# Wireless Capsule Endoscopy of the Small Intestine in Children

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**ABSTRACT**

Wireless capsule endoscopy (CE) for the diagnosis of small-bowel disease has been in clinical use for more than a decade, and is no longer an emerging technology, but rather one that has reached fruition. This noninvasive technology has been readily embraced by both physicians and patients. Used in the diagnosis of inflammatory bowel disease, for locating sources of obscure gastrointestinal bleeding, and for assessing small-bowel polyp burden in polyposis syndromes as well as for less common indications, CE has transformed the diagnostic algorithms of small-bowel investigations. Although already in widespread use, the technology incorporated into the various CE platforms continues to improve and expand. Here, we briefly review the indications, limitations, and advances in video capsule technology, with an emphasis on its use in pediatrics.

**Key Words:** bleeding, Crohn, inflammatory bowel disease, pediatric, PillCam, polyposis

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Since its original approval by the Food and Drug Administration (FDA) in 2001, capsule endoscopy (CE) has provided gastroenterologists with a safe, accurate, and noninvasive method of viewing the intestinal mucosa. The capsule, which consists of a camera, light source, battery, and radio transmitter packaged into a pill-sized capsule, has undergone several improvements. These include improved optics, wider angle of vision, increased battery life, increased dynamic imaging speeds, and better real-time viewing, as well as other hardware and software improvements, which have led to improved quality of images in addition to enhanced accuracy and speed of interpretation to increase diagnostic yield. There are a number of commercialized capsule endoscopes, but to date the vast majority of procedures have used the Given Imaging (Yoqneam, Israel) platform. PillCam SB is FDA approved for use in children from 2 years of age, but case reports have demonstrated uneventful use in younger children, down to 8 months (1), or 7.9 kg (2). The aim of the present review is to provide an up-to-date, concise summary of the indications, bowel preparations, and complications of CE, with an emphasis on use in pediatrics.

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## METHODS

MEDLINE and Cochrane databases were searched for studies including the term "capsule endoscopy" between 2004 and November 2014. Few prospective randomized pediatric studies are available in the literature, and most published reports are of small- to medium-sized case series from single or multiple centers, or small comparative studies. As such, the relevant evidence is based largely on the descriptive data from pediatric series and trials, as well as more extensive data from adults.

## CE TESTING

The CE platform includes the capsule, an external sensor worn by the patient, and a recorder device carried on a shoulder strap during the full recording period. Patients are instructed to swallow the capsule with water. Swallowing of the capsule has been shown to be feasible in children <4 years old (3). Practicing swallowing candy or jellybeans of gradually increasing size has been used to help children prepare for the test (4). Patients who are unable to swallow the capsule (because of age constrictions, swallowing difficulty, or aspiration risk) or with poor gastric emptying may have the capsule placed endoscopically with the use of a basket, snare, or a dedicated introducer.

## INDICATIONS

CE has been shown to have added value in the investigation of obscure gastrointestinal bleeding (OGIB), in inflammatory bowel disease (IBD), and in the surveillance of polyposis syndromes. In a meta-analysis of 723 pediatric CEs, Cohen and Klevens (5) found that the most common indications in children were suspicion of Crohn disease (CD) and investigation of IBD (54%), OGIB and iron deficiency anemia (17%), abdominal pain and diarrhea (13%), and polyposis (11%). Of these pediatric CEs, 65% yielded positive findings. This differs from adults in whom the most common indication, from a review of 22,840 reported CEs, is OGIB (66%), followed by investigation of clinical symptoms (10.6%) and of known or suspected IBD (10.4%) (6). In children <8 years old, in whom CD is less common, OGIB was the most common indication (36%) (5). Table 1 provides a list of indications in which CE has been used (more common being lymphangiectasia and vascular malformations and less common indications and findings including Meckel diverticulum). Of note, celiac disease suspected based on the serological studies and symptoms or signs, but not identified in duodenal biopsies, may be identified by the characteristic scalloping of duodenal folds on CE (7). In addition, findings in CE are not limited to the small intestine, and often gastric and colonic disease missed in other studies may be noted during the examination (8).

