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Should the MUHC Approve the Video Capsule Endoscopy System in the Diagnosis of Small Bowel Abnormalities?

A Technology Assessment

by

The Technology Assessment Unit (TAU)

of the McGill University Health Centre

(MUHC)

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Invitation. This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be *deeply appreciated* if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.

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Executive Summary

The capsule endoscopy is a wireless diagnostic tool that has been recently introduced primarily to investigate the cause of recurrent chronic gastrointestinal bleeding, particularly of the small bowel, which could not be determined by current diagnostic modalities.

The evaluation of a diagnostic tool is in many respects more difficult than evaluating therapeutic interventions. In general, study design of diagnostic tools is often inherently weak. The interpretation of results are limited by a lack of randomized trials, of a defined gold standard, of limited follow-up periods with no standardized assessment either of improved patient outcomes, or diminished resource utilization. This is the case for the video capsule.

Our systematic review of the capsule endoscopy literature suggests that the diagnostic yield in patients with comparable characteristics to those studied in the literature (patients with recurrent, severe gastrointestinal bleeding suspected to be located in the small bowel), is increased from approximately 30% with conventional diagnostic modalities to approximately 50% (Risk Difference 0.21 95% CI (0.12 – 0.31). Moreover, the video capsule has good performance standards (5% failure rate), excellent patient tolerability and a good safety profile (risk of intestinal obstruction < 1%, providing a small bowel series is initially performed).

Study limitations have precluded providing estimates of improved patients outcomes either in the short or long-term or estimates of decreased resource utilization or associated

savings. At present, the video capsule appears unlikely to replace current diagnostic modalities. Because of this lack of demonstrated benefit, evaluations carried by the The Comité d'Évaluation et de Diffusion des Innovations Technologiques (CÉDIT), and the American Society for Gastrointestinal Endoscopy Technology Assessment Committee did not endorse the use of the capsule for routine clinical use. No other report on the capsule endoscopy carried out by other technology assessment agencies was found. . Finally, the small number of MUHC patients who might benefit, the acquisition cost ($62,000) and the substantial physician time required for interpretation are additional impediments to recommending this technology.

However, the potential of this innovative technology is recognized and a later re-evaluation in light of more data may be performed. Moreover, the acquisition of this technology through research programs or private donations to help in better defining its future role could be considered.

Based on the above considerations TAU, while recognizing the innovative characteristics of the capsule endoscopy does not feel that there is sufficient evidence to recommend either the hospital purchase of this technology or its incorporation into routine clinical practice.

Foreword

On November 14, 2002 the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from Dr. Ewa Sidorowicz, Assistant Director, Professional Services, requesting the TAU to "give its opinion" concerning the use of endoscopic video capsule in the diagnosis of small bowel disorders. The objective of this report is therefore to evaluate the current available literature regarding the capsule endoscopy and to make recommendations regarding its use.

1. Introduction

1.1 Background

The endoscopic examination of the small bowel is necessary particularly for the evaluation of obscure gastrointestinal (GI) bleeding, but also in the diagnosis of small bowel tumors, polyposis syndromes, and inflammatory diseases of the small bowel [1].

More than 90% of the cases of chronic gastrointestinal bleeding (CGB) can be explained by using upper gastrointestinal endoscopy or colonoscopy. However, in cases of CGB where the source is suspected to be in the small bowel, success rates with conventional diagnostic procedures can be as low as 10-20%, although one study has demonstrated a successful rate of 60% [2]. Among the patients presenting obscure GI bleeding with normal upper GI endoscopy and colonoscopy findings, a small-bowel source can be identified in up to 40% of the cases with push, or sonde enteroscopy [3].

Difficulties in examining the small bowel arise due to a variety of reasons, such as, remoteness from the mouth and anus, its length (3.35-7.85m), and the presence of mesenteric attachments and multiple complex looped configurations [3]. Arteriovenous malformations, i.e., angyodysplasias of the

small bowel are detected in 31-46% of the patients by push enteroscopy, however, these figures may be overestimated as they can be mistaken with traumatic lesions [4].

Cancer of the small bowel is uncommon, but, unfortunately, due to the limitations of diagnostic testing, it historically carries a poor prognosis; some studies have shown that if it is diagnosed early, the prognosis is improved. Studies have shown that 10% of patients with obscure bleeding have a tumor of the small bowel [5].

Diagnosis of obscure bleeding may take a long time after the onset of the disease, which may result in high costs with diagnostic procedures, hospital admissions and blood transfusions. Studies in the literature found that the median time to diagnosis of obscure-overt bleeding was 2 years, with a range of 1 month to 8 years, and that patients with obscure bleeding requiring intraoperative enteroscopy had a mean of 5 hospital admissions (range 2-20), and a mean of 46 units of blood transfused (range 6-200) before surgical intervention [6].

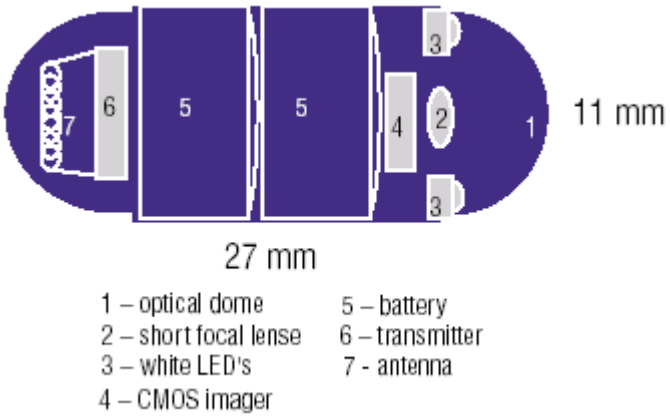
Appendices 1 and 2 present an algorithm for the evaluation of occult and obscure bleeding respectively, as recommended by the American Gastroenterological Association [7]; however, these algorithms do not include the capsule endoscopy as they were published before its use in patients.

1.2 The Capsule Endoscopy System

The capsule endoscopy system is produced by Given® Diagnostic Imaging System, and it consists of a capsule measuring 11mm x 26mm. The system includes an optical dome, lens, illuminating disk, imager, battery, transmitter and antenna (see Figure 1). Some investigators prefer to do a bowel purge in order to clear the distal small bowel [8]. Once ingested, the capsule travels through the small intestine, capturing two images per second and transmitting video signals that are received by relay sensors attached to the patient's body. The sensors send signals to a wireless data recorder in a belt worn

by the patient. After the image recording is complete, data are downloaded from the recorder to a workstation that produces a video record of the images from the small intestine. The capsule battery life is about eight hours, which is sufficient for imaging of the small intestine, but not long enough to provide images of the large intestine. The capsule is excreted after 8 to 72 hours [9]. The images provided are time coded [10].

Figure 1 Capsule endoscopy system [11].



Besides the time required to complete the examination, the time required to view the images produced may take up to 2 hours. However, as the reader gains more experience, this time may be reduced to about 1 hour[4].

The design of the capsule endoscopy is only suited for imaging of the small bowel as it passes too quickly through the esophagus to obtain adequate imaging. The stomach is incompletely imaged due to its large lumen, and the colon has not being imaged satisfactorily yet [8].

Health Canada, in July 2001, issued a Class II medical licence for the Given® Capsule endoscopy, as an adjunctive tool in the detection of gastrointestinal disorders and diseases. And the US Food and Drug Administration (FDA) approved it in August 2001. The product has also been granted

approval in Israel, the European Union, and Australia [9]. According to the manufacturer, the Given® capsule endoscopy has been approved in countries in Latin America, and Africa.

Contraindications to its use are the use of cardiac pacemakers or other implanted devices, known intestinal obstruction or significant intestinal strictures or fistulas. Physicians are warned to perform a contrast x-ray series in patients with suspected strictures or fistulas prior to the use of the capsule endoscopy, as the capsule may lodge in these areas, requiring surgical removal in rare instances. It must also be born in mind that the variation in the patients GI motility may decrease the length of the small bowel that is imaged [12]. Due to the size of the capsule, it cannot be used in children under approximately 10 years old [13].

