ALBERTA HEALTH TECHNOLOGIES DECISION PROCESS

Double Balloon Endoscopy\Enteroscopy (DBE) for the Diagnosis and Treatment of Conditions of the Small Intestine

Final Report

(submitted by Dev Menon,
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EXECUTIVE SUMMARY

Introduction

Double balloon endoscopy/ enteroscopy (DBE) is a non-surgical approach that provides access to the entire inner mucosal surface of the small intestine for endoscopic visual examination, biopsy and treatment. DBE is being heralded as a breakthrough technology because accessing the deep small intestine endoscopically has largely been unsuccessful by conventional approaches.

Objective

To review the safety, efficacy and effectiveness of DBE and examine the potential social, fiscal and economic impact should it become a publicly funded health service in Alberta.

A Rapidly Emerging Technology

DBE has diffused rapidly since it was developed in Japan and first reported in 2001. The Netherlands and Germany were early adopters. Four centres in Canada had DBE capacity mid 2007 (Toronto, Montreal, Regina, Vancouver). In mid-September, the first diagnostic DBE procedure in Alberta was done in Calgary Health Region using a Fujinon device under research protocol. An Olympus single balloon device was used as a comparator however there is little published data on this competing device. If adopted, provision of DBE is likely to be limited to one or two facilities in the two major urban centres. Capital Health is interested in obtaining DBE capability.

Who Stands to Benefit

Patients obtaining DBE are a highly select group with conditions of the small intestine that are challenging to diagnose and treat. They are often highly tested first with a variety of conventional imaging and laboratory tests. Although obscure gastrointestinal bleeding (OGIB) is the most frequent indication, in one large case series 32 final diagnoses were revealed after DBE testing for the non specific indications of bleeding, pain, diarrhoea or obstruction. Possible therapeutic interventions include coagulating bleeds, resecting lesions and releasing strictures.

Alternative, complementary and comparator technologies

DBE is complementary to existing technologies rather than being strictly a substitute or an add-on. It fits into existing care pathways between video capsule endoscopy (VCE) and surgery. Though its diagnostic capabilities are compared to VCE, VCE does not have biopsy or therapeutic capabilities. In many series VCE is done prior to DBE and afterwards only about 50% of cases still require DBE to access the small intestine for biopsy and/or therapeutic intervention. DBE can circumvent in most cases but not totally eliminate the need for surgical intervention. Tumours for example may still require surgical resection. As patients progress through care pathways they obtain the next most invasive approach only as necessary based on their clinical needs. The true comparisons therefore are alternate care pathways with and without DBE.

DBE for Many Indications, Diagnoses and Therapies

A narrowly focused systematic review question would omit evidence on important impacts and resource implications were DBE to become a publicly funded service in Alberta. The focus of this HTA was therefore broad as all the capabilities of DBE are likely to be used if available.

Methods (Appendix A)

Systematic search for clinical research and relevant analyses revealed 388 citations of which 256 were targeted for retrieval. One draft health technology assessment (HTA) report was identified. The Australian Medical Services Advisory Committee (MSAC) HTA on DBE for OGIB

provided a baseline literature review to May 2006. This was updated to April 2007 and expanded to include conditions other than OGIB. Local data resources including clinical experts were consulted.

FINDINGS

Following application of preset criteria 81 papers reporting clinical research were included. The highest level of available evidence is Level IV prospective or retrospective uncontrolled case series and case reports – a relatively low level of evidence.

Social and System Demographics

Indications (section 3.4)

Obscure gastrointestinal bleeding (OGIB) was the most common indication for DBE (60%) with angiodysplasias (vessel malformations causing bleeding) as the most common finding after DBE. Tumours at <5% are less common but potentially of greater consequence.

The other 40% of cases are referred for chronic abdominal pain plus other symptoms (10%), polyposis syndromes (9%), Crohn's disease (8%) and other more uncommon indications (13%) including foreign bodies, protein-losing enteropathy, structural malformations and radiation enteritis.

The Potential Need for DBE

The need in Alberta is estimated to be 193 procedures a year for obscure GI bleeding based on the MSAC analysis estimates for Australia. If DBE were used for the other 40% of indications (as suggested by case series not limited to OGIB) this number could rise to 322 procedures a year or more given higher reported Canadian incidence rates for inflammatory bowel diseases.

Technological Effects and Effectiveness

Complication Rates (section 3.5 and 3.6)

A post-polypetectomy bleeding rate of 10.8% reported in one case series of therapeutic DBE procedures study raises a safety alarm. Innovation to decrease this rate are underway however unmitigated this risk is unacceptably high.

Major complications resulting from DBE to identify and treat OGIB are less than 1% based on Level IV case series data from 24 studies reporting on 2,175 patients. Perforation, pancreatitis and segmental enteritis are the major complications identified and reported that are directly related to DBE for diagnostic use. The rate of reported minor complications was 8.7% (139 in 1525 procedures). Performing DBE under conscious sedation mitigates risks associated with anaesthesia use.

Therapeutic Success Rate (section 3.7)

The 97% reported success rate of DBE enabled therapeutic interventions is based on 19 studies reporting on 442 procedures. Success as defined in the available level IV case series is primarily procedural success (ie the bleed stopped, the polyp removed) not true measures of health outcomes based on patient experience of symptom reduction. One study reported a 91% improvement or elimination of symptoms using a scoring system to evaluate GI bleeding. Reduced transfusion requirements after DBE for OGIB were identified in five case studies: 67% did not require further transfusion in during follow-up periods averaging 4 and 5 months.

Diagnostic Yield (section 3.8)

DBE has high reported diagnostic yield for detecting the source of OGIB and for diagnosing other conditions of the small intestine: 75% (range 52 to 93%) from case series with quality scores of 2 to 3. This is comparable to VCE.

Technical Failure (section 3.10)

Acute technical failure was experienced in 6 of 178 (3.3%) therapeutic interventions undertaken from a population of 353 (Level IV evidence from one case series, quality score of 3/3). Equipment failure was reported in 4 of 508 (0.8%) procedures in 3 case series reporting on both diagnostic and therapeutic use.

Procedure Time (section 3.11)

The procedure time for DBE is approximately 73.5 minutes ± 25 (range 25-131).

Economic and Social Considerations (section 4.0)

As DBE takes approximately four times as colonoscopy it is likely to remain a scarce resource even if publicly funded. Relatively few gastroenterologists will be interested in doing this time intensive procedure according to a local gastroenterology expert.

Rigorous economic evaluations of DBE have not been conducted. The MSAC HTA compared the cost of DBE with laparotomy and intra-operative enteroscopy. They found the costs were comparable at $1,363 DBE versus $1,348 laparoscopy without therapy and $1,830 versus $1,678 with therapy in Australian dollars. A reasonable conclusion is therefore that DBE is not more expensive and prevents surgical intervention.

Substituting current Alberta component costs, DBE is estimated to cost $2,181 per procedure without therapy and $2,715 with therapy assuming DBE is done under conscious sedation on an ambulatory care basis (as experts envision). Equipment acquisition cost is approximately $140,000 including monitoring and computer components with other uses.

By comparison, the inpatients costs of treating GI bleeding were on average $3,619 but ranging from $3,002 to $11,146 based on 2004 data (Health Cost 2005 for Alberta).

It is reasonable to assume that DBE will be more costly than VCE but provide greater benefit in terms of diagnostic (biopsy) and treatment capability when that is required for optimal patient care. It is also reasonable to assume that DBE will be less costly than surgical interventions done on an inpatient basis given the high cost of hospital care.

Unknown is the extent to which a decrease in the costs of other tests and treatments would offset the costs of adding DBE to the current care pathways. Besides equipment costs, introducing DBE requires that specialists leave the province to train in centres with experience in DBE. Nursing assistants also require training.

DBE is not associated with contentious social, legal and ethical issues. Patients would generally prefer to swallow a capsule compared to the relatively more invasive endoscopy and prefer to avoid surgery. As the role of DBE is between these two options in a clinical pathway for investigating and treating conditions of the small intestine then these preferences are satisfied.

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Glossary[1]

Diagnostic yield is the number (percentage) of all cases examined by a test that result in a diagnosis.

Endoscopy is the general term for the use of an endoscopy to visualize internal body structures. An endoscope is a medical device consisting of a camera mounted on a flexible tube. Small instruments can be used to take samples of suspicious tissues through the endoscope.

Enteroscopy is the specific term for endoscopy used to view the lumen or interior surface of the intestine.

Hemotochezia is the passage of bloody feces.

Ileus is a temporary arrest of intestinal peristalsis known to occur when the intestines have been manipulated.

Laparotomy: surgery that opens the abdominal cavity

Laparoscopic endoscopy is endoscopy performed through smaller incisions into the abdominal cavity to be minimally invasive.

Meckel's diverticulum is an outpouching of the small intestine that sometimes contains gastric mucosa, which can cause local ulcers and bleeding; detected by diagnostic imaging.(1)

Melena are bloody or tarry stools

Obscure gastrointestinal bleeding (OGIB) is bleeding of unknown origin that persists or recurs after a negative initial or primary endoscopy.

Push Enteroscopy uses special endoscopes specifically designed to access the small intestine by advancing (pushing). They are longer with special tips, overtubes and viewing tubes that balance flexibility and rigidity. They are 'push' not 'push pull' because they are not designed to draw the intestine back over the overtube.

Push Pull Enteroscopy is the technique of drawing sections of the intestine back over the enteroscope to move the scope through the length of the small intestine. DBE is a push pull enterescopy technique.

Video capsule endoscopy (VCE) is a procedure in which the person swallows a battery-powered capsule. The capsule contains one or two small cameras, a light, and a transmitter. Images of the lining of the intestines are transmitted to a receiver worn on the person's belt or in a cloth pouch. Thousands of pictures are taken.

Intraoperative endoscopy (IOE) is endoscopy/enteroscopy done during the course of a surgical operation. It is synonymous with laparoscopic endoscopy.

[1] mercksource.com was the source for the definition of glossary terms unless otherwise referenced.

1.0 Technology Overview

1.1 Small Intestine as Frontier

The benefits of using endoscopes to visualize and treat lesions from within the gastrointestinal tract do not therefore currently extend to the entire length of the small intestine. The small intestine has therefore been characterized as a final frontier. The tortuously looped and accordion-like structure of the small intestine snags the tip of the regular endoscope. This stretches the walls, impedes movement and risks damage to the vulnerable blood rich mucosal lining. Being in the middle of the gastrointestinal tract, the small intestine requires the longest reach being farthest from either oral or anal endoscopy entry points. Manoeuvering through and around the pyloric valve and Treitz ligament pose extra challenges. A significant length of small intestine in the middle generally cannot be reached by either oral or anal approaches with regular endoscopy. This stretch can be visualized less directly through other imaging technologies or accessed through invasive and risky surgical laparoscopic endoscopy or laparotomy.

1.2 Double Balloon Endoscopy: The Technological Innovation

Double balloon endoscopy/ enteroscopy (DBE) is a modification that makes the entire inner surface of the small intestine accessible to endoscopic visual examination, biopsy and treatment. The double balloon extension of the endoscope is the innovation that fixes the endoscope at various points along its length allowing deeper insertion and avoiding stretching and looping the small intestine as it progresses. There are two types of Double Balloon Endoscopes, one for general diagnostic use and the other offers treatment capabilities. The major difference between the two devices is that the general use endoscope is a slightly thinner device.

With both balloons deflated and the overtube back, the tip of the endoscope is inserted orally or anally and advanced to the small intestine. Then the overtube balloon is inflated to fix the enteroscope in place while the tip continues to advance to a second position and is inflated. Then the overtube balloon is deflated and slides forward to the tip and is reinflated. It is the gentle withdrawal of the overtube that folds or pleats the intestine onto the overtube preventing looping. This manoeuver can be repeated until the entire small intestine has been traversed. In practice the entire small intestine may not be visualized given the time duration. Bidirectional endoscopy (one approach via oral and one via the anal route) may be done to visualize the entire length of the small intestine. Or a lesion is found or specific area targeted, viewing the entire small intestine may not be necessary.

1.3 Current Use

Hironori Yamamoto invented the DBE technique and technology in Japan in the late 1990s. His first clinical report appeared in English in 2001.(2) DBE has diffused rapidly since then with case reports and case series from the Netherlands, Germany, and United States of America, Mexico, Spain, Taiwan and China.

DB Endoscopes are licensed for sale by Health Canada as a Class 2 device. Fujinon Inc. is the patent holder and manufacturer. The Food and Drug Administration has approved the technology for sale in the USA. Fujinon devices are available in Canada through Carson Medical Inc.