TABLE 1. Indications for pediatric capsule endoscopy and selected findings

| |
|---|
| Intestinal inflammation |
| Crohn disease |
| Celiac disease |
| Obscure intestinal bleeding and iron deficiency anemia |
| Vascular malformations |
| Angiodysplasia |
| Blue rubber bleb nevus syndrome |
| Arteriovenous malformations |
| Cavernous hemangioma |
| Hemangioma |
| Vasculitis (Henoch-Schönlein purpura) |
| Meckel diverticulum |
| Intestinal parasites |
| Protein-losing enteropathies |
| Intestinal lymphangiectasia |
| Miscellaneous |
| Peutz-Jeghers syndrome |
| Familial and nonfamilial polyposis |
| Eosinophilic enteropathy |
| Infantile myofibromatosis |
| Food allergy |
| Mucosal injury |
| Drugs |
| Chemotherapy |
| Radiotherapy |
| Graft-versus-host disease |
| Malignancy |
| Primary intestinal (gastrointestinal stromal tumor, adenocarcinoma, leiomyoma) |
| Lymphoproliferative (lymphoma) |
| Metastatic |
| Extraintestinal with mass effect (Castleman disease) |
| Chronic abdominal pain |
| Growth failure |

## INFLAMMATORY BOWEL DISEASE

In the investigation of IBD, CE may be used at different times in the disease course, including diagnosis, differentiating ulcerative colitis (UC), or indeterminate colitis (IBDU) from CD, investigating the disease extent, activity, response to treatment (9), or later in the disease course to differentiate active disease from comorbid functional complaints. In a study of 66 children with CD and 17 with suspected IBD, 86% of those with established disease were found to have abnormal CE, of which three-fourths subsequently underwent treatment escalation. Additionally, negative studies were found in 94% of those with suspected IBD, effectively ruling out the condition following upper and lower endoscopy (10). Cohen and Klevens (5) reported 75% to 92% of known CD pediatric patients undergoing CE had treatment changes performed based on the CE results. Of note, their meta-analysis was performed before the broad availability of magnetic resonance enterography (MRE). In another study, UC and IBDU were reclassified into CD based on CE in 5 of 7 pediatric patients (11). There are no clear accepted criteria for CE-diagnosed CD in children, and characteristic findings, for example, aphthae, ulcerations, and strictures, can also be found in other inflammatory diseases and during nonsteroidal anti-inflammatory drug use (Fig. 1). The Lewis Score (12) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) (13) assess disease activity in adults, but have not been adequately validated in pediatrics. In addition, neither an association between CE findings and symptoms nor the response to changes in treatment made in response to CE findings have been reported.

In a study comparing CE, MRE, and small intestinal contrast ultrasonography (SICUS) in 34 pediatric patients with known or suspected CD, CE was found to be as sensitive, but less specific than the other 2 modalities in the diagnosis of CD without a statistically significant difference in the overall identification of active disease. Noteworthy was that 9 of 34 patients were unable to undergo CE because of strictures identified on MRE (14). In contrast, Lai et al (15) retrospectively compared CE, MRE, and barium swallow with small-bowel follow-through and demonstrated sensitivities of 94.6%, 85.7%, and 71.1%, respectively, and specificities of 72.7%, 70%, and 40%, respectively. MRE and CE performed with similar sensitivity in the retrospective pediatric study by Kovanlikaya et al (16) (75% vs 77.8%, respectively), noting that the tests are complementary with mild mucosal disease identified in more patients by CE and full thickness and extraintestinal involvement by MRE. Another pediatric study comparing MRE and CE in 60 children (37 of 60 underwent CE) demonstrated that both methods are accurate for diagnosis; however, Casciani et al (17) recommended MRE as the initial test to assess small-bowel strictures, which could be a contraindication for CE.

