



WIRELESS CAPSULE ENDOSCOPY IN THE EVALUATION OF ESTABLISHED AND SUSPECTED CROHN'S DISEASE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum has been asked to review the peer reviewed scientific literature on the efficacy and safety of Wireless Capsule Endoscopy in the evaluation of established and suspected Crohn's Disease.

BACKGROUND

Crohn's disease (CD) is a chronic, recurrent inflammatory disease of uncertain etiology that may occur throughout the gastrointestinal tract. Patients generally present with chronic or nocturnal diarrhea, abdominal pain, bowel obstruction, weight loss, fever, night sweats, or symptoms of underlying intestinal inflammation (Hanauer, 2001). The inflammation and ulceration characteristic of CD may lead to fibrosis, stricture, bowel abscess, fistula formation and perforation if not promptly diagnosed and treated. The small bowel is affected in approximately 70% of patients, and up to 30% of patients have disease limited to the small bowel, particularly the distal ileum (Leighton, 2005). Patients with ileal disease have an increased probability of surgery compared with other bowel segment involvement (Carter, 2004). Approximately 20 percent have disease limited to the colon. A small percentage of patients have predominant involvement of the mouth or gastroduodenal area, while fewer patients have involvement of the esophagus and proximal small bowel (Carter, 2004).

Diagnosis of CD is based on a combination of clinical findings, elevated serum inflammatory markers and characteristic endoscopic, radiologic and histopathologic findings. Colonoscopy with intubation of the terminal ileum is the major tool used to establish the diagnosis of ileocolonic CD. Radiologic studies (such as small bowel follow through or enteroclysis) may be useful in documenting the length and location of strictures in CD and when CD involves segments of the gastrointestinal tract, such as the small bowel, not accessible by colonoscopy. The initial diagnosis of CD in symptomatic patients is often delayed; one study estimated that the time between the onset of symptoms and diagnosis of CD was almost eight years (Pimental, 2000). Delayed diagnosis may lead to greater complications and the need for more invasive

interventions, including surgery for some patients (Sands, 2003). There has been much interest in emerging technologies and diagnostic tests that may allow for earlier and more accurate diagnosis in patients with CD, particularly those with possible small bowel involvement.

Wireless Capsule Endoscopy

Capsule endoscopy allows examination of the small intestine, which is otherwise inaccessible by means of traditional endoscopic methods. The Given Diagnostic Imaging System (Given Imaging Ltd, Norcross, GA) is the only wireless capsule endoscopy (WCE) system that has FDA approval. Another system is being used in Europe and should be available soon in the United States. The Given capsule endoscopy system is composed of a disposable plastic capsule (PillCam SB), two data recorders, a customized PC workstation and propriety software to process and display the images. The capsule itself measures 11mm by 26 mm and weighs 3.7 gm. It contains a complementary metal oxide silicon chip camera, six light emitting diodes, two silver oxide batteries and a UHF band radio telemetry transmitter (Hara, 2005; Bhuket, 2005).

The capsule is swallowed by the patient after a ten to twelve hour fast and is propelled by peristalsis through the gut transmitting images at two frames per second until the battery expires after about seven to eight hours. It has a 140 degree field of view and a minimum size of detection of 0.1 mm. Images are transmitted by a digital radio frequency communication channel to an external data recorder unit. Patients can continue most of their regular activities, although they are encouraged to avoid exercise or other activities that may cause the sensor to detach during passage of the capsule. Patients can resume a light meal four hours after ingestion of the capsule. In some reports, patients have preferred the capsule over the alternatives presumably because it is more convenient and less invasive than traditional endoscopy (Swain, 2003). A disadvantage of WCE is that it is purely a diagnostic test with no capability of biopsy or therapeutic intervention (Cave, 2006).

Bowel preparation may affect the sensitivity of the WCE exam, but there is not consensus as to the optimal bowel preparation (Raju and Nath, 2005). The manufacturer recommends a ten hour fast without bowel purge prior to the exam, while others have tested preparations of polyethylene glycol, colonoscopy type preparations, sodium phosphate preparations and others (Keroack, 2004).

WCE is widely used for the evaluation of obscure gastrointestinal bleeding presumed to be of small bowel etiology (e.g.: Tatar, 2006; Hara, 2004; Fireman, 2004; Lewis, 2005). WCE has been as successful and frequently is more successful than push enteroscopy in finding the cause of obscure gastrointestinal bleeding (Marmo, Rotondano et al., 2005). Its use is being investigated for evaluation of other GI pathology,

including esophagitis and Barretts esophagus (Eliakim, 2005; Sharma, Eliakim, et al. 2005) and other small bowel pathology, such as tumors (Schulman, 2003; Cobrin, 2006) and celiac disease (Green 2005), and for detecting small bowel lesions in patients with seronegative spondyloarthropathies (Eliakim, 2005).