According to the manufacturer, a new feature of the capsule that will allow physicians to identify the bleeding sites in the small intestine with greater precision will be available in the future (from the company website).

According to CCOHTA [9], the reported cost of the equipment was CDN$ 35,000, plus CDN$ 900 per single-use capsule in 2001, however, presently, the cost of the equipment has been reported to be approximately CDN$ 62,000, as per the information given by the representative, Mr. Jacques Binette from the distributor Southmedic. This price includes 10 capsules, but the cost of each capsule purchased separately is approximately CDN$ 900.00.

1.3 Alternative Methods

Push enteroscopy is a procedure in which the enteroscope is pushed through the mouth, via the upper GI tract, into the small bowel, it is the most commonly used endoscopic diagnostic procedure for examining the small bowel [14]. It is usually proposed only after other endoscopic procedures fail to locate the source of bleeding, as it is a more invasive procedure and may require deep sedation or general

anesthesia [15]. The examination takes 15-45 minutes and requires a skilled endoscopist; it can also be uncomfortable and even painful for some patients. With this diagnostic procedure, between 80 and 120 cm beyond the ligament of Treitz can be examined [3]. Some advantages of push enteroscopy are that it allows for biopsies to be taken in order to confirm the diagnosis, also permitting treatment measures such as hemostasis of active bleeding, and thermal destruction of potential bleeding sources [2]. The diagnostic yield of push enteroscopy is around 15-35% for obscure bleeding of the small bowel [14], although in some uncontrolled prospective studies, its diagnostic yield has been up to 50%. Push enteroscopy is considered to be the most effective diagnostic method for the diagnosis of CGB [2].

Small bowel series, i.e., x-rays after ingestion of a contrast medium, have been shown to have a low diagnostic yield, 5%, and a high false negative rate of 41.7% [14]. Small barium series are not able to demonstrate flat lesions, or angyodysplasias, one of the most common pathologic lesions found [3].

Enteroclysis is a type of x-ray in which the contrast medium is administered via a small tube placed directly in the proximal intestine [14]. It may have a diagnostic yield of up to 90% in patients with small bowel tumors and Crohn's disease, on the other hand, in patients with unexplained GI bleeding, the diagnostic yield drops to around 10-20% [4]; when compared to the small bowel series, enteroclysis presents some disadvantages such as a greater exposure to radiation, greater patient discomfort and longer procedure time [14].

Sonde enteroscopy involves transnasal insertion of a longer enteroscope, which is advanced through the digestive tract to the distal portion of the small bowel by peristalsis, over an approximately 8-hour period. It has the potential to examine the entire small bowel, however, the procedure takes 6-8 hours to be completed, it is uncomfortable and often painful. Sonde enteroscopy is currently rarely performed [3]. Its overall diagnostic rate ranges from 26% to 54% [6].

Intraoperative enteroscopy is considered to be the "gold standard" for small bowel examination because most, if not all of the small bowel can be visualized, with a reported diagnostic yield of 70-100%. As this is an invasive procedure, posing a risk of complications to the patients, it is most often used in patients with obscure bleeding, who, after multiple testing, remain undiagnosed and continue to require blood transfusions. Complication rates range from 0% to 52%, and mortality related to the procedure or to postoperative complications can be up to 11% [6].

Radionuclide scanning has a sensitivity of 50-90%, providing that there is active bleeding. In order to produce a positive scan result, there has to be a bleeding rate of 0.1 to 0.4 ml/min [14].

Angiography may be used as a diagnostic tool in gastrointestinal bleeding, although the accuracy is highest with active bleeding of at least 0.5 ml/min. It can also diagnose lesions that are not actively bleeding, such as vascular ectasia or tumors [16], and has the advantage of accurately defining the site of the pathology. Data pooled from studies involving 675 patients who underwent angiography, showed a mean positivity rate of 47%; the rate of positive tests may increase to 61-72% if only patients who are actively bleeding are used, as defined by the number of transfusions or hemodynamic compromise [17]. The patient population in these studies may also have included patients with colonic sources of bleeding in addition to small-bowel sources, which may differ from the patient population that will use the capsule endoscopy.

2. Literature Review

2.1 Method

The main database used for the literature review was MEDLINE, but other databases such as the Cochrane Library, and Technology Assessment Agencies sites were also searched. The keywords used for the search were "video capsule", "capsule endoscopy", "wireless endoscopy", and "m2a" (M2A™ disposable imaging capsule). There were no limitations as to language or year of publication.

2.2 Pre-clinical studies

Appleyard et al [3], compared the capsule endoscopy with push enteroscopy in animals. Colored beads were sewn (3-6 mm in diameter) into 9 canine small bowels. A total of 89 beads, 9-12 in each animal, were inserted in a pre-determined randomized order; half of the beads were inserted within a meter of the pylorus, within the reach of the push entereoscope. A week later, push enteroscopy was performed once for each animal, and capsule endoscopy examinations were performed 1-3 times for each animal in a random order. Two experienced endoscopists evaluated the capsule endoscopy images, and the histological appearance of the small intestine was interpreted by a pathologist. The endoscopists who evaluated the images of the capsule endoscopies were blinded to the push enteroscopy findings.

A median of 3 (interquartile range - IQR 3-4) beads per animal was detected by push enteroscopy, compared to a median of 6 (IQR 6-7) beads for the capsule endoscopy ($p < 0.001$). In total, for the 9 push enteroscopy examinations, 33 of the 89 implanted beads (37%) were detected, while the capsule endoscopy identified 143 of the 225 beads (64%) during the 23 examinations; this difference was statistically significant ($p < 0.0001$). The capsule's sensitivity in detecting beads sewn in the full length of the small bowel was 64% compared to 37% for push enteroscopy, their specificity were 92% and 97% respectively. The push enteroscope had a sensitivity of 94% in identifying beads within its range, compared to an overall sensitivity of 53% for the capsule within the same range; according to the authors, the sensitivity of the capsule in this range may have been underestimated given the likelihood of the first 1 or 2 beads in the duodenum to be missed, and the loss of some beads in one of the dogs during the second capsule endoscopy. Capsule endoscopy was able to identify beads sewn beyond the reach of the push enteroscope [3].

Comments: The color and order of the beads sewn in the dogs intestines was done in a pre-determined randomized order, and the endoscopists and enteroscopists were blinded to each others' findings. The capsule endoscopy was able to identify more beads than the push enteroscope overall,

however, if the region within reach of the push enteroscope is considered, the latter had a higher sensitivity, although no statistical significance test result was reported for this comparison.

2.3 Clinical studies

The first study in humans was done by Iddan et al. [18] in 10 healthy volunteers. No complication with the capsule was reported, and the images were visualized without problems.

Appleyard et al. [19] first reported results of the capsule endoscopy in patients with obscure gastrointestinal bleeding. Four patients were studied, and all of them considered the capsule as easy to swallow, painless, and preferable to conventional endoscopy. The information obtained with the procedure apparently helped in directing further treatment in those patients.

Lewis and Swain [10] conducted a prospective pilot study to compare the number of lesions identified by the capsule endoscopy and push enteroscopy in patients with GI bleeding of obscure etiology. Twenty-one patients between 21 and 80 years of age who were referred for enteroscopy were included in the study. In order to be eligible for the study, patients should have undergone colonoscopy, upper endoscopy, and a small bowel series, all of which with negative results. Patients with a history of bowel obstruction were excluded from the study due to a risk of acute bowel obstruction caused by lodging of the capsule; diabetic patients were excluded from the study because of a concern that a delay in gastric emptying could reduce recording time available for the small bowel; patients with pacemakers and those who were pregnant were also excluded as a precaution as this was an initial pilot study. Following the capsule endoscopy examination, the patients underwent push enteroscopy with a 2.5-meter push enteroscope without an overtube; a moderate level of sedation was needed in all patients for the push enteroscopy. Two investigators independently reviewed the capsule images, and the second investigator was blinded to the medical history of the patients, to the push enteroscopy findings, and to the review of the capsule endoscopy images by the first investigator; push enteroscopy was reviewed by one

investigator. The patients answered a telephone-administered questionnaire with information about their impressions of the procedures after the capsule endoscopy, after the capsule retrieval, and after the push enteroscopy; the questionnaire was administered one day after the enteroscopy was performed.

