Capsule endoscopy in the diagnosis of Crohn’s disease

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Abstract: Crohn’s disease is a chronic inflammatory disorder affecting any part of the gastrointestinal tract, but frequently involves the small and large bowel. Typical presenting symptoms include abdominal pain and diarrhea. Patients with this disorder may also have extraintestinal manifestations, including arthritis, uveitis, and skin lesions. The PillCam™SB capsule is an ingestible disposable video camera that transmits high quality images of the small intestinal mucosa. This enables the small intestine to be readily accessible to physicians investigating for the presence of small bowel disorders, such as Crohn’s disease. Four meta-analyses have demonstrated that capsule endoscopy identifies Crohn’s disease when other methods are not helpful. It should be noted that it is the best noninvasive procedure for assessing mucosal status, but is not superior to ileocolonoscopy, which remains the gold standard for assessment of ileocolonic disease. Mucosal healing along the small bowel can only be demonstrated by an endoscopic procedure such as capsule endoscopy. Achievement of long-term mucosal healing has been associated with a trend towards a decreased need for hospitalization and a decreased requirement for corticosteroid treatment in patients with Crohn’s disease. Recently, we have developed and validated the Capsule Endoscopy Crohn’s Disease Activity Index (also known as the Niv score) for Crohn’s disease of the small bowel. The next step is to expand our score to the colon, and to determine the role and benefit of a capsule endoscopy activity score in patients suffering from Crohn’s ileocolitis and/or colitis. This scoring system will also serve to improve our understanding of the impact of capsule endoscopy, and therefore treatment, on the immediate outcome of this disorder. As the best procedure available for assessing mucosal status, capsule endoscopy will provide important information about the course and outcome of Crohn’s disease.

Keywords: capsule endoscopy, Crohn’s disease, mucosal healing, Capsule Endoscopy Crohn’s Disease Activity Index, Niv score

Introduction
Crohn’s disease is a chronic, inflammatory disorder affecting any part of the gastrointestinal tract, but frequently involves the small and large bowel. The etiology of Crohn’s disease is unknown. It affects populations around the globe, with one million patients affected in the US in 2006, and a prevalence of 65 per 100,000 in Israel in 2007.1,2 It occurs at any age, but has a predilection for those aged 15–35 years. While about one half of patients have involvement of the ileum and large bowel, another third have disease confined to the small bowel. Crohn’s disease in the small bowel can often be difficult to diagnose using the traditional methods of evaluation, including colonoscopy with ileoscopy and contrast radiography. Mucosal features of Crohn’s
disease are often subtle and difficult to identify on a small bowel follow-through. The small bowel follow-through has traditionally been relied on to evaluate the small intestine for evidence of Crohn’s disease, but has been shown to have a relatively low accuracy of only 30%, so is no longer relied on. Computed tomographic and magnetic resonance enterography are the preferred radiology procedures.

The PillCam™SB capsule (Given Imaging Ltd, Yokneam, Israel) is an ingestible disposable video camera that transmits high quality images of the small intestinal mucosa. This enables the small intestine to be readily accessible to physicians investigating for the presence of small bowel disorders, such as Crohn’s disease. Four meta-analyses have demonstrated that capsule endoscopy identifies Crohn’s disease when other methods are not helpful. Very high diagnostic yields have been reported that were significantly better than other methods. It should be noted that it is the best noninvasive procedure to assess mucosal status, but is not superior to ileocolonoscopy, which remains the gold standard for assessment of ileocolonic disease. The usual medications used in Crohn’s disease are mesalazine, steroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and biologics (infliximab, adalimumab, natalizumab). The diagnostic procedure includes colonoscopy with ileoscopy, gastroscopy, or enteroscopy, with or without biopsies, small bowel follow-through, computed tomographic or magnetic resonance enterography, barium enema, and blood tests as indicated.