Most patients with a classic presentation of CD can be diagnosed by conventional endoscopy and radiologic imaging consisting of a small bowel series or CT. For the one-third of patients who present exclusively with ileitis and are not definitely diagnosed with ileoscopy and/or small bowel radiography, the diagnosis may be more elusive and could benefit from other diagnostic modalities, such as WCE.

This review evaluates the current peer reviewed evidence for the use of WCE in the following circumstances:

1. Patients with suspected CD being evaluated for small bowel involvement.
2. Patients with established CD being evaluated for small bowel involvement.
3. Patients with indeterminate colitis.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1 Does the technology have final approval from the appropriate government regulatory bodies?

On August 1, 2001, the FDA Center for Devices and Radiological Health cleared the Given Diagnostic Imaging System classified as a class II device under the generic name of Ingestible Telemetric Gastrointestinal Capsule Imaging System with special controls. The FDA used the de novo process which is neither PMA nor 510(K) and is used for the approval of low-risk devices when neither of the other processes are deemed appropriate. The device is intended to be used for visualization of the small bowel mucosa as an adjunctive tool in the detection of abnormalities of the small bowel.

On July 1, 2003, the FDA removed the wording regarding use "as an adjunctive tool" and noted that "It may be used as a tool in the detection of abnormalities of the small bowel".

TA criterion 1 is met.

TA Criterion 2 **The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words "capsule endoscopy", wireless capsule endoscopy" and videocapsule endoscopy", cross referenced with the keywords "Crohn's Disease", Inflammatory Bowel Disease" and "small bowel". The bibliographies of systematic reviews and key articles were manually searched for additional references. Abstracts of citations were reviewed and all relevant articles reviewed in full.

There are at least 17 publications in the peer reviewed literature that compare outcomes of WCE with other endoscopic and/or radiographic modalities in the evaluation of patients with suspected CD, known CD or indeterminate colitis. There are no randomized clinical trials; most of these trials are prospective non-randomized clinical trials in which consecutive patients, generally at a single center, are evaluated with different techniques and the diagnostic yield for detection of lesions in the small bowel consistent with CD is then compared. In addition to diagnostic yield, eight studies report on clinical management and patient outcomes on the basis of information from WCE.

Level of evidence: 3 and 5

TA Criterion 2 is met

TA Criterion 3 **The technology must improve the net health outcomes.**

For diagnostic tests, there is evidence that use of the test would result in improved medical management in a way that will benefit the patient.

Non-randomized series

Costamagna (2002) reports on an early study that compared small bowel follow through (SBFT) with WCE in 20 patients with suspected small bowel disease. They found that SBFT showed ileal nodularity in three patients while WCE was positive in 17 patients (diagnostic in nine patients, suspicious in eight and failed in three). No information is provided regarding clinical decision-making.

Fireman (2003) reports on 17 patients with a high clinical suspicion of CD who underwent WCE after a normal small bowel series and colonoscopy (15 of 17 patients). However, ileoscopy was performed in only

six patients. The mean duration of symptoms before diagnosis was 6.3 years. Twelve of the 17 patients (71%) had lesions on WCE consistent with CD, such as mucosal erosions, ulcers and strictures. These patients were started on steroids and 5-ASA; ten patients showed "good" clinical improvement while two showed "some improvement" with a mean follow-up of four months.

Herrerias (2003) reports on 21 patients with suspected CD but with unremarkable colonoscopy and small bowel series. In nine patients, WCE found lesions consistent with CD. The authors report that these patients were started on therapy for CD and all had disease remission by three months. One review paper asserts that some of the images displayed in the paper had "superficial mucosal changes of dubious clinical significance" (Legnani and Kornbluth, 2005).

Eliakim (2003) reports on a blinded study comparing WCE to small bowel radiography in patients with suspected CD. Twenty patients with suspected CD underwent small bowel follow through followed by WCE and CT enteroclysis. Patients with stricture were eliminated (though the authors provide no information on how many patients were evaluated to enroll the 20 patients they report on in the study). Mean patient symptoms were eight months and 17 of 20 had undergone colonoscopy prior to the study; visual endoscopy was not repeated as part of this study. None were on medications, including NSAIDs. Capsule findings were identified as "medically significant or explained the patient's reason for referral" in 14 of 20 patients (70%), though some authors point out that some of the findings considered significant could be considered normal in a healthy patient (Voderholzer, 2006). Radiography found abnormalities in ten of 20 patients (50%) ($p < 0.04$). There is little information on clinical follow up.