On average, before entering the study, the patients had been bleeding for 36.5 months (2-144 months), with an average of 2.9 hospitalizations for bleeding, and an average of 28 units of packed red cells (range 0-300 units) transfused. The average lowest hemoglobin level was 6.4 g/dL. The patients had undergone extensive evaluation before study entry, including 78 colonoscopies, 83 upper endoscopies, 19 small bowel series, 4 enteroclysis examinations, 22 push enteroscopies among others; except for an enteroclysis study that revealed a possible polyp in the jejunum, all other exams were negative. No complications occurred during the examinations, however, 3 capsules did not reach the colon within the 8-hours acquisition time, limiting the time available for the imaging of the small bowel. Due to a processing error in one of the examinations, the data for this patient was eliminated from the analysis, therefore 20 of 21 capsules were studied. The capsule images were considered of good to excellent quality by both investigators, and they reported similar findings after reviewing the images. Push enteroscopy identified the source of obscure bleeding in 6 out of 20 patients (30%), compared to 11 out of 20 (55%) for the capsule endoscopy. However, this difference was not statistically significant ($p=0.0625$). The capsule endoscopy found a source of bleeding in a region of the small intestine that could not be reached by an enteroscope in 5 out of 14 patients (36%) who had normal push enteroscopy. No additional lesions were identified by push enteroscopy in the small intestine that had not been visualized by the capsule endoscopy. All of the patients preferred the capsule endoscopy to enteroscopy. According to the authors, the results of this study need to be confirmed by larger, comparative studies, as well as studies that evaluate if the capsule endoscopy contributes to the subsequent management of the patients.

Comments: The study was not randomized, however, the patients acted as their own controls; the three investigators who evaluated the images were reported to be blinded to each others' findings. The patients

had undergone several diagnostic examinations prior to study entry, none of which had a definite positive finding; the study population was small as this was a pilot study, and it seems that the patients presented with severe GI bleeding, as judged by the mean time of bleeding prior to study entry, hemoglobin level, and need for blood transfusions. The capsule identified more lesions than push enteroscopy, although this result was not statistically significant; the capsule was able to identify lesions not identified by push enteroscopy, and the latter did not identify any lesion that had not been identified by the capsule. The images of the capsule endoscopy could not be reviewed in one patient (5%) due to processing errors, and, although the data from this patient were excluded from the comparative analysis, the result of push enteroscopy for this patient could have been reported, and perhaps included in the study as a failure for the capsule endoscopy, and the actual result for the push enteroscopy. Three capsules did not reach the colon within the 8 hours battery life, constraining the length of the small bowel examined. The authors reported that the images of the capsule endoscopy were used to guide therapy, but no mention was made as to whether the images of the enteroscope would have been able to guide therapy as well. None of the patients had any complication in this study. In 14% of the examinations (3/21), the time of imaging of the small bowel was limited due to a longer transit time, and the authors also mentioned that tumbling of the capsule in the small bowel is infrequent, but possible, decreasing thus the quality of the images.

Ell et al. [2] compared the results of the capsule endoscopy to push enteroscopy in 32 patients with CGB in whom the bleeding source was suspected to be in the small bowel. Patients had to present CGB for at least 6 months, and episodes of active bleeding within the preceding 6 months; patients with known consumption of non-steroidal anti-inflammatory drugs, hemoglobin > 10 g/dl, and with bleeding sources outside of the small bowel were excluded from the study. The patients referred to the clinic due to CGB and guaiac-positive stool test during the study period, i.e., from April 2001 until October 2001, underwent the department's standard work-up, consisting of upper gastrointestinal endoscopy, colonoscopy, enteroclysis, abdominal angiography, blood pool scintigraphy, and Meckel scintigraphy; diagnostic procedures that had been carried-out in the previous 6 months, and for which the reports were available

and with good quality, were not repeated. Blood pool scintigraphy was only performed when there were signs of active bleeding (13 patients), angiography was not done in 6 patients due to known allergy to the contrast medium, and Meckel scintigraphy was only performed in patients under 60 years of age (21 patients). From the 65 patients referred, 33 patients were excluded from the study, either due to exclusion criteria, or pathological findings during previous procedures, and 4 of them refused to undergo complete work-up. Thus, 32 patients underwent the full diagnostic work-up, capsule endoscopy and push enteroscopy examination.

The average age was 61 $\pm$ 14 years and, on average, prior to entering the study, the patients had been bleeding for 29 $\pm$ 24 months, the average lowest hemoglobin level was 5.9 $\pm$ 1.4g/dl, an average of 17 $\pm$ 18 blood units had been transfused, and an average of 6 $\pm$ 7 hospitalizations had been required to treat and diagnose the bleeding source, with an average of 14 $\pm$ 9 diagnostic tests. Enteroclysis and Meckel scintigraphy were negative in all patients examined, blood pool scintigraphy showed positive results that correlated with the push enteroscopy and the capsule endoscopy in one patient, and mesenteric angiography produced positive findings in four patients. In total, the conventional examination procedures identified a lesion in 5 out of 32 patients (16%). The capsule endoscopy found a definite evidence of a bleeding source in 21 out of 32 patients (66%), whereas push enteroscopy found a definite evidence of a bleeding source in 9 out of 32 patients (28%), and a questionable evidence in an additional 3 patients (9%); all clear-cut findings obtained with push enteroscopy were also seen with the capsule endoscopy, either unambiguously (6 patients), or questionably (3 patients). The difference in definite bleeding sources identified by the two techniques was statistically significant ($p < 0.0001$). The capsule endoscopy did not demonstrate a biopsy-proven lymphoma in the upper third of the small bowel, however it was able to find a malignant stenosis in the mid-part of the small bowel in the same patient. On the other hand, push enteroscopy only demonstrated 8 of the 21 findings identified on the capsule endoscopy. The capsule endoscopy procedure had to be repeated in 2 patients, in one due to a technical problem, and in the other patient, due to an active bleeding in the small bowel; delayed passage of the capsule was

observed in two patients, i.e., 4 and 10 weeks after its ingestion. In one patient with a small-bowel lymphoma, the capsule did not pass a distally located stenosis and was surgically removed 6 months later. According to the authors, in this trial, the capsule endoscopy was found to be more effective than push enteroscopy. The authors also mentioned that part of the efficacy of the capsule endoscopy is due to the fact that patients were carefully selected, and presenting with severe CGB, however, it is not possible to say if the same diagnostic yield would be seen in patients with guaiac positive mild iron-deficiency anemia. Still according to the authors, the indication for capsule endoscopy presupposes careful selection of the patients and accurate prior upper and lower gastrointestinal endoscopy examinations; they also expected that the capsule endoscopy would help reduce the number of diagnostic procedures, and could become the initial diagnostic choice in patients with CGB and negative upper and lower gastrointestinal endoscopy. Nevertheless, the authors believe that further studies are necessary in order to confirm the findings [2].

Comments: As in the previous study the patients acted as their own controls. Infrequent technical problems and delayed passage of the capsule occurred. Generalization of the study results is difficult due to the small selected population. It was not clear if the investigators assessing the images were blinded to the findings obtained with the other procedures. The capsule endoscopy identified a statistically significant higher number of lesions than the push enteroscopy (66% versus 28% respectively). The authors did not mention if the identification of the lesions caused any change in the patients treatment, or if the delay passage of the capsule in the 3 patients compromised the small bowel imaging.