Recently, we have developed and validated the Capsule Endoscopy Crohn’s Disease Activity Index (CECDAI, also known as the Niv score) for Crohn’s disease of the small bowel. The next step is to expand our score to the colon, and to determine the role and benefit of capsule endoscopy activity scoring in patients suffering from Crohn’s ileocolitis and/or colitis. The idea is to have one score for the gastrointestinal tract for every patient with Crohn’s disease. Today one cannot evaluate a patient with substantial small and large bowel disease using presently available scores. As the best procedure available for assessing mucosal status, capsule endoscopy will provide important information about mucosal healing. Patients will fill out questionnaires allowing assessment for a possible correlation between CECDAI according to findings on capsule endoscopy and changes in the Crohn’s Disease Activity Index (CDAI) and Inflammatory Bowel Disease Quality of Life scores. Further, our research will evaluate the immediate benefit of treatment following findings of capsule endoscopy on the clinical outcome for the patient.

Clinical spectrum of Crohn’s disease
Patients with Crohn’s disease can generally be categorized based on disease presentation, ie, small bowel disease alone (30%–35% of cases), small and large bowel disease (45%–50%), or colon alone (20%). The clinical presentation of Crohn’s disease is often insidious and may fluctuate throughout the course of the disease. Symptoms may include diarrhea, abdominal pain, weight loss, fever, and blood in the stool. In addition, patients with Crohn’s disease may develop either strictures of the intestinal tract leading to obstructive symptoms or they may develop fistulae presenting with pneumaturia, an intra-abdominal abscess, or an enterocutaneous fistula. There are also extraintestinal manifestations, including rashes, arthritis, and uveitis, as well as perirectal disease. Complications of Crohn’s disease can include malnutrition, malabsorption, small bowel obstruction, anemia, malignancy of both intestinal and extraintestinal origin, and bowel perforation. Crohn’s disease is a chronic illness without a cure. Despite surgical resection of the involved intestinal segment, clinical recurrence of disease is common. Although rarely fatal, Crohn’s disease is associated with high patient morbidity, and due to the early age of onset, can profoundly affect the patient’s physical, social, occupational, and emotional well being.

Diagnosis of Crohn’s disease
A range of diagnostic tools can be used to determine the presence of Crohn’s disease, including radiology, endoscopy, and serum antibody tests. Unfortunately, these diagnostic tools are often associated with low diagnostic yields and may require repeated testing before a diagnosis is even established. None of these tools represents a gold standard, and the diagnosis is usually established through assessment of the clinical presentation in combination with radiographic, endoscopic, and if possible, pathologic findings. Since no single sign, symptom, or test definitively establishes the diagnosis of Crohn’s disease, standard procedures for identifying the disease can be challenging. The National Cooperative Crohn’s Disease study reported an average lag time of 36 months between onset of symptoms and the presence of abnormal findings on diagnostic evaluation.

Symptoms of the disease cannot occur without the presence of mucosal changes. At the same time, not all mucosal disease is associated with symptoms. This has led physicians to treat symptoms of the disease only because there has been no way to identify mucosal disease of the small bowel readily. This underlines the need for a gold standard test to diagnose and measure Crohn’s mucosal disease correctly in the small bowel.
Indices of Crohn’s disease activity

With these difficulties in mind, a variety of disease activity indices have been developed over many years.12–15 These instruments are based on symptoms, blood work, and endoscopic findings, either alone or in combination. For most, they have been designed as a research tool to determine drug response, while others have been designed for clinical utility in measuring disease activity to aid in patient management decisions. The most recognized scoring index for Crohn’s disease is the CDAI. This index summarizes symptoms over a one-week period and measures the number of liquid stools, severity of abdominal pain, general well being, number of complications, use of antidiarrheal medication, abdominal mass, anemia, and body weight. Due to the subjective nature of the symptoms, the CDAI has high interobserver variability. In addition, although liquid stools may be an important symptom, they may not be secondary to disease activity but rather to altered anatomy secondary to surgery or ileal scarring. It is also considered quite difficult to calculate in routine practice because it is measured over one week.