Argueles-Arias (2004) report on 12 pediatric patients with suspected CD. All patients had undergone extensive evaluation prior to WCE; but only six of the 12 had successful ileal intubation. WCE revealed abnormalities in seven of the 12 patients on the basis of ulceration in the small bowel. Patients with positive findings were treated with prednisone and mesalamine, and the authors report all had clinical remission by a median follow-up of three months. This small study provides evidence that information derived from WCE can lead to improved outcomes in patients with suspected CD, though the lack of successful ileoscopy in half the patients may account for the findings.

Ge (2004) evaluated 20 patients with WCE who had prior normal colonoscopy and small bowel series within the previous six months. Patients with strictures on the small bowel series or had used NSAIDs in the prior year were excluded. WCE identified inflammatory lesions in 13 of 20 patients. These patients were treated

with standard CD medication and 11 of 13 “showed a good clinical improvement.” They report that three patients experienced capsule retention, although all had had normal small bowel series.

Mow (2004) report retrospectively on the experience with 50 patients who underwent WCE for: 1) evaluation for small bowel involvement in patients with inflammatory bowel disease (n=22), 2) determination of the extent of small bowel disease in patients with CD (n=20), and 3) workup of suspected CD (n=8). Outcome measures were “diagnostic” when multiple ulcerations were present, “suspicious” when less than three ulcerations were present, “nonspecific” and “normal”. Most patients (40/50) had undergone at least one SBFT in the prior year. WCE findings were diagnostic for CD in 20 patients and suspicious in ten patients. Twenty patients were evaluated for continued symptoms; most had recent negative small bowel series and ileocolonoscopy. Of these, 18 of 20 had ileocolitis and eight of these had findings considered diagnostic for CD. Seven of these patients had a change in medical therapy as a result of the WCE results and all had clinical improvement (no further details are provided).

Eliakim (2004) report on 35 consecutive patients with suspected CD. All patients had SBFT, CT enteroclysis and then WCE if no stricture was identified. The radiologic studies revealed abnormalities in 23% (for SBFT) and 20% (CT tomography) of exams, compared with WCE that identified abnormalities consistent with CD in 77% ($p < 0.05$). Some of the WCE findings (e.g. “erythema” in 22%) are reported as diagnostic but are not necessarily diagnostic of CD. Change in patient management is not reported.

Buchman (2004) reports on a prospective, blinded study of 42 patients with known CD in whom recurrent CD was suspected based on abdominal pain, diarrhea, anemia and/or arthralgias. Patients underwent small bowel series followed by WCE if no stricture was present. For SBFT, studies were graded as grade 0 (normal), grade 1 (minimal nodularity, ulcerations), grade 2 (more extensive ulcers, minimal luminal narrowing), or grade 3 (fistula, skip areas, extensive ulceration). WCE was performed within one week of SBFT. WCE findings were graded as grade 0 (normal) grade 1 (erythema, isolated villi loss), grade 2 (erosion, no ulcer) or grade 3 (ulcers, bleeding and/or stricture). Twelve patients were excluded on the basis of strictures. Of the remaining 30 patients, WCE identified inflammatory lesions consistent with active CD in 21 patients, compared with 20 patients with the small bowel series. Complete agreement between procedures occurred in 13 of 30 studies. There was good agreement between WCE and the small bowel series. Interestingly, neither WCE nor SBFT results correlate with biological or clinical indices of disease activity. A survey at the conclusion of the study found higher patient satisfaction with WCE than with radiography. No clinical decision making outcomes are reported. The authors conclude that WCE and SBFT have similar sensitivity and accuracy for the diagnosis of CD.

Kalantzis (2005) evaluated 193 patients with WCE for suspected small bowel disease. Most patients (N = 108) presented with obscure gastrointestinal bleeding. They report that in patients referred for established or suspected CD, WCE was compatible with the diagnosis in five of six patients with established and eight of 22 with suspected CD.

Voderholzer (2005) reports on a study whose aim was to evaluate the gain in information and therapeutic impact of WCE in patients with established and suspected CD. Fifty-six consecutive patients were first evaluated with CT enteroclysis; patients with strictures greater than 10 mm were excluded (15 patients). All eligible patients (N=41) underwent EGD, ileocolonoscopy, CT enteroclysis and WCE within two weeks. Each technique was evaluated by one investigator blinded to the results of the other investigators. Of the 41 patients, 23 were female, the average age was 36, the average duration of symptoms was one year and 33 had active disease with CDA1 > 150. Small intestinal involvement was found by WCE in 25 (61%) of the patients, compared with 12 patients for CT enteroclysis ($p < 0.004$), and detected ileocecal/neoterminal ileal involvement in 24 (43%) of patients compared with CT enteroclysis which detected inflammatory lesions in 20 patients ($P = NS$). The capsule became impacted in two patients, and one of these had to be removed by push enteroscopy. Treatment was changed based on the results of the WCE in ten patients; in five of these patients the diagnosis of CD was established by WCE based on the presence of multiple aphthous or erosive lesions. In the five patients with established CD, therapeutic strategies were changed due to the results of the WCE. The authors report that all ten patients improved clinically. They conclude that WCE is superior to CT enteroclysis in diagnosis of small bowel lesions consistent with CD in patients with known or suspected CD, and the results lead to enhanced clinical decision-making for these patients.