Costamagna [4] evaluated 22 consecutive patients with suspected small bowel disease by performing a barium follow-through, followed by capsule endoscopy 4 days later. Patients who were pregnant, under 18 years of age, using cardiac pacemakers or other implanted eletromedical devices, with suspected or documented intestinal obstruction or strictures were excluded from the study. Two patients were excluded from the study after the barium follow-through examination revealed a sub-clinical ileal

stenosis. Therefore, the results of barium follow-through and the capsule endoscopy were compared in 20 patients, i.e., 13 with obscure GI bleeding, 3 with suspected Crohn's disease/recurrence, 1 with suspected sarcoma recurrence, 1 with unexplained chronic diarrhea, 1 with familial adenomatous polyposis, and 1 with small bowel polyps; multiple diagnostic procedures had been performed in these 20 patients, without any positive finding. The endoscopists and radiologists were aware of the identity and clinical presentations of the patients. However, the endoscopists were blinded to the results of the barium follow-through study. The barium radiographs required 30-120 minutes to be completed, and an additional 15 minutes for the interpretation, whereas for the capsule endoscopy, the examination took 8 hours, and approximately 2 additional hours for the verification of the images. The barium follow-through was considered diagnostic in 6 out of 22 patients (27%), whereas the capsule endoscopy was considered diagnostic in 9 patients (45%), suspicious in 5 patients (40%), and failed in 3 patients (15%); the statistical significance of the difference in total diagnostic yield between the two procedures was not reported. If only the 13 patients with obscure bleeding were considered, the capsule endoscopy was considered diagnostic in 4 patients (31%), compared to 1 patient (8%) in the barium radiography group. The capsule endoscopy showed angiodysplastic lesions in 8 out of 13 patients (62%) with obscure GI bleeding. In this study, no complications were reported, except for a capsule endoscopy battery dysfunction after 5 hours in one patient. The authors considered the capsule endoscopy to have advantages such as a good diagnostic yield, convenience, comfort, repeatability, and ability to be performed on an outpatient basis; on the other hand, some disadvantages included non-ability to take biopsy specimens, difficulties in determining the exact site of the bleeding within the small bowel, and a possible need for a preparation before the examination, as some patients were not cleaned enough to see the entire small bowel; furthermore, for an inexperienced reader, it can take up to 2 hours to view the film, although this can be decreased to approximately 1 hour after some experience is gained. Certain patients may need a barium study evaluation before the capsule endoscopy examination in order to avoid the risk of a possible intestinal obstruction by the capsule.

Comments: As with the previous studies, because of the small number of patients no definite conclusions can be drawn.

Scapa et al. [1] examined the capsule endoscopy in 35 patients aged 18-75 years who suffered from unexplained bleeding of an undetermined nature from the GI tract and/or suspected illness of the small bowel. A small bowel x-ray was performed in all patients in order to screen for intestinal obstruction; patients with history of intestinal obstruction or major abdominal surgery, diabetes mellitus and pregnant women were excluded from the study. All patients had undergone other diagnostic procedures without any positive finding before entering the study. Abnormal findings with the capsule endoscopy were found in 29 of 35 patients (82.9%). However, significant pathological findings that explained the clinical background of the patient were found in 22 of the 35 patients (62.9%); the capsule endoscopy found the source of bleeding in 15 out of 20 patients with iron deficiency anemia (hemoglobin=9.2 g/dL). One patient with lymphangiectasia, diagnosed in childhood, showed normal small bowel with the capsule examination, in one patient with celiac disease, the capsule did not detect a small bowel polyp suspected by small bowel CT. Mild transient abdominal pain was reported by two patients, possibly connected to the procedure in one, and with a remote association to the capsule endoscopy ingestion in the other; no other complications were reported within one month of the capsule ingestion. The authors believed that the capsule endoscopy could be used before the push enteroscopy as it is noninvasive, painless, does not require hospitalization, is safer, and is possibly a more accurate procedure; nevertheless, they also mentioned that future studies should evaluate if the capsule endoscopy changes the natural history of small bowel diseases not diagnosed by any other measure. The authors also reported that some patients diagnosed by the capsule received definitive treatment for the first time in their medical history.

Comments: This was a within patient comparison of the capsule with traditional diagnostic procedures. Its patient population was not described in detail, making it difficult to generalize its results to

other populations. The authors mentioned that the diagnosis made by the capsule changed the treatment of many patients, but they did not specify the exact number of patients in which this occurred.

Abstracts: Most of the clinical studies that were found in the literature have appeared as abstracts in conferences. Table 1 summarizes these abstracts. Overall, the investigators involved in these studies reported a positive experience with the use of the capsule endoscopy, and, in general, in the comparative studies, found that it was superior to other diagnostic procedures, with the exception of one study, Van Gossum et al [20]. However, as discussed by some of the authors, further studies are needed. Some authors, such as Chutkan et al [21], and Lim et al [22] consider that long-term studies are necessary in order to assess the clinical significance of these findings. These results should also be interpreted with caution, as the information available in abstracts is limited. Three abstracts of studies performed in Canada were found in the literature, two of them were performed at St. Michael's Hospital in Toronto[23] [24], and the third one was performed at St. Justine's Hospital in Montreal [25].

Table 1 – Clinical Studies published as abstracts

Comparison (reference)	# Patients	Population	Results	Country – Year of Publication
Small bowel enteroscopy [26]	12	Obscure gastrointestinal bleeding or Iron deficiency anemia	Abnormal findings found in: PE – 4 (33%) VC - 10 (83%) No statistical test reported	Italy 2002
Push Enteroscopy [27]	29	Obscure GI bleeding with previously normal endoscopies	Etiology discovered in : PE – 8 (28%) VC 17 (59%) $p < 0.05$	Italy 2002
Push Enteroscopy [28]	57	Chronic anemia or Obscure occult/overt digestive bleeding with negative endoscopies	Detection of lesions in: PE - 32/57 (56%) VC - 43/57 (75%) p=0.04	France 2002
Push-Enteroscopy [20]	21	Unexplained iron-deficiency anemia or Digestive blood loss	Detection of lesions in PE – 16 (83%) VC – 13 (69%) No statistical test reported	Belgium 2002
Barium Follow-through / Entero CT [29]	20	Suspected Crohn's Disease	Detection of lesions in: VC – 70% Barium – 37% Entero CT – 32%	Israel 2002
- [30]	12	Suspected occult GI bleeding with prior negative endoscopy	Detection of lesions in: VC – 9/12 (75%)	Germany 2002
- [31]	17	Suspected Crohn's Disease that cannot be confirmed by other standard modalities	Detection of lesions in: 12/17 (70.6%)	Israel 2002
- [25]	9	Children with occult Crohn's disease, intestinal poyposis, GI bleeding	Detection of lesions in: Occult bleeding – 2/3 Crohn's disease – 2/2 Polyposis – 3/3 1 jejunal stricture	Canada 2002 (St. Justine Hospital – Montreal)
- [23]	8 (4 controls)	Celiac Disease	All 4 cases of histologically proven of villous atrophy were identified by reviewing the capsule endoscopy images No statistical test was reported	Canada 2002 (St.Michael's Hospital – Toronto)
- [32]	40	Chronic iron deficiency anemia Chronic abdominal pain	Detection of lesions in Chronic iron deficiency anemia – 16/36 (44%) Chronic abdominal pain – ¼ (25%)	US 2002
- [33]	45	Obscure GI bleeding	Abnormalities found in 85% of the cases	US 2002
Small Bowel follow-through CT scan [34]	48	GI bleeding of unknown origin Inflammatory bowel disease Iron deficiency anemia Chronic abdominal pain	CE identified significant lesions missed on CT scans and small bowel follow through	US 2002
- [35]	16	Prior evaluations with inconclusive results Obscure bleeding/abdominal pain	Detection of lesions in 14 (88%) patients	US 2002
- [21]	70	Prior evaluations with inconclusive results Obscure GI bleeding	58% positive findings	US 2002
Push Enteroscopy [22]	20	Obscure GI bleeding	Detection of lesions in: VC – 14 (70%) PE - 9 (45%) No statistical test was reported	US 2002
Small bowel follow through [36]	11	Crohn's disease	Sensitivity of VC was higher than small bowel follow through	US 2002
Push Enteroscopy [24]	10	Chronic obscure GI bleeding	Detection of lesions in: VC – 50% PE – 30% No statistical test was reported	Canada 2002
- [37]	21	Obscure / overt GI bleeding	VC detects small bowel abnormalities in a significant number of patients with obscure GI bleeding	US 2002
- [38]	140	Crohn's disease	66% of patients with positive findings	US 2002

Although mainly used for the diagnosis of small bowel abnormalities, a case of identification of obscure bleeding in the right colon by capsule endoscopy has been reported in the literature. However, colonoscopy plus retrograde ileoscopy had to be performed in order to confirm the diagnosis, which was found to be a Dieulafoy lesion. The capsule endoscopy has not been approved for the diagnosis of lesions in the colon [15].