A simple method known as the Harvey-Bradshaw index was developed to limit the difficulty in measuring disease activity. This index uses five variables, including well being, abdominal pain, number of stools, abdominal mass, and complications. Although easier to calculate, it is also subject to interobserver variability. To avoid the score being based predominantly on patient symptoms, another index utilizing laboratory values was developed. This instrument, known as the Van Hees (or Dutch) index adds serum albumin, erythrocyte sedimentation rate, height to weight ratio, physical examination of a mass, and temperature, along with consistency of stools and extraintestinal manifestations. With addition of laboratory values, this index does not correlate with the CDAI or the Harvey-Bradshaw index. In an effort to measure mucosal disease directly, an endoscopic index of colonic disease activity has been developed and validated. The Crohn’s Disease Endoscopic Index of Severity can only be used to assess those with isolated colonic and terminal ileal disease. In the index, ulcers are counted and measured and the presence of stenosis and ulcerated stenosis are also weighed. The Rutgeerts score is used to measure mucosal activity in patients following ileocolic surgery and is based on counting the number of aphthous lesions in the neoterminal ileum. These tools measure colonic and terminal ileal changes in patients who have had surgery, but ignore many patients who have only small bowel disease.

Capsule endoscopy of the small bowel

New technology has emerged in an attempt to improve visualization and diagnosis within the small bowel. An endoscopic capsule (Given Imaging™, Yokneam, Israel) was developed to obtain images from the entire small bowel. The capsule, measuring 11 mm × 26 mm, contains six light emitting diodes, a lens, a color camera chip, two silver oxide batteries, a radiofrequency transmitter, and an antenna. The camera is a complementary metal oxide semiconductor chip. This chip requires less power than the charged coupled device chips presently found on video endoscopes and digital cameras, and can operate at very low levels of illumination. The capsule obtains two images per second and transmits the data via radiofrequency to a recording device worn about the patient’s waist. This recording device is a minicomputer with 5 GHz of memory, allowing storage of the 57,600 images obtained during a typical eight-hour examination. Once the study is completed, the recording device is downloaded to a computer workstation, the software in which provides the images on the computer screen. The capsule is disposable, does not need to be retrieved by the patient, and is passed naturally. The current model is the SB2, with the SB3 model to become available in the near future.

Mucosal healing in Crohn’s disease

The advent of capsule endoscopy has improved our understanding of the lining of the small bowel. Extensive research has shown that capsule endoscopy identifies ulcerating lesions of the small bowel better than any previous technology. This is true for nonsteroidal anti-inflammatory enteropathy and Crohn’s disease.16–19 At the same time, this advantage can be misleading, because research has shown that normal healthy individuals can have mucosal breaks in the small bowel.19 A celecoxib capsule trial only acted to open the door for insecurity in diagnosing Crohn’s disease and nonsteroidal anti-inflammatory enteropathy.19 Although the investigators routinely felt that mucosal breaks seen in the volunteers were single, small, and clinically insignificant, the trial made no effort to assess the size or extent of these lesions. However, this study showed that up to 13% of healthy volunteers had mucosal breaks in the small bowel. It also became clear that capsule endoscopy has several limitations. The focal length of the camera is too short to measure the size of lesions seen reliably. In addition, because the capsule is propelled by peristalsis, one cannot reliably count the exact number of lesions present. Indeed, this is the problem faced when trying to assess the severity of nonsteroidal anti-inflammatory
enteropathy or Crohn’s disease in clinical trials as well as in clinical practice.

The traditional target of therapy in Crohn’s disease has been relief of symptoms and clinical remission, measured by the CDAI.\textsuperscript{20} Most of the factors in the CDAI are subjective measures of patient symptoms. Over the past few years, the importance of more objective therapeutic endpoints, such as mucosal healing, has been emphasized. New biologic treatments, such as infliximab, demonstrated higher mucosal healing rates than steroids, and raised the question of whether mucosal healing should be the goal of treatment rather than clinical remission. Is there a correlation between clinical remission, as expressed in a CDAI < 150, and mucosal healing rates?