Dubcenco (2005) reports on WCE findings in patients with suspected and established CD compared with findings from radiologic and endoscopic techniques. Fifty-four consecutive, symptomatic patients were enrolled, 43 with known and 11 with suspected CD. All patients underwent ileocolonoscopy with biopsies from the terminal ileum followed by small bowel radiologic studies before WCE. Small intestinal strictures were radiologically identified in 14 out of 54 patients with a prior history of CD; 12 out of 14 had previously undergone small bowel resections. These patients were excluded from WCE. One patient had an incomplete WCE, so data was analyzed for 39 patients. The final diagnosis of CD of the small bowel was made in 29 of 39 patients, 23 of whom had previously established CD and six had suspected CD (all of whom improved after initiation of treatment for CD). WCE showed the correct diagnosis in 26 of 29 patients and radiologic studies (SBFT or small bowel enema) showed the correct diagnosis in eight of 29 patients.

Difference in the diagnostic yield of the two tests was significant (Fisher exact test, $p < 0.0001$). There were no reported complications with the WCE.

Chong (2005) prospectively evaluated 22 patients with known CD (group 1) and 21 patients with suspected small bowel CD (group 2) with push enteroscopy, enteroclysis and capsule endoscopy. Examiners were blinded to results of other investigations. In patients with known CD, WCE detected small bowel CD in 77% of patients in group 1 and 10% in group 2. It detected more erosions than did push enteroscopy or enteroclysis ($p < 0.001$) in group 1; there were no significant differences between the procedures in group 2. Referring physicians reported that findings from WCE changed management for 30 of the 43 patients. The authors conclude that WCE has a higher yield than push enteroscopy and enteroclysis in patients with known CD when small bowel mucosal disease is suspected.

Marmo (2005) report on a prospective comparison of double contrast enteroclysis and WCE to assess the extent of small bowel involvement in 31 patients with histologically proven CD. Patients had previously undergone upper and lower endoscopy with ileoscopy and the diagnosis of CD was confirmed by histologic examination of biopsy specimens. They found that WCE identified small bowel lesions in 71% of patients and enteroclysis identified lesions in 26% ($p < 0.001$). Most of the lesions identified by WCE were in the distal small bowel. The authors state that findings from WCE in these patients "could alter treatment recommendations", but no further details are offered.

Albert (2005) reports on a prospective comparison of WCE with MRI and fluoroscopic enteroclysis in consecutive patients hospitalized with suspected or clinically worsening CD. Eighty-one consecutive patients were identified and patients were then excluded if they had dysphagia, known GI obstruction and/or ileus, pregnancy or an implanted electromedical device. Fifty-two patients underwent WCE, MRI and fluoro-enteroclysis. Of these, 25 had suspected CD and 27 had established CD with recurrent or worsening symptoms. Small bowel CD was diagnosed in 41 of 52 patients; of these, 14 had strictures and did not undergo WCE. The remaining 27 patients received WCE, MRI and fluoro-enteroclysis with diagnostic yields of 25 (93%), 21 (78%) and 33% respectively. There was not a statistically significant difference between MRI and WCE. Patient clinical outcomes are not discussed. The authors conclude that WCE and MRI are complementary tests and that addition of WCE to MRI findings is not likely to alter decision-making.

Hara (2006) compared CT enterography, WCE, SBFT and ileoscopy in 20 consecutive patients with known or suspected CD who had been referred to an inflammatory bowel clinic. Inclusion criteria included known or suspected CD based on imaging, pathologic findings or prior endoscopy. Exclusion criteria were pregnancy,

presence of cardiac pacemakers, small bowel strictures, obstruction or swallowing disorder. Findings were considered “positive” if they demonstrated “any lesion in the small bowel consistent with CD—for WCE these consisted of erosions, ulcers or strictures”. Seventeen of the 20 patients enrolled in the study (nine with established CD and eight with suspected CD). Small bowel findings consistent with CD were present in 12/17 (71%) with WCE, 11/17 with ileoscopy (65%), 9/17 with CT enterography (53%) and 4/17 with SBFT (24%). Differences in detection did not reach statistical significance. In addition, five patients had incomplete examinations of the distal ileum, two with WCE and four with ileoscopy. They conclude that the yield of ileoscopy is similar to WCE and that SBFT is inferior to the other techniques.