In 2009, the World Organization of Digestive Endoscopy (OMED) and the European Crohn's and Colitis Organization (ECCO) recommended that in children, CE can be performed for the diagnosis of CD when conventional upper and lower endoscopy and radiographic imaging are not conclusive (18). In addition, ESPGHAN-revised Porto criteria for the diagnosis of pediatric IBD (19) have included CE as the small-bowel imaging of choice when MRE is not available or possible. Performing MRE before CE may lessen, although not eliminate, the risk of retained capsules in bowel strictures. Levine et al (19) noted not only the advantages of CE such as the ease of performance and the ability to identify mucosal lesions but also the main disadvantages such as possible capsule retention and a high rate of false-positive examinations. CE has also been used in a clinical trial to monitor the mucosal improvement in response to treatment (20). Findings on CE were found to correlate with C-reactive protein (CRP) and fecal calprotectin in adults with CD followed over time with sequential CE, CRP, and calprotectin (21). In contrast, Kopylov et al (22) found that at a single time point, CE findings did not correlate well with CRP or fecal calprotectin levels in established adult CD. Significant small-bowel findings could be seen despite normal marker levels. Thus, these markers should not be the sole basis for choosing patients for CE.

## OBSCURE GASTROINTESTINAL BLEEDING

OGIB, whether occult or apparent, is the most frequent indication for CE in children <8 years old (5). At times, the bleeding source may only be seen in a single image (Fig. 1), making the reading of tests performed for this indication more time consuming than those for IBD. Positive findings have been reported in 42% of pediatric patients (5) compared to 60% in adults with OGIB or persistent iron deficiency anemia (6). Higher diagnostic yields are found if CE is performed early (within 1 week) of overt OGIB (23). In adults, pooled results from multiple studies have shown that angiodysplasia is the most common finding (50%), followed by inflammation/ulcers (26.8%) and neoplastic lesions (8.8%). Pooled pediatric diagnoses are shown in Table 2 (24–27).

A meta-analysis of adult studies comparing the diagnostic yield of CE and double-balloon enteroscopy (DBE) demonstrated similar results (pooled odds ratio of diagnostic yield with CE compared to DBE 1.48 (95% confidence interval [CI] 0.9–2.43; $P = 0.16$) (28). Similarly, Urs et al (29) reported similar diagnostic yields in CE and DBE (77.7% vs 70.7%, respectively) for all