The first DBE procedure was conducted in the Calgary Health Region mid September 2007 as part of an evaluation and acquisition decision process. It was compared with a competitor's new product – the Olympus single balloon endoscope (SBE). The single balloon design with the one balloon on the over tube seeks to obtain the same functionality as the DBE without violating patent restrictions. Capital Health Region has also expressed interest in obtaining DBE technology.

In Canada, Toronto has the most experience with DBE technology. Norm Marcon with the University of Toronto, Department of Gastroenterology is currently leading research comparing DBE and VCE. Vancouver, Montreal and Regina have recently obtained DBE with 3 additional sites expected for 2007 including Calgary. [2] Canadian experience with DBE has not been reported in the peer-reviewed literature.

The current medical procedure list and fee structure do not currently include DBE as a funded service. In addition, if DBE is were to be introduced into Alberta in addition to the equipment costs there are significant training costs given the learning curve required by endoscopists learning to use the new approach. Nursing assistants would also require special training.

2.0 Topic Specific Challenges in Assessing DBE

The topic specific challenges of reviewing this emerging technology identified at the outset were:

- Multiple conditions potentially detected by DBE therefore restricting scope of the research question may omit important uses;
- Use for both diagnosis and treatment therefore assessment of both functions required;
- Multiple comparators represented including video capsule endoscopy and surgical interventions; and

2.1 Multiple conditions

The symptoms associated with conditions of the small intestine (bleeding, pain, diarrhoea) are not condition specific and so it is not possible to directly correlate symptoms with underlying small intestinal disease. Bleeding, for example, may be related to any of the diagnoses presented in Table 1. Specifically, the indications for DBE may include signs of gastrointestinal bleeding (like melena or hemotochezia) as well as, abdominal pain, chronic diarrhoea, signs of obstruction or laboratory indicators of malabsorption.(3) Likewise a large number of diagnoses are possible post-test as non specific symptoms are investigated and diagnosis is achieved.

Available case series confirm that investigation of obscure gastro-intestinal bleeding (OGIB) is the most common reason DBE is performed: 60% versus 40% for 'other' non-OGIB indications (section 3.4). There is considerable overlap between the causes of OGIB (ie post-test diagnoses with DBE) and 'other' non-OGIB indications for DBE testing. This is not surprising given that OGIB is a clinical condition needing a more precise diagnosis for adequate management.

[2] Carsen Medical Inc

The American Gastroenterological Association (AGA) defines occult and obscure gastrointestinal bleeding (OGIB) as:

> bleeding of unknown origin that persists or recurs (i. e., recurrent or persistent iron−deficiency anemia, fecal occult blood test positivity, or visible bleeding) after a negative initial or primary endoscopy (upper and/or lower gastrointestinal endoscopy).(4)

The common causes of OGIB from ICCE consensus on OGIB are presented in Table 1. (5) The eventual diagnoses represent a wide range of pathologies and etiologies. Therefore a focus on OGIB encompasses all these 13 common causes and the variety of care pathways they represent.

Table 1: Common Causes of Obscure Gastrointestinal Bleeding in the Small Intestine

Duodenum	Small Bowel (jejunum, ilium)
• Ampullary neoplasm • Distal duodenal neoplasias • Aortoenteric fistula (3rd portion of the duodenum) • Hemosuccus pancreaticus (pancreatic aneurysm) • Hemobilia (trauma, stone)	• Angiodysplasias • Primary neoplasias (leiomyoma, leiomyosarcoma, carcinoid) • Metastasis (lung cancer, breast cancer, renal cell carcinoma, melanoma) • Polyposis syndromes • Meckel diverticulum • Medication-induced mucosal lesions (NSAIDs, KCl) • Crohn's disease • Portal hypertensive intestinal vasculopathy

Pennazio M, Eisen G, Goldfarb N. ICCE consensus for obscure gastrointestinal bleeding. Endoscopy 2005; 37:1046-1050.

The incidence of OGIB has been estimated at about 5 episodes per 100,000 per year based on Goldfarbs estimate that the incidence of GI bleeding is about 100 episodes per 100,000 population and 5% of these are OGIB.(6) In Alberta with a population of over 3.4 million this would represent 3,400 GI bleeds annually of which 170 or more would be cases of OGIB.

Besides finding and treating the lesions associated with OGIB, there are other indications for DBE. Removing foreign objects or retained video capsule endoscopes are relatively rare indications but ones for which surgical intervention would otherwise be required. As the research presented in section 3.4 indicates, approximately 40% of conditions that DBE is being used for are non-OGIB. Some also appear in Table 1 as causes for OGIB. For example, an active bleed may be the reason DBE is done and following the DBE test a diagnosis of Crohn's disease may be made. Or a patient with known Crohn's disease may have a DBE to release strictures resulting from their disease and in this case the indication for DBE would be categorized as Crohn's disease.

Preconditions for small intestine pathology are widespread and provide little opportunity for prevention beyond the nutritional types of advice for good health. Diverticulosis is an example of

an age related condition that in some cases may cause life-threatening conditions but are largely 'silent' – that is, they may not cause symptoms that require treatment.

> Small intestinal diverticulosis is rare, and 60–70% of cases are asymptomatic. The incidence ranges from 1.1% to 2.3% at enteroclysis, during postmortem examination or during surgical procedures. Most cases are found in patients who are in their seventh decade of life or older… Symptomatic diverticula have either acute or chronic manifestations. Chronic complications include malabsorption, chronic abdominal pain, intestinal pseudo-obstruction and chronic gastrointestinal bleeding. Acute complications include diverticulitis, abscess, perforation, intestinal obstruction and massive gastrointestinal bleeding. (7)

There are claims in the DBE literature that inflammatory bowel disease (IBD) is increasing. Whether the increase is due to better awareness and detection or a true increase is beyond the scope of this report but it does highlight the challenge of delineating disease patterns for conditions of the small intestine as well as contributing factors. (8) Research done using an emerging Canadian dataset indicate that published Canadian rates for IBD are the highest in the world and Alberta rates are highest in western Canada.(9) Whether the reported rates are actually higher than other countries or the result of better detection and documentation is not clear. As well the factors that might cause higher rates in some populations (like conditions are 'too clean' to stimulate optimal immune responses in childhood like the 'too clean' hypothesis) is not known. Hypotheseis like are under investigation.

Injuries of the small intestine that are related to pharmaceutical use are an important association to note because they are iatrogenic – that is, medically caused.

> Anticoagulants and NSAIDs are widely prescribed and the increasing consumption of these drugs might be associated with the increasing incidence of their well-known small intestinal complications, such as intestinal inflammation, protein loss, blood loss, ulcerations, perforation, narrow-based ileal stenosis, and strictures. It has previously been demonstrated that small intestinal large erosion/ulcer is seen in approximately 25% of chronic NSAID users without melena and hematochezia…(10)

DBE capability may permit better understanding, detection and management of drug-induced injuries to the small intestine.(11)

As experience with DBE has grown, condition specific, non OGIB case series have appeared in addition to case series of only or mostly OGIB cases. These include case series on refractory celiac disease, Crohn's disease, primary intestinal follicular lymphoma and cases where tumors were missed with VCE. These represent indications for which DBE may come to play an important and perhaps standard role in the future. (Appendix D).

Finally, numerous case reports have appeared describing the pivotal role DBE played in resolving particularly challenging cases. Pungpagpong et al (12) from the Mayo Clinic, for example described an unusual case of protein-losing enteropathy from eosinophilic enteritis which was causing bilateral lower extremity oedema for 1 month. Whereas no one of these cases represent a

population of patients large enough in number to be the focus of a case series let along a systematic review, they are useful for illustrating the useful or even critical role DBE may play in the management of particular clinical circumstances. (Appendix E).

2.2 Alternative, complementary and comparator technologies

A key question is whether a new health technology is an 'add-on' or substitute for alternate modalities as this has important resource implications for health systems. Rather than being an 'add-on' or substitute, DBE appears to fit into existing care pathways between near alternatives of video capsule endoscopy (VCE) and surgical intervention (intraoperative endoscopy or laparotomy). VCE does not have the ability to selectively visualize, biopsy or treat lesions. Surgery has risks such as post operative infections. Patients with difficult to diagnose intestinal disorders progress from more accessible and less invasive imaging modalities (Table 2) to VCE then DBE then surgery with fewer patients progressing at each stage as clinical problems are resolved.

Testing prior to DBE: Other diagnostic and imaging modalities are typically used prior to DBE. Patient with conditions of the small intestine are often intensively worked up because the nature of their condition and its location resists diagnosis and treatment. Other tests are required for a definition of OGIB. Hsu et al enumerated the diagnostic tests that had been done prior to DBE from a recent case series of 20 patients (Table 2). (13)

Table 2 Tests used for diagnostic evaluation or OGIB prior to DBE

Method	*No. of examinations*	*No. of patients*
Esophagogastroduodenoscopy	31	20
Colonoscopy	20	18
Radionuclide bleeding scan	16	14
Small bowel follow-through	14	13
Visceral angiography	7	6
Abdominal computed tomography	6	6
Capsule endoscopy	5	5
Lower gastrointestinal contrast	3	3
Meckel's scan	3	3
Push Enteroscopy	3	3
Upper gastrointestinal series	1	1

There is a funnelling that takes place as patients progress along a clinical pathway investigating conditions of the small bowel. Daperno 2007 describes the clinical strategy of narrowing indications for endoscopy:

> Endoscopy is an essential tool for diagnosis, management and prognostic evaluation of inflammatory bowel disease. However discomfort, potential risks and costs associated to endoscopic examinations should contribute to the narrowing of indications to those cases in which the result of endoscopy is essential to determine a variation in the management strategy. (14)

Video capsule endoscopy (VCE): VCE was the first breakthrough technology to reliably obtain images from the length of the small intestine and therefore contribute to diagnosis. It appeared on the North American market a few years ahead of DBE. Swallowing a capsule containing a camera that relays images from the small intestine is generally preferred by patients to undergoing a procedure. In Alberta, VCE is done primarily under research protocol.

If DBE is not a substitute for VCE then the debate on which has the marginally superior diagnostic yield is not of central concern for public policy decisions. Though DBE is frequently compared to VCE, VCE is only comparable for visual inspection. VCE does not have biopsy or therapeutic capabilities. If both VCE and DBE are available, VCE tends to be used first with only about 50% of patients going onto DBE for further visual inspection, biopsy or therapy. For the purposes of making a public policy decision to fund DBE therefore, the difference in diagnostic yield found in some comparative studies is not central to the decision as DBE provides endoscopic access for biopsy and therapeutic intervention over and above the visual inspection provided by VCE. Nonetheless, given the relative convenience of VCE for both provider and patient provides VCE with advantages unmatched by DBE. Therefore, it is most likely that they will both become part of clinical care pathways for management of small intestinal pathology.

It is not within the scope of this report to review the literature comparing DBE to VCE which is of greater importance for clinical decision making. The range of reported diagnostic yield from case series of the two modalities overlap. The diagnostic yield of VCE has been reported to be in the range of 50 to 81%.(15) The overall diagnostic yield for DBE was in the range of 52 to 93%. (section 3.8) Yield will vary depending on the indication, population and provider characteristics. Rigorous and comparative evaluations as a diagnostic test against a gold standard or reference test to determine test parameters such as sensitivity, specificity, positive and negative predictive values are not in evidence. While the available studies have limitations, there is some evidence that VCE performs better than DBE in terms of overall diagnostic yield in direct comparison(16) (See appendix G).

Intra-operative endoscopy (IOE):
The Australian Medical Services Advisory Committee assert that laparotomy or laparoscopic endoscopy are the appropriate comparators for DBE. Laparoscopic endoscopy and IOE are both terms that refer to the same practice of accessing the small bowel through surgical incisions into the small intestine through the abdominal cavity. The rationale is that surgery is the only way to access the small intestine for biopsy and treatment without a less invasive technology such as DBE. It is generally accepted that surgery is the most invasive therefore it carries greater risk of harm. There is little research data on this however. Given the risks it would not be appropriate to use surgical intervention as a gold standard reference test or comparator in populations not requiring surgery. There is no research comparing IOE to DBE directly.

Jacobs et al 2006(17) contribute this perspective on intra-operative endoscopy vis-a-vis DBE (IOE):

> Studies comparing IOE with DBE have not yet been conducted. Such studies may never be performed because patients with a diagnostic DBE do not need an IOE and vise versa.