De Bona (2006) reports on 38 patients with suspected CD who were studied with WCE after negative evaluations with upper and lower EGD, ileoscopy and SBFT. Patients were divided into two groups: Group 1 consisted of 12 patients with ongoing symptoms and Group 2 consisted of 26 patients with symptoms and biochemical markers of inflammation. WCE findings were classified as diagnostic (multiple erosions/ulcerations), suspicious (< or = 3 erosions/ulcerations), non-specific and normal. WCE findings were diagnostic for CD in 13 patients (34%), suspicious in two, non specific in four and normal in 19, for a detection rate of 39% (diagnostic + suspicious). Diagnostic yield was higher in Group 2 than Group 1. The authors report that WCE “directly affected the management of 15 out of 38 patients”, including one who was found to have GI lymphoma. Specific treatments and patient outcomes are not reported.

Other indications in CD

There are other potential uses of WCE in the evaluation of patients with established CD. First, there may be a future role for WCE in the evaluation of patients with indeterminate colitis who are failing medical therapy and for whom surgery is being considered (Legnani and Abreu, 2006). Second, it has been proposed as a way to evaluate patients with possible post operative recurrence of CD (Bourreille, 2006; De Palma, 2004). And finally, WCE may be useful to assess patient response to medical therapy and to optimize therapy as needed. At the current time there is insufficient literature to evaluate the role of WCE for these potential indications.

Meta-Analyses

Marmo, Rotondano et al (2005) report on a meta-analysis of WCE vs. conventional modalities in the diagnosis of small bowel diseases. Overall, they found that WCE provided a significant diagnostic gain over both enteroclysis and SBFT in the diagnosis of small bowel CD. A subgroup analysis found a significant difference in diagnostic yield between WCE and SBFT in patients with suspected recurrence of CD, but no statistically significant difference in diagnostic yield in patients with suspected CD. WCE also led to

significantly increased diagnostic yield compared to CT enteroclysis and when compared to colonoscopy/ileoscopy. Overall, they conclude that in patients with known or suspected CD, WCE has a higher yield than enteroclysis or push enteroscopy when mucosal disease is suspected, and that WCE alters the knowledge of the presence and/or extension of disease in about half of the patients with CD, leading to a relevant change in therapeutic strategy.

Leighton (2006) reports on a meta-analysis of published studies and abstracts of WCE in the evaluation of obscure gastro-intestinal bleeding and in CD. They analyzed 11 studies of 309 patients with suspected or established CD. They identified nine trials that compared WCE with small bowel radiography. The yield of WCE for findings consistent with CD in all patients was 64% vs. 24% for small bowel radiography ($p < 0.001$; 95% CI, 28%-51%) and a NNT of 3 (95% CI, 2-4). They further analyze their findings based on whether the WCE was done to evaluate patients with suspected CD (six studies with 97 patients) or to evaluate suspected small bowel recurrence in patients with established CD (seven studies with 134 patients). They report that WCE had a 43% yield in patients with suspected CD, compared with 13% for small bowel radiography. This was statistically significant with the fixed effects model, but the incremental yield of WCE decreased with a random effects model and was not statistically significant ($p = .09$; 95% CI, -3%--51%). In patients with recurrent CD, WCE had a yield of 78% vs. 32% for small bowel radiography, for an incremental yield of 46%; in contrast with the CD suspect analysis, this yield increased to 51% with the random effects model and remained statistically significant ($p < 0.001$; 95% CI, 31%-70%) with a NNT of two for an additional positive finding (95% CI, 1-3). They report on four trials with 114 patients that compared WCE with ileo-colonoscopy. Overall, they found that WCE had a 61% yield vs. 46% for ileo-colonoscopy ($p = .02$; 95% CI, 2%-27%). In patients with suspected CD, WCE had a yield of 33% vs. 26% ($p = \text{NS}$). In patients with known CD being evaluated for recurrent disease, WCE had a yield of 86% vs. 60% for ileo-colonoscopy ($p = .002$; 95% CI, 9%-43%). The NNT for an additional finding was seven for all patients and four in patients with established CD. They report on three trials with 93 total patients that compared WCE with CT enteroclysis or enterography. For all patients (suspected and known CD), WCE again had a higher yield (69% vs. 30%). When a random effects model was applied these differences were no longer statistically significant in the suspected CD subgroup but persisted in the known CD group.

Case Reports

Barkay et al (2005) report on the use of WCE in successfully diagnosing Crohn's disease in two adolescents with atypical presentations.

