysis reveals that SBCE can lead to significant long-term savings and improved patient outcomes. The upfront cost of SBCE typically includes the price of the capsule, the equipment for image acquisition, and the analysis of the recorded data. In Italy, the cost of performing SBCE on inpatients is estimated at €1,775.90, while for outpatients, the cost reduces to €800–€1,000.[50,51]

In contrast, traditional upper endoscopy with biopsies involves costs related to sedation, facility fees, and potential complications associated with invasive procedures, which in Italy (Lombardy region) is reimbursed at €172.95.[51]

Despite these initial expenses, SBCE's ability to provide a noninvasive diagnostic option can reduce the overall need for multiple invasive procedures, thereby mitigating long-term costs. Furthermore, early and accurate diagnosis through SBCE can lead to timely interventions, such as dietary changes, which may ultimately reduce the incidence of complications and associated healthcare costs.

Regarding environmental sustainability, the single-use nature of capsule endoscopy poses a challenge. The scientific community is working toward defining a standardized approach to report the carbon footprint of endoscopic procedures. A recent study by Pioche et al. addressed the gap in identifying the net greenhouse gas emissions of SBCE, calculated in kilograms of carbon dioxide equivalents ($kgCO_2e$), with an overall carbon footprint estimated at 20 $kgCO_2e$. Moreover, the study explored the potential benefits of capsule

retrieval and recycling through simulations based on data available in the literature, as there are currently no ongoing recycling programs. Theoretical yearly emissions reductions of 1854 kgCO_2e (equivalent to 8427 km driven in a fossil-fuel car) and 2251 kgCO_2e (equivalent to 10,232 km driven in a fossil-fuel car) were identified with magnet and capsule recycling, respectively.[52]

Conclusion

In conclusion, SBCE plays a valuable role in the diagnosis and management of CeD by offering a noninvasive, comprehensive visualization of the entire SB, especially in case of seronegative CeD or RCeD, where traditional diagnostic methods may fall short. While not a replacement for biopsy, SBCE serves as a complementary tool, enhancing the clinician's ability to assess disease extent, monitor response to treatment, and identify potential complications. Further research is warranted to refine its indications and optimize its integration into clinical practice. Ongoing developments, including the integration of AI and enhancements in capsule maneuverability and functionality, might further boost its relevance.

In addition, although a few studies reported a higher environmental impact of SBCE, the debate about its contribution to the planet's sustainability is still open.[52]

Looking ahead, it will be crucial to delve deeper into this challenge to collect more quantitative data to inform decision-making. This body of evidence will offer a clearer understanding of how sustainable these technologies are over time and whether SBCE can contribute to a more sustainable future by applying circular economy principles to care delivery.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Matilde Topa: Conceptualization; Writing – original draft; Writing – review & editing.

Mattia Corradi: Writing – original draft.

Luca Elli: Supervision; Writing – review & editing.

Yasmine Raji: Writing – original draft.

Emanuele Lettieri: Writing – original draft.

Nicoletta Nandi: Writing – review & editing.

Lucia Scaramella: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

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