> Nevertheless, further studies should be carried out to redefine the role of the invasive IOE procedure in the new era of wireless capsule endoscopy and DBE. (17) p 316

The clinical community appears to need no convincing or quantification to accept that the harm benefit profile of DBE will be more advantageous than IOE, which may be the reason the motivation to conduct research of the respective roles of VCE, DBE and IOE is lacking. The key issue is the investigation funnel (clinical pathway) that sorts patients until a highly select group for the more invasive and uncomfortable DBE testing. What is generally required of diagnostic tests is that competing comparator tests are evaluated against a gold standard test. A representative and identifiable population defined by rigorously applied selection criteria are then tested with 2 or more comparators. The gold standard of laparotomy or laparoscopic endoscopy is too invasive to be considered an acceptable gold standard test so this strategy is unlikely to be applied to a population representative all those suitable for less invasive testing. So other research strategies are needed to provide an evidence base in support of the respective roles of DBE, VCE and IOE which seem to be evolving in the absence of good evidence.

In conclusion, it appears that DBE can circumvent in most cases but not totally eliminate the need for surgical intervention. Tumours for example may still require surgical resection. DBE may be useful prior to surgery to tattoo the relevant section of the bowel to streamline the surgical intervention. VCE may have a superior diagnostic yield but the evidence appears to be preliminary. Yet VCE does not have biopsy or therapeutic capacity and so it is a poor comparator overall. As patients progress through care pathways they obtain the next most invasive approach only as necessary based on their clinical needs. The true comparisons therefore are alternate care pathways with and without DBE.

2.3 DBE's Role in diagnosis and treatment

DBE has a potential role to play in both the diagnosis and treatment of many conditions of the small intestine. It may be more useful to think about and investigate DBE as embedded within care pathways with other modalities in series rather than in parallel as this is how they are used in practice. Not only can DBE can be manipulated to more completely visualize lesions or areas of interest, lesions so identified may be immediately accessible to treatment. Video capsule endoscopy provides images from the entire length of the small intestine but has no capability to target an area of interest for more complete imaging or treatment. Surgical intervention is inherently riskier. A more reasonable comparison is care pathways (including both VCE and IOE) with and without DBE. Evaluating DBE by comparing it to other modalities that cannot perform the same functions or roles is not optimal. Whereas supportive research has not been done, there is some agreement and support for the new care pathways that are possible with DBE and VCE availability.

Swain et al, 2004 suggest a clinical pathway incorporating VCE demonstrating both parallel and serial testing strategies depending on availability and findings. (18) A limitation of VCE is its inability to precisely locate a lesion, biopsy or treat.(19)

The MSAC put forward a clinical pathway with an explicit role for DBE. This pathway assumes that conventional endoscopy has been done prior to a decision to offer VCE but that it has been negative. DBE enters the MSAC pathway after determining that there is a bleed that cannot be

treated medically, cannot be accessed with standard endoscopy and surgery is not clearly indicated.

In Alberta, clinical experts agree that DBE is likely to be used following VCE in most cases however as DBE is not available here and VCE use is largely restricted to research protocols no clinical pathway has been established. Local expert gastroenterologists would prefer a care pathway that reflects different pathways for active versus inactive bleeds. It may be clinically advantageous for active bleeds to proceed directly to DBE.

Figure 1 A clinical care pathway for OGIB using video capsule endoscopy

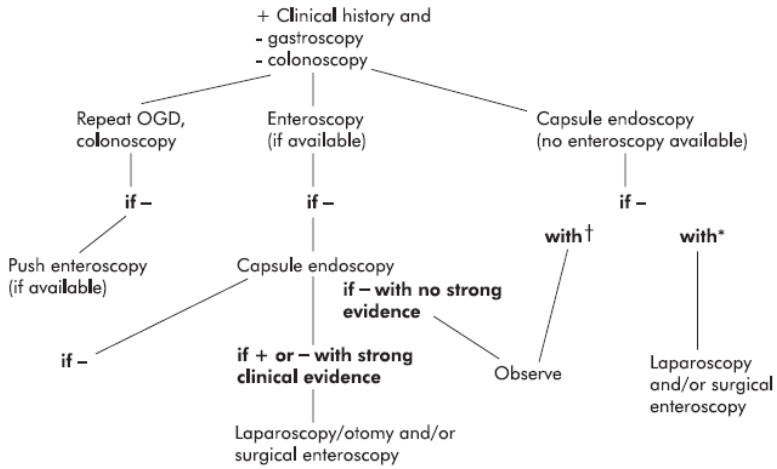
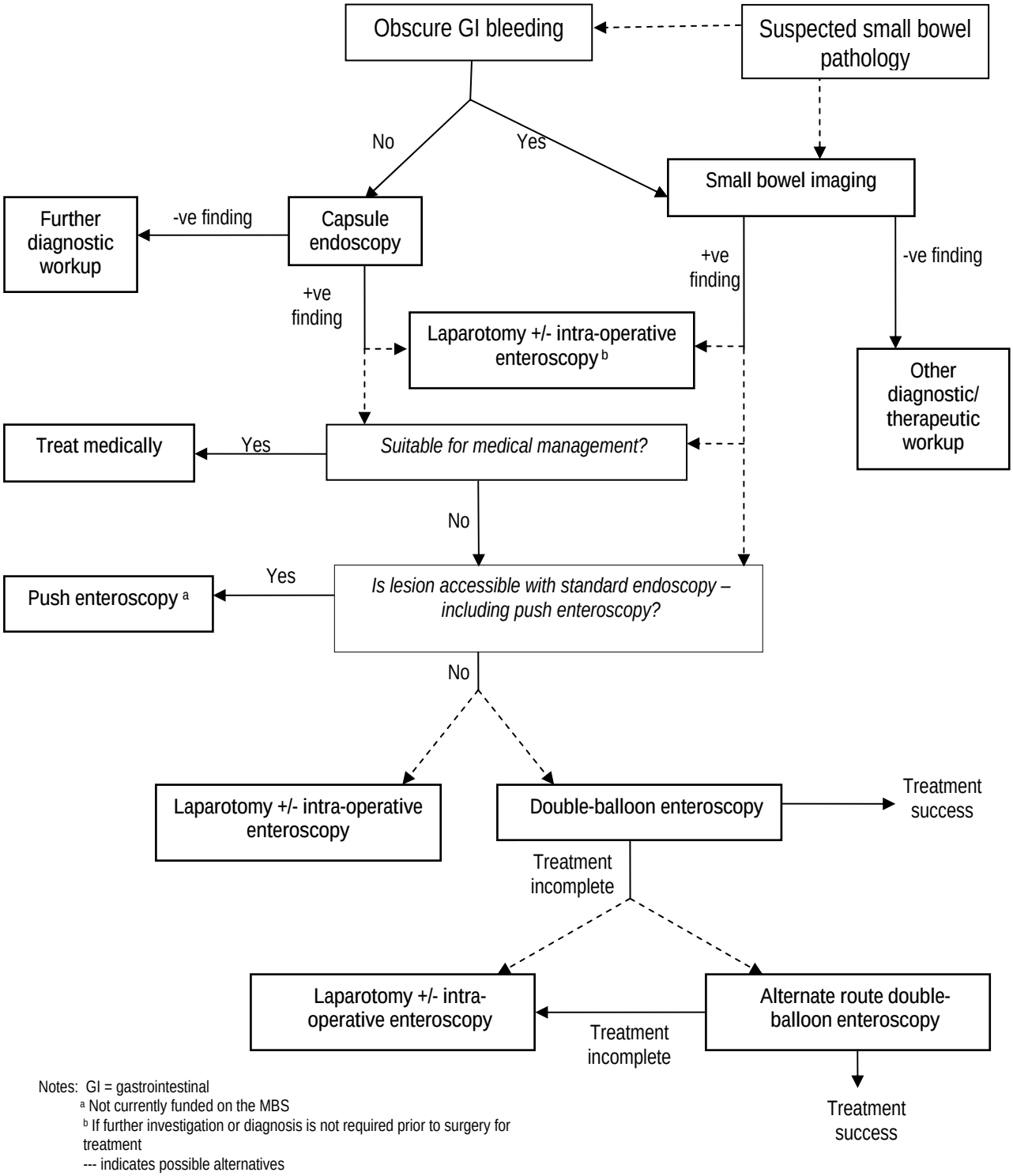


Figure 8 Algorithm for investigation of patients with obscure bleeding. *Short history of bleeding, continued bleeding (transfusion dependent), weight loss, and other abnormal blood tests. †Long history of bleeding, >2 years anaemia corrected with iron, no weight loss, and no other abnormal blood tests.

Figure 2: A clinical care pathway for DBE for OGIB



Notes: GI = gastrointestinal
[a] Not currently funded on the MBS
[b] If further investigation or diagnosis is not required prior to surgery for treatment
--- indicates possible alternatives

The available clinical pathways are proposals. No standard has been established. Though an DBE as a first test has been considered this practice is not evident in available series.(20) With OGIB representing only 60% of all cases referred for DBE, clinical pathways whether implicit or explicit will be required for the many other diagnoses that DBE may contribute to. For example Cheng et al report on the use of DBE in identifying primary gastrointestinal neuroendocrine tumors. (21) For this purpose, Cheng reports high sensitivity and specificity given the added advantage of taking biopsies with DBE. VCE and endoscopic ultrasound have complementary roles and are suggested only when DBE is negative. While this suggested clinical pathway requires validation it does illustrate the ways that DBE is likely to be implicated in many, not just one clinical pathway. DBE is still in relatively early stages of use and there are many reports of novel uses. Gay et al, for example report its usefulness for difficult colonoscopies. (22) (Appendix F)

2.4 Therapeutic uses of DBE

The major advantage of DBE over the diagnostic modalites discussed above is that it enables a variety of treatments including stopping bleeding with argon plasma coagulation, resecting polyps, releasing strictures or stenting to provide structural support. Therapeutic endoscopy adds to medical treatment options. For example for OGIB therapeutic modalities including iron replacement, combined hormones and octreotide acetate.(23)

DBE would not completely replace the need for surgery in all cases but can be useful in preparing for surgery. For example, if a lesion cannot be removed endoscopically its location can be more precisely located and readied for surgical resection by tattooing the site for easy identification during surgery.

DBE is also emerging as a tool for research. For example, Nakamura et al, 2007 (24) have used DBE to investigate the features of intestinal follicular lymphoma. While this was possible at autopsy, DBE permitted this research to catalogue and describe endoscopic features to provide other clinicians with better information with which to diagnose. This knowledge could lead to better management though at present this is not proven.

3.0 Findings

3.1 The Growing Body of Evidence on DBE

The state of the science on DBE is relatively immature notwithstanding the rapid rate of uptake in some centres. The earliest 'proof of concept' report in an English language peer reviewed journal by inventor/ investigator Yamamoto is a case series of 4 demonstrating that 'total enteroscopy with a nonsurgical steerable double-balloon method' was possible. A key piece of evidence was a radiographic image of the enteroscope threaded through the entire small intestine and emerging through the iliocecal valve.(2) This illustration of technical feasibility represents a fairly low level of evidence.

The body of evidence is growing quite quickly with 81 clinically relevant reports making up the body of research evidence and expert opinion on DBE. The methods we use to identify and appraise this body of evidence is described in Appendix A. Included in Appendix A is the Hierarchy of Evidence we used to evaluating DBE as a therapeutic intervention. With the lack of an appropriate gold standard to calculate diagnostic test parameters and the panoply of candidate conditions considering DBE as a therapeutic intervention has the advantage of focusing on the global health affects as well as system challenges of the introduction of DBE into clinical pathways. While less than optimal for determining causation it might be the most feasible HTA strategy given the nature of the intervention and the state of the science (see also discussion in Section 2)

As a therapeutic intervention, the evidence for DBE safety and effectiveness rates low on standard hierarchies of evidence based on the ability of the research design employed to determine causation. That is the study designs used provide little safeguard that the effects seen are due to the intervention and not to confounding factors known or unsuspected.

Though there are some attempts to compare DBE with VCE the comparator is arguably inadequate. The argument that the appropriate comparator is laparotomy or laparoscopic enteroscopy is mute from the standpoint of evaluating the research -- no research with a surgical comparator has been done or would ever be done in all likelihood. Furthermore, the body of evidence, being predominantly case series with only post test evaluation and short follow-up, provides little more value in scientific terms than observations of what was done.

While observations provide a description of how DBE is used and therefore its feasibility and safety, for providing conclusive proof of causality the available evidence can only be considered inadequate. Still there is a case for judging this as a body of evidence on its strength (level quality and statistical precision), size of effect and relevance as the MSAC has done.