Although steroids are effective at suppressing acute inflammation, they have shown no benefit in maintaining remission or inducing mucosal healing.\textsuperscript{20} D’Haens et al demonstrated that early immunosuppression had a beneficial effect on mucosal healing, with 73% in an early immunosuppression group healed at the end of the study versus only 30% in a conventional step-up treatment group.\textsuperscript{20} In this landmark study, there was no association between remission as defined by CDAI and mucosal healing. The lack of correlation between clinical and endoscopic findings in patients with Crohn’s disease is well known to experienced gastroenterologists, and was described earlier. The endoscopic substudy of ACCENT I (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen I) demonstrated that, at week 10, only 36% of patients with mucosal healing were in remission as defined by the CDAI, 40% of patients in clinical remission by CDAI did not have endoscopic remission, and at week 54, 67% of patients with mucosal healing were in remission by CDAI, while 56% of patients in remission by CDAI did not have mucosal healing.\textsuperscript{21} Similar findings have been described for ulcerative colitis.\textsuperscript{22} In the first Active Ulcerative Colitis Trial (ACT I), clinical remission at week 8 for placebo, 5 mg/kg, and 10 mg/kg, was 15%, 39%, and 32%, respectively, whereas mucosal healing was 34%, 62%, and 59%, respectively. Can active disease be present if the mucosa is healed? Other causes of diarrhea should be taken into account, such as infection, bacterial overgrowth, cholestatic diarrhea, and irritable bowel syndrome. In the patient with Crohn’s disease, proximal inflammation outside the reach of the endoscope and stricture disease must be ruled out. Another aspect of this discrepancy is the patient in symptomatic remission without corticosteroids but also without mucosal healing. Both the patient and physician may feel reluctant to increase therapy without clear data indicating a real benefit with respect to disease progression. Achievement of long-term mucosal healing has been associated with a trend toward a decreased need for hospitalization and a decreased need for corticosteroid treatment in patients with Crohn’s disease.\textsuperscript{24}

**Niv score for Crohn’s disease of the small bowel**

The Niv score was devised to measure mucosal disease activity using capsule endoscopy. This scoring index is based on inflammatory score parameters, ie, erythema, hyperemia, edema, denudation, nodularity, aphthae, erosion, ulcer, bleeding; extent score: Focal, patchy, diffuse; and stricture score: Single-passed, multiple-passed, obstruction. The higher the score, the more involvement is observed. The advantage of this index is that it actually measures disease activity and not symptoms, and in an easy noninvasive manner. For assessing Crohn’s disease, mucosal healing can be seen directly, and if there is no mucosal disease, there can be no symptoms secondary to inflammatory bowel disease. The subjective nature of indices of disease activity is avoided, as is the problem of disease without symptoms. It is envisioned that the Niv score could diagnose Crohn’s disease (excluding normally occurring mucosal breaks), identify damage induced by nonsteroidal anti-inflammatory drugs, measure disease activity and severity, measure drug response for clinical trials and in practice, and guide medical management for the patient with Crohn’s disease of the small bowel.

The Niv score for capsule endoscopy in Crohn’s disease of the small bowel (ie, CECDAI) was developed\textsuperscript{4} and validated in a multicenter study.\textsuperscript{9} In these studies, the CECDAI was not correlated with the clinical score (CDAI) or the quality of life score (Inflammatory Bowel Disease Quality of Life), and specific ranges for remission or relapse (mild, moderate, and severe) were not established. The main problem in this regard is the lack of an accurate gold standard for disease behavior, and the lack of correlation between mucosal healing and clinical scores. The new generation of capsule that examines the small bowel and colon enables development of a new score that will cover Crohn’s disease at both sites and give a better answer than the Niv or Lewis score for the small bowel.\textsuperscript{9,23}

**Capsule endoscopy for Crohn’s disease: the new generation**

Recently, a new generation of capsule endoscopy was developed by Given Imaging, dedicated to inflammatory bowel disease, with new functions and abilities. This capsule has
two heads, with one camera at each end, and wider angle lenses of 172 degrees. In addition, there is a new recorder, transmission between the capsule and the recorder, and the number of frames per second is directly correlated with the velocity of the capsule. The new capsule will enable development of a new score that will be a summation of small bowel and colonic pathology.

Disclosure
The author is a principal investigator of two studies sponsored by Given Imaging.

References