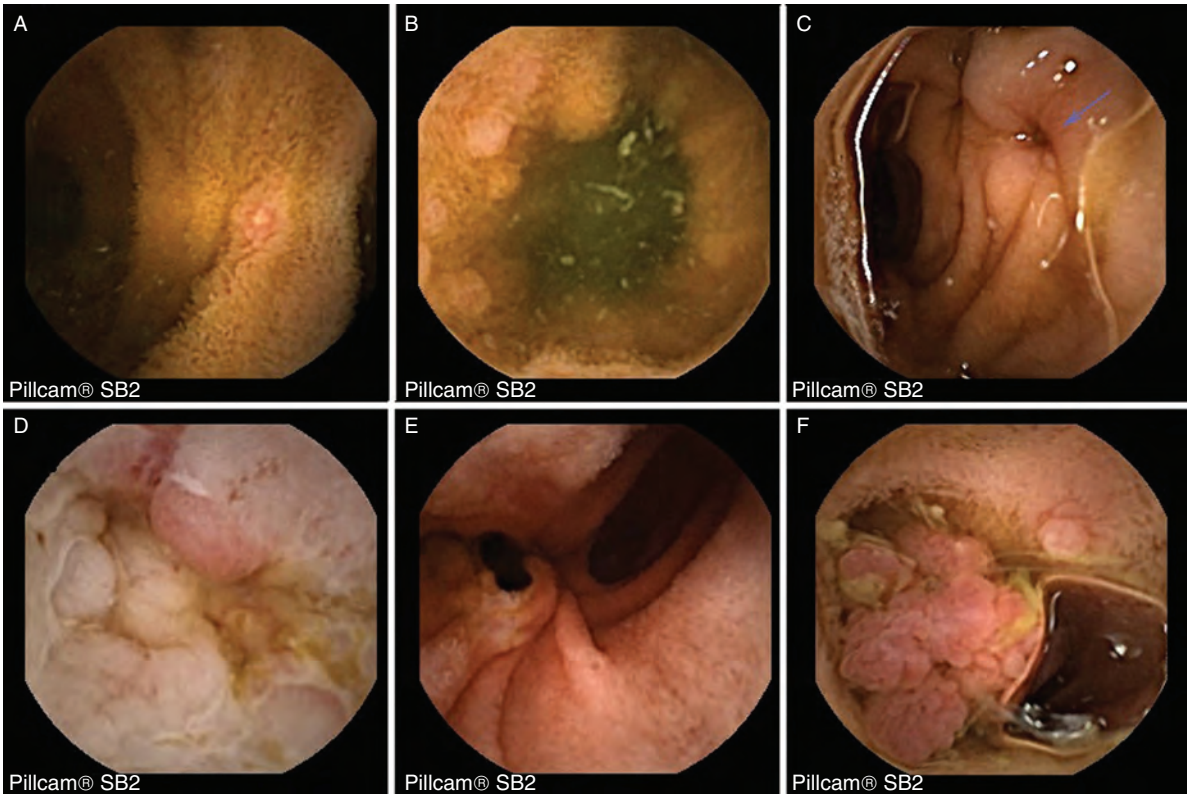


**FIGURE 1.** Findings in capsule endoscopy. A, Aphthous ulcer. B, Lymphoid hyperplasia. C, Duodenal ulcer (seen in only a single image). D, Ulcerated stricture in Crohn disease. E, Bile discharged from duodenal papilla (normal finding). (F) Jejunal polyp in an adolescent.

purpose diagnosis, though DBE could be used for intervention, which is lacking in CE. Furthermore, CE is unable to accurately assess the location of disease identified during the procedure, and is therefore unable to assist later surgical interventions as may be done with enteroscopic procedures. CE was inferior to DBE in an adult study assessing the identification of Meckel diverticulum (30); however, although DBE has the potential of therapeutic intervention, the technology is not readily available in pediatric centers, and may carry with it more risk than CE. Because OGIB is a frequent indication for CE in young children, the need for anesthesia for capsule placement should be kept in mind when planning the diagnostic workup and treatment of the patient.

## PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome (PJS) is associated with a high rate of intussusception, with polyps acting as leading points and a need for emergent surgery, as well as malignant transformation of polyps. Polyps of concern are generally those larger than 10 mm. Guidelines recommend screening patients with PJS every 2 to 3 years beginning around age 8 years for small-bowel polyps (31,32). Dutch surveillance recommendations are to screen children at age 10 with CE, followed by MRE in the event that polyps are noted to determine exact localization and size to determine the need for removal (33). Beggs et al (31) also recommended screening asymptomatic patients by CE, however beginning at 8 years old,

TABLE 2. Small bowel findings in children undergoing capsule endoscopy for obscure gastrointestinal bleeding

| Study | n | Crohn disease | Polyps | Vascular lesion | Angiodysplasia | Gastro-enteropathy | GVHD | Ulcers | Lymphoid nodular hyperplasia | Other* |
|---|---|---|---|---|---|---|---|---|---|---|
| Antao et al (24) | 7 | | | | 2 | 2 | | | | 3 |
| Cohen et al (8) | 27 | 4 | 3 | 1 | | | | | | 9 |
| Ge et al (26) | 12 | 4 | 1 | 2 | 2 | | | | | 1 |
| Jensen et al (27) | 18 | | | 5 | | 5 | 1 | | | 1 |
| Nuutinen et al (1) | 18 | 1 | 1 | | | | 1 | 1 | 1 | 3 |
| Oliva et al (25) | 22 | 1 | 1 | | 9 | | | 4 | 3 | 1 |
| Total | 104 | 10 | 6 | 8 | 13 | 7 | 2 | 5 | 4 | 18 |
| % | 100 | 9.6 | 5.8 | 7.7 | 12.5 | 6.7 | 2.0 | 4.8 | 3.8 | 17.3 |