The Australian MSAC analysis plays a key role in this University of Alberta HTA. Though not yet publicly released, their draft has been generously shared. In addition to providing a methodological approach that has been endorsed by a community of Australian experts it provided a baseline review of evidence to May 2006. Our efforts could therefore leverage this core analysis to update and extend the analysis to conditions other than OGIB. The result is a methodologically rigorous approach that combines the strength of two organizations.

Any approach to reviewing research has limitations. In focusing their review on OGIB the Australian efforts revealed to us the limitation of focusing the topic of DBE on the most common indication. The problem is that OGIB is an interim diagnosis in search of a more definitive cause of the bleed and final diagnosis. For example, a study by Hadithi was excluded as it attempted a comparison with VCE and the MSAC focused question had a laparotomy or laparoscopic enteroscopy as the appropriate comparator.(25) However this study is influential in the clinical community. It demonstrates how VCE and DBE are being used in combination in series rather than in parallel. As this is the preferred strategy of local Alberta based clinical experts, to omit this case series makes it inaccessible for consideration for health policy formulation. The omission of this study was understandable given the stated goals of the MSAC systematic review methodology however given that the MSAC positive funding recommendation is based largely on a cases pre-screened by videocapsule endoscopy (as in the Hadithi study) the boundaries created by using a narrowly focused question resulted in the inability to consider evidence relevant to the policy decision. This is also the case for the many non-OGIB conditions for which DBE may make an impact. These also warrant inclusion and consideration.

3.2 Case study appraisal

Studies were ranked on quality appraisal criteria that indicated the use of study design features that protect against bias. Specifically the studies were appraised as to whether they collected data prospectively, were consecutive cases or representative of patient population and specified how long the patients were followed-up after the test. Table 3 provides an overview of the quality of studies that updated and expanded the MSAC report.

Table 3 Appraisal of DBE case studies using study design quality criteria

Quality criteria Study Author/year	Prospective measurement of outcomes before and after intervention using clear criteria defined a priori	Case selection consecutive or unbiased, evidence cases not significantly different from whole population	Follow-up adequate including specification of losses to follow-up
Akahoshi et al 2007(27)	0.5	0.5	0
Ang et al 2007(28)	0.5	0.5	1
Cazzato et al 2007(29)	1.0	1.0	0
Hadithi et al, 2007(30)	1	1	0
Hadithi et al, 2006(31)	1	1	1
Hsu et al 2007(13)	0.5	1.0	1
Li et al 2007(32)	0	0.5	0
Manabe et al, 2006(33)	0	1.0	1.0
Manner et al 2006(34)	0.5	0	1
May et al 2007(26)	1.0	1.0	1.0
Mehdizadeh et al 2007(35)	0.5	1.0	0
Oshitani et al, 2006(36)	0.5	0.5	0
Pérez-Cuadrado et al, 2006(37)	1.0	1.0	0

Table 3 Continued

Sun et al, 2006(38)	0	0.5	1.0
Suzuki et al 2007(10)	0	1.0	1.0
Zhong et al 2007(39)	0	0.5	1

Only the study by May et al, 2007 met all criteria and this study primarily reported on the procedural success of therapeutic intervention.(26) Therefore, not only was does the body of evidence rank low on a hierarchy of evidence scale but many of the studies also rank low on simple criteria for assessing the quality of the study design and execution.

3.3 Overview

To leverage the systematic review conducted by MSAC, the University of Alberta HTA critiqued, leveraged, updated, supplemented and contextualized the MSAC HTA for Alberta decision makers. In the presentation of the findings that follow, the University of Alberta updated the set of studies focused on or including cases of OGIB. This is then followed by older and often smaller sets of case series reviewed by MSAC to spring of 2006. Finally additional cases series and case reports of non-OGIB conditions of the small intestine are presented.

This HTA report has the following objectives in relation to the primary and secondary research

1. To review the safety and effectiveness of DBE in visually inspecting the small intestine and possibly collecting biopsy samples where indicated to aid in diagnosis.
2. To review the safety and effectiveness of DBE in treating lesions of the small intestine identified at the time of endoscopy.

Following is a presentation of the available clinical evidence from DBE from peer reviewed research published and indexed from 2001 through April 2007 on the following dimensions directly relevant to safety and effectiveness:

Indications
Major complications
Minor complications
Symptom reduction/ therapeutic success
Diagnostic yield
Transfusion requirement
Technical failure

3.4 Indications for DBE

Evidence Statements

Considerable experience with DBE has accumulated in Europe and Asia. The largest case series are those most likely to have stable utilization patterns. Therefore reported indications for DBE were taken from the 3 reported case series with 200 or more cases. (26, 39, 40)

60% of DBE were for OGIB in the case series of May et al 2007 and Heine et al 2006.

Zhong et al 2007 reporting a rate of 51% is from China and therefore may not be generalizable to the Canadian setting. 32 distinct final diagnoses were enumerated in this study.

For the non-OGIB cases, May et al 2007 report the following indications for therapeutic DBE: chronic abdominal pain plus other symptoms (10%); polyposis syndromes (9%), Crohn's disease (8%) and other indications (13%).

Suspected Crohn's disease was an indication for 21% of the case series reported by Heine et al, 2006.

Table 4 Indications for and diagnoses following DBE from case studies > 200 cases

Indications for DBE(numbers, %)	Diagnosis Following DBE
May et al 2007 (N=353)	
Midgastrointestinal bleeding=210 (60%) Chronic abdominal pain plus other symptoms=35 (10%), Polyposis syndrome=33 (9%) Crohn's disease=27 (8%) Other indications=48 patients (13%).	Incompletely enumerated

Table 4 continued

Heine 2006 (N=275)	
OGIB=168 (61%)	Andiodysplasia=60 Tumors=8
Celiac disease/suspected EATL=25 (9%)	28% EATLs
Abnormal CT or small bowel follow-through=23 (8%)	Duodenal diverticulum, lymphoma, metastases
Peutz-Jeghers syndrome=14 (5%) FAP/Gardner syndrome=6 (2%)	Previously diagnosed
Suspected Crohn's disease=13 (21%) General malaise=11 (4%) Foreign body=3 (1%) Protein-losing enteropathy=3 (1%) Pre-operative evaluation and tattoo=2 (0.7%) Radiation enteritis=2 (0.7%)	1 Celiac disease
Zhong 2007 (N=378)	
OGIB = 191 (51%)	OGIB Ulcers and/or erosions=48 Crohn's 27 of 48 Tumors and/or polyps=37 GIST= 19 of 37 Vascular/lymphatic=32 Angiodysplasia=17 of 32 Structural disorders=18 Diverticula/diverticulosis = 15 of 18 Infections=9 Others=10
Pain = 69 (18%)	Pain Ulcers and/or erosions=12 Crohn's 8 of 12 Tumors and/or polyps=5 Vascular/lymphatic=1 Structural disorders=4 Postoperative adhesion 3 of 4 Infections=4
Diarrhea= 63 (17%)	Diarrhea Ulcers and/or erosions=9 Crohn's 5 of 12 Tumors and/or polyps=2 Vascular/lymphatic=2 Infections=2 Celiac disease=1 Primary hypoglobinemia=2 Malabsorption=5
Obstruction=48 (13%)	Ulcers and/or erosions=12 Crohn's 10 of 12 Tumors and/or polyps=18 Vascular/lymphatic=1 Structural disorders=5 Others=3

3.5 Safety of DBE to Visually Inspect, Biopsy or Treat Lesions of the Small Intestine

Major Complications

Evidence Statements

Major complications resulting from DBE to identify and treat OGIB are less than 1% based on Level IV case series data from 24 studies reporting on 2,175 patients.[3]

Perforation, pancreatitis and segmental enteritis are the major complications identified and reported directly related to DBE for diagnostic use.

Post-polypetectomy bleeding is the major complication associated with a therapeutic use of DBE. Data from the largest study with 3/3 quality ranking for case series reports that the majority of the 6 major complications in 635 procedures were post polypectomy (5 of 46 or 10.8%)(26) This rate is unacceptably high. By comparison a recent case series including polypectomies done by colonoscopy had a bleeding rate of 0.46%.(41)

General anaesthesia is the cause of further major complications related to DBE however as the DBE would most likely be done with conscious sedation in Alberta, these risks are likely to be limited to a small proportion of cases. Reported anaesthetic complications are seizure, aspiration pneumonia following seizure and desaturation after bronchus obstruction by a dislodged cannula.

Only one major complication was reported in 83 procedures from 3 case series including condition-specific but non-OGIB cases (1.2%). This perforation was from a Level IV case series (quality rating 1/3) of 40 patients with Crohn's disease. (36)

The available case reports do not provide additional information on types of complications and cannot contribute to an estimation of the rate of complications.

A total of 24 studies contributed information on major complications resulting from DBE for OGIB or from series with large numbers of OGIBs. These were all case studies representing Level IV evidence; that is they are uncontrolled and data was collected post-test. Data and appraisal on 13 studies were obtained from the MSAC HTA representing searches to May 2006. Data and appraisal on 11 studies were obtained from the University of Alberta HTA representing searches from May 2006 to April 2007 (See Appendix A).

In addition, the studies were ranked on criteria that indicate they were conducted with features that protect against bias. Specifically the studies were appraised as to whether they collected data prospectively, were consecutive cases or representative of patient population and specified how long the patients were followed-up after the test.

[3] Denominator: UAlberta – 907; MSAC – 1268; Total – 2175

Nine of the studies were rated 3/3 meaning the study protocol adequately met all 3 criteria, 3 were rated 2.5/3, 7 were rated 2/3, 3 were rated 1.5/3 and 2 were rated 2/3. The MSAC scores were somewhat higher but without reviewing all or resolving through discussion it is unclear whether this is a true difference.

The most thorough analysis of major complications comes from the May et al, 2007 case series (n=352) which has a quality ranking of 3/3 because it was prospective, enrolled consecutive patients and followed-up for an average of 9 months. The majority of the 6 major complications in 635 procedures were post polypectomy (5 of 46 polypectomy procedures or 10.8%) [May et al 2007]

Also noteworthy is a case report by Attar et al, 2005 reporting a case of paralytic intestinal ileus following DBE that was unresolved one week later but later fully resolved without further events over a five month follow-up period.(42)

A further 3 case series which did not include OGIB cases were identified for the time period 2001 to Apr 2007 (see table 7). These contribute information from case series including respectively patients with Crohn's disease (2) and suspected Meckel's Diverticulum. There was 1 major complication with DBE for Crohn's disease among 77 procedures (1.3%). With no reported follow-up period and the retrospective analysis quality scores were 1/3 and 2/3. No major complications resulted in the 6 procedures done with 3 patients with suspected Meckel's Diverticulum during 6 to 9 months of follow-up .

Manabe et al, 2007 claim that 2 cases in 64 procedures in which signs of cardiac failure appeared during the procedure were unrelated to the procedure.