Patient Safety

Overall, about 200,000 capsules have been deployed worldwide with no deaths reported (Cave, 2006). The manufacturer of the Given Diagnostic Imaging System (Given Imaging Ltd, Norcross, GA) states that use of capsule endoscopy in patients with pacemakers or other implanted devices is contraindicated, though patients with pacemakers were not systematically excluded from many of the studies (ASGE Report, 2006). Other contraindications to WCE include patients with swallowing disorders, those with known or suspected gastrointestinal obstruction, fistula or stricture, and pregnancy. Patients with dementia may not be capable of cooperating with WCE.

The major potential adverse event associated with WCE is capsule retention. This is an infrequent event occurring in approximately 0.7% - 13% of patients; the risk of capsule retention is higher in patients with CD but generally reported to be in the 2% - 4% range (Lewis, 2006). One study found that capsule retention occurred in 13% of patients with known CD but only in 1.6% with suspected CD (Cheifetz, 2006). Other risk factors for capsule retention or entrapment include use of non-steroidal anti-inflammatory drugs, prior abdominal radiation, Crohn's enteritis and prior major abdominal surgery (Remedios and Appleyard, 2005). Capsule entrapment almost always occurs at the site of small bowel pathology so that surgical intervention to remove the capsule may then also address the underlying problem (Carey, 2005). Marmo, Rotondano et al (2005) report on a meta-analysis of 526 patients evaluated by WCE for obscure bleeding (N=289) and CD (N=237). Overall, adverse events were recorded in 29 patients. In the population with CD, there were seven adverse events, all related to capsule retention. Of these, five necessitated a surgical removal, one an endoscopic retrieval and one passed spontaneously after steroid treatment. Dissolvable "patency capsules" are being used in Europe that are swallowed first by the patient and can then identify the site of entrapment via a radiofrequency signal before the capsule dissolves (Lewis, 2006; Signorelli, 2006). They are not yet approved for use in the United States (ASGE Report, 2006). One recent review of contraindications to capsule endoscopy concluded that the procedure can be performed safely in almost all clinical settings and that the only "true" remaining contraindications are obstruction/pseudo-obstruction and pregnancy (Storch and Barkin, 2006).

In sum, the accumulated peer reviewed evidence and meta-analyses suggest that WCE is more sensitive in detecting small bowel lesions than radiography and at least as sensitive as ileoscopy when it can be performed. However, more research is needed to better define the clinical significance of the small bowel findings on WCE. Few studies included specific and reproducible diagnostic criteria for WCE in CD. As evidence accumulates that WCE detects small bowel abnormalities in 10% to 20% of persons without IBD (Goldstein, 2005), it is critical that rigorous diagnostic guidelines for WCE in CD be developed and tested. In

addition, several studies present outcomes that suggest that information derived from WCE results in improved medical management in ways that benefit patients with known or suspected CD. Unfortunately, these outcomes are generally poorly documented and described in the majority of these studies. In spite of these problems, overall, there is sufficient evidence from the peer reviewed literature that use of WCE improves medical decision making and management in ways that benefit patients.

TA Criterion 3 is met.

TA Criterion 4 The technology must be as beneficial as any established alternatives.

The conventional diagnostic evaluation of patients for suspected CD, in addition to serum tests as indicated, consists of upper and lower endoscopy, including ileoscopy, small bowel imaging and SBFT, or CT enterography for patients suspected of having small bowel involvement. Most patients can be accurately diagnosed with this combination of tests. Below is brief overview of the conventional tests that may be alternatives or complementary to WCE.

Colonoscopy and Retrograde Ileoscopy

Colonoscopy with ileoscopy is a standard endoscopic/imaging test to be performed in the evaluation of patients with suspected CD, or in patients with known CD to evaluate for recurrent disease. If negative, the patient will likely undergo small bowel radiography (SBFT or enteroclysis). For most patients this combination of tests will suffice. However, imaging with radiologic techniques may fail to detect flat lesions and is an insensitive method of detecting fine mucosal disease and raised lesions (Marmo, Rotondano et al, 2005). Further, the small intestine is relatively inaccessible to endoscopic examination. WCE has been proposed as an alternative or adjunctive test for the evaluation of patients with suspected or known CD and small bowel involvement.

Radiologic Imaging of the Small Bowel

Radiologic studies (such as upper gastrointestinal series with SBFT and/or enteroclysis) are the current gold standard for evaluating CD of the small bowel not diagnosed by endoscopy (Papadakis, 2005). These studies are useful in documenting the length and location of strictures in CD and when CD involving segments of the gastrointestinal tract not accessible by colonoscopy is suspected. Double contrast enteroclysis has been found to be superior to small bowel follow through in detection of extraluminal and other complications of CD (Carucci, 2002).