2.4 Safety

According to Given Imaging, lodging of the capsule within the GI tract requiring surgical removal occurs in approximately 0.5% of the ingestions, but this rate is expected to be higher in patients with Crohn's disease or obstructive symptoms [8]. In an abstract published by Barkin et al.[39], 0.75% of 937 patients worldwide who ingested the capsule required surgical intervention to remove the capsule from the gastrointestinal tract.

Lewis [40] studied the use of the capsule endoscopy in 75 patients who had certain contraindications to its use such as, diabetics, patients using pacemakers and patients who had a history of previous intra-abdominal surgery. Patients with gastrointestinal obstruction were not included in the study. Gastric and small bowel emptying was similar in all patients, and no difference in emptying times was seen between diabetic and non-diabetic patients; no complication occurred in patients using pacemakers. The author concluded that diabetes, use of pacemakers, and previous abdominal surgery do not appear to be contraindications to the capsule endoscopy use. However, patients must be careful not to disconnect the recording device. In one-third of the exams, the capsule may not reach the colon within 8 hours, and, therefore, a longer acquisition time should be considered. The information was published as an abstract, thus detailed information about the patient population was not available; there were no pregnant women in this study.

Smith et al. [41] studied the safety of capsule endoscopy in 71 adult subjects. Some complications were reported such as; three capsule failures requiring a repeat examination; one capsule did not pass beyond the pylorus at the end of the exam, one capsule was retained in the anastomosis of an esophago-jejunostomy; five exams were compromised by transmission gaps lasting from 1 minute to 2.5 hours. The large bowel was not reached in 12 out of 67 patients (18%) within the 8-hours recording time; surgical removal of the capsule was necessary in two patients (3%), one who presented symptomatic capsule retention, consisting of abdominal distension, nausea and pain, and another patient who did not pass the capsule two weeks after the exam due to small bowel stricture.

2.5 Technology Assessment Agencies Reviews

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) issued a communication bulletin in November 2001, stating that capsule endoscopy is a significant extension to the methods available for examination of the small intestine, and that it may be mainly used in major centers with expertise in gastrointestinal endoscopy. According to CCOHTA, the review of the images produced by capsule endoscopy requires considerable physician time and experience, but patient reports indicate that capsule endoscopy examination is preferred to traditional endoscopic procedures [9].

The Comité d'Évaluation et de Diffusion des Innovations Technologiques (CÉDIT) has issued a Recommendation Report [42] on the capsule endoscopy. Stating. According to CÉDIT, it allows physicians to conduct out-patient exploration of the entire small intestine without the need for anesthesia or sedation, but, when compared to enteroscopy, its images have a lower quality, and it has the disadvantage of not allowing for biopsies or treatment-related procedures to be performed. CÉDIT also considered that the assessment of its reliability was poorly documented. According to CÉDIT, tolerance to the capsule endoscopy exam appears to be satisfactory, but its use has not yet been sufficiently evaluated to warrant recommendation of it widespread use. CÉDIT therefore supported a study with the capsule endoscopy in

order to gather information on its efficacy in patients with obscure gastrointestinal bleeding (CÉDIT). This study has not been published at this point.

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Assessment Committee [43] considered that further research and experience are required to assess the role of the capsule endoscopy in the evaluation and management of digestive tract disorders.

2.6 Economic studies

No study that evaluated the cost-effectiveness of capsule endoscopy compared to other diagnostic procedures was found in the literature.

Goldfarb et al. [14] discussed the economic implications of the use of the capsule endoscopy for the diagnosis of obscure bleeding. However, a full cost-analysis was not performed. This study presents a model based on literature review and information given by specialists; the model presented shows how current diagnostic tools and protocols impact on costs (see Appendix 3). The author also considers that capsule endoscopy has the potential for cost savings due to the following factors:

- improved diagnostic yield
- reduction in the number of inconclusive tests, as the capsule traverses the entire small bowel
- earlier diagnosis of potentially adverse conditions, such as malignancies of the small bowel
- reduced complications, such as intestinal tears resulting from placement of the enteroscope and/or infection
- reduced pain and discomfort associated with the diagnostic procedure
- reduced losses in productivity as a result of undergoing multiple testing

Comments: The author provides a model that identifies possible contributors to direct and indirect costs associated with diagnosing obscure bleeding. The model was developed based on the literature and

consultation with clinicians. No evidence of the possible cost savings mentioned by the author were found in the literature. Moreover, the author did not include possible complications that may arise as a consequence of the use of the capsule in the discussion.

3. Summary of the Literature Review

Capsule endoscopy was able to identify a higher proportion of lesions than push enteroscopy and barium follow-through in the few studies published so far. However, in the case of a diagnostic test, the biggest concern is with its specificity and sensitivity, which are obtained through comparisons with a gold standard, i.e., surgical enteroscopy in this case. Unfortunately, such studies are not feasible as only some of the patients who could use the capsule endoscopy would be able to undergo surgical enteroscopy, due to the invasiveness of this procedure. Without having information on the sensitivity and specificity of a test, the medical community has to judge its efficacy based on its diagnostic yield, which is contaminated by the presence of false positives and false negatives [8]. Appendix 4 presents a summary of the results of the clinical studies found in the literature and demonstrates a consistently superior diagnostic yield with the capsule endoscopy.

It is expected that the population of patients who will likely benefit from this new technology will be those with bleeding of obscure origin or severe iron deficiency anemia caused by chronic GI blood loss, and, in this population, the capsule endoscopy is expected to identify lesions that may be causing the bleeding in 50% of the cases. Although precise localization of these lesions will be difficult, the localization of a general region of the small bowel might be helpful for those patients who require surgery, as it allows the surgeon to limit the extent of the small bowel exploration. If a lesion is found with capsule endoscopy, it is also necessary to evaluate if diagnosis improves the patient's outcome. It is not expected that capsule endoscopy will replace other diagnostic procedures such as barium examination and push enteroscopy as the barium examination still precedes capsule endoscopy in order to screen for

possible obstructions or strictures, and, as push enteroscopy also allows for some biopsies and treatments to be performed. The capsule endoscopy will also likely not replace scintigraphy or angiography in the acute setting due to the time required to complete the examination, i.e., 8 hours [8]. The considerable physician time and training to review the images produced by the capsule should also be taken into account, as well as the fact that, presently, there is no billing code for reimbursement of the procedure to the physicians.

Capsule endoscopy is an innovative procedure that does not require hospitalization. However, some technological aspects still need improvements such as, random image sampling, lack of control over the progress of the capsule through the small bowel, restricted field of view, limited battery life of 8 hours, and lack of precise information about the capsule's localization in the small intestine. There have been cases in which the capsule was lodged in strictures or fistulas, requiring surgical removal. Patient preparation before the exam, using a purge, is considered necessary by some investigators. The quality of the video images transmitted by the capsule were considered to be slightly poorer than those of the new video push enteroscopes, but better than those obtained with sonde enteroscopes. Despite these limitations, some authors believe that the capsule endoscopy might be placed alongside push enterosocopy for the diagnosis of diseases of the small bowel [44]. A low rate of processing errors with the capsule endoscopy system, i.e., approximately 5%, was seen in some of the articles published. Patient tolerability was good, and the patients preferred the capsule endoscopy to other procedures.