Table 5 Major complications resulting from DBE May 2006 to April 2007

Study	Level and quality	Population	Major complications per procedure
Quality score:	**3/3**		
Manabe et al 2006	Level IV: Uncontrolled post-test case series Quality score: 3/3	31 patients	2/64 (3%) procedures 'Signs of mild cardiac failure' … 'not related to the procedure'=2
May et al 2007	Level IV: Uncontrolled post-test case series Quality score: 3/3	353 patients	6/ 635 (0.9%) procedures 6/ 178 (3.4%) therapeutic procedures 5/46 (10.8%) polypectomy procedures 4 of 139 patients (2.9%) Post-polypectomy (large polyps >3cm in size) Bleeding = 2 Perforation = 3 Segmental enteritis after APC = 1
Quality score:	**2.5/3**		

Hsu et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	20 patients	0/29 (0%) procedures
Quality score:	**2/3**		
Ang et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	30 patients	0/34 (0%) procedures
Cazzato et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	100 patients	0/118 (0%) procedures
Pérez-Cuadrado et al 2006	Level IV: Uncontrolled post-test case series Quality score: 2/3	44 patients	2/44 (4.5%) 1 Anesthetic: desaturation abdominal relaxation pushed cannula into right main bronchus 1 Perforation requiring surgery
Suzuki et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	19 patients	0/19 diagnostic procedures
Quality score:	**1.5/3**		
Mehdizadeh et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	56 patients	1/59 (1.7%) procedures Tear of an ileal pouch anal anastomosis from a prior ileostomy
Sun et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	153 patients	0/191 (0%) procedures
Zhong et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	378 patients	2/378 patients Severe pain and intraperitoneal gas = 1 Bleeding after adenoma removal = 1
Quality score:	**1/3**		
Akahoshi et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1/3	60 patients	0/103 (0%) procedures
Quality score:	**0.5/3**		
Li et al 2007	Level IV: Uncontrolled post-test case series Quality score: 0.5/3	51 patients	0/64 (0%) procedures

Table 6 Major complications resulting from DBE 2001 to May 2006 (MSAC review)

Study	Level and quality	Population	Major complications per procedure
Quality score:	**3/3**		
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	1/247 (0.04%) procedures: Epileptic seizure as a result of propofol sedation=1
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	1/147 (0.06%) procedures: Aspiration pneumonia resulting from epileptic seizure caused by propofol sedation=1
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	0/47 procedures
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	1/62 (1.61%) procedures: Perforation=1
(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17 patients	0/19 procedures
(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients	0/12 procedures
(Ohmiya et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	2 patients	0/5 procedures
Quality score:	**2.5/3**		
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients	3/316 (0.09%) procedures: Pancreatitis=3
(Yamamoto et al 2001)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	4 patients	0/4 procedures
Quality score:	**2/3**		
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients OGIB=66 Obstructive symptoms=22 Suspicion of intestinal tumour=11 Other indications=32 (note: some overlap in indications)	1/178 (0.06%) procedures: Perforation=1
(Zhi et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 2/3	57 patients	0/72 procedures
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients	1/70 (1.43%) procedures: Post-polypectomy bleeding=1
Quality score:	**1.5/3**		
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients	0/89 procedures

OGIB=obscure gastrointestinal bleeding; GI=gastrointestinal; FOBT=faecal occult blood test; IBD=inflammatory bowel disease; N/A=not applicable

Table 7: Major complications resulting from DBE 2001 to April 2007 in non OGIB case series

Study	Level and quality	Population	Major complications per procedure
Quality score:	**?/3**		
Hadithi et al, 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	21 patients with refractory celiac disease investigated for high risk lesions	0/24 (0%) procedures
Manner et al 2006	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	3 patients with suspected Meckel's diverticulum	0/6 (0%) procedures
Oshitani et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1/3	40 patients with Crohn's disease	1/53 (1.9%) procedures Perforation
Ross et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1/3	3 patients with Peutz-Jeghers syndrome treated with laparoscopic assisted DBE and polyp resection	2/3 (67%) procedures Ileus

Table 8: Major complications resulting from DBE identified by case reports

Study	Study design	Population	Major complications per procedure
(Attar et al 2005)	Case report	1 patient	1/1 procedure: Small bowel ileus=1
(Gasbarrini et al 2005)	Case report	1 patient with abdominal pain, GI bleeding and syncope	0/2 procedures
(Groenen et al 2006)	Case report	2 patients: Anaemia and melaena=1 Anaemia only=1	2/2 (100%) procedures: Acute severe pancreatitis=1 Mild pancreatitis=1
(Honda et al 2006)	Case report	1 patient with tarry stool and severe anaemia	1/2 procedures: Severe pancreatitis=1
(Sunada et al 2004)	Case report	1 patient with Crohn's disease with jejunal strictures	0/1 procedure

GI=gastrointestinal

3.6 Minor Complications

Evidence Statements

The rate of reported minor complications was 8.7% (139 in 1525 procedures) in the 13 level IV case series that quantified minor complications (see tables 9 to 12) The lack of standardization in what is considered a minor complication and indications of under reporting undermine the accuracy of this estimate.

Continued

Reported minor complications ranged from 0.06 to 59% indicating the variation of threshold. The 59% report was from a study that combined all minor complications as well and included dizziness which was not reported by any of the other studies. The reported 0.06% was from a study that reported only one minor complication of fever combined with abdominal pain.

The breakdown of minor complications was as follows. There were 47 reports of mucosal bleeding or redness (2 studies); 40 reports of abdominal pain/distention (9 studies); 39 representing all minor complications combined (1 study); 8 reports of sore throat of which 1 required medical treatment (3 studies); 3 reports of fever (3 studies); 2 report of vomiting (1 study) and 1 reported overnight stay due to prolonged sedation.

One study of refractory celiac disease investigated for high-risk lesions reported a 25% rate of minor complications in this special population. This study highlights that DBE is likely to have different minor complication rates depending on the underlying condition under investigation.

As experience with DBE increases the minor complication rate may improve. Research is underway on a new strategy – CO2 insufflation to decreasing abdominal pain following DBE. While promising, this is not currently proven or standard practice.

The threshold for determining whether to report a minor complication was determined by each set of researchers. Not all of the published case series report on minor complications but this may be more that particular research groups did not consider them to be of sufficient importance or did not record minor complications in the records they retrospectively consulted. As Zhong et al, 2007 report from their case series of 378 patients:

> Most of the patients experienced mild to moderate abdominal distension and pain that resolved spontaneously a few hours later. Sore throat was frequently observed in patients examined via the oral route, but no specific treatment was needed.(39) p 213

This account may reflect the true situation however this is impossible to evaluate on the basis of the available data. Only the case studies that did report minor complications were used to calculate the rate at which they occur. No case reports of minor complications were encountered that contributed to available evidence from case series. See MSAC case reports on minor complications (table 10).

DBE is frequently a companion technology to therapeutic interventions. Therefore minor complications may also vary by intervention and the additional procedure time as well as related factors that may not be well understood at this time given the state of the science.

It is likely that minor complications have been under reported in this literature which includes studies which have less that full 3/3 quality scores as they may variously have lower scores because they are retrospective, non consecutive with no reported follow-up time. On the other hand, given the weakness of the post test case series design and given that patients with

conditions of the small intestine may have symptoms like abdominal pain pre DBE cases without new pain could conceivably be erroneously contributing data to the minor complication rate.

Finally, the current estimated rate may decrease over time as experience with DBE increases. For example, self-limiting abdominal pain after DBE results in part from the air that is used to insufflate the small intestine during the relatively long procedure times. This minor complication may be ameliorated in the future by innovations to practice. Bretthauer et al 2007 are conducting a randomized clinical trial to investigate whether the use of carbon dioxide (CO2) insufflation will lead to reduced abdominal pain as compared to the use of air.(43) It is difficult to predict whether this intervention will be proven successful and diffuse into practice causing a decrease in the minor complication of abdominal pain. It may also be true that average clinicians will not be able to reproduce the complication rates of experts researching and publishing data.

Table 9: Minor complications resulting from DBE May 2006 to April 2007

Study	Level and quality	Population	Minor complications per procedure
Quality score:	**2/3**		
Cazzato et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	100 patients	18/118 (15%) procedures: Abdominal pain=14 Sore throat not requiring medical therapy=4
Quality score:	**1.5/3**		
Mehdizadeh et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	56 patients	1/59 (1.7%) procedures: Mild self-limiting abdominal pain=1 2/25 (8%) procedures (first in series) Vomiting=2 before nasogastric tube became part of standard procedure
Sun et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	152 patients	23/191 (15%) procedures: Self-limiting mucosal bleeding
Quality score:	**0.5/3**		
Li et al 2007	Level IV: Uncontrolled post-test case series Quality score: 0.5/3	53 patients	39/66 (59%) procedures: 'Reported dizziness, light pharyngalgia, distention, light abdominal pain, nausea, or vomiting after '=39

Table 10: Minor complications resulting from DBE 2001 to May 2006 (MSAC review)

Study	Level and quality	Population	Minor complications per procedure
Quality score:	**3/3**		
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	37/247 (15.0%) procedures: Reddening of mucosal tissue=24 Abdominal pain and/or sore throat=12 Fever=1
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	12/147 (8.2%) procedures: Abdominal pain=9 Sore throat requiring medical therapy=1 Fever=1 Vomiting after procedure=1
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	2/47 (4.3%) procedures: Abdominal discomfort/ bloating=2
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	3/62 (4.8%) procedures: Overnight stay due to prolonged sedation=1 Sore throat and swollen uvula=3
(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17patients	0/19 procedures
(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients	0/12 procedures
(Ohmiya et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	2 patients	1/5 procedures: Abdominal tenderness and fever=1
Quality score:	**2.5/3**		
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients	8/316 (2.5%) procedures: Abdominal tenderness=3
(Yamamoto et al 2001)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	4 patients	0/4 procedures
Quality score:	**2/3**		
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients	1/178 (0.06%) procedures: Post-operative fever and abdominal pain=1
(Zhi et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 2/3	57 patients	0/72 procedures
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients	0/70 procedures:
Quality score:	**1.5/3**		
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients	3/89 (3.3%) procedures: Abdominal pain=3

Table 10 Continued

Quality score:	**1/3**		
(Groenen et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 1/3	2 patients	0/2 procedures:

Table 11: Minor complications resulting from DBE from condition specific studies (not including OGIB) 2001 to April 2007

Study	Level and quality	Population	Minor complications per procedure
Quality score:	**2/3**		
Hadithi et al, 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	21 patients with refractory celiac disease investigated for high risk lesions	6/24 (25%) procedures: Self-resolving abdominal pain

Table 12: Minor complications resulting from DBE identified by case reports

Study	Study design	Population	Major complications per procedure
(Attar et al 2005)	Case report	1 patient	0/1 procedure
(Gasbarrini et al 2005)	Case report	1 patient with abdominal pain, GI bleeding and syncope	0/2 procedures
(Honda et al 2006)	Case report	1 patient with tarry stool and severe anaemia	0/2 procedures
(Sunada et al 2004)	Case report	1 patient with Crohn's disease with jejunal strictures	0/1 procedure

3.7 Symptom reduction / therapeutic success with DBE enabled interventions

Evidence Statements

97% success rate of DBE enabled therapeutic interventions based on 19 studies reporting on 442 procedures.

Success in this set of studies primarily refers to procedural success (ie the bleed stopped, the polyp removed) not true measures of health outcomes based in patient experience of symptom reduction.

Zhong et al, 2007, provided an exception. This research group estimated that 91% (190/208) of patients with a confirmed diagnosis who were treated specifically (not all with DBE) had a improvement or elimination of their symptoms. A scoring system to evaluate GI bleeding severity and treated developed and applied finding that 154 patients with positive findings prior

Continued

to treatment had a statistically significant reduction in their bleeding severity afterwards. This study had a quality score of 1.5/3.

50% of all DBE procedure led to a therapeutic intervention in the large series by May et al, 2007 (quality rating 3/3) . This appears to be the best estimate of mature therapeutic use of DBE in a tertiary referral centre.

Argon plasma coagulation or some other modality to stop bleeding was the most common procedure enabled by DBE. Dilation/stricture release and polyp removals were also common.

Follow-up times were relatively short or not reported in this set of case series therefore there is little hard evidence of impact over time.

Validated outcome measurement is lacking in the evaluation of DBE enabled therapeutic intervention. Whereas it would appear to be self evident that finding the source of bleeding and stopping it would be curative and symptom relieving, well designed rigorous studies with adequate comparisons, validated outcome measures and follow-up periods are required to know the true therapeutic impact of DBE enabled therapeutic interventions. The health impacts of bleeding from the small intestine, for example, can vary from life threatening to self limiting and non recurring. Chronic conditions undermine health and well-being. The evidence from this set of case series cannot provide a true gauge of the health impact of DBE.

Zhong et al, 2007 reporting with a large sample size that measured severity of GI bleeding before and after DBE. Treatment may have been endoscopic, medical or surgical with the assumption that the capabilities provided by DBE led to more specific and therefore effective management. The bleeding severity score was based on 5 scales representing the following dimensions: hemoglobin values, duration of the disease, frequency of defecation/ stools, consistency and features of stool and blood transfusion.

> The mean score (± standard deviation) for the severity of gastrointestinal bleeding in the 154 patients with positive findings before DBE was 6.8 ± 2.2, and this dropped to 1.5 ± 0.5 ($P < 0.01$) in patients who underwent specific treatments, to 3.6 ± 0.7 ($P < 0.05$) in patients who received symptomatic relief, and to 3.9 ± 0.9 ($P < 0.05$) in patients who received no treatment.

The quality score achieved by the study would have been improved had it been clear that patients were selected and enrolled prospectively and what population they were drawn from.

No case series of condition specific (non OGIB) DBE use reported on symptom reduction with DBE enabled interventions.

There are many case reports of therapeutic uses of DBE however while these demonstrate feasibility they provide a very low level of evidence for symptom reduction/ therapeutic impact for patient populations.

