Double-balloon enteroscopy

November 2006

MSAC Application 1102

Assessment report

ISBN 1-74186-207-8

ISBN (Online) 1-74186-208-6

ISSN (Print) 1443-7120

ISSN (Online) 1443-7159

First printed April 2007

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

The Secretary
Medical Services Advisory Committee
Department of Health and Ageing
Mail Drop 106
GPO Box 9848
Canberra ACT 2601

Enquiries about the content of the report should be directed to the above address.

The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared on behalf of the Medical Services Advisory Committee by Ms Elizabeth Buckley, Ms Skye Newton, Ms Hedyeh Hedayati, Ms Tracy Merlin, Mr John Moss and Professor Janet Hiller from Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, University of Adelaide. The report was edited by Ms Jo Mason, Mason Edit, South Australia. The report was endorsed by the Minister for Health and Ageing on 5 February 2007.

Publication approval number: P3-1291

Contents

Executive summary vi

Introduction 1

Rationale for assessment 1

Background 2

Small bowel 2

Small bowel disorders 2

Double-balloon enteroscopy 3

Intended purpose 3

Diagnostic modalities for small bowel disorders 4

Therapies for small bowel disorders 5

Comparator techniques 8

Marketing status of the technology 8

Current reimbursement arrangement 8

Approach to assessment 9

Objective 9

Expert advice 9

Review of literature 9

Assessment of the body of evidence 13

Results of assessment 15

Clinical need for double-balloon enteroscopy 15

Safety of double-balloon enteroscopy 16

Primary safety outcomes 16

Secondary safety outcomes 19

Effectiveness of double-balloon enteroscopy 23

Primary effectiveness outcomes 23

Secondary effectiveness outcomes 28

Economic considerations associated with double-balloon enteroscopy 34

Other relevant considerations 40

Discussion 42

Is double-balloon enteroscopy safe? 42

Is double-balloon enteroscopy effective? 42

Economic considerations of double-balloon enteroscopy 43

Conclusions 45

Safety 45

Effectiveness 45

Economic considerations 46

Recommendation 47

Appendix A MSAC terms of reference and membership 48

Appendix B Advisory panel **50**
Appendix C Search strategies **51**
Appendix D Internet sites searched **54**
Appendix E Critical appraisal checklist **58**
Appendix F Studies included in the review **59**
Appendix G Excluded studies **67**
Appendix H DBE safety and effectiveness data in conference abstracts **72**
Glossary and abbreviations **75**
References **77**

Figures

Figure 1 Human gastrointestinal tract 2

Figure 2 Double-balloon enteroscope 3

Figure 3 Clinical pathway for use of double-balloon enteroscopy 7

Figure 4 Study selection process 10

Tables

Table 1 Number of citations initially retrieved and then retained at each phase 11

Table 2 Evidence dimensions 11

Table 3 Designations of levels of evidence (adapted from NHMRC 2005) 12

Table 4 Body of evidence assessment matrix 14

Box 1 Study selection criteria to determine the safety of double-balloon enteroscopy 16

Table 5 Major complications resulting from double-balloon enteroscopy 17

Table 6 Major complications resulting from double-balloon enteroscopy identified by case reports 19

Table 7 Minor complications of double-balloon enteroscopy 20

Table 8 Minor complications resulting from double-balloon enteroscopy identified by case reports 21

Box 2 Study selection criteria to determine the effectiveness of double-balloon enteroscopy 23

Table 9 Reduction of symptoms after therapeutic intervention by double-balloon enteroscopy 24

Table 10 Biopsy yield / diagnostic yield of double-balloon enteroscopy 26

Table 11 Transfusion requirement after double-balloon enteroscopy 28

Table 12 Examination time of double-balloon enteroscopy 28

Table 13 Completion of double-balloon enteroscopy procedures 30

Table 14 Technical failure of double-balloon enteroscopy 32

Table 15 Unit costs of pre-procedural workup and post-procedural care for double-balloon enteroscopy and its two comparators 34

Table 16 Cost per unit of additional capital equipment and maintenance for double-balloon enteroscopy 35

Table 17 Unit cost of double-balloon enteroscopy per procedure in a private day hospital facility 35

Table 18 Unit cost per procedure of comparator technique – laparotomy for a private patient in a private hospital 36

Table 19 Unit cost per procedure of comparator technique – laparotomy with intra-operative enteroscopy for a private patient in a private hospital 37

Table 20 Comparison of MBS item costs for double-balloon enteroscopy and laparotomy with or without intra-operative enteroscopy..... 38

Table 21 Assessment of body of evidence for effectiveness of double-balloon enteroscopy 43

Table 22 Major complications resulting from double-balloon enteroscopy (conference abstracts)..... 72

Table 23 Minor complications of double-balloon enteroscopy (conference abstracts)72

Table 24 Reduction of symptoms after therapeutic intervention by double-balloon enteroscopy (conference abstracts) 73

Table 25 Biopsy yield / diagnostic yield of double-balloon enteroscopy (conference abstracts)..... 73

Table 26 Examination time of double-balloon enteroscopy (conference abstracts).... 74

Table 27 Completion of double-balloon enteroscopy procedures (conference abstracts)..... 74

Executive summary

The procedure

Double-balloon enteroscopy (DBE) is a procedure which can be used for the diagnostic and therapeutic benefit of patients with obscure gastrointestinal bleeding (OGIB) and/or small bowel pathologies. DBE is unique in that it provides the ability to examine the entire small bowel using either an oral or anal approach, as well as perform therapeutic interventions.

The double-balloon enteroscope comprises a high-resolution videoendoscope with a flexible overtube. Latex balloons attached to the tip of both the endoscope and overtube are inflated and deflated, providing 'fixation points' that overcome the problem of mobility of intestinal loops and enable advancement of the endoscope through the small bowel.

Various devices can be attached to the endoscope, such as an argon plasma probe, snares, injection needles and a pneumatic balloon. These enable therapeutic interventions to be carried out by the endoscopist during the procedure.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Adelaide Health Technology Assessment (AHTA) at the Discipline of Public Health, University of Adelaide, was engaged to conduct a systematic review of the literature on the DBE for patients with obscure gastrointestinal bleeding or suspected small bowel disease. An advisory panel with expertise in this area then evaluated the evidence and provided advice to the MSAC.

MSAC's assessment of double-balloon enteroscopy

Clinical need

Without readily available data to indicate the incidence of OGIB, assessment of the clinical need for DBE has been based on the prevalence of OGIB and small bowel pathologies, for which standard enteroscopy is not possible due to its inability to examine the entire small bowel.

The number of capsule endoscopies performed in the 2004-05 financial year was 2,556 (Medicare Australia 2005a). With an assumption of one capsule endoscopy per patient, data from the PillCam Endoscopy Register indicates that 66 per cent of these procedures have a positive finding in the small bowel (Given Imaging 2005). Allowing for the number of patients who would be suitable for medical treatment, whose lesion is expected to be within reach of a standard enteroscope, or who would be candidates for

surgery, it is estimated that 843 patients would be suitable for DBE. It is also expected that 100–200 cases per year of small bowel pathology would be identified by alternative methods. Along with an anticipated 10 per cent of patients requiring application of both an oral and anal DBE approach, this would result in an estimated maximum of 1,147 procedures being performed in Australia annually.

Safety

Assessment of the safety of DBE identified 14 uncontrolled case series and four case reports which reported on this aspect of the procedure.

In relation to major complications such as perforation, sepsis, ileus and death, 12 complications were reported from 1,276 procedures. This is a major complication rate of less than 1 per cent. No deaths were reported in the studies identified and the most common cause of major complication was pancreatitis (6 cases), of which all but one case were resolved with conservative therapy.

Sixty-seven minor complications such as abdominal pain, sore throat or fever were reported from 1,276 procedures (7.2%), the majority of which were self-limiting. A high incidence of minor complications was reported in one study (May et al 2005a), which could reflect discrepancies in reporting between different groups and is not necessarily a true indication of the safety of DBE.

Although no safety data relating to the comparator has been included in the systematic review, the expert opinion of the Advisory Panel indicates that the more invasive procedures of laparotomy with or without intra-operative enteroscopy are associated with a higher incidence of major complications than DBE.

Overall, without direct comparative safety data, it is not possible to conclude that DBE is as safe as, or safer than, laparotomy with or without intra-operative enteroscopy. However, it does appear that, due to its much less invasive nature, fewer complications would arise as a result of using DBE. It is the strong view of the Advisory Panel, therefore, that DBE is a safer technique than laparotomy with or without intra-operative enteroscopy.

Effectiveness

Eleven uncontrolled case series were identified that reported effectiveness outcomes of DBE.

Ten case series reported the success of therapeutic intervention, ranging from 77 to 100 per cent success, with six studies reporting 100 per cent success of the treatments used. Two studies did not adequately report the success of treatments.

Biopsy yield or diagnostic yield was reported in 11 case series and ranged between 68 and 93 per cent.

Transfusion requirement after DBE was poorly reported, with only one study providing data on this outcome. This study (Kaffes et al 2006) reported a 70 per cent reduction in the number of patients requiring transfusion after treatment by DBE.

Examination time for DBE ranged from 55 to 90 minutes using an oral approach, and 55 to 110 minutes using an anal approach. The relevance of examination time as an outcome of effectiveness is arguable due to the procedure being terminated once a lesion had been identified. Examination time, therefore, was often dependent on the location of lesions and not the ability to examine the small bowel. A similar argument can be applied to the length of insertion of the enteroscope as an outcome. The mean range of insertion for an oral approach was 200 to 270 cm, and for an anal approach 70 to 180 cm. Again, this does not necessarily reflect the ability to insert the enteroscope, but is more likely to be a function of the location of small intestinal lesions.

The ability to examine the entire small bowel varied among the studies identified. Yamamoto et al (2004a) reported an 86 per cent (24/28) success rate when attempting to examine the entire small intestine. However, other studies did not report any success on this outcome (Kaffes et al 2006). The outstanding success of Yamamoto et al (2004a) is likely to reflect the extensive experience that the authors have obtained since pioneering this procedure in 2001. It is also important to note that unlike many other countries, capsule endoscopy is not easily accessible in Japan, and therefore DBE is used as a primary diagnostic procedure. This explains the need to often examine the entire small bowel.

Only one study (of 248 procedures) reported a technical failure of the equipment. The cap of the enteroscope was lost upon withdrawal from the small bowel but was successfully recovered.

As no data compared DBE with laparotomy with or without intra-operative enteroscopy, no conclusions can be drawn regarding the comparative effectiveness of the procedure. However, on the basis of the evidence identified, DBE appears to be effective at providing therapies to small bowel lesions.

Economic considerations

As there was no evidence comparing DBE with laparotomy with or without intra-operative enteroscopy, it was not possible to determine if the procedure was as effective as, or more effective than, the comparator. As a consequence, a financial incidence analysis has been performed to identify the expenditures related to this procedure.

It was estimated that the unit cost per DBE procedure is $2,505 ($2,972 with therapy) compared to between $3,968 and $4,763 for laparotomy with or without intra-operative enteroscopy.

The financial implications to the Australian government for each DBE diagnostic procedure (performed in the private sector) would range between a cost of $481 and a saving of $315 relative to the comparators (and a cost of between $152 and $948 for DBE with therapy).