Push Enteroscopy

Push enteroscopy is commonly used to examine the small bowel, particularly in the evaluation of obscure bleeding when upper endoscopy and colonoscopy have failed to find the source of blood loss (Wilmer and Rutgeerts, 1996; Saurin, 2005; Adler, 2004). Enteroscopes are significantly longer than colonoscopies, but the outer diameters and internal chamber diameters are similar. At maximal depth of insertion, over 250 cm of small intestine remain unexamined (Carey, 2005). The use of an overtube can increase insertion depth by 10-25 cm, but this practice has become less common as overtubes contribute to complications (such as Mallory-Weiss tears and pancreatitis) and to patient discomfort. Push enteroscopy is rarely used in the evaluation of patients with possible CD.

Double Balloon Enteroscopy

Double balloon push enteroscopy (DBE) was introduced in 2001 and allows for visualization and endoscopically directed therapy of the entire small bowel (Yamamoto and Kita, 2005; Yamamoto, 2003; Yamamoto, 2003). A push and pull method with inflation and deflation of the balloon allows for pleating of the small bowel onto the overtube. As this procedure is repeated, the endoscope, which is inserted either rectally or orally, can be pushed much further into the small intestine than its 200 cm length and 145 cm flexible overtube would otherwise permit (Leighton and Loftus, 2005). To date, DBE has been mainly used in the evaluation of obscure GI bleeding. In CD, a potential advantage of DBE over WCE is that it can obtain biopsies and deliver local therapy (Heine, 2006). May (2005) reports that DBE had an overall diagnostic yield of 80% when performed on 137 patients with suspected small bowel disease, most of whom had chronic GI bleeding, who were studied after a negative evaluation with other modalities. Of these, 27% (29 patients) were found to have erosions and ulcerations, and of these, 18 were diagnosed with CD. There are no comparative studies of DBE and WCE in the evaluation of patients with suspected or known CD. At present, DBE is more likely to be used in research settings to allow for confirmatory histologic diagnosis of small bowel CD as it is a time consuming procedure not currently performed in many centers.

Intraoperative Enteroscopy

Intraoperative enteroscopy is the gold standard of small bowel imaging, but is considered a procedure of last resort because of its extreme invasiveness (Hartmann, 2005). It is performed with a gastroenterologist and a surgeon in the operating room with the patient under general anesthesia. This procedure is rarely used in patients with CD.

Emerging Technologies

Emerging endoscopic technologies include chromoendoscopy, magnification endoscopy, which allows for greater magnification of intestinal mucosa, and confocal laser microscopy, narrow band imaging that uses filters and xenon light source to enhance surface structures and microvasculature and optical spectroscopy (Leighton and Loftus, 2005). Radiologic technologies being investigated for the evaluation of patients with inflammatory bowel disease include CT and MR colonography, MR enterography and positron emission tomography. More research is needed on the role of all of these technologies.

Serum Tests

Several auto-antibodies can be found in patients with CD, some of which may be clinically useful for establishing the diagnosis. Two commonly used antibody tests are antineutrophil cytoplasmic antibodies (P-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA), the combination of which have been proposed as a means for diagnosing IBD and distinguishing CD from ulcerative colitis (Ruemmele, 1998). The role of antibody tests in the initial evaluation and ongoing monitoring of patients with known or suspected CD is still evolving. They should be used only as an adjunct to conventional testing and clinical diagnosis.

TA criterion 4 is met

TA Criterion 5 The improvement must be attainable outside the investigational settings.

Guidelines have been suggested for credentialing and granting privileges to perform capsule endoscopy (ASGE Guideline, 2005). Specifically, they call for formal training in capsule endoscopy during GI fellowship and/or completion of an eight hour CME course and review of the first ten capsule studies by a credentialed capsule endoscopist. Although in the studies discussed above WCE results were all read by investigators with extensive experience reading capsule endoscopy (Legnani and Kornbluth, 2005), these guidelines are attainable outside the investigational setting and WCE is currently being used extensively outside of investigational settings.

TA criterion 5 is met

CONCLUSION

Colonoscopy with ileoscopy is generally the first endoscopic/imaging test to be performed in the evaluation of patients with suspected CD, or in patients with known CD to evaluate for recurrent disease. If negative, the patient will likely undergo small bowel radiography (SBFT or enteroclysis). For most patients, this

combination of tests will suffice. However, imaging with radiologic techniques may fail to detect flat lesions and is an insensitive method of detecting fine mucosal disease and raised lesions (Marmo, Rotondano et al, 2005). Further, the small intestine is relatively inaccessible to endoscopic examination. Therefore, WCE has been proposed as an alternative or adjunctive test for the evaluation of patients with suspected or known CD.