Table 13: Reported symptomatic reduction/ therapeutic success with DBE enabled interventions May 2006 to April 2007

Study	Level and quality	Population	Therapeutic intervention	Successful intervention/ Reduction of symptoms
Quality score:	**3/3**			
May et al 2007	Level IV: Uncontrolled post-test case series Quality score: 3/3	353 patients	Overall=178 APC=102 (57%) Injection therapy=2 APC+injection therapy = 6 Polypectomy=46 Dilation=18 Foreign body extraction=3 Stent placement=1	Overall=172 (97%) APC=101 Injection therapy=2 APC+injection therapy = 6 Polypectomy=41 Dilation=18 Foreign body extraction=3 Stent placement=0 With success defined as no complications with success procedural
Quality score:	**2.5/3**			
Hsu et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	20 patients	Overall=11 Heater probe coagulation=9 Polypectomy=1 Mucosal resection=1	Overall=9 (82%) Heater probe coagulation=7 (2 required surgery with subsequent rebleeding in patients with treated angiodysplasias of 20% (3 of 15 including medically treated) Polypectomy: results not reported Mucosal resection: results not reported
Quality score:	**2/3**			
Cazzato et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	100 patients	Overall=41 Argon plasma coagulation (APC) =32 Polypectomy=9	Overall=41 (100%) with success defined as procedure performed with no complications.
Manabe et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 2/3	31 patients	Overall=3 with follow-up data Thermal coagulation=2 Obliteration=1	Overall=2 (67%) Coagulation=1 Obliteration=1
Pérez-Cuadrado et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 2/3	44 patients	Overall=24 Argon plasma coagulation=19 Polypectomy=4 Capsule removal=1	Overall=24 (100%) post DBE Argon plasma coagulation=19 Polypectomy=4 Capsule removal=1
Suzuki et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients	Overall=3 Electrocoagulation=3	Overall=3 (100%)

Table 13 Continued

Quality score:	**1.5/3**			
Mehdizadeh et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	56 patients	Overall=16 Argon plasma coagulation=10 Dilation of strictures to remove retained capsules=2 APC plus clips=1 Not specified=3	Overall=16 (100%) with success defined as procedure performed with no complications.
Sun et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	153 patients	Overall=18 Argon plasma coagulation=most common Hemoclips	Overall=18 (100%) with success defined as no complications otherwise success reports not linked to specific endoscopic procedures
Zhong et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	378 patients	In 208/247 patients with a confirmed diagnosis (84.2), specific treatments were performed. *Not enumerated by procedure	Symptoms disappeared or improved in 190/208 patients (91.3
Quality score:	**1/3**			
Akahoshi et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1/3	60 patients	Overall=9 Hemostasis=1 Polypectomy=5 Balloon dilatation=1 Mucosal resection=1 Lithotripsy=1 Additional: Tattooing=33	Overall=9 (100%)

Table 14: Symptomatic reduction/ therapeutic success with DBE enabled interventions 2001 to May 2006 (MSAC review)

Study	Level and quality	Population	Therapeutic intervention	Successful intervention/ Reduction of symptoms
Quality score:	**3/3**			
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	Overall=57 Argon plasma coagulation=44 Polypectomy=7 Foreign body extraction=3 Balloon dilation=2 Injection of epinephrine solution=1	Not stated
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	Overall=42 Argon plasma coagulation=37 Polypectomy=2 Dilation=2 Removal of foreign body=1	Overall=42 (100%)
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	Overall=11 Argon plasma coagulation=10 Polypectomy=1	Overall=10 (91%) Argon Plasma coagulation=9 Polypectomy=1
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	Overall=13 Diathermy=10 Polyp tattooing=2 Polypectomy=1	Overall=10 (77%) Diathermy=7 Polyp tattooing=2 Polypectomy=1

Table 14 Continued

(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17patients	Overall=7 Balloon dilation of strictures=4 Tattooing=3	Overall=7 (100%)
(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients	Overall=5 Local injection of diluted bosmin solution=4 Tattooing=1	Overall=4 (80%) Local injection of diluted bosmin solution=4 Tattooing=1
Quality score:	**2.5/3**			
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients	Overall=82 Argon plasma coagulation=61 Polypectomy=10 Tattooing=8 Removal of foreign body=3	Overall=unable to determine exact numbers Argon plasma coagulation=unable to determine exact numbers Polypectomy=9 Tattooing=8 Removal of foreign body=2
Quality score:	**2/3**			
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients	Overall=21 Electrocoagulation=12 Balloon dilation=6 Stent placement=2 Mucosal resection=1 Stent placement=2 Mucosal s	Overall=21 (100%)
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients	Overall=14 Argon plasma coagulation=7 Polypectomy=3 Electrocoagulation=4	Overall=14 (100%)
Quality score:	**1.5/3**			
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients	Overall=26 Argon plasma coagulation=26	Overall=26 (100%)

EMR=endoscopic mucosal resection

3.8 Diagnostic Yield

DBE is one possible step in a multistep process or clinical pathway for diagnosing and treating conditions of the small intestine. Patients are highly selected and the more rigorous the selection criteria for obtaining DBE the more likely the DBE will yield a positive diagnosis.

DBE has generally been used after more widely available diagnostic and imaging modalities have been done without providing adequate information for diagnosis or treatment. More traditional and available upper GI endoscopy (esophagogastroduodenoscopy) and lower GI endoscopy may have been done as well as radiological, ultrasound or nuclear imaging tests.

The test characteristics of prior tests will have an impact on yield with DBE. Ang provides this summary of modalities for small intestinal diseases including reported diagnostic yields from the literature:

(a) conventional barium follow-through with a diagnostic yield of 0–20%;

(b) angiography with a diagnostic yield of 40–60%, which although allowing for therapeutic intervention, requires active bleeding at 3–5 ml/min during the study time; and
(c) technetium (Tc) 99m-labelled red blood cell scintigraphy with a diagnostic yield of 20–40% but requires active bleeding of 0.1–0.5 ml/min.
(d) Traditional forms of push enteroscopy using either standard colonoscopies (160 cm) or specifically designed small intestinal endoscopes (200–270 cm) yielded diagnostic rates of 30% to 50%
(e) Sonde enteroscopy which has a longer instrument length (270– 400 cm) and traverses the small intestine by peristalsis, achieved diagnostic rates between 23% and 33%(13,14) but did not gain wide acceptance in view of the lack of therapeutic capability and poor luminal visualisation.
(f) Intraoperative endoscopy, while allowing for immediate surgical intervention, is by far the most invasive of all investigations. (28)

Diagnosis may require the additional information provided by biopsy during the DBE procedure.

The referral pathway will also determine test parameters. Given that DBE is being introduced through specialized, tertiary and university affiliated centres, it can be expected that patients prescreened in the primary and secondary health care centers are more likely to test positive with DBE.

Video capsule endoscopy, which emerged a few years ahead of DBE, is variously portrayed in the literature as a comparator or as a complementary diagnostic procedure. The MSAC clinical pathway assumes CE will be done prior to DBE in 90% of cases and that 50% of those who have CE will be referred for DBE.(44) See discussion section 2.2 for the challenges of comparing DBE to a gold standard reference test.

Evidence Statements

DBE has high reported diagnostic yield for detecting the source of OGIB and diagnosing other conditions of the small intestine: 71% overall (range 41 to 93%) in case series of hierarchy of evidence Level IV with quality ratings from 3/3 to 0.5/3. If only case series with quality scores of 2 to 3 are considered the average increases to 75% with a range from 52 to 93% (see tables 15 and y).

Diagnostic yield is simply the number of diagnoses made per cases tested. It does not reflect how accurate diagnoses are. Generally diagnostic tests may be evaluated by calculating test parameters of sensitivity, specificity and predictive value. This requires a gold standard reference test and the attempt to provide this for DBE have not been of high quality.

Patient receiving DBE are highly selected. Diagnostic yield is a function of the selection process and therefore dependent on referral patterns, the results of prior investigations and selection criteria as much as the technical performance of DBE equipment and operator. Variance is both expected and difficult to precisely explain with available data.

Continued

The series that define the upper and lower range of diagnostic yield are illustrative. The study that provided the highest diagnostic yield at 93% was one with prior CE or suspected intestinal stenosis precluding CE and in which DBE was required for biopsy or for angiodysplasias to be treated with argon plasma coagulation.(45) By contrast DBE was done without prior CE and without stringent criteria in the study with the lowest reported diagnostic yield (41%).

A series, which included only patients with refractory celiac disease and seeking to identify high-risk lesions, had a diagnostic yield of 33%.

Reported diagnostic yields (tables 16-17) also reveal the variation in taxonomies and range of conditions of the small intestine conditions detected. Whether the diagnoses are accurate and conform to a standard clinical category with predicted outcomes cannot be determined from this data.

Finally, the diagnostic yield data does not reveal how accurate the diagnosis is or whether patients were better off as a result of having been diagnosed with DBE and if so how much their health status improved.

Table 15: Biopsy yield / diagnostic yield of double-balloon enteroscopy May 2006 to Apr 2007 in series containing OGIB (UAlberta HTA)

Study	Level and quality	Population	Biopsy yield / diagnostic yield
Quality score:	**3/3**		
May et al 2007	Level IV: Uncontrolled post-test case series Quality score: 3/3	353 patients Mid midgastrointestinal bleeding=210 (60%). Primarily reporting on therapeutic intervention	Overall 265/353 (75%)
Quality score:	**2.5/3**		
Hsu et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	20 patients Angiodysplasias=9 GISTs[4]=2 Ulcers=2 Polyps=2	Overall 15/20 (75%)
Quality score:	**2/3**		
Ang et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	30 patients OGIB=18 Erosions/ ulcerations=7 GI Pathology ruled out=3	Overall 20/30 (67%)
Cazzato et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	100 patients Angiodysplasias=39 Erosions/ ulcerations =21 Tumors=7 Ileostenosis with Crohn's suspicion=2	Overall 69/100 (69%)

[4] Gastrointestinal stromal tumors (GISTs)

Table 15 Continued

Manabe et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 2/3	31 patients Ulcers or erosions=11 Polyps or tumors=9 Vascular abnormalities=2 Other=1	Overall 23/31 (74%)
Pérez-Cuadrado et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 2/3	44 patients Angiodysplasias=19 Other=4	Overall 23/44 (52%)
Suzuki et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	19 patients Small intestinal tumors=6 Angiodysplasia=5 Submucosal tumors=3 Small intestinal cancer=1	Overall 21/27 (78%)
Quality score:	**1.5/3**		
Mehdizadeh et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	56 patients Arteriovenous Malformation=8 Ulcerated mass=5 Nonulcerated polypoid lesion=4 Ulcer Small bowel stricture with retained capsule=2 Small bowel diverticula=2	Overall 26/56 (46%)
Sun et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	153 patients Small bowel tumors=45 Angioectasia=35 GISTs=21 Crohn's Disease=18 Ulcers/erosions=13 Adenocarcinomas=5 Adenoma (tubular)=4 Submucosal tumor=4 Other=15	Overall 115/152 (76%)
Zhong et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	378 patients Ulcers and or erosions =85 Crohn's disease=52 Tumors and or polyps=63 GIST=24 Vascular/lymphatic=36 Angiodysplasias=17 Structural disorders=27 Diverticula/diverticulosis=18	Overall 247/378 (65%) OGIB 153/191(81%) Abdominal pain 26/69 (38%) Diarrhea 23/63(37%) Small bowel obstruction 39/48(81%) Others 5/7 (71%)
Quality score:	**1/3**		
Akahoshi et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 1/3	46 patients in which small intestine investigated Abnormalities = 20	Overall 20/46 (43%)
Quality score:	**0.5/3**		
Li et al 2007	Level IV: Uncontrolled post-test case series Quality score: 0.5/3	51 patients Malignancy=7 Crohn's Disease=7 Isolated ulcer=2 Angiodysplasias=2 Parasitic infection=2 Inflammatory lump=2	Overall 21/51 (41%)

Table 16: Biopsy yield / diagnostic yield of double-balloon enteroscopy 2001 to May 2006 (MSAC HTA)