Overall, the cost to the Australian healthcare system, based on the clinical need for DBE (see clinical need section) would range between $2,873,235 and $3,408,884. In comparison, the cost to the healthcare system for the comparators would be between $4,551,296 and $5,273,906. The difference in overall costs between the procedures is largely due to the 4-day hospital stay required after surgery for the comparators. As a result, the overall cost savings to the Australian healthcare system of performing DBE rather than the comparators would be between $1,142,412 and $2,400,671.

Expert opinion

It is the strong opinion of the Advisory Panel that DBE is an effective tool for the diagnosis and treatment of small bowel pathologies that may or may not present initially with occult bleeding. It is unclear whether DBE is as or more effective than laparotomy with or without intra-operative enteroscopy, but it does appear to be safer. The adverse events associated with the surgical techniques means that DBE should be considered as a first option when surgery in not immediately indicated. DBE would be contraindicated in those rare patients with known latex allergy. In general, it is also the opinion of the Advisory Panel that patient preference would favour DBE at the expense of the more invasive surgical intervention.

Recommendation

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 intra-operative enteroscopy.

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

DBE is effective in allowing enteroscopic assessment and some treatment of the entire small intestine.

Although more costly to Medicare than intra-operative 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.

The Minister for Health and Ageing accepted this recommendation on 5 February 2007.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of double-balloon enteroscopy (DBE) for the diagnosis and treatment of patients with obscure gastrointestinal bleeding or suspected small bowel disease. The MSAC evaluates new and existing health technologies and procedures for which public funding is sought under the Medicare Benefits Scheme (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC's terms of reference and membership are at Appendix A. The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

Rationale for assessment

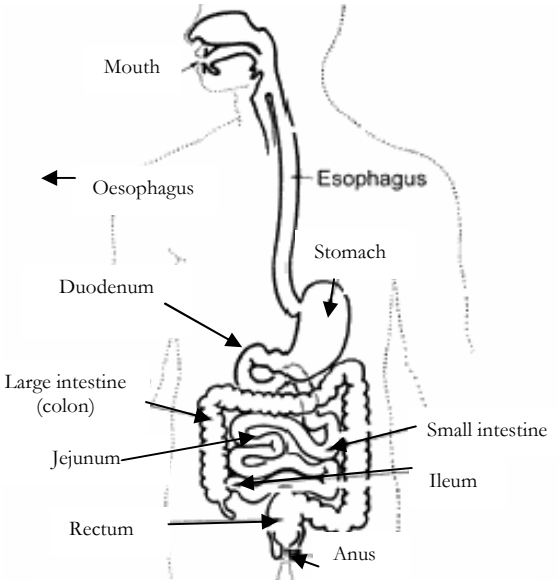
An application has been made to the MSAC by Fujinon Australia for the listing of double-balloon enteroscopy (DBE) under Medicare. Currently, there is no specific item or descriptor for DBE. However, procedures currently listed on the MBS that are related to this procedure (30473, 30475, 30476, 30478, 32090 and 32093) may cover DBE. DBE would be used for therapeutic intervention or biopsy of identified or suspected small bowel pathology.

In order to consider this application for public funding, the MSAC has commissioned an independent evaluator to assess the safety, effectiveness and cost-effectiveness of DBE.

Background

Small bowel

The small bowel (otherwise known as the small intestine) is the longest portion of the gastrointestinal tract (Figure 1). It is labelled 'small' as it is the narrowest portion of the bowel, but it is over five metres long (Tilson & Saltzman 2006). The small bowel is the primary site for nutrient digestion and absorption into the body. It is divided into three sections which have complementary functions: the duodenum, the jejunum and the ileum (Gray 1977). While the duodenum is fixed, the remainder of the bowel is not, making endoscopic examination difficult.



Available from :
http://www.acg.gi.org/patients/gihealth/smallbowel.asp

Figure 1 Human gastrointestinal tract

Small bowel disorders

Gastrointestinal bleeding is a widespread problem that frequently requires hospitalisation (Jensen & Freese 2006). Symptoms of gastrointestinal bleeding can vary depending on the cause and severity. Although 3 to 5 per cent of gastrointestinal bleeding is known to occur in the small bowel, determining the origin of the bleeding is one of the major challenges that face gastroenterologists (Tilson & Saltzman 2006). The major cause of bleeding in the small bowel (significant enough to warrant investigation) is from angioectasia, which do not show on standard x-rays. Other pathologies include benign tumours (eg adenoma, intestinal leiomyoma, polyps), malignant tumours (eg lymphoma, intestinal leiomyosarcoma, gastrointestinal stromal tumour), Crohn's disease (inflammatory bowel disease) and ulcers (Tilson & Saltzman 2006).

Occult bleeding may be characterised by a positive faecal occult blood test and/or iron deficiency anaemia (Kendrick et al 2001). Symptoms of obscure gastrointestinal bleeding that warrant investigation include: melaena (blood coating or mixed in the stool); or haematemesis (the vomiting of either bright red blood or blood with a coffee-grounds appearance). Upper gastrointestinal endoscopy and colonoscopy can exclude occult bleeding pathology that occurs in the upper gastrointestinal tract and large bowel.

Double-balloon enteroscopy

The double-balloon enteroscope was designed and introduced by Yamamoto et al (2001) to examine the entire small bowel using the push-and-pull technique (Kaffes et al 2006). It combines the characteristics of the capsule endoscope and push enteroscopy, being able to visualise the small bowel, perform biopsies and carry out therapeutic interventions (May et al 2005b). It is made up of a high-resolution videoendoscope (2 m long, 8.5 mm diameter) and a flexible overtube (1.4 m long, 12 mm diameter). Two latex balloons (Figure 2) are attached to the tip of the enteroscope and can be inflated and deflated by means of a pressure-controlled pump system (May et al 2005a). These act as 'fixation points' for the small bowel, solving the problem associated with mobility of the intestine (Fujinon Australia 2005). The system is advanced or withdrawn by deflating or inflating the balloons respectively. The double-balloon enteroscope may use either the oral or anal route to the small bowel (May et al 2005a). The procedure has the ability to search the entire small intestine without the invasiveness of intra-operative enteroscopy, and conduct both therapeutic and diagnostic interventions. The enteroscope may also include a range of devices, including an argon plasma probe, snares, injection needles and a pneumatic balloon, as attachments (Di Caro et al 2005). DBE requires the same preparation and sedation as upper gastrointestinal endoscopy and colonoscopy procedures (Ell et al 2005).

Intended purpose

DBE is indicated for patients with identified or suspected small bowel pathology requiring therapeutic intervention or biopsy for histopathological diagnosis before treatment (Ell et al 2005). Small bowel pathology may be identified or suspected after use of an appropriate diagnostic modality, such as capsule endoscopy or small bowel imaging.

Obscure gastrointestinal bleeding is the most frequent indication for DBE but other indications may include obstructive symptoms or suspicion of intestinal tumour (Yamamoto 2005).

Available from: www.fujinon.com.sg/index.php?display=78&action=cat

Figure 2 Double-balloon enteroscope

Previous history of abdominal surgery may be a contraindication for DBE due to presence of adhesions, and would require careful clinical judgement of risk and benefit (Fujinon Australia 2005).

Diagnostic modalities for small bowel disorders

It is important to access the small bowel in order to localise the bleeding site but with minimal risk and discomfort to the patient. Historically, the small bowel has been difficult to investigate via either the mouth or the anus because the instruments must either pass through the stomach or the large intestine (Tilson & Saltzman 2006). A number of enteroscopy techniques have been established to access the small intestine, including push enteroscopy, capsule endoscopy, sonde enteroscopy and the double-balloon method, which is the latest technique. Previously, the only other option was to access the small bowel surgically through the abdomen, either with open surgery (laparotomy) or keyhole surgery (laparoscopy), or by using a combination of these approaches with enteroscopy (intra-operative enteroscopy).

Following is a non-comprehensive summary of historic and current diagnostic approaches. Some rare indications may lead to alternative diagnostic modalities.

Push enteroscopy

Push enteroscopy is a procedure for locating the intestinal bleeding site, and may be used to examine the small intestine, biopsy the site and provide therapeutic intervention (Fujinon Australia 2005). On its own it can only access 50 to 150 cm of the small intestine, and therefore lesions located in distal sections of the intestine cannot be visualised (Gerson & Van Dam 2004). The use of a flexible overtube that attaches to the enteroscope may enable better visualisation and improved diagnostic yield. However, it also has complexities, not only reducing the mobility of the enteroscope, but also possibly causing significant patient discomfort and complications (Carey & Fleischer 2005). This procedure is currently not funded by the MBS.

Capsule endoscopy

As its name suggests, this technique uses an endoscope in the shape of a capsule. This technology was designed to allow complete visualisation of the small intestine in a non-invasive manner. Capsule endoscopy works by means of a wireless video capsule endoscope that is ingested by the patient after an overnight fast. As normal peristaltic action of the intestine pushes this capsule along the tract, the capsule camera takes two images per second. These images are transmitted to an external data recorder unit via a radio frequency communication channel (Carey & Fleischer 2005). The capsule has a battery life of 8 hours and there is no requirement for the patient to be in the physician's presence while the examination takes place. Due to the characteristics of this endoscope, it cannot be used for therapeutic or biopsy purposes and is solely a non-invasive diagnostic procedure (Carey & Fleischer 2005). Capsule endoscopy has revolutionised the investigation of small bowel pathology due to the painless and non-invasive nature of the capsule and its high diagnostic yield (Gerson & Van Dam 2004).

Small bowel series

The small bowel series is an x-ray of the small bowel taken after barium dye has been swallowed. The barium appears white on the x-ray and shows irregularities of the bowel wall as it passes through the small intestine. The test is painless but the barium is unpleasant to drink and may cause constipation (Brown 2004).

Computed tomography

Computed tomography (CT) is an imaging technique whereby a large series of two-dimensional x-rays are used to create a cross-sectional image of the anatomy. Contrast medium may be used to enhance the detail of the scan (Beckmann 2006).

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has recently been supported for its ability to detect small bowel disorders (Bernstein et al 2005). However, due to the high cost and lack of incremental gain over a CT scan, MRI is not frequently used for this purpose (Ros et al 2005). MRI that uses an orally administered contrast is called magnetic resonance enterography (MRE) (Gourtsoyiannis et al 2006). Compared to small bowel series and CT scans, MRI has the benefit of no radiation (Bernstein et al 2005). MRI is currently not funded by the MBS for small bowel pathology.

Sonde enteroscopy

This form of endoscopy involves a thin enteroscope extending 2.7 m in length with a balloon attached to the tip. The balloon attaches itself to the intestinal lumen and by means of peristaltic action the enteroscope moves through the small intestine (Carey & Fleischer 2005). The instrument is usually positioned in the morning and the examination takes place 6–8 hours later. Although this technique allows for visualisation of the entire small intestine, the automatic movement of the enteroscope does not allow for focusing on a particular area. In addition, the examination can be significantly time consuming and uncomfortable for the patient. With improvements in techniques for endoscopic visualisation of the small bowel, sonde enteroscopy is no longer favoured (Carey & Fleischer 2005) or in use in Australia.

Therapies for small bowel disorders

Following is a non-comprehensive summary of current treatment approaches for small bowel disorders. The clinical decision-making process concerned with small bowel pathologies is illustrated in Figure 3.