There are a number of clinical and methodological shortcomings of the current peer reviewed literature. First, as the meta-analysis data illustrates, there is significant heterogeneity in the study design and populations studied in the current literature making it difficult to compare results between trials (Leighton, 2006). This meta-analysis failed to find a significant difference between small bowel radiography and WCE in the subgroup analysis of patients with suspected CD. Second, the current research is suffering from a lack of standardization of diagnostic criteria of CD in WCE. Less than half of the trials present any diagnostic criteria a priori and there is a gold standard pathologic diagnosis used in only one of the trials (Marmo, 2005,). This problem is compounded by a lack of blinding of radiologists in several of the studies to the patients clinical history or to others interpretation of test results. The lack of a diagnostic gold standard is a significant limitation in assessing the sensitivity, specificity and predictive value of WCE compared to other modalities. As DBE is further refined, it could serve as a means of direct visualization and biopsy of small bowel lesions and provide a "gold standard" against which other modalities can be compared. At the current time, the outcomes reported in the existing peer reviewed literature of diagnostic "yield" and "positive" findings are inexact measures that allow for significant variation in interpretation among the various studies. Third, there is growing awareness that asymptomatic patients will have small bowel lesions seen on WCE of unclear clinical significance. We must further elucidate which patients are to be labeled as having CD and treated with potentially harmful agents on the basis of WCE results. Most trials did not eliminate patients taking NSAIDS, a known cause of benign small bowel inflammation, as part of the exclusion criteria. Breaks in the small bowel mucosa are not in themselves diagnostic of CD. Other causes of ulcerations include infections, ischemia and drugs; and 10% to 21 % of normal asymptomatic individuals may have mucosal breaks and other non-specific lesions on WCE (Goldstein, 2005; Graham, 2005). More research is needed to better characterize the specificity of small bowel erosions on WCE in the absence of other more definitive signs and symptoms of CD. Fourth, although patient outcomes are a more useful standard for the assessment of WCE than diagnostic yield (Rastogi, 2004), most of the studies to date do not adequately assess or report on the impact of WCE on clinical decision-making and clinical outcomes.

The existing evidence does not support the use of WCE as a first line diagnostic test for the evaluation of patients with suspected or known CD. However, in spite of existing uncertainties about the ultimate place of

WCE, there is sufficient evidence to support the use of WCE for patients with suspected or known CD who have undergone prior negative evaluation usually consisting of ileo-colonoscopy and SBFT or CT enterography. For these patients, there is sufficient evidence that results from WCE provides additional information that contributes to medical decision making in a manner that will benefit the patient. Further, when stricture is ruled out on the basis of small bowel radiography, WCE has proven to be a very safe technology with no reported deaths to date.

We emphasize that the evidence for this conclusion is not strong, and urge that further trials be undertaken that examine the impact of WCE on clinical decision making and most importantly, on patient outcomes. More information does not always translate into improved quality of care. Randomized trials could be designed that examine clinical decision making and patient outcomes with and without the inclusion of information obtained from WCE. In this way, we can further elucidate the role of WCE in the evaluation of patients with known or suspected CD.

RECOMMENDATION:

Use of Wireless Capsule Endoscopy meets CTAF criteria 1-5 for evaluation of patients in whom there is a clinical suspicion of small bowel CD and for whom conventional testing is negative.

The California Technology Assessment Forum panel voted unanimously in favor of this recommendation.

October 18, 2006

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

In 2003, the BCBSA Technology Evaluation Center Medical Advisory Panel determined that the use of wireless capsule endoscopy for initial diagnosis in patients with suspected Crohn's disease without evidence of disease on conventional diagnostic tests such as SBFT and upper and lower endoscopy meets TEC criteria.

Centers for Medicare and Medicaid Services (CMS)

CMS NHIC California provides for coverage of capsule diagnostic imaging endoscopy when performed with FDA approved devices for recurrent acute small bowel GI bleeding of chronic occult GI bleeding and for Crohn's disease. There is a draft update currently being considered.

American Society of Gastrointestinal Endoscopy (ASGE)

The ASGE has four guidelines regarding the use of capsule endoscopy. An ASGE representative was not in attendance to participate at the meeting.

American Gastroenterological Association (AGA)

The AGA has not issued a formal position paper regarding the use of wireless capsule endoscopy for the evaluation of patients with suspected inflammatory bowel disease. A representative was not in attendance to participate at the meeting.

California Radiological Society (CRS)

The CRS does not have a statement on the use of this technology. A representative will not attend the meeting.

Crohn's & Colitis Foundation of America (CCFA)

The CCFA Northern California Chapter has been invited to provide an opinion regarding this technology and to have representation at the meeting.

ABBREVIATIONS

CD: Crohn's Disease

WCE: Wireless Capsule Endoscopy

DARE: Database of Abstracts of Reviews of Effects

SBFT: Small bowel follow through

DBE: Double balloon push enteroscopy

P-ANCA: Antineutrophil cytoplasmic antibodies

ASCA: Anti-Saccharomyces cerevisiae antibodies

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