GVHD = graft-versus-host disease.
* Other—Meckel diverticulum 2, eosinophilic gastroenteropathy 1, lymphangiectasia 1, small bowel varices 1, villous atrophy 1, active bleeding—no source 1, gastric/proximal duodenal lesions—8, colon lesions—3.

and earlier if symptomatic. They did not advocate DBE because of the lack of published evidence. Tomas et al (34) have raised concern about the use of CE for polyp screening because of the reports of proximal jejunal and duodenal polyps and tumors that were missed by CE and properly identified by DBE. Ohmiya et al (35) compared CE to DBE in 18 patients (median age 15.1 years) with PJS. They found no difference in the detection rates of either all polyps or large (>10 mm) polyps (interclass correlation coefficient 0.832). In PJS, CE was able to identify a similar number of polyps >10 mm compared to barium enterography in 11 children, but more small polyps (<10 mm) were seen on CE ($P = 0.02$). Moreover, CE was preferred by the patients (36). Gupta et al (37) compared CE and MRE with DBE as the comparative standard in 19 adults with PJS and found no significant differences between the 2 in regard to the identification of either small or large polyps. Three large polyps (>15 mm) seen in MRE were not detected by CE. Patients found CE more comfortable, but there was no difference in final patient preference. Studies in children and adults with PJS and other small-bowel polyposis syndromes will need to be performed to clarify the relative roles of DBE, CE, and MRE in these conditions. It is possible that rotating the type of screening procedures through life may increase the diagnostic yield.

## ABDOMINAL PAIN

Functional abdominal pain is appropriately considered to be a condition not generally necessitating any invasive investigation. Despite this, Gijsbers et al (38) reported that the Rome III criteria are insufficient to rule out the organic causes of abdominal pain, even when alarm symptoms are absent. CE has been anecdotally studied in small series of children. Of the 16 children studied with CE (ages 5–16 years), 7 were found to have lymphoid nodular hyperplasia of uncertain significance, 1 had oxyuris in the cecum, and only 1 had aphthous lesions in the ileum, suggestive of CD (39). Shamir et al (4) reported gastritis in 4 of 10 children with abdominal pain (only 1 identified by endoscopy), and 1 of 10 with small-bowel and cecal CD on CE. Similarly, Urbain et al (40) reported that 3 of 7 children undergoing CE for recurrent abdominal pain had significant findings (2 CD, 1 patient with persistent ileoileal invaginations that led to laparoscopy and findings of significant adenitis). These reports indicate that although CE should not be routinely recommended for abdominal pain, limited use, in highly selected cases, may have a role in differentiating functional from nonfunctional disease in children.

## BOWEL PREPARATION

Once the capsule is swallowed, visualization of the mucosa is dependent on the bowel preparation and capsule position (which cannot be controlled with the available capsules). Several studies have addressed the best method of bowel cleansing for small-bowel CE. A meta-analysis of adult studies demonstrated that compared to no bowel preparation, a protocol including polyethylene glycol (PEG) and simethicone appears to be the best approach; however, ideal dosages have yet to be determined (41). Oliva et al (42) in their randomized single-blind study of children demonstrated that low volume PEG (25 mL $kg^{-1}$) the evening before the study and 376 mg simethicone in 20 mL water 30 minutes before the procedure achieved better visualization scores than PEG alone, simethicone alone, or a 12-hour clear liquid diet. No significant differences were found in the diagnostic yields between protocols. A 10- to 12-hour fast before the testing is generally recommended in all but the youngest children to increase visualization of the distal and terminal ileum, and in clinical practice, some physicians require only an overnight fast without any preparation. At present, no conclusive recommendations can be provided on the best method of bowel preparation in children.