Medical therapy

Medical therapy for bleeding is used: to treat anaemia; when there are multiple vascular lesions in the small intestine; when lesions are inaccessible or inappropriate for endoscopic intervention; or when bleeding continues despite endoscopic or surgical intervention (Fujinon Australia 2005). Therapies used include hormone therapy, iron supplementation, correction of any coagulation or platelet abnormalities, and blood transfusion if anaemia cannot be controlled by iron supplementation (Mitchell et al 2004). These may be effective if the blood loss is slow, if the patient is elderly, or if the risk of surgery is greater than the risk of non-specific management (Fujinon Australia 2005). Occasionally, anti-inflammatory or blood-thinning medications (eg aspirin) may aggravate gastrointestinal bleeding (Jensen & Freese 2006). Management of such bleeding would include withdrawal of the medication. Medical therapy for the most common form of gastrointestinal bleeding, angioectasia, is seldom effective.

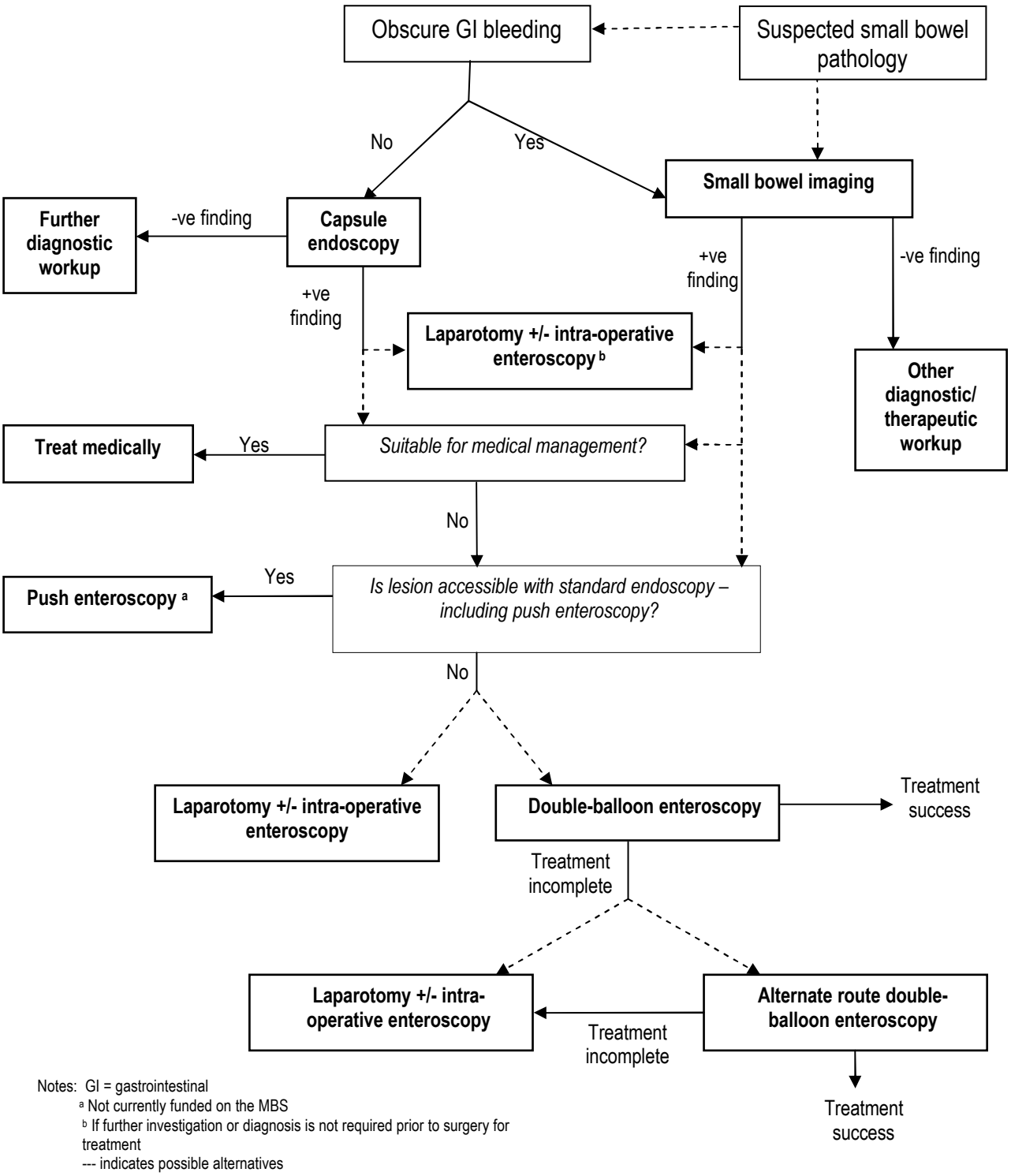
Medical therapy may be used to treat pathologies such as inflammatory bowel disease and lymphoma. Treatment can include a range of medications, including corticosteroids and antibiotics (Brown 2004).

Push enteroscopy

Push enteroscopy (as described in the diagnostic modalities section above) may be used for both direct visualisation and intervention. While not currently funded by the MBS, push enteroscopy may be an appropriate treatment tool if prior capsule endoscopy or imaging has shown that the pathology is within reach of push enteroscopy.

Surgery

Surgery for small bowel pathologies is designated as the comparative treatment for DBE, and descriptions are included under the 'Comparator techniques' section (page 8).



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

Figure 3 Clinical pathway for use of double-balloon enteroscopy

Comparator techniques

The proposed comparators to DBE are laparotomy, with and without intra-operative enteroscopy.

Laparotomy

A laparotomy involves a large surgical incision through the abdominal cavity enabling the surgeon to explore the underlying organs. Once a problem has been identified, laparotomy allows the option to treat immediately or to delay treatment until a subsequent operation (Department of Human Services 2000). A laparotomy is performed under general anaesthesia.

Intra-operative enteroscopy

The most invasive yet the most sensitive method of small bowel imaging is intra-operative enteroscopy, which is performed during open laparotomy or, less commonly, via laparoscopy (Yamamoto et al 2001). This technique requires the patient to be under general anaesthesia as the surgeon inserts the enteroscope either transanally and/or transorally or through an operative enterotomy, depending on the area of interest and physician preference. Through an abdominal incision, the surgeon then guides the intestine over the endoscope (Carey & Fleischer 2005). This procedure can be used for diagnostic or therapeutic purposes, and was the only endoscopic option for removing lesions beyond the reach of push enteroscopy prior to the development of DBE. While intra-operative enteroscopy is the gold-standard for therapeutic interventions of the small bowel, it is not without significant morbidity and mortality due to the invasive nature of the surgery (Carey & Fleischer 2005).

Marketing status of the technology

The Double Balloon method Electronic Enteroscopy System is registered on the Australian Register of Therapeutic Goods (ARTG No 100358 – Enteroscope, flexible, video and ARTG No 100389 – Pump, general purpose).

Current reimbursement arrangement

There are no items currently listed on the MBS which specifically cover DBE. The comparator technique, laparotomy with or without intra-operative enteroscopy, is listed on the MBS under the following item numbers:

Item 30387:	Laparotomy involving operation on abdominal viscera (including pelvic viscera), not being a service to which another item in this Group applies (Anaes.) (Assist.) Fee: $549.55
Item 30568:	Intraoperative enterotomy for visualisation of the small intestine by endoscopy (Anaes.) (Assist.) Fee: $628.35
Item 30569:	Endoscopic examination of small bowel with flexible endoscope passed at laparotomy, with or without biopsies (Anaes.) (Assist.) Fee: $320.40
Item 30373:	Laparotomy (exploratory), including associated biopsies, where no other intra-abdominal procedure is performed (Anaes.) Assist.) Fee: $418.25

(Medicare Australia 2005b)

Approach to assessment

Objective

To determine whether there is sufficient evidence, in relation to clinical need, safety, effectiveness and cost-effectiveness, to have DBE for obscure gastrointestinal bleeding or suspected small bowel disease listed on the Medicare Benefits Schedule.

Research questions

1. Is double-balloon enteroscopy as safe as, or safer than, laparotomy with or without intra-operative enteroscopy at identifying and treating obscure gastrointestinal bleeding or suspected small bowel disease?

2. Is double-balloon enteroscopy as, or more, effective at identifying and treating obscure gastrointestinal bleeding or suspected small bowel disease compared to laparotomy with or without intra-operative enteroscopy?

3. Is double-balloon enteroscopy as, or more, cost-effective at identifying and treating obscure gastrointestinal bleeding or suspected small bowel disease compared to laparotomy with or without intra-operative enteroscopy?

Expert advice

An advisory panel with expertise in gastroenterology, surgery and consumer issues was established to evaluate the evidence and provide advice to the MSAC from a clinical perspective. In selecting members for advisory panels, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies concerning DBE for the period between 2001 and May 2006, as DBE was first reported in 2001. Appendix C describes the electronic databases that were used for this search and the other sources of evidence that were investigated.

The search terms used to identify literature in electronic databases on the safety and effectiveness of DBE are also presented in Appendix C.

Inclusion/Exclusion criteria

The criteria for including articles in this report varied depending on the type of research question being addressed. Often a study was assessed more than once because it addressed more than one research question. One researcher applied the inclusion criteria to the collated literature. If there was any doubt concerning inclusion of papers, this was

resolved by group consensus to ensure that all potentially relevant studies were captured. In general, studies were excluded if they did not:

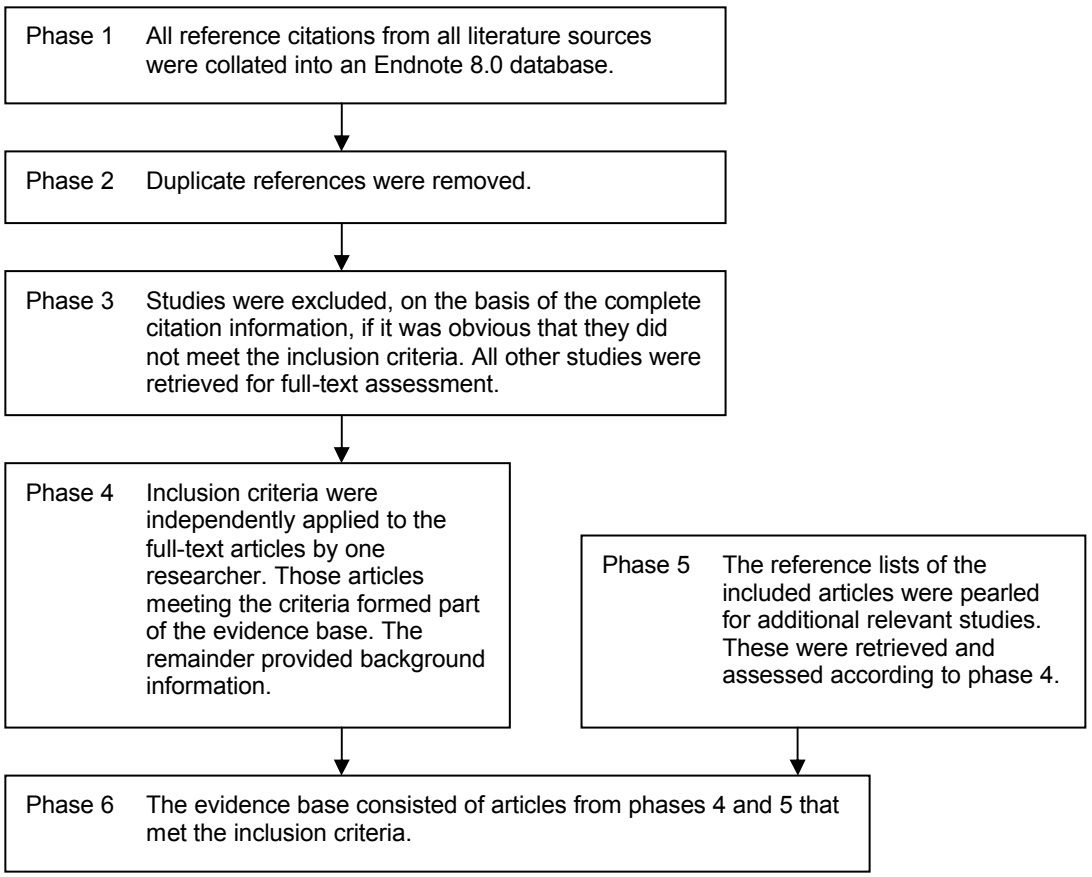
- address the research question;
- provide information on the pre-specified target population;
- include one of the pre-specified interventions;
- compare results to the pre-specified comparator;
- address one of the pre-specified outcomes and/or provided inadequate data on these outcomes (in some instances, a study was included to assess one or more outcomes but had to be excluded for other outcomes due to data inadequacies); or
- have the appropriate study design.