4. Discussion

The capsule endoscopy presents some advantages, such as, not being an invasive procedure, its ability to be performed on an outpatient basis, and, from the patients perspective, being less uncomfortable and painful than the other procedures, as reported in the literature. However, the use of the capsule endoscopy is not possible in children of less than 10 years of age [13]. By considering the results of the studies published, it can be estimated the capsule endoscopy diagnosed approximately 21% (95% CI:

0.12 , 0.31) more lesions than the other diagnostic procedures in the selected population studied (Appendix 5). However, the lack of negative, or even equivocal studies may suggest the possibility of publication bias. Furthermore, it must also be considered that these estimates are subject to the shortcomings of the studies published, which were previously pointed out. Studies with larger samples, and studies that evaluate the long-term outcomes are still needed.

A low rate of occurrence of technical problems, about 5%, was reported in the literature Specifically, these were usually due to battery malfunction, or the capsule not reaching the colon within the battery life, i.e., 8 hours, due to delayed GI motility even in non-diabetic patients. Also, lodging of the capsule in the small intestine requiring surgical intervention was seen in rare cases (about 1 in 200). The time required to complete the examination is approximately 8 hours, and another 1-2 hours are necessary to review the images. Training of an endoscopist to view the images is also necessary.

It hasn't been defined what the role of the capsule endoscopy will be, although some authors place it alongside or before push enteroscopy. Nevertheless, it is unlikely that the capsule endoscopy will replace barium radiography, as it is necessary in order to screen for intestinal strictures. Push enteroscopy will still often be required for biopsies and specific treatments to be performed.

It seems unlikely that capsule endoscopy is going to cause cost savings in the short-term, as it does not replace other diagnostic procedures. However, there may be a decrease in the number of procedures performed, as well as in recurrent treatments such as transfusions and hospitalizations in some patients, which may result in long term cost savings. Some authors also argued that, allowing an early diagnosis of malignancies might impact the patient outcomes, which may influence the treatment costs on the long run. Unfortunately, there is not enough evidence in the literature to confirm if these cost savings caused by the use of capsule endoscopy will occur, and if so, if they will overcome its costs, such as

equipment (CDN$ 62,000), capsule (CDN$ 900.00), and personnel costs. The capsule endoscopy procedure presently doesn't have a billing code at the RAMQ.

To evaluate the number of MUHC patients who might be prospective candidates for this technology, we examined the MED-ECHO administrative hospital discharge database. Between April 1st 1996 and March 31st 2001, there were 316 hospitalizations in the Royal Victoria Hospital and Montreal General Hospital due to undiagnosed GI bleeding (ICD-9 code:578.9), and blood in stool (ICD-9 code:578.1); among these hospitalizations, 286 patients had only one hospitalization, 23 had two hospitalizations, 4 patients had three hospitalizations, 2 patients had four hospitalizations, and 1 patient had 5 hospitalizations. The length of stay was approximately 7 to 8 days, and 50% of the patients stayed in hospital for 5 days or less. The total number of days spent in hospital for these patients was 2,457. Ninety-two patients stayed in the intensive-care unit (ICU), adding to a total of 328 days in the ICU. Therefore, we identified only 7 patients in this time frame who had recurrent non-diagnosed GI bleeds on a severity to require more than 2 hospitalizations.

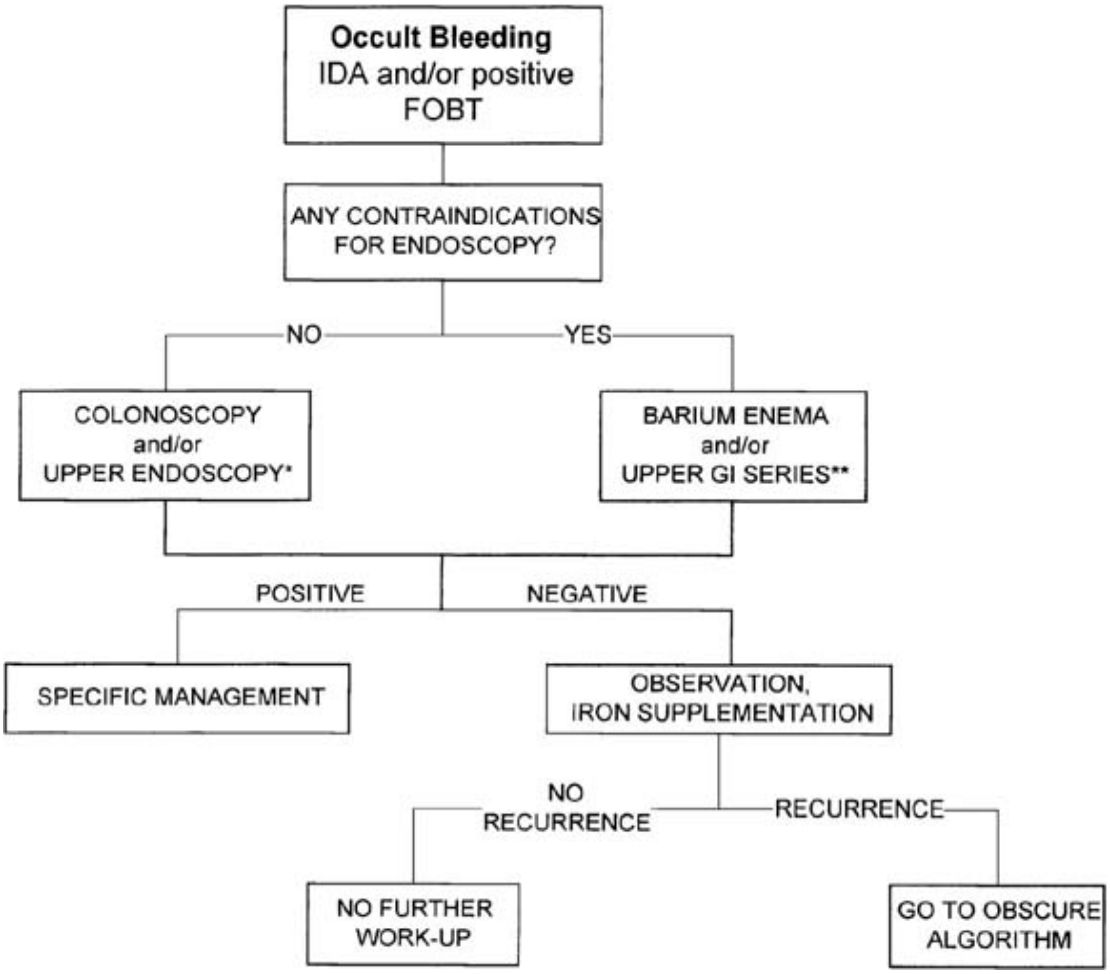
Although this approach may well underestimate the number of patients who could benefit from the improved diagnostic capabilities of the capsule endoscopy (since patients not requiring hospitalization cannot be traced), it does suggest that current diagnostic tools are adequate for the great majority of MUHC patients.

Recommendation

Based on the above considerations TAU, while recognizing the innovative characteristics of the capsule endoscopy does not feel that there is sufficient evidence to recommend either the purchase of this technology or its incorporation into routine clinical practice.

Appendix 1 – Algorithm for evaluation of occult bleeding

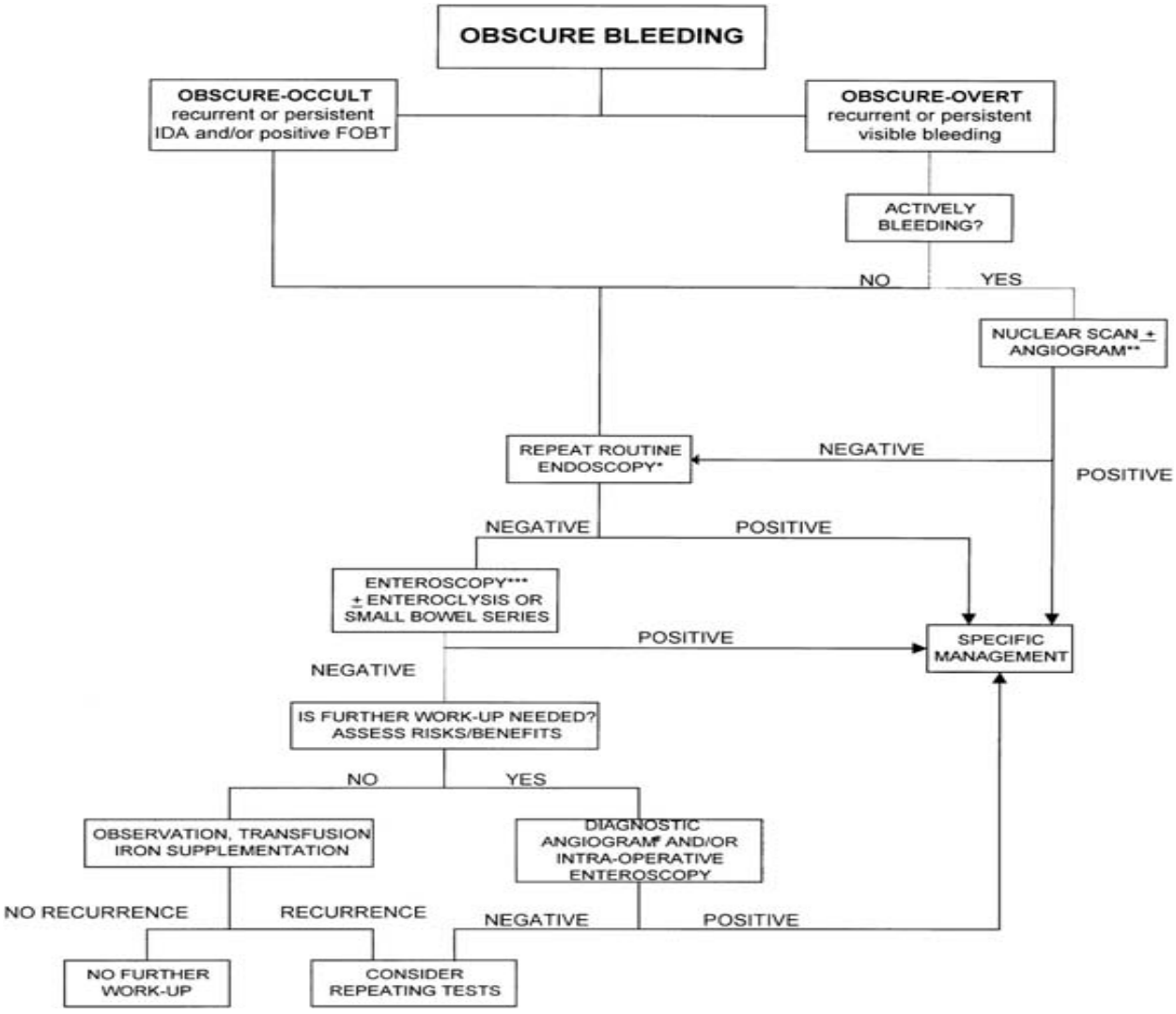
Algorithm for evaluation of occult bleeding. *The indication and sequence of endoscopic procedures may be directed by patient age, symptoms, and comorbid conditions; small bowel biopsy is indicated at this juncture only in the presence of clinical or endoscopic evidence of celiac sprue. **Radiological studies may be indicated when comorbid conditions make endoscopy risky or when endoscopy is incomplete; small bowel follow-through radiographs have a very low yield unless clinical evidence exists for small bowel disease.



Source: American Gastroenterological Association Medical Position Statement (2000) [7]

Appendix 2 – Algorithm for evaluation of obscure bleeding

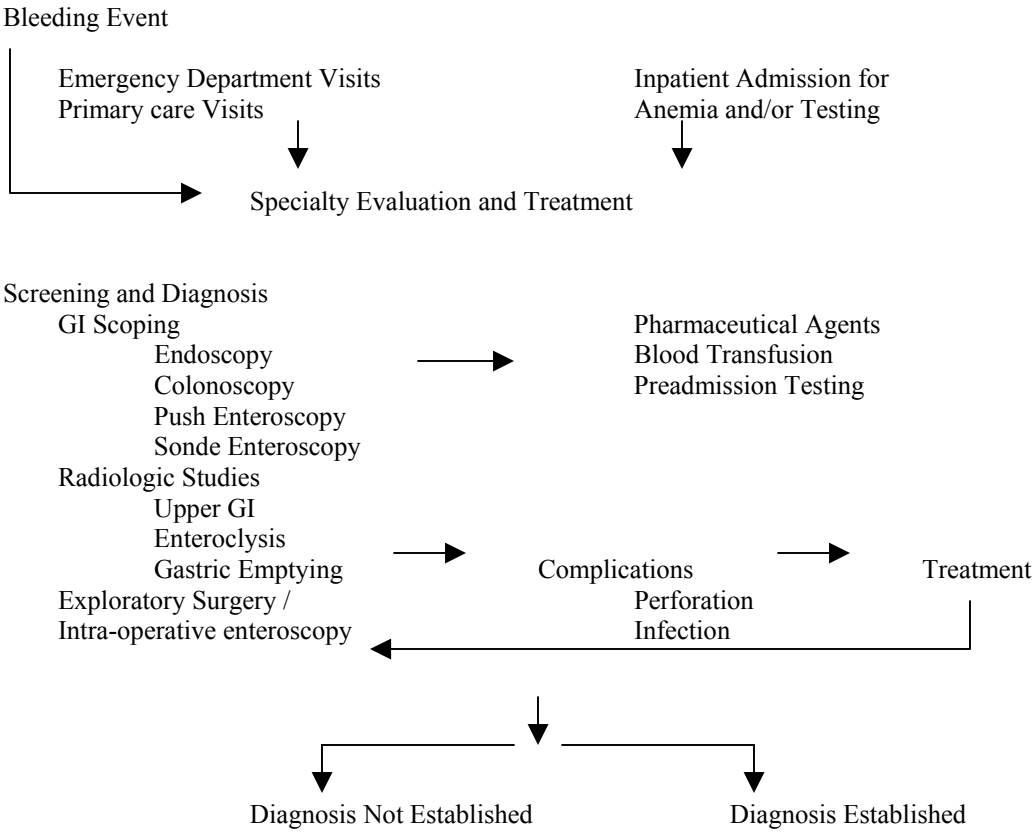
Fig. 2. Algorithm for evaluation of obscure bleeding. *The decision to repeat upper endoscopy and/or colonoscopy may depend on the skill and expertise of the initial endoscopist; push enteroscopy can replace upper endoscopy at this juncture; and small bowel biopsy is indicated in patients with clinical or endoscopic evidence of celiac sprue or unexplained IDA. **Repeat routine endoscopy may be performed in actively bleeding patients at the discretion of the endoscopist. ***Push enteroscopy and/or Sonde enteroscopy may be performed, depending on operator and institution expertise; enteroclysis can complement enteroscopy and improve the diagnostic yield. #Angiography performed electively may demonstrate typical findings of angiodysplasia or a tumor blush.



Source: American Gastroenterological Association Medical Position Statement (2000) [7]

Appendix 3 – Model of Costs associated with diagnosing obscure bleeding

A – Direct Medical Costs



B – Other medical costs

Delay in diagnosis of progressing disease

C – Non-Medical Costs

Lost productivity
Discomfort and worry
Preparation time and cost for screening
Travel and incidentals (child care, etc.)

Source: Goldfarb et al (2002) [14]

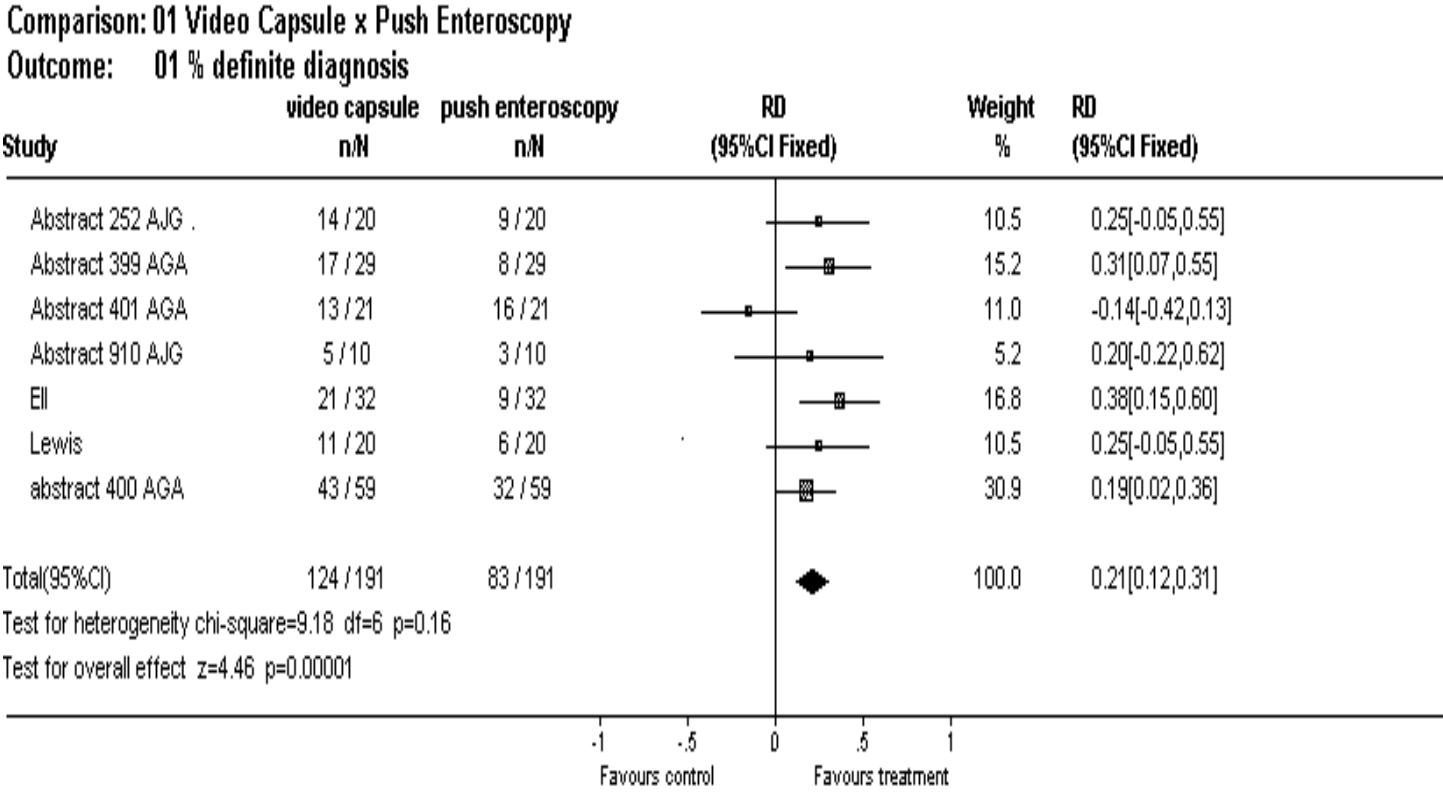
Appendix 4 – Summary of the Clinical Studies

# Patients Studied / Reference	Comparator	Previous Diagnostic tests	Baseline characteristics	Reason for diagnostic test	Results	Extra lesions identified by the Capsule endoscopy	Extra treatment received (Y/N)	Long-term Extra benefit
20 / Costamagna et al [4]	Barium Radiograph	**SB follow-through**: 13 (11 patients) **Gastroscopy:** 87 (17 patients) **Colonoscopy:** 82 (17 patients) **PE:** 13 (9 patients) **Intraop. Enterosc.:** 1 **Angiography :** 5 (5 patients) **Radionuclide scan.:** 9 (9 patients)	**Mean # bleeding episodes:** 8.5 (1-40) **Mean # blood units transfused:** 10.6 (0-77)	Obscure GI bleeding – **13** S. Crohn's disesase – **3** S. Sarcoma recurrence –**1** Unexpl. Chronic diarrhea – **1** Familial adenomatous polyposis – **1** Small bowel polyps **- 1**	*Definitive diagnostic:* Barium follow-through: 5% VC: 31% p<0.05 Difference in diagnostic yield for the capsule endoscopy (95% CI): **26% (-2% , 54%)** According to information in the article, the percentage of definitive diagnosis for **Barium follow-through** should be 8% instead of 5% Difference in diagnostic yield for the capsule endoscopy (95% CI): **23% (-7% , 53%)**	*Definite Diagnosis* Total # extra lesions: 5 *Obscure Bleeding (3):* Distal ileal ulcer Jejunal and ileal angiodysplasia Giant ileal angiodysplasia *Fam. adenomatous polyposis(1)* *S. Crohn's recurrence (1)*	 Not clear Not reported Y	Not reported
32 / Ell et al [2]	PE	**SB enema** : 32 patients **Blood pool scintigraphy** : 13 patients **Meckel scintigraphy:** 21 patients **Selective celiac and mesenteric angiography**: 26 patients	**Mean Bleeding time:** 29 ± 24 months **Mean lowest Hb:** 5.9 ± 1.4 g/dl **Mean # blood units transfused:** 17 ± 18 **# Hospitalizations:** 6 ± 7	Patients with severe CGB in whom the bleeding source was suspected to be in the small bowel	*Definite Diagnostic:* VC: 66% PE: 28% p=0.0001 Difference in diagnostic yield for the capsule endoscopy (95% CI): **38% (14% , 62%)**	*Definite Diagnosis* Total # extra lesions: 12 Chornic inflammatory bowel disease (2) Angiodysplasia (10)	Not reported	Not reported

# Patients Studied	Comparator	Previous Diagnostic tests	Baseline characteristics	Reason for diagnostic test	Results	Extra lesions identified by the Capsule endoscopy	Extra treatment received (Y/N)	Long-term Extra benefit
20 / Lewis and Swain [10]	PE	**Colonoscopy**: 78 **Upper endoscopy**: 83 **SB series** : 19 **Enteroclysis**: 4 **PE**: 22 **Nuclear bleeding scan**:10 **Nuclear scans for Meckel's diverticulum**: 2 **Angiograms**: 3	**Mean bleeding time:** 36.5 months (2-144) **Mean lowest HB**: 6.4 g/dl (2-8) **Mean # blood units transfused**: 28 (0-300)	GI bleeding of obscure origin	**Definitive Diagnostic:** VC: 55% PE: 30% Difference in diagnostic yield for the capsule endoscopy (95% CI: **25% (-5% , 55%)**	Total # of extra lesions: 5 SB carcinoid (1) Ileal angioectasia or bleeding sites (2) Multiple angioectasia of the jejunum (1) Diffuse angioectasias of SB (1)	 Y Y Y N	Not reported
35 / Scapa et al [1]	-	**Colonoscopy** : 42 (33 patients) **Gastroscopy :** 33 (31 patients) **SB x-ray:** 35 (35) **Abdominal CT:** 16 (17 patients) **PE :** 8 (9 patients) **Nuclear medicine :** 1	Not reported	Unexplained bleeding from the GI tract and/or suspected illness of the SB of an undetermined nature	Significant pathological findings: VC - 62.9%	Not comparative – Lesions found in 29 out of 35 patients: Ulcers - 11 patients Other – 16 patients Erosions – 8 patients Angiodysplasia: 5 patients Polyps 3 patients Blood or clots : 3 patients Edema: 2 patients Nematodes: 1 patient	The authors mentioned that the diagnosis of lesions helped guiding further treatment, but gave no specific information	Not reported

CGB = chronic gastrointestinal bleeding
PE = push enteroscopy
S = suspected
SB = small bowel
CI: Confidence interval

Appendix 5 – Results of Published Studies



AJG= American Journal of Gastroenterology / AGA=American Gastroenterology Society / CI=confidence interval

References:
Abstract 252 AJG [22] / Abstract 399 AGA [27] / Abstract 401 AGA [20]
Abstract 910 AJG [24] / Ell [2] / Lewis [10] / Abstract 400 AGA [28]

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