## COMPLICATIONS, COMPLETION, AND RETENTION

Two complications have been noted in CE, namely capsule retention and capsule aspiration. Capsule aspiration is an extremely rare event and to the best of our knowledge has not been reported in children. Capsule retention, defined as nonexpulsion of the capsule within 2 weeks or the need for directed intervention before that time, was reported in 22 of 1013 pediatric patients (2.3%, 95% CI 1.5–3.4), 4 of these were gastric retention (43). Retention rates differ based on the indication for the procedure, with CD carrying the highest risk 13 of 596 (2.2%), followed by OGIB 2 of 144 (1.4%) and polyposis 1 of 81 (1.2%) (43). These rates are similar to those reported in adults for similar indications (6), although the overall retention rates in children are higher, mostly because of the higher representation of studies performed for CD. Retained capsules may pass with time, whether in the stomach or in the intestine, and therefore if bowel obstruction does not occur, removal may be delayed. Capsules retained in small-bowel strictures, causing bowel obstruction, may need to be removed endoscopically or surgically; however, if an inflammatory stricture is suspected and the clinical scenario permits, medical treatment of the underlying condition (eg steroids for inflammatory strictures) may be attempted before surgical intervention (44). CE completion rates are relatively stable in childhood and adults at around 80% of capsules capturing images through to the cecum (5,6). Newer capsules, with longer capturing times, will most likely increase the number of completed tests.

The Agile patency capsule was developed to lower the risk of retained capsules, which may cause bowel obstruction, necessitating surgical or medical intervention and mitigate the need for MRE. The patency capsule is a dissolvable capsule that contains a radiofrequency identification tag, which begins dissolving 30 hours following ingestion if it is not successfully passed in that time. The patency capsule can be detected either with a radiofrequency detector or with an abdominal x-ray. Cohen et al (8) reported that patency testing allowed for 19 of 23 patients to undergo CE. Of these, 1 had capsule retention despite the patency test, which highlights that the test is not a guarantee of successful test completion. Interestingly, some suggest that in specific cases CE can be used to identify suspected strictures in the small bowel missed by radiology to help localize the responsible disease (45).

## NEW CAPSULES ENDOSCOPES AND FUTURE APPLICATIONS

In the last several years, new wireless capsule applications have been developed. The colon capsule (PillCam Colon, Given Imaging, Yoqneam, Israel), which was approved by the FDA in adults for use following incomplete colonoscopy while screening for colorectal carcinoma (46), has been assessed as a surrogate to colonoscopy in both adult (47,48) and pediatric (49) ulcerative colitis. An esophageal capsule (PillCam ESO Given Imaging, Yoqneam, Israel) may be used to identify esophageal varices (50,51) and screen for Barrett esophagus (though with a lower sensitivity and specificity than endoscopy) (52) and esophagitis (53). Both of these capsules have both forward and reverse facing cameras to increase the surface mucosa viewed during data analysis. Neither of the new capsules has been adequately studied in children, and therefore recommendations for their use cannot be made at this time for the identification of colonic polyps, macroscopic ulcerative colitis, esophageal varices, or Barrett esophagus.

Improvements to small-bowel CE have included a 4-camera 360° imaging CE (CapsoCam SV-1, CapsoVision, Saratoga, New York) which has demonstrated better landmark assessment, but at the same time requiring capsule retrieval (54). In addition, magnetically maneuverable (55) and self-propelling capsules (56) have also been developed. Coupling real-time viewing with the ability to sample tissue or target drug delivery into pathological lesions has not yet been brought into clinical practice.

In conclusion, in the last decade, CE has become part of the diagnostic toolbox available for the investigation of small-bowel disease and is a valid alternative imaging method. The strengths and weaknesses of CE must be kept in mind when selecting patients for the procedure. Future studies should delineate the role of CE in the diagnostic algorithm of current indications as well as the role of improved capsules in the diagnosis and follow-up of pediatric conditions, for example, celiac disease, colonic disease, motility disorders, and other diagnoses based on the CE pill performance.

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