The inclusion criteria relevant to each of the research questions posed in this assessment are provided in Boxes 1 and 2 in the results section of this report.

Search results

The process of study selection went through six phases (Figure 4).

Figure 4 Study selection process



The results of the process of study selection – collation of the evidence base of safety and effectiveness criteria in assessing DBE – are provided in Table 1.

Table 1 Number of citations initially retrieved and then retained at each phase

Search	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
DBE safety and effectiveness	139	129	99	27	0	27

Data extraction and analysis

A profile of key characteristics was developed for each included study (Appendix F).

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 2) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 2 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design. [a]
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

[a] See Table 3

Strength of the evidence

Level

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 3.

Table 3 **Designations of levels of evidence** (adapted from NHMRC 2005)

Level	Intervention [b]
I [a]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial [c] Cohort study Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single-arm studies [d] Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

[a] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.
[b] Definitions of these study designs are provided in NHMRC 2000, pp 7–8.
[c] This also includes controlled before-and-after (pre-test/post-test) studies as well as indirect comparisons (ie using A vs B and B vs C to determine A vs C).
[d] Comparing single-arm studies, ie case series from two studies.
Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.
Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Quality

The appraisal of intervention studies pertaining to treatment effectiveness was undertaken using a checklist developed by Downs and Black (1998). This checklist is suitable for trials and cohort studies and has been psychometrically assessed to have overall high internal consistency, good test–re-test and inter-rater reliability, and high criterion validity (Downs & Black 1998). The modified checklist produced an overall Quality Index score (total=27), along with subscale scores (Reporting, External Validity, Bias and Confounding). Information on specific methodological components shown empirically to impact on treatment effect sizes were also included in this checklist – specifically, concealment of allocation, blinding and completeness of data (Juni et al 2001; Moher et al 1998; Schulz et al 1995).

Uncontrolled before-and-after case series are a poorer level of evidence for the assessment of effectiveness. The quality of this type of study design was assessed according to a checklist developed by the West Midlands Development and Evaluation Committee (Young & Ward 1999). A maximum quality score of three can be achieved.

Study quality was, however, presented in the assessment report in terms of the components of quality (eg selection bias, misclassification bias, reviewer bias) as well as the overall quality score.

Statistical precision

Statistical precision was determined using statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000).

Size of effect

For intervention studies on DBE it was important to assess whether statistically significant differences are also clinically important. The size of the effect needed to be determined, as well as whether the 95% confidence interval included only clinically important effects. Rank scoring methods were used to determine the clinically important benefit of the size of the effect in studies, as well as the clinical relevance of the evidence in controlled studies (NHMRC 2000).

Relevance of evidence

Similarly, the outcome being measured should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000). When assessing the safety and effectiveness of DBE, rank scoring methods were used to determine the clinical relevance of the outcome being assessed in any controlled studies (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2005). Five components are considered essential by the NHMRC when judging the body of evidence:

- the volume of evidence – which includes the number of studies sorted by their methodological quality and relevance to patients;
- the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogenous findings;
- the potential clinical impact – appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test;
- the generalisability of the evidence to the target population; and
- the applicability of the evidence – integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 4) (NHMRC 2005).

Table 4 Body of evidence assessment matrix

Component	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence is/are the same as the target population	Population(s) studied in body of evidence is/are similar to the target population	Population(s) studied in body of evidence is/are different to target population for guideline but it is clinically sensible to apply this evidence to target population	Population(s) studied in body of evidence is/are different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

SR=systematic review

Results of assessment

Clinical need for double-balloon enteroscopy

The clinical need for double-balloon enteroscopy (DBE) is dependent on the prevalence of small bowel pathologies that are beyond the reach of push enteroscopy and require therapeutic intervention (resection, removal of foreign body or ablation) or biopsy for histopathology diagnosis before treatment. Once a capsule endoscope (or other imaging technique) has found small bowel pathology (ie a lesion) inaccessible to push enteroscopy, the only treatments available are intra-operative enteroscopy via either laparotomy or (less commonly) laparoscopy, or DBE.

Data on the incidence of obscure gastrointestinal bleeding are not readily available (MSAC 2003). In the financial year 2004–05, 2,556 capsule endoscopies were performed in Australia (Medicare Australia 2005a). Assuming one capsule endoscopy per patient, it is estimated that positive findings in the small bowel would be identified in approximately 66 per cent of these patients (1,687 cases) (Given Imaging 2005). Approximately 50 per cent of those would be managed by medical treatment or push enteroscopy, or would have an obvious need for surgical intervention (Fujinon Australia 2005). It is therefore expected that the remainder of these patients (843 cases) would be candidates for DBE.

In addition, it is expected that there may be another 100 to 200 cases each year that would benefit from DBE (Fujinon Australia 2005). This would include patients with small bowel mucosal disease, for which capsule endoscopy is not publicly funded, and therefore the majority would require investigation by other imaging modalities.

Expert opinion of members of the Advisory Panel suggests that 10 per cent of patients suitable for DBE would require the use of both oral and anal approaches. This would result in an additional 94–104 procedures per year. Therefore, the maximum number of DBE procedures expected to be performed in Australia is approximately 1,147 per year.

Safety of double-balloon enteroscopy

Double-balloon enteroscopy (DBE) was assessed in terms of possible patient harms that may result from the procedure. Studies addressing this issue were assessed for inclusion in this report according to the criteria delineated *a priori* in Box 1.

Box 1 Study selection criteria to determine the safety of double-balloon enteroscopy

Research question	
Is double-balloon enteroscopy as safe as, or safer than, laparotomy with or without intra-operative enteroscopy at identifying and treating gastrointestinal bleeding of obscure origin or suspected small bowel disease?	
Selection criteria	**Inclusion criteria**
Population	Patients with obscure gastrointestinal bleeding or suspected small bowel disease
Prior tests	Capsule endoscopy, CT scan, small bowel barium series, angiography, radio-labelled red blood cell nuclear scanning
Intervention	Double-balloon electronic enteroscopy (per-oral or per-anal approach depending on location of identified or suspected small bowel pathology)
Comparators	Laparotomy with or without intra-operative enteroscopy
Outcomes	Primary – major complications such as perforation, post-polyp sepsis, ileus, abscess, intestinal haematoma, haemorrhage, intussusception, infection (eg peritonitis), death
	Secondary – minor complications such as pain (ie sore throat, abdominal discomfort), fever, low-grade infection
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs
Search period	2001–5/2006 [a]
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence base

[a] DBE was first reported in 2001.

Complications were classified as either primary or secondary, based on the severity of the adverse event (Box 1).

This review does not include systematic assessment of the safety of the comparator. The safety of DBE relative to the comparator was initially planned but no comparative studies were identified. An indirect comparison was attempted but the data extracted were not comparable. Therefore, an overview of the safety considerations concerning laparotomy with or without intra-operative enteroscopy informed by expert opinion is presented in the section 'Other relevant considerations'.

Primary safety outcomes

Major complications

There were no comparative studies identified that fitted the selection criteria determined *a priori* for assessing the safety of DBE. A literature search was therefore performed to determine whether good quality information on the safety of the comparator techniques was available in order to perform a naive indirect comparison with DBE. No studies were identified that provided safety data on laparotomy with or without intra-operative enteroscopy relevant to patients with obscure gastrointestinal bleeding or suspected small bowel disease. Therefore, only the studies identified in the initial search on DBE have been presented.

Thirteen descriptive studies report major complications as a result of DBE (Table 5). These are all low level uncontrolled post-test case series (level IV intervention evidence).

Four case reports were also identified as reporting major complications following this procedure (Table 6). The study profiles for all included studies are shown in Appendix F.

The largest case series of procedures identified in the literature (level IV evidence) was by Heine et al (2006). This good quality study reported three major complications from a total of 316 DBE procedures. These were all instances of pancreatitis, of which two were mild and one was of intermediate severity. The patient with intermediate pancreatitis also underwent a laparotomy (which proved to be unnecessary) as a small bowel perforation was also suspected. All three patients recovered from these episodes after receiving conservative therapy (Heine et al 2006).

In the second largest good quality case series no major complications were attributable to DBE (247 procedures); however, one patient did suffer an epileptic attack as a result of the administration of propofol (May et al 2005a). The authors report that this is recognised as a rare adverse event with the use of propofol for sedation. The only major complication reported by Ell et al (2005) was one case of epileptic seizure following propofol administration in the 147 procedures performed in their high quality study. It was not possible to determine conclusively whether there was any overlap between patient populations in this study and that of May et al (2006), although given the rarity of this adverse event it is likely that the patient series is duplicated to some extent.

In the high quality study reported by Yamamoto et al (2004a), the single major complication in the case series was of multiple intestinal perforations in a patient with intestinal lymphoma. This was attributed to chemotherapy that the patient had undergone.

Post-polypectomy bleeding was reported in one patient after DBE by Mönkemüller et al (2006) in a good quality case series involving 70 procedures. Bleeding was stopped by endoscopic epinephrine injection without a significant decrease in haemoglobin levels or requirement for transfusion (Mönkemüller et al 2006).

Overall, fewer than 1 per cent of procedures resulted in major complications in the reported case series. Case reports were also included but provided less information than uncontrolled case series because it was impossible to determine the denominator, ie how many patients received the procedure and were at risk of harm but did not necessarily have any adverse events. Case reports only provide descriptive information as to the possible types of adverse events.

One case report describes DBE on two patients, both of which experienced pancreatitis post-procedurally. Groenen et al (2006) have suggested that this may be a complication of the procedure and a consequence of increased duodenal intraluminal pressure (when both balloons are inflated), which results in reflux of the duodenal fluids into the pancreatic duct.

Table 5 Major complications resulting from double-balloon enteroscopy [a]

Study	Level and quality	Population	Major complications per procedure
Quality score: 3/3			
(May et al 2005a) [b]	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	1/247 (0.04%) procedures: 1 epileptic seizure as a result of propofol sedation
(Ell et al 2005)	Level IV: Uncontrolled post-	100 patients	1/147 (0.06%) procedures:

Study	Level and quality	Population	Major complications per procedure
[b]	test case series Quality score: 3/3		Aspiration pneumonia resulting from epileptic seizure caused by propofol sedation
(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: 3 cases pancreatitis
(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: 1 case perforation
(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: 1 case post-polypectomy bleeding
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

[a] Data extracted from conference abstracts are included in Appendix H (Table 22). These data have not been included in the assessment of the safety of DBE.