Study	Level and quality	Population	Biopsy yield / diagnostic yield
Quality score:	**3/3**		
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients Chronic or acute recurrent GI bleeding=90 Abdominal pain=11 Polyposis syndromes=14 Chronic diarrhoea/malabsorption=3 Non-Hodgkin's lymphoma=3 FOBT negative iron deficiency anaemia=2 Subileus or severe abdominal pain in Crohn's disease=6 Intestinal obstruction from capsules/ dentures=3 Other=5	Overall 109/137 (80%)
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients GI bleeding=64 Polyposis=8 Abdominal pain=7 Suspected Crohn's disease=7 Chronic diarrhoea=7 Other=7	Overall 72/100 (72%)
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients Suspicion of tumour=13 Coeliac disease=4 Crohn's disease=3 AVM=10 Obscure GI bleeding=3 Obstructive symptoms=4 Other=5	Overall 39/42 (93%)
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients OGIB=18 IDA=6 Anaemia of chronic disease=4 Acute OGIB=4 Abdominal with other symptoms=4 Crohn's disease=3 Abdominal pain alone=1	Overall 30/40 (75%)
(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17patients Bowel obstruction=12 Abdominal tumour=2 Anaemia=1 Hematochezia=1 Low protein=1	Overall 12/17 (71%)
(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients Chronic or recurrent GI bleeding=5 Acute GI bleeding=5	Overall 8/10 (80%)

Table 16 continued

Quality score:	**2.5/3**		
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients Suspected small bowel bleeding=168 Celiac disease / suspected EATL=25 Abnormalities on CT or small bowel follow-through=23 Peutz-Jeghers syndrome=14 Suspected Crohn's disease=13 General malaise=11 FAP / Gardner syndrome=6 Foreign body=3	Unable to extract reliable data
Quality score:	**2/3**		
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients OGIB=66 Obstructive symptoms=22 Suspicion of intestinal tumour=11 Other=32	GI bleeding 50/66 (76%) Obstructive symptoms 17/22 (77%)
(Zhi et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 2/3	57 patients Clinically suspicious intestinal haemorrhage=57	Overall 52/57 (91.2%)
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients GI bleeding=29 Suspected Crohn's disease=6 Abdominal pain=4 Polyp removal or evaluation=6 Chronic diarrhoea=4 Surveillance or tumour search=4	Overall 36/53 (68%)
Quality score:	**1.5/3**		
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients OGIB=33 Chronic diarrhoea=5 IDA and positive FOBT=5 Refractory or suspected celiac disease with negative gastro copy=4 Abdominal pain=3 FAP=3 Impaired clinical conditions in Crohn's disease=3 Follow-up of GI tumours=3 PeutzJeghers syndrome=2 Gardner's syndrome=1	GI bleeding 29/33 (89%) IDA 1/5 (20%) Chronic diarrhoea 3/5 (60%) Abdominal pain 2/3 (66%) GI cancer 2/3 (66%) Peutz-Jegher's syndrome, Gardner's syndrome and FAP 6/6 (100%) Suspected or refractory celiac disease 3/4 (75%) Crohn's disease 2/3 (66%)

EATL=enteropathy associated T-cell lymphoma; IDA=iron deficiency anaemia; FAP=familial adenomatous polyposis; N/A=not applicable; FOBT=faecal occult blood test; GI=gastrointestinal; AVM=arteriovenous malformations; OGIB=obscure gastrointestinal bleeding; CT=computed tomography

Table 17: Diagnostic yield from studies with inclusion criteria of small bowel condition specific excluding OGIB

Study	Level and quality	Population	Biopsy yield / diagnostic yield
Quality score:	**3/3**		
Hadithi et al, 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	21 patients with refractory celiac disease investigated for high risk lesions Enteropathy-associated T-cell lymphoma=5 Ulcerative jejunitis=2	Overall 7/21 (33%)

3.9 Transfusion Requirements after DBE

Transfusion requirement is a surrogate health outcome as it does not directly report on a physiological or subjectively experienced health state. In the cases where the natural history of a GI bleed is to continue to bleed and require blood transfusion at regular intervals then transfusion requirement may be a good though indirect measure of improvement. However in some cases the natural history of the bleed may have been self limited and so investigation and treatment did not cause the improvement.

Evidence Statements

There is evidence of reduced transfusion requirements after DBE from five case studies (quality rating ranging from 2.5 to 3. Of 50 patients for whom there is clear data from individual before and after DBE on transfusion status 33 patients (67%) did not require further transfusion in during follow-up periods averaging 4 and 5 months. This is an indirect measure of the therapeutic impact of DBE on bleeding.

Table 18: Transfusion requirements after double-balloon enteroscopy May 2006 to Apr 2007 in series containing OGIB (UAlberta HTA)

Study	Level and quality	Population	Transfusion requirements	
			No. of patients with previous history transfusion	No. of patients with successful reduction in requirement for transfusion
Hadithi et al, 2006	Level IV: Uncontrolled post-test case series Quality score: 3/3	35 patients	30	26
Manabe et al 2006	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	20 patients	23	Up to 21 (no rebleeding average follow-up of 8.5 mo. but not identified by prior transfusion status)
Hsu et al 2007	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	20 patients	11	Up to 13 of 20 (no rebleeding average follow-up of 1 year but not identified by prior transfusion status)

Table 19: Transfusion requirements after double-balloon enteroscopy 2001 to May 2006 (MSAC HTA)

Study	Level and quality	Population	Transfusion requirements	
			No. of patients with previous history transfusion	No. of patients with successful reduction in requirement for transfusion
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	20	7
(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients	5	Not stated

3.10 Technical failure of double-balloon enteroscopy

Evidence Statements

Acute technical failure was experienced in 6 of 178 (3.3) therapeutic interventions undertaken from a population of 353 (Level IV evidence from one case series, quality score of 3/3) (see tables 20 and 21).

Equipment failure was reported in 4 of 508 (0.8%) procedures in 3 case series reporting on both diagnostic and therapeutic use.

Procedural failure has a technical component although operator experience and anatomical challenges also contribute. Mehdizah et al, 2007 specifically investigated procedural success in retrograde DBE in gaining access higher than the terminal ileum. This study revealed failure in 12 of 58 procedures (21%). (35)

To be included in this section the authors must have explicitly reported on technical failures. There is a discrepancy in what researchers count as technical failure. Whereas May et al, 2007 (26) define technical failure as equipment failure as well as procedural failure, Mehdizah counts failure of DBE to reach a desired location within the small intestine thereby perhaps failing to diagnose the source of bleeding.(35) Both perspective contribute to valid information about DBE. Authors

Mehdizah et al, 2007 indirectly addresses the issue of operator contribution to procedural failure.

> Yamamoto et al[6] were able to insert the endoscope beyond the ICV in all 89 patients, including patients with prior laparotomy. The Japanese group has the most experience in the world, and their success may be explained by their vast DBE experience.

We identified prior abdominal or pelvic surgery as a major contributor to rDBE failure. DBE, in principle, requires the bowel to be mobile within the abdominal cavity for endoscope advancement and shortening. Adhesions that fixate loops of bowel are the likely reason for procedure failure in patients with prior surgery. Distal ileal angulation and fixation by scar tissue may render the already difficult ileal intubation impossible to perform. We also showed that stable small-bowel intubation is significantly more prolonged in patients with prior abdominal or pelvic surgery….

Our results show a learning curve specific to rDBE. The failure rate was minimized after performance of 40 procedures. Likewise, the farthest reach of the endoscope within the small bowel was most satisfactory after 40 procedures were performed. (35)

Table 20: Technical failure of double-balloon enteroscopy May 2006 to Apr 2007 in series containing OGIB (UAlberta HTA)

Study	Study design	Population	Major complications per procedure
May et al 2007	Level IV: Uncontrolled post-test case series Quality score: 3/3	353 patients	6/178 therapeutic interventions (3.4%) 1. Failed Polypectomy due to 'unstable position of the scope','invagination of the small bowel' and 'huge polyp size of 8 cm.' Surgicaly resected 2. Electrosurgical cutting effect failed completely during resection of a large polyp (5 cm) due to a break in the snare. It had to be left in place and removed surgically next day with no further complications 3-5. DBE overtube could not be positioned correctly in 3 attempted dilations of stenoses perhaps because close to the ileal value (pediatric colonoscope successful) 6. An attempt 'to place a self-expending stent failed because of anatomical conditions and the insertion catheter could not be inserted through the working challen of the t-type enteroscope'
Mehdizadeh et al 2007	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	56 patients	12/58 (21%) retrograde (anal approach) DBE failed to reach higher than TI (terminal ileum) 1/58 'In 1 instance, 1 of 2 endoscope lights failed during small-bowel advancement. The procedure was terminated…'

Table 21: Technical failure of double-balloon enteroscopy 2001 to May 2006 (MSAC HTA)

Study	Study design	Population	Major complications per procedure
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	Overall 1/ 248 (0.4 %) procedures Loss of cap attached to tip of scope upon withdrawal of scope. Cap was recovered and extracted

Table 22: Technical failure of DBE with inclusion criteria of small bowel condition specific (excluding OGIB)

Study	Study design	Population	Major complications per procedure
Hadithi et al, 2007	Level IV: Uncontrolled post-test case series Quality score: 2/3	21 patients	Overall 0/24 procedures (0%)

3.11 Examination time and completion

Evidence Statements

DBE is a time consuming procedure and therefore it is resource intensive on human and space resources as well as equipment.

May et al, 2005 report on procedure time among 137 consecutive patients. Either the oral or anal approach take between 70 and 75 minutes with a range of between 25 and 131 minutes. (46)

The variation in procedure time is explained in part because it is unnecessary to complete a transverse of the small intestine if a source lesion has been identified.

Table 23: Examination time of double-balloon enteroscopy

Study	Level and quality	Population	Mean examination time (minutes) by approach	Number of approaches used per patient
Quality score:	**3/3**			
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	Oral and anal: 73.5 ± 25 (range 25-131) Oral=72.5 ± 23 (range 30-131) Anal=75 ± 28 (range 25-130)	Single approach=57/137 (42%) Both approaches=80/137 (58%)
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	Oral and anal: 75 ± 19 (range 32-150)	Not stated
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	Oral=55 ± 21 Anal=61 ± 27	Not stated
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	Not stated	Single approach=19/40 (48%) Both approaches=21/40 (53%)
(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17patients	Not stated	Single approach=15/17 (88%) Both approaches=2/17 (12%)

Table 23 continued

(Su et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	10 patients	Not stated	Single approach=8/10 (80%) Both approaches=2/10 (20%)
Quality score:	**2.5/3**			
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients	Oral=90 ± 42 Anal=110 ± 34	Not stated
Quality score:	**2/3**			
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients	Oral and anal (median): 123 (range 77-180)	Not stated
(Zhi et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 2/3	57 patients Clinically suspicious intestinal haemorrhage=57	Oral and anal: 80.2 (range 12-180)	Single approach=42/57 (74%) Both approaches=15/57 (26%)
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients	Oral=72 (range25-180) Anal=55 (range 25-90)	Not stated
Quality score:	**1.5/3**			
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients	Oral=70 ± 30 Anal=90 ± 35	Single approach=35/62 (56%) Both approaches=27/62 (44%)

EMR=endoscopic mucosal resection

Table 24: Completion of double-balloon enteroscopy procedures

Study	Level and quality	Population	Mean length of insertion (mean ± SD cm)	Total enteroscopy	Termination of DBE procedure
Quality score:	**3/3**				
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	Oral=240 ± 100 (range 40 -550) Anal=120 ± 90 (range 50 -350)	25/55 (oral only=2, oral and anal=23)	Intolerance despite increased sedation=1 Inadequate bowel preparation=4
(Ell et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	Overall=200 ± 70 Oral=220 ± 90 Anal 130 ± 80	16 (16%) (oral and anal=14, oral only=2) Procedure was stopped once diagnosis was made	Active bleeding in duodenal bulb=1 Bleeding source found in colon=1 Anatomical conditions=5
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	Not stated	Not stated	Not stated
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	Not stated	0/10 (0%)	Not stated

Table 24 continued

Quality score:	**2.5/3**				
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2.5/3	275 patients	Oral=270 ± 104 Anal=156 ± 116	26/62 (42%) (oral and anal=12)	Not stated
Quality score:	**2/3**				
(Yamamoto et al 2004a)	Level IV: Uncontrolled post-test case series Quality score: 2/3	123 patients	Not adequately stated	24/28 (oral only=2, oral and anal=22)	Not stated
(Zhi et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 2/3	57 patients Clinically suspicious intestinal haemorrhage=57	Not stated	Not stated	Not stated
(Mönkemüller et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 2/3	53 patients	Oral=200 (range 30-470) Anal=70 (range 1-220)	4/53 (oral only=2, oral and anal=2)	No attempt at small bowel inspection=1 Multiple adhesions prevented passage of scope=1 Not able to tolerate procedure=1 Anatomical conditions=3
Quality score:	**1.5/3**				
(Di Caro et al 2005)	Level IV: Uncontrolled post-test case series Quality score: 1.5/3	62 patients	Oral=254 ± 174 Anal=180 ± 150	10 (16.2%)	Subclinical ileal stenosis=5 Excessive looping of colon=5

3.12 Australian MSAC HTA Recommendations

The Medical Services Advisory Committee (MSAC) contracted the Adelaide Health Technology Assessment (AHTA) at the Discipline of Public Health, University of Adelaide to provide a synthesis of the evidence in support of DBE for OGIB. The Adelaide HTA unit was to report on the research relating to the safety, effectiveness and cost-effectiveness and evaluate under what circumstances public funding should be supported.