[b] May be overlap between patient series

Table 6 Major complications resulting from double-balloon enteroscopy identified by case reports

Study	Study design	Population	Major complications per procedure
(Attar et al 2005)	Case report	1 patient	1/1 procedure: 1 small bowel ileus
(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 1 case anaemia and melaena 1 case anaemia only	2/2 (100%) procedures: 1 case acute severe pancreatitis 1 case mild pancreatitis
(Honda et al 2006)	Case report	1 patient with tarry stool and severe anaemia	1/2 procedures: 1 case severe pancreatitis
(Sunada et al 2004)	Case report	1 patient with Crohn's disease with jejunal strictures	0/1 procedure

GI=gastrointestinal

Secondary safety outcomes

Minor complications

Fourteen descriptive studies reported minor complications following DBE (Table 7). These 14 studies were all level IV intervention evidence. Three case reports were also identified in the literature as reporting on minor complications following DBE. The study profiles for all the included studies are shown in Appendix F.

Minor complications occurred in up to 20 per cent of procedures reported in the case series. May et al (2005a) report 37 minor complications in the 247 procedures performed on 137 patients. The majority of these (24) were for reddening of the mucosal tissue with or without intramucosal haemorrhage, while 12 patients reported abdominal pain and/or sore throat. One patient developed fever (39°C) following DBE, but it had resolved by the next day without the use of antibiotics (May et al 2005a).

A relatively high incidence of minor complications was also reported in the high quality study by Ell et al (2005) but these appear to be of little clinical consequence. Twelve minor complications were reported with the majority (9) being abdominal pain. One case each of brief fever, vomiting after the procedure and a sore throat requiring treatment were also reported. It is important to note that it is possible that there is some overlap between the population studied by Ell et al (2005) and that of May et al (2005a).

Heine et al (2006), the authors of another large good quality case series, reported only eight minor complications in 316 procedures performed. All eight complications were due to abdominal tenderness, which were subsequently investigated for possible perforation by radiography and computed tomography. No perforations were identified (Heine et al 2006).

Of the 178 procedures performed by Yamamoto et al (2004a) on 123 patients, one patient reported minor complications. This patient had Crohn's disease and reported post-operative fever and abdominal pain.

Overall, in the 14 case series and three case reports identified, including a total of 1,276 procedures in 926 patients, there were reports of 67 minor complications. This equates

to minor complications occurring at rates of up to 20 per cent in the individual studies; or, overall, in 7.2 per cent of DBE procedures.

Table 7 Minor complications of double-balloon enteroscopy [a]

Study	Level and quality	Population	Minor complications per procedure
Quality score: 3/3			
(May et al 2005a) [b]	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	37/247 (15.0%) procedures: 24 cases reddening of mucosal tissue 12 cases abdominal pain and/or sore throat 1 fever
(Ell et al 2005) [b]	Level IV: Uncontrolled post-test case series Quality score: 3/3	100 patients	12/147 (8.2%) procedures: 9 cases abdominal pain 1 sore throat requiring medical therapy 1 fever 1 case of vomiting after procedure
(Gay et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	42 patients	2/47 (4.3%) procedures: 2 cases abdominal discomfort/bloating
(Kaffes et al 2006)	Level IV: Uncontrolled post-test case series Quality score: 3/3	40 patients	3/62 (4.8%) procedures: 1 overnight stay due to prolonged sedation 2 cases sore throat and swollen uvula
(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	1/5 (20%) procedures: 1 case abdominal tenderness and fever
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: 8 cases abdominal tenderness
(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 (0.05%) procedures: 1 case post-operative fever and abdominal pain
(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: 3 cases abdominal pain
Quality score: 1/3			
(Groenen et al	Level IV: Uncontrolled post-test case series	2 patients	0/2 procedures

Study	Level and quality	Population	Minor complications per procedure
2006)	Quality score: 1/3		

[a] Data extracted from conference abstracts are included in Appendix H (Table 23). These data have not been included in the assessment of the safety of DBE.
[b] May be overlap between patient series.

No minor complications were reported in the included case reports (Table 8).

Table 8 Minor complications resulting from double-balloon enteroscopy identified by case reports

Study	Study design	Population	Minor 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

Summary – Is double-balloon enteroscopy as safe as, or safer than, laparotomy with or without intra-operative enteroscopy for patients with obscure gastrointestinal bleeding of the small bowel?

No comparative data were identified which reported the safety of double-balloon enteroscopy (DBE) against laparotomy with or without intra-operative enteroscopy; however, based on the limited amount of evidence, DBE appears to cause few major or minor complications.

Of the 14 case series (level IV evidence) and four case reports identified, with a combined total of 1,276 procedures, only one study reported a patient requiring surgery as a result of complications following DBE. This patient had suffered pancreatitis and it was suspected that small bowel perforation may also have occurred. It was subsequently shown (through laparotomy) that this was not the case.

Pancreatitis was the cause of the majority of major complications (6 reported cases). With the exception of the patient described above, these complications were treated and resolved with conservative therapy.

One serious adverse event reported in the studies identified was epileptic seizure; however, this was not attributable directly to the DBE procedure, but rather to the administration of propofol for sedation.

The majority of minor complications reported, including abdominal pain, sore throat and brief fever, were self-limiting and did not require medical intervention.

The high incidence of minor complications in the study by May et al (2005a) highlights the difficulty in comparing outcomes of uncontrolled case series for which there is no common reference group. Results may be skewed due to different methods of reporting adverse

events as well as variation among operators performing the procedure. Caution should be exercised when considering these results as the higher reported incidence of minor complications in the study by May et al (2005a) are of little clinical consequence and may not be truly indicative of the safety of DBE.

There are no comparative data on which to draw evidence-based conclusions regarding the comparative safety of DBE.

Effectiveness of double-balloon enteroscopy

Studies were included in this assessment of the effectiveness of double-balloon enteroscopy (DBE) according to the criteria outlined in Box 2.

Box 2 Study selection criteria to determine the effectiveness of double-balloon enteroscopy

Research question	
Is double-balloon enteroscopy as, or more, effective at identifying and treating gastrointestinal bleeding of obscure origin or suspected small bowel disease compared to laparotomy with or without intra-operative enteroscopy?	
Selection criteria	**Inclusion criteria**
Population	Patients with obscure gastrointestinal bleeding or suspected small bowel disease
Prior tests	Capsule endoscopy, CT scan, small bowel barium series, angiography, radio-labelled red blood cell nuclear scanning
Intervention	Double-balloon electronic enteroscopy (per-oral or per-anal approach depending on location of identified or suspected small bowel pathology)
Comparators	Laparotomy with or without intra-operative enteroscopy
Outcome	Primary – reduction of symptoms, reduction in gastrointestinal bleeding, biopsy yield / diagnostic yield (of findings that could explain symptoms, ie arteriovenous malformations, erosions, ulcers, epithelial tumours, polyps), transfusion requirement
	Secondary – examination time, completion of procedure, length of hospital stay, re-admission, further diagnostic workup technical (equipment) success/failure
Study design	Randomised or non-randomised controlled trials or cohort studies, uncontrolled before-and-after case series of at least 10 participants or systematic reviews of these study designs
Search period	2001–5/2006 [a]
Language	Studies in languages other than English were only translated and included if they represented a higher level of evidence than that available in the English language evidence base

[a] DBE was first reported in 2001.

Primary effectiveness outcomes

A total of 10 descriptive studies were identified which reported on the effectiveness of DBE in identifying and treating obscure gastrointestinal bleeding or suspected small bowel disease. These 10 studies were all uncontrolled post-test case series and low level evidence of effectiveness (level IV intervention evidence). The study profiles for all the included studies are shown in Appendix F.

Reduction in symptoms

The 10 descriptive studies which reported on the reduction of symptoms after therapeutic intervention by DBE showed that 77 to 100 per cent of treatments were successful (Table 9). Six studies showed successful treatment or reduction in symptoms in all therapeutic interventions, with the number of treatments performed in each of these studies ranging from 5 to 42.

A study by Gay et al (2006) reported success in 10 of 11 treatments (91%), with one patient requiring further argon plasma coagulation to treat arteriovenous malformations. Kaffes et al (2006) had success in 10 out of 13 patients treated; three of the patients who were treated by diathermy did not have a successful resolution of their anaemia.

Two studies did not report the success rate of all treatments performed during DBE (May et al 2005a; Heine et al 2006). Heine et al (2006) reported that argon plasma coagulation was performed in 61 patients; on average, 1.2 consecutive DBE sessions were required before the need for blood transfusion ceased during the follow-up period

of 1 month after DBE treatment. This indicates that argon plasma coagulation was not performed successfully and often required a follow-up procedure to ensure cessation of bleeding and transfusion requirement. The authors also reported that of 10 polypectomies performed, nine were successful and one required surgical removal due to an inability to advance the endoscope. Furthermore, of three foreign body extractions, two were successful and in the third the foreign body had already migrated into the intra-abdominal space (Heine et al 2006). May et al (2005a) reported that 57 therapeutic interventions were performed during their study but no indication was given as to the success of these procedures.

Table 9 Reduction of symptoms after therapeutic intervention by double-balloon enteroscopy [a]

Study	Level and quality	Population	Therapeutic intervention	Successful intervention / reduction of symptoms [b]
Quality score: 3/3				
(May et al 2005a) [c]	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) [c]	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
(Sunada et al 2005b)	Level IV: Uncontrolled post-test case series Quality score: 3/3	17 patients	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=0
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 Tattooing=8 Polypectomy=10 Removal of foreign body=3	Overall=unable to determine exact numbers Argon plasma coagulation=unable to extract data Tattooing=8 Polypectomy=9 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	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

[a] Data extracted from conference abstracts are included in Appendix H (Table 24). These data have not been included in the assessment of the symptom reduction after DBE.

[b] Patients with successful therapeutic intervention / reduction of symptoms (% treated successfully).

[c] May be overlap between patient series.

Biopsy yield/diagnostic yield

Eleven descriptive studies (level IV intervention evidence) reported on the biopsy yield and diagnostic yield of DBE (Table 10). Within these 11 studies the diagnostic yield ranged between 68 and 93 per cent.

The largest diagnostic yield (93%) was seen in the high quality case series of 42 patients described by Gay et al (2006). In this study the authors looked at the value of using capsule endoscopy to determine the indication for DBE. Of the 164 patients included in the study, 38 had DBE performed after it had been indicated by capsule endoscopy and 4 had DBE without prior capsule endoscopy as it had been contraindicated. Suspected lesions were found in 39 of 42 patients examined by DBE. Zhi et al (2005) also reported a high diagnostic yield (91%) in a good quality study of 57 patients with suspected small bowel bleeding.

Another high quality case series of 275 patients examined the use of DBE in suspected small bowel disease (Heine et al 2006). In this study the authors reported that a presumptive diagnosis was made in 114 patients (56%) and that it was not possible to make a diagnosis in 21 per cent of patients (Heine et al 2006). However, it is important to note that a number of patients were previously diagnosed with small bowel disease prior to DBE and underwent this procedure for the purpose of therapeutic intervention or surveillance alone. Furthermore, it was not possible to extract consistent data from this study and some inconsistencies in the reporting of the data were apparent. As a consequence, the exact diagnostic yield of this study was not able to be determined. Similarly, in the study by Yamamoto et al (2004a), a retrospective case series of 123 patients, there is overlap among a small number of patients having multiple indications. The diagnostic yields in this study were only reported by their indication and not by the number of patients within the study, making it unclear as to the exact diagnostic yield of this procedure.

Without a comparator or reference standard in these studies, however, it cannot be determined whether the diagnostic yield captures most or all of the suspect lesions presented by the patients in these series.

Table 10 Biopsy yield / diagnostic yield of double-balloon enteroscopy [a]

Study	Level and quality	Population	Biopsy yield / diagnostic yield
Quality score: 3/3			
(May et al 2005a) [b]	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 Others=5	Overall 109/137 (80%)
(Ell et al 2005) [b]	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	17 patients Bowel obstruction=12 Abdominal tumour=2 Anaemia=1 Hematochezia=1 Low protein=1	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%)

Study	Level and quality	Population	Biopsy yield / diagnostic yield
Quality score: 2.5/3			
(Heine et al 2006)	Level IV: Uncontrolled post-test case series Prospective study except for first 30 patients. 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%) [c] Obstructive symptoms 17/22 (77%) Suspected small intestinal tumour 8/11 (73%) Other 15/32 (47%)
(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 gastroscopy=4 Abdominal pain=3 FAP=3 Impaired clinical conditions in Crohn's disease=3 Follow-up of GI tumours=3 Peutz-Jeghers 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-Jeghers 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

[a] Data extracted from conference abstracts are included in Appendix H (Table 25). These data have not been included in the assessment of the biopsy/diagnostic yield of DBE.

[b] May be overlap between patient series.

[c] Some overlap exists in a small number of patients with multiple indications.

Transfusion requirement

Of the two case series (level IV intervention evidence) that indicated patients with a previous history of transfusion (Table 11), only one study (Kaffes et al 2006) reported

the need for transfusion after DBE. The high quality study reported that of 40 patients in the study, 20 had required previous blood transfusion; and of 10 patients who underwent diathermy, seven had cessation of their transfusion requirements.

In a small series of 10 patients with obscure gastrointestinal bleeding, Su et al (2005) reported five requiring blood transfusion. Eight of the 10 patients had a bleeding site identified, of which five underwent successful haemostasis by endoscopic therapy. Two patients with submucosal tumours received laparoscopic surgery and one patient with active bleeding underwent surgery after failed hemostasis following Indian ink tattooing (Su et al 2005). The authors did not report on the need for blood transfusion after DBE.

Table 11 Transfusion requirement after double-balloon enteroscopy

Study	Level and quality	Population	Transfusion requirement	
			No. of patients with previous history of 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

Secondary effectiveness outcomes

Examination time and procedural completion

Examination time, as reported by the eight descriptive studies described in Table 12 (level IV intervention evidence), shows that the mean examination time ranged from 55 to 90 minutes in an anterograde approach and 55 to 110 minutes in a retrograde approach. However, the relevance of this data is debatable as examinations were often terminated once a lesion had been found. The examination time was therefore often dependent on the location of small intestinal lesions.

The number of approaches used per patient was reported in six descriptive studies (level IV intervention evidence), as described in Table 12. The number of patients requiring a single approach (either orally or anally) ranged between 42 and 88 per cent. Consequently, the number of patients requiring both approaches (oral and anal) ranged between 12 and 58 per cent.

Table 12 Examination time of double-balloon enteroscopy [a]

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) [b]	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)	Single approach=57/137 (42%) Both approaches=80/137 (58%)

			Anal=75 ± 28 (range 25–130)	
(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	17 patients	Not stated	Single approach=15/17 (88%) Both approaches=2/17 (12%)
(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	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 (range 25–180) 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%)

[a] Data extracted from conference abstracts is included in Appendix H (Table 26). These data have not been included in the assessment of the examination time of DBE.

[b] May be overlap between patient series.

Length of insertion and completion of procedure

Data describing the completion of DBE, including the length of insertion of the endoscope, were reported in seven descriptive studies (level IV intervention evidence) (Table 13). The length of insertion (mean ± standard deviation) for anterograde approaches ranged from 200 ± 70 cm to 270 ± 104 cm. Anally, the length of insertion of the endoscope (mean ± standard deviation) ranged from 70 cm (no standard deviation reported) to 180 ± 150 cm. Due to examinations often being terminated once a lesion was found, the relevance of this data is unclear.

The ability to examine the entire small intestine varied greatly between the seven studies that reported this data. Yamamoto et al (2004a), the pioneer of this procedure, reported success in examining the entire small bowel in 24/28 procedures (86%). Of these, 22 required both oral and anal approaches, while two examinations required only the oral approach.

Reasonable success was also achieved by Heine et al (2006) and May et al (2005a), with 26/62 (42%) and 25/55 (45%) respectively. Examination of the entire small intestine by Heine et al (2006) required both approaches on 12 occasions and therefore a single approach on 14 occasions. May et al (2005a) required a single approach (oral) on two occasions compared to both approaches on 23 attempts.

Low success was reported by the high quality study of Kaffes et al (2006), with zero successful examinations of the small intestine in 10 attempts. In the average quality study by Mönkemüller et al (2006) four successful examinations of the entire small intestine were made in 53 attempts.

Two studies, Di Caro et al (2005) and Ell et al (2005), reported similar success with 16 per cent of procedures examining the entire small intestine. However, neither study reported the total number of attempts.

The early termination of DBE was reported in four studies. The low quality study of Di Caro et al (2005) indicated that the procedure was stopped on 10 occasions out of 89 procedures performed, five times due to subclinical ileal stenosis and five times due to excessive looping of the colon.

In a high quality study by Ell et al (2005) DBE was terminated early in 7 of 147 procedures performed. The early terminations were a result of active bleeding in the duodenal bulb (1), bleeding source located in the colon (1) and anatomical conditions (5). May et al (2005) reported that the procedure was halted early due to a severe nose bleed in the patient (1), intolerance of the procedure (1) and inadequate bowel preparation (4). It should be noted that in this study the procedure halted due to intolerance was successfully completed using the anal approach, and that the other five early terminations were also successfully repeated (May et al 2005a).

Mönkemüller et al (2006) reported the early termination of DBE on six occasions. One instance was the result of multiple adhesions (the patient had a previous history of four exploratory laparotomies) preventing further passage of the endoscope, and the other was due to intolerability of the procedure. Three procedures were terminated due to anatomical conditions preventing entry into the terminal ileum more than 1–2 cm. In addition, one patient had undergone a Merendino operation to replace a diseased segment of lower oesophagus with a segment of the upper small bowel, and the main objective was to examine the remaining stomach. No attempt was made to examine the small bowel any further (Mönkemüller et al 2006).

Table 13 Completion of double-balloon enteroscopy procedures [a]

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) [b]	Level IV: Uncontrolled post-test case series	137 patients	Oral=240 ± 100 (range 40 –550)	25/55 (oral only=2, oral	Severe nose bleed=1 [c]

	Quality score: 3/3		Anal=120 ± 90 (range 50–350)	and anal=23)	Intolerance despite increased sedation=1 [d] 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
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	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 [e] 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

[a] Data extracted from conference abstracts is included in Appendix H (Table 27). These data have not been included in the assessment of the procedural completion.
[b] May be overlap between patient series.
[c] Procedure was successfully repeated.
[d] DBE successfully completed via the anal approach.
[e] Underwent Merendino operation and objective of DBE was to inspect remaining stomach.

Technical failure

Only one study reported any data in relation to a technical failure of DBE (Table 14). May et al (2005a), in a high quality study that examined a series of 137 patients in 248 procedures, reported one technical problem where the cap at the tip of the scope was lost during withdrawal of the endoscope into the duodenum. The cap was easily recovered and extracted with no further technical difficulties.

Table 14 Technical failure of double-balloon enteroscopy

Study	Level and quality	Population	Technical failure
(May et al 2005a)	Level IV: Uncontrolled post-test case series Quality score: 3/3	137 patients	Loss of cap attached to tip of scope upon withdrawal of scope. Cap was recovered and extracted.

Summary – Is double-balloon enteroscopy as, or more, effective for patients with obscure gastrointestinal bleeding of the small bowel compared to laparotomy with or without intra-operative enteroscopy?

No comparative studies were identified which reported the effectiveness of double-balloon enteroscopy (DBE) against the comparator, laparotomy with or without intra-operative enteroscopy.

All descriptive studies which reported effectiveness outcomes of DBE were level IV intervention evidence.

Therapeutic interventions by DBE were reported in 10 case series, of which six indicated 100 per cent success of all treatments used. The success of therapeutic interventions ranged from 77 to 100 per cent, with the most utilised intervention being argon plasma coagulation for the cessation of bleeding in the small intestine.

It is important to note that of the four studies that did not report 100 per cent success of all interventions, only two reported the success of the therapeutic interventions as being less than 100 per cent (Gay et al 2006; Kaffes et al 2006). The remaining two studies either failed to report the success of the therapy (May et al 2005a) or reported the average number of procedural sessions required to successfully treat the patient, which in itself indicates that the success of the therapeutic interventions was not 100 per cent (Heine et al 2006).

Eleven descriptive studies reported biopsy yield or diagnostic yield of findings that could explain symptoms, which ranged from 68 to 93 per cent.

Transfusion requirement after DBE was not widely reported in the studies included in this report. Only one study reported this outcome and indicated that seven out of 10 patients who had a previous history of transfusion no longer required transfusion after therapeutic DBE.

The secondary effectiveness outcomes assessed include examination time, completeness of procedure and technical failure.

The mean examination time was reported in eight case series and ranged from 55 to 90 minutes for the anterograde approach and 55 to 110 minutes for the retrograde approach.

As the examination of the small intestine was often halted after a lesion had been found, the relevance of this data is questionable as it was, in many cases, dependent on the location of small intestinal lesions.

Similarly, data describing the length of insertion of the endoscope, which was reported in seven descriptive studies, may not be relevant as the extent of the examination was often dependent on finding a lesion. After finding the lesion, the examination of the remaining small intestine was often not completed. The length of insertion (mean ± standard deviation) for anterograde approaches ranged from 200 ± 70 cm to 270 ± 104 cm. Anally, the length of insertion of the endoscope (mean ± standard deviation) ranged from 70 cm (no standard deviation reported) to 180 ± 150 cm.

Successful examination of the entire small intestine varied greatly between the seven descriptive studies which reported this outcome. Kaffes et al (2006) reported no success in 10 attempts. However, Yamamoto et al (2004a), the pioneer of DBE, reported good success, with 24 successful examinations of the entire small bowel from 28 attempts. Interestingly, early termination of the procedure was often reported to be due to anatomical conditions such as extensive looping of the colon, ileal stenosis or adhesions, whereas intolerance of the procedure was reported on only two occasions.

The use of an oral and/or anal approach showed large variability between the six studies for which it was reported. This may be an indication of the experience of the operators and the learning curve associated with this procedure; or it may simply reflect the variability in the small bowel lesion site in presenting patients.

Technical failure as an outcome was only reported in one study, which described 248 procedures. During one procedure the cap at the tip of the endoscope was lost during withdrawal from the duodenum but was successfully recovered without further consequences.

Economic considerations associated with double-balloon enteroscopy

The purpose of economic evaluation is to assist decision-makers in ensuring that society's ultimately scarce resources are allocated to those activities from which we will get the most value. That is, it seeks to enhance economic efficiency.

A cost-effectiveness analysis is only undertaken if there is evidence that the procedure under consideration is more effective than the designated comparator. Otherwise, an estimate of the financial incidence of the new procedure is all that is required by the MSAC.

Due to a lack of comparative evidence, it is not possible to conclude whether or not double-balloon enteroscopy (DBE) is as effective, or more effective than, laparotomy with or without intra-operative enteroscopy. Therefore, an analysis of the expenditures associated with the new procedure relative to the comparator has been conducted.

Financial incidence analysis

Likely number of procedures in a typical year

It is anticipated that the number of procedures which would be performed annually across Australia would be no greater than approximately 1,147. As previously described in the section addressing clinical need (see page 15), this estimate is based on the assumption that approximately 50 per cent of small bowel lesions identified by capsule endoscopy would be suitable for DBE. In addition, it is likely another 100 to 200 patients would be identified via other imaging techniques, and approximately 10 per cent of all patients would require both an oral and anal approach when DBE is undertaken.

Pre-procedural and post-procedural unit costs

The pre-procedural workup for both DBE and laparotomy with or without intra-operative enteroscopy is the same, involving identification of small bowel lesions in most instances by capsule endoscopy. However, should this be contraindicated (due to suspicion of intestinal stenosis), identification would occur via CT scan and/or small bowel series. The post-procedural care and post-hospital costs are the same for both DBE and the comparator, laparotomy with or without intra-operative enteroscopy. The unit costs of the pre-procedural workup and post-procedural care are presented in Table 15.

Table 15 Unit costs of pre-procedural workup and post-procedural care for double-balloon enteroscopy and its two comparators

Item	Source of estimate	Schedule fee
Pre-procedural workup		
CT scan	MBS Item 56407	$360
Capsule endoscopy	MBS Item 11820	$1,765
Small bowel series, barium	MBS Item 58915	$79
Pre-anaesthetic consult	MBS Item 17603	$37
Post-hospital costs		
Follow-up consult	MBS Item 108	$69

Medicare Benefits Schedule (MBS) Items at November 2005.

Unit costs of the procedure

The unit costs of DBE are presented in Table 16 and Table 17. These tables include all relevant costs regardless of the agency that bears them.

The costs associated with the additional capital equipment required for DBE are presented in Table 16. In performing the financial incidence analysis two assumptions have been made: that DBE is performed in a day facility, and that efficient throughput would see 100 to 150 of such procedures per instrument performed each year. Under these assumptions the equivalent annual cost of the equipment would be $23,485, the annual maintenance costs $6,406 and the estimated cost per procedure $299.

Table 16 Cost per unit of additional capital equipment and maintenance for double-balloon enteroscopy

Item	Estimate	Source of estimate
Purchase price	$106,764	Fujinon Australia
Estimated clinical life of equipment	5 years	Fujinon Australia
Annual equivalent cost of equipment	$23,485	Annuity at 5% p.a for 5 years payable in advance
Annual maintenance costs	$6,406	Fujinon Australia
Total major capital equipment cost p.a.	$29,891	
Estimated annual volume of procedures	100 (150 maximum)	Expert opinion of GESA [a] nominees on MSAC Advisory Panel
Estimated cost per procedure	$299	

[a] GESA=Gastroenterological Society of Australia

It should be noted that if, for example, DBE facilities were available in each capital city, it is likely that some would not be working at efficient capacity because of low patient numbers.

Table 17 Unit cost of double-balloon enteroscopy per procedure in a private day hospital facility

Item	Estimate	Source of estimate
Equipment cost: capital and maintenance per procedure [a]	$299	Table 16 (above)
Professional fee- surgeon	$1,157 ($1,624 with therapy)	Expert opinion [b] indicates that the procedural time for DBE is approximately four times that of colonoscopy and that therefore it would be reasonable to multiply the fee for colonoscopy by four. MBS Item 32090 (or 32093 with therapy)
Anaesthesia initiation	$86	MBS Item 20740
Anaesthesia time units	$103	Expert opinion [b] indicates that the average procedural time is 90 minutes. MBS Item 23063
Modifier (if required)	$17	Anaesthesia, perfusion or assistance at anaesthesia where the patient is less than 12 months of age or 70 years of age or greater (1 basic unit). MBS Item 25015
Cost of associated disposables [a]	$329 $30	Overtube (Fujinon Australia) Balloon for enteroscope (Fujinon Australia)
Cost of day hospital facility services [a]	$484	Total average charge per AR-DRG V4.2 Private Hospitals Data Bureau; G44C – other colonoscopy, sameday [c].
Total	$2,505 ($2,972 with therapy)	

Medicare Benefits Schedule (MBS) Items at November 2005.
[a] Items not covered by Medicare.

[b] Gastroenterological Society of Australia nominee on MSAC Advisory Panel.
[c] Department of Health and Ageing 2005.

The unit costs of the two comparators, laparotomy and laparotomy with intra-operative enteroscopy, each for a private patient in a private hospital, are presented in Table 18 and Table 19.

Table 18 Unit cost per procedure of comparator technique – laparotomy for a private patient in a private hospital

Item	Estimate	Source of estimate
Professional fee – surgeon	$550	MBS Item 30387
Anaesthesia initiation	$103	MBS Item 20840
Anaesthesia time units	$103	MBS Item 23063
Modifier (if required)	$17	Anaesthesia, perfusion or assistance at anaesthesia where the patient is less than 12 months of age or 70 years of age or greater (1 basic unit) MBS Item 25015.
Surgical assistant	$110	MBS Item 51303
Cost of hospital services [a]	$3,085	Total average charge per AR-DRG V4.2 Private Hospitals Data Bureau; G11A Anal & stomal procedures + CSCC. ALOS 4.16 days [b]
Total	$3,968	

Medicare Benefits Schedule (MBS) Items at November 2005.
[a] Item not covered by Medicare
[b] Department of Health and Ageing 2005.
ALOS=average length of hospital stay

Table 19 Unit cost per procedure of comparator technique – laparotomy with intra-operative enteroscopy for a private patient in a private hospital

Item	Estimate [a]		Source of estimate
	Laparotomy with intra-operative enteroscopy only	Laparotomy with intra-operative enteroscopy and additional abdominal procedure(s) [b]	
Professional fee – surgeon	$628 [c]	$903 [d]	MBS Item 30568 and 30387
Professional fee – gastroenterologist	$320	$320	MBS item 30569
Anaesthesia initiation	$103	$103	MBS Item 20840
Anaesthesia time units	$154	$154	MBS Item 23091
Modifier (if required)	$17	$17	Anaesthesia, perfusion or assistance at anaesthesia where the patient is less than 12 months of age or 70 years of age or greater (1 basic unit). MBS Item 25015
Surgical assistant	$126	$181	MBS Item 51303
Cost of hospital services [e]	$3,085	$3,085	Total average charge per DRG V4.2 Private Hospitals Data Bureau; G11A – Anal & stomal procedures+CSCC. ALOS 4.16 days [f].
Total	$4,433	$4,763	

Medicare Benefits Schedule (MBS) Items at November 2005.
[a] Note the capital equipment costs for intra-operative enteroscopy have not been included, and are likely trivial given the use of this equipment for other indications and procedures.
[b] Where the surgeon performs additional procedures within the abdominal cavity in addition to intra-operative enteroscopy.
[c] MBS item 30568 only.
[d] Calculated using MBS items 30568 and 30387 and the multiple operation formula.
[e] Item not covered by Medicare
[f] Department of Health and Ageing 2005.
ALOS=average length of hospital stay

In summary, the cost per procedure of performing a single approach DBE is estimated to be $2,505 (or $2,972 with therapy); the cost per laparotomy procedure is estimated at $3,968; and the cost per laparotomy with intra-operative enteroscopy is estimated at $4,433 (or $4,763 if the surgeon performs any procedures in the abdominal cavity in addition to the intra-operative enteroscopy). These estimates are for a private patient in a private facility. It is important to note that the cost of doing both oral and anal approaches for DBE would be twice that of a single approach as the second approach requires scheduling at a later date.

Cost to the Australian Government

The Australian Government will be responsible for payment of the rebate on items from the Schedule of Medicare Benefits. On the assumption that the DBE will be performed in a day hospital facility, the rebate will be 75 per cent of the schedule fee – as it will also be for services for a private patient in a private hospital.

A comparison of MBS item payments associated with the techniques is presented in Table 20. As illustrated, the estimated costs of MBS items for DBE with biopsy or

therapeutic intervention are $1,363 and $1,830 respectively. In comparison, the cost for surgery would be between $882 and $1,678. Thus, DBE *with therapy* would result in an additional *cost* to the Australian Government per procedure of between $152 and $948 relative to its comparators. The corresponding estimates for DBE *without therapy* range from a *cost* of $481 to a *saving* of $315 relative to the comparators.

Table 20 Comparison of MBS item costs for double-balloon enteroscopy and laparotomy with or without intra-operative enteroscopy

	Double-balloon enteroscopy (with therapy)	Laparotomy	Laparotomy with intra-operative enteroscopy
Item			
Professional fee	$1,157 ($1,624)	$550	$948 [a] $1,223 [b]
Anaesthesia	$206	$223	$274
Surgical assistance	N/A	$110	$126 [a] $181 [b]
Total cost	$1,363 ($1,830 with therapy)	$882	$1,348 [a] $1,678 [b]

N/A=not applicable
[a] Laparotomy with intra-operative enteroscopy only.
[b] Laparotomy with intra-operative enteroscopy and additional procedures performed by the surgeon.

Australian Refined Diagnosis Related Group (AR-DRG) round 8 cost estimates indicate that the public to private patient splits for a comparable procedure (same day colonoscopy) are 30 per cent and 70 per cent respectively. It is therefore possible to assume that 70 per cent of DBE procedures would be eligible for MBS reimbursement, with the remaining 30 per cent coming under the Australian Health Care Agreements between the States/Territories and the Commonwealth. As it is estimated that there will be no more than approximately 1,147 procedures being performed annually, 802 of these procedures would be eligible for MBS reimbursement.

To calculate the financial implications to the Commonwealth of subsidising DBE, the estimated cost per procedure is multiplied by the expected uptake of the procedure in private hospitals. In this calculation the assumption has been made that of the laparotomies with intra-operative enteroscopy that are performed, 50 per cent would entail the surgeon performing additional procedures within the abdominal cavity in addition to the intra-operative enteroscopy. The remaining 50 per cent would be laparotomy with intra-operative enteroscopy alone. As 802 procedures are expected to be performed annually in the private sector, a total *cost* of between $254,234 and $760,296 for DBE *with therapy* per year would be incurred by the Commonwealth relative to laparotomy with or without intra-operative enteroscopy (depending on the nature of the comparator procedure). For DBE *without therapy*, the implications to the Commonwealth would range between a *cost* of $385,762 and a *saving* of $120,300 per year relative to the comparators.

Total cost to the Australian healthcare system overall

The total cost to the Australian healthcare system would include copayments, costs of disposables, hospital services and capital equipment as well as medical services. For 1,147 DBEs performed annually in the healthcare system, the total cost is estimated to range from $2,873,235 to $3,408,884, depending on whether or not therapy is carried out with the diagnostic procedure.

The total cost to the Australian healthcare system for approximately 1,147 *comparator* procedures performed annually in the healthcare system ranges from $4,551,296 to $5,273,906. This greater total expenditure on the comparators is largely a consequence of the 4.16 days average post-surgery hospital stay, whereas DBE is a 1 day stay procedure.

The total *cost savings* for the public sector (ie approximately 345 of 1,147 procedures) are likely to be absorbed by other services if public hospitals are working close to capacity. These cost savings would range between $470,235 and $631,350 per year depending on the procedures performed.

Other relevant considerations

This section provides information that does not fit with the evidence-based assessment of the safety and effectiveness of double-balloon enteroscopy (DBE), but nevertheless impacts on this assessment.

Access to DBE by the general Australian population is an important issue when assessing the procedure. Although the demand for DBE is not considered high, to provide equitable access it would be considered necessary that a system would be in use in each major capital city in Australia. Should this provision occur, it is likely that the units would be under-used.

Performing DBE is considered to be a difficult and complex procedure, requiring extensive training and accreditation by appropriate training bodies and craft groups. The learning curve associated with the procedure is considerable. As this procedure is relatively new (first being performed in 2001), all included studies in this systematic review have incorporated a learning curve. It would not be considered unreasonable to expect fewer complications to occur as experience with this procedure increases. Further, it would be expected that fewer patients would require both approaches (anal and oral) to be used as experience is gained in not only examining the small bowel but also determining the best approach from prior diagnostic imaging modalities (eg capsule endoscopy).

Evidence relating to the safety of the comparators has not been included in the systematic review as no comparative data for DBE and laparotomy with or without intra-operative enteroscopy is available. Despite this, safety concerns regarding laparotomy with or without intra-operative enteroscopy should be noted. The widely accepted risks of the comparators include wound infection, prolonged ileus (which would extend the length of stay in hospital), morbidity from use of general anaesthetic, intra-abdominal infection, perforation and small bowel obstruction.

A number of studies have reported development of abdominal adhesions, occurring in up to 94 per cent of patients following abdominal surgery (Becker & Stucchi 2004). Adhesions are associated with complicated subsequent surgeries, infertility, chronic abdominal pain and adhesive small bowel obstruction. The widely accepted principles of adhesion prevention – gentle handling of tissues, careful control of bleeding, excision of necrotic tissue and prevention of infection – have done little to curb their incidence (Becker & Stucchi 2004).

The expert opinion of the Advisory Panel suggests that the risk of perforation as a result of DBE would be similar to that of colonoscopy. Iqbal et al (2005) reported the risk of perforation during colonoscopy to be between 0.03 and 0.19 per cent.

The possibility of intra-abdominal infection is real for any patient who has undergone abdominal surgery (Cheadle & Spain 2003). This is particularly so for patients involving resection or perforation of the gastrointestinal tract. The mortality rate for such a complication may be as high as 30 to 35 per cent depending on the cause and severity of the illness (Aprahamian & Wittmann 1991; Cheadle & Spain 2003).

Complications associated with intra-operative enteroscopy include perforation, prolonged ileus, intestinal ischaemia and wound infection, and have been reported to range between 0 and 52 per cent (Hartmann et al 2005). Mortality as a direct

consequence of either the procedure or post-operative complications is not widely reported. However, some studies have reported mortality as being up to 11 per cent (Hartmann et al 2005). Hartmann et al (2005) themselves reported a death as a result of post-operative complications in the series of 47 patients which they studied.

Laparotomy with or without intra-operative enteroscopy is considered to be the definitive treatment for this population. It is likely, however, that patient preference will influence the uptake of DBE. The less-invasive nature of the procedure, as well as cosmetic reasons, may be appealing to all patients. Although fit and younger patients would be expected to recover more easily and quickly from laparotomy, their preference may be for DBE. There is no scar associated with the procedure; there is a lower likelihood of complications; and a day procedure would result in minimal loss of income due to recovery time and hospital stay. Older, frailer patients may prefer DBE rather than laparotomy with or without intra-operative enteroscopy because they may expect to recover more easily from a less invasive procedure.

It is possible that latex allergy may be a concern in relation to DBE. The balloons attached to the tip of the enteroscope and overtube are made of latex and could therefore present a risk to patients who suffer from latex hypersensitivity. It has been reported that direct mucosal and parenteral exposure to latex during medical procedures could elicit a fatal response in such patients (Taylor & Erkek 2004). However, it is important to note that no allergic reactions resulting from latex hypersensitivity have been reported after DBE. In addition, these concerns would also be relevant for patients receiving laparotomy with or without intra-operative enteroscopy due to the widespread use of latex surgical gloves. If the allergy is known, modifications can be made to the surgical procedures; however, they cannot be made to the DBE procedure itself.

It appears that the complications associated with laparotomy with or without intra-operative enteroscopy are of a more severe nature than those in DBE. With this in mind, it is reasonable to assume that if DBE could provide an acceptable level of efficacy, patient preference (and that of the clinician) would be for DBE.

Discussion

Is double-balloon enteroscopy safe?

Fourteen case series (level IV intervention evidence) assessed the safety of double-balloon enteroscopy (DBE). The available evidence does not provide an indication of the comparative safety of DBE. However, less than 1 per cent of procedures were associated with major complications, and they appeared to be resolved with conservative therapy.

Of eight major complications reported, six were due to pancreatitis. One theory put forward by Groenen et al (2006) suggests that this may be due to reflux of duodenal fluids into the pancreatic duct as the intraluminal pressure increases. This pressure increase occurs when both balloons are inflated within the duodenum, occluding the segment between the two balloons. Heine et al (2006) suggest, however, that it may result from the prolonged mechanical stress placed on the pancreas due to repeated stretching of the endoscope. Regardless of the cause, it would appear that pancreatitis may be a complication associated with DBE.

May et al (2005a) reported a higher incidence of minor complications than any other study. This may be a reflection of particularly stringent reporting of adverse events in this study and/or differences between operators performing the procedure. Caution should be taken when considering these results as the higher reported incidence of minor complications in this study may not be truly indicative of the safety of DBE.

Latex allergy may be a concern for a small group of patients due to the use of latex balloons on the enteroscope and overtube. However, there are no reports to date of adverse reactions resulting from latex hypersensitivity.

Although there are no comparative data to suggest that DBE is safer than laparotomy with or without intra-operative enteroscopy, it would follow that, due to its much less invasive nature, fewer complications would arise as a result of this procedure.

Is double-balloon enteroscopy effective?

Eleven case series (level IV intervention evidence) assessed the effectiveness of DBE. There was no evidence available which compared the effectiveness of this procedure to laparotomy with or without intra-operative enteroscopy.

A major advantage of DBE is the ability to perform therapeutic interventions once lesions have been identified. Successful reduction of symptoms was achieved in the vast majority of interventions. One study (Kaffes et al 2006) did not report as high a success rate as the other studies, and three out of ten treatments with diathermy in this study were unsuccessful. Although the authors did not put forward any explanation for this, it was noted that one major complication (perforation of the small bowel) occurred in this study as a consequence of diathermy treatment. It is possible that this may have led to caution when applying this treatment in subsequent procedures, resulting in less than successful outcomes.

The ability to examine the entire small bowel varied greatly among the studies assessed and may be dependent on two factors: the skill level required to manipulate the

enteroscope through the small bowel, and differences in patient ethnic group. The greatest success in achieving total examination of the small bowel has been attained by Yamamoto et al (2004a), the pioneer of this procedure and, one would expect, the most experienced in performing it. Kaffes et al (2006) noted that diverticular disease and redundant looping of the colon appeared to be more prevalent in their study of a Western cohort compared to the population studied by Yamamoto et al. However, the ability to examine the whole small bowel may not be necessary once a lesion has been located. Further examination would only be required if it was suspected that the patient was suffering from multiple lesions.

Expert opinion among members of the Advisory Panel suggests that in Japan the DBE experience may be different from that in other countries. Capsule endoscopy is not yet widely available in Japan and hence DBE is used as a primary diagnostic modality for the small intestine. As a result, the frequency with which the procedure is done in both directions is higher in Japanese patients than elsewhere, where the findings of capsule endoscopy can be used to determine the initial approach of DBE. It is also likely that the frequency with which both approaches are required will fall as experience with the procedure is achieved and depth of insertion increases.

An overall evaluation of the body of evidence supporting the effectiveness and use of DBE for obscure gastrointestinal bleeding or suspected small bowel disease is provided in Table 21.

Table 21 Assessment of body of evidence for effectiveness of double-balloon enteroscopy [a]

Component	A Excellent	B Good	C Satisfactory	D Poor
Volume of evidence				Level IV studies, or level I to III studies with high risk of bias
Consistency		Most studies consistent and inconsistency may be explained		
Clinical impact		Substantial		
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 13.

Economic considerations of double-balloon enteroscopy

The financial incidence analysis indicates that the cost to the Commonwealth would be greater for DBE than laparotomy with or without intra-operative enteroscopy. However, the overall financial burden to the Australian healthcare system would be greater for the comparator procedures.

The procedural costs of DBE with therapy are greater than those of the comparator, reflecting the duration and complexity of the procedure involved. Laparotomy with or without intra-operative enteroscopy, while also a complex procedure, may not be of the same duration, in particular if intra-operative enteroscopy is not performed.

Costs of hospital services (which are not incurred by the Commonwealth) are a significant factor, particularly as DBE is performed as a day-only procedure while the comparator involves an average 4-day stay in hospital. However, in general, the cost of hospital services are borne by the private health insurers or occasionally by the individual.

Conclusions

Safety

The small volume of evidence which assessed the safety outcomes of double-balloon enteroscopy (DBE) was of a low level (level IV intervention evidence) and provided no comparative data in relation to laparotomy with or without intra-operative enteroscopy.

In general, the evidence reported consistent findings with respect to safety of DBE, with small numbers of major complications reported. Major adverse events reported were small bowel ileus, pancreatitis ranging from mild to severe, perforation, post-polypectomy bleeding and epileptic seizure as a result of propofol sedation. It is important to note that epileptic seizure is a rare but recognised side effect of propofol sedation and is not directly attributable to the DBE procedure.

Minor complications were more commonly reported and included abdominal pain, sore throat, fever, vomiting and reddening of mucosal tissue. These events were of a self-limiting nature and often did not require medical therapy.

In general, the evidence was consistent in the reporting of minor complications. However, one good quality uncontrolled case series reported a higher incidence of minor complications than any other study. The majority of these complications were reddening of the mucosal tissue. This variation could be an indication of differences in reporting of complications, or could reflect the skill level and/or learning curve required of the endoscopist performing the procedure.

Overall, DBE appears to be a safe procedure with few reported major complications. However, with no evidence comparing the safety of this procedure with laparotomy with or without intra-operative enteroscopy, it cannot be concluded that DBE is as safe as, or safer than, the comparator.

Effectiveness

The volume of evidence used to assess the effectiveness of DBE consisted solely of low level uncontrolled post-test case series (level IV intervention evidence) and is therefore considered to be of poor methodological value. However, the populations of the studies examined were generalisable to the target population within Australia, ie patients with obscure gastrointestinal bleeding or other small bowel pathology that requires treatment or biopsy. The results of the studies are applicable to the Australian healthcare context, with most studies being conducted in developed countries with similar standards of practice in the treatment of small bowel pathology.

The majority of the evidence reported that the reduction in symptoms and success of therapies performed was very high; however, some inconsistencies were apparent