The MSAC An advisory panel of national experts from a variety of disciplines reviewed the HTA report and advises the Minister for Health and Ageing on whether to provide funding as part of the Australian Medicare system. Here are their recommendations.

Recommendations of the MSAC report[5]

This assessment was considered by the MSAC at the 15 November 2006 meeting

Double Balloon Enteroscopy (DBE) is a safe, minimally invasive technique for examining endoscopically the whole of the small intestine, allowing biopsy and certain therapeutic procedures at the same time. The most appropriate comparator is intraoperative enteroscopy.

While there is no direct comparative data, it is likely to be safer to perform than the alternative, intraoperative enteroscopy.

DBE is effective in allowing enteroscopic assessment and some treatment of the entire small intestine. Although more costly to Medicare than intraoperative enteroscopy, DBE is potentially cost saving for the entire health funding system.

MSAC **recommends public funding** for DBE for the diagnosis and treatment of patients with obscure gastrointestinal bleeding.

Endorsed by the Minister for Health and Ageing on 5 February 2007

[5] MSAC Draft report available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/AD35ED216E990FC7CA2571420004A192/$File/DBE%20report%20print%20ready%20Nov%2006.pdf

4.0 Economic and Social Considerations

Our search did not reveal a full economic evaluation of DBE published in the peer-reviewed literature. The MSAC reported a cost comparison that informed our analysis. MSAC states that the appropriate comparator for DBE is a surgical alternative; that is, laparoscopy or interoperative enteroscopy.(44)

4.1 Canadian DBE unit costs

The costs of acquiring the technology to perform DBE were estimated to be $140,344 total purchase price including GST and the cost of ancillary computer hardware. This works out to approximately $667 per procedure assuming that each enteroscope would perform 50 or more procedures per year, that the equipment would have a working life about 5 years over a 5 year budget period and with financing costs of 5% per annum. (Table 25).

Acquisition costs in Canadian dollars were obtained directly from representatives of Fujinon – suppliers of DBE technology in Canada. The MSAC model for calculating unit costs of DBE equipment was used. As Canadian expert gastroenterologists would prefer DBE to be done under conscious sedation as a day procedure our calculations do not reflect anaesthesia costs.

When physician, facility (including assistant staff costs) as well as the variable costs of disposables per patient are included then the total per unit costs for DBE conducted on an outpatient basis with conscious sedation were estimated to be $2,181 without therapy and $2,715 with therapy (Table 26).

The Alberta Health Care Insurance Plan (AHCIP) base fee code 01.22 for Nonoperative endoscopy of lower gastrointestinal tract was used to estimate the specialist fees. The current fee schedule was used for all fee codes.[6] This code has four related additional codes that can be billed with this which represent therapeutic manoeuvers. The highest rate of $88.96 for one so this was used multiplied by 4 (representing the difference in the time to do a DBE versus colonoscopy) to calculate the rate with therapy.

[6] Medical Procedure List available at http://www.health.gov.ab.ca/professionals/SOMB_Procedure_List.pdf

Table 25: Cost per unit of DBE equipment and maintenance

Item	Estimate	Source of estimate
Purchase price • DBE enteroscope (EN-450T5) • Balloon Pump Controller (PB-20) Equipment essential for DBE Subtotal Non essential items with research and other uses • Processor (EPX-4400) • Cart (PC-30) • Monitor (19" Radiance monitor NDS[7]) GST Total	 $55,750 $26,750 $82,500 38,750 5,750 5,400 132,400 7,944 140,344	Carsen Medical Inc, Canada distributor of Fujinon DBE technology
Estimated clinical life of equipment	5 years	Carsen Medical Inc
Annual equivalent cost of equipment	$ 30,872	Annuity at 5% p.a. for 5 years
Annual maintenance costs	$2,500	Carsen Medical Inc estimate over 5 years with lower estimated costs in the first and second years of operation
Total major capital equipment cost per annum	$33,372	
Estimated annual volume of procedures	50 plus	Alberta expert advisor estimate on annual use per DBE site
Estimated cost per procedure for equipment and maintenance	$667	

Table 26: Total cost per unit of DBE equipment, specialist and day facility costs

Item	Estimate	Source of estimate
Equipment cost: capital and maintenance per procedure	$667	Table 25 (above)
Specialist fees	$633.60 (including biopsy) ($989.44 with therapy)	Clinical experts concur that the procedural time for DBE is approximately four times that for colonoscopy and that therefore it would be reasonable to multiply the fee for colonoscopy by four. AHCIP fee code 01.22
Cost associated disposables[8]	$344.5 $39.75	Carsen Med Inc, Canada Overtube TS-13140 Carsen Med Inc, Canada Balloon for enteroscope BS-2 (10 ballons per package with 1 used per procedure)
Cost of day hospital facility services	$496	GI endoscopy Low: (highest cost) based on relative resource use: p 282 Health Costing 2005.
Total	$2,181 $2,715	Without therapy With therapy

[7] National Display Systems (NDS) is designed to provide superior images for any medical application
[8] Including GST

4.2 Canadian intra-operative enteroscopy costs

When ongoing signs and symptoms are acute or serious and if small intestinal pathology is implicated but cannot be diagnosed with conventional modalities (including increasingly VCE) then the only currently available means of accessing the small intestine for diagnosis and treatment is generally surgical intervention with laparotomy or intra-operative enteroscopy.

Precisely estimating the numbers of surgical interventions currently occurring in Alberta that could potentially be replaced by DBE is challenging as administrative datasets as the procedure and diagnostic codes in routine use do not precisely identify the subset of patients receiving surgical interventions specifically for small bowel procedures because they cannot be diagnosed with conventional means or treated endoscopically.

This report has benefited from the extensive work done by the Alberta Costing Project which produced average costs for common diagnostic and procedural categories. [9] This effort compiles data from the Capital Health and Calgary Regions to estimate the average cost of hospital-based inpatient activity.

Given that 60% of the cases from large case series are referred to DBE for mid GI bleeding, it seems reasonable to assume that this subgroup will be well represented in the category of GI hemorrhage. With an average cost of 3,619 and a range of average cost per complexity level of $3,002 to $11,143 it appears that inpatient surgical intervention for GI Hemorrhage is likely to be slightly more costly than DBE. (Table

Is it likely that interoperative endoscopy are less costly than DBE. This assumes that DBE will not in most cases be additive to surgery. That is, provided that therapeutic interventions can successfully be performed with DBE then the DBE procedure will replace surgery for most cases. Tumors are an example of a clinical circumstance where surgery may still be performed following DBE. There may still be the opportunity for DBE to add value to the surgery by tattooing. Tattooing permits more efficient location of the target area for surgery and therefore may decrease invasiveness and time spend in surgery and therefore complications.

All costed categories which embrace diagnoses within the yield and therapeutic range of DBE were overall more expensive than DBE. This includes stricture release for GI obstruction. The average cost of inpatient treatment of GI Obstruction is $2,949 with a range of $2,638 to $12,214 (Table 28).

There are 3 other categories under which operative alternatives to DBE may be captured in the administrative dataset. 'Other GI Diagnoses' includes foreign body entering through natural orifice category which may also be retrieved by DBE. This procedure has average costs of $3,418 with a range from $2,831 to $14,113. Digestive system malignancies have an average range of $5,005 to 14,699. Laparotomy has an average cost of $2,061 with a range of $1,703 to 5,297. This latter category is the only one that overlaps with the estimated cost of DBE ($1,703 versus

[9] Alberta Health and Wellness. "Health Costing in Alberta: 2005 Annual Report" October, 2005. Available at www.health.gov.ab.ca/resources/publications/Health_Costing_2005.pdf.

$2,181. Therefore, is a possibility that a simple laparotomy could be cheaper than DBE but overall it appears that most surgical interventions will be more costly.

Table 27: G.I. Hemorrhage

Complexity Level	Average Length of Stay	Average Direct Cost	Average Indirect Cost	Average Cost	Cost per Day	Number of Costed Cases
	4.5	2,761	858	3,619	800	2,324
Plx 1	3.9	2,286	716	3,002	776	1,855
Plx 2	7.3	4,412	1,385	5,797	796	221
Plx 3	9.0	5,768	1,776	7,544	840	156
Plx 4	10.9	8,638	2,505	11,143	1,051	105

p. 93 Other diseases of the digestive system (K90-K93); includes at least 75% of principal diagnoses within CMG; One of top 5 CMGs based on activity for medical partitions

Table 28: GI Obstruction

Complexity Level	Average Length of Stay	Average Direct Cost	Average Indirect Cost	Average Cost	Cost per Day	Number of Costed Cases
	4.3	2,205	744	2,949	690	1,821
Plx 1	3.9	1,970	669	2,638	684	1,622
Plx 2	6.8	3,697	1,268	4,065	735	104
Plx 3	11.4	5,017	2,013	7,030	697	56
Plx 4	14.2	9,250	2,064	12,214	862	35

Other diseases of intestines (K55-K63)

These costs include all direct costs including provider costs, direct supervision, supplies, and equipment costs. As well the indirect costs include administrative and facility overhead costs.

The Australian comparison of costs for DBE and laparotomy with or without intraoperative enteroscopy and with or without therapy find the total costs are not greatly different. In Australian dollars they estimated total costs for DBE of $1,363 without and $1,830 with therapy. Simple laparotomy was the cheapest option at $882. Laparotomy with intra-operative enteroscopy was $1,348 without and $1,678 with therapy.(44)

4.3 Estimating the need for DBE

There are no estimates of DBE use per population with proper denominator data. Nor is the good epidemiological data on the subset of all patients requiring investigation of small intestinal pathology. The best estimate for population based need for DBE is probably based on the MSAC analysis as this calculation was for the whole country. The MSAC analysis is based on the estimate that only 1,147 DBE procedures would be required for a population of over 20 million -- 57 DBE procedures per million. This number was obtained by using actual rates of capsule endoscopy from billing data. It was assumed that 50% would identify small bowel lesions that

would be suitable for DBE. In addition 100-200 would be identified by other imaging techniques. Finally, 10% would require both oral and anal DBE approach.

4.4 Data from peer-reviewed literature

Researchers have reported data on the economic considerations in introducing DBE into a system.

DBE is acknowledged to be a resource intensive procedure. Gerson, 2005 summarizes key resource requirements:

> As noted by May et al, double-balloon enteroscopy requires additional staffing, typically either two physicians (one to control the enteroscope and the second to assist with the overtube) or an additional nursing assistant. Compared with intraoperative enteroscopy, however, double-balloon enteroscopy appears to be equally as effective for the management of small-bowel lesions, associated with fewer complications, and most likely will be less expensive, because it is an outpatient procedure.(47)

Lo & Mehdizadeh, 2006 describe DBE as expensive given that it requires…

> …fluoroscopy, extended anesthesia support, long procedure time, significant capital investment, and a team of three or four people (endoscopist, anesthesiologist, nurse).(48)

The reports from US for profit centres are that DBE can be revenue positive though there are also concerns that DBE is 'poorly reimbursed relative to time investment'.(48) Etzkorn et al 2006 claims that over a 1 year of follow-up in a private setting they tracked savings in blood transfusions, hospital days, ER visits, laboratory, repeat endoscopies and contrast and nuclear studies. (49) Ross et al, 2006 report that the downstream revenue of $100,000 was generated for a total of 82 inpatient days in DBE and related hospital services. (50)

4.5 Social considerations

DBE is without contentious ethical or legal issues though reimbursement has been raised as an access issue. Patients would generally prefer to swallow a capsule compared to the relatively more invasive endoscopy and prefer to avoid surgery. As the role of DBE is between these two options in a clinical pathway for investigating and treating conditions of the small intestine then these preferences are satisfied. Given that DBE will only be available in relatively few tertiary centres generic issues of accessibility may arise depending on equity in referral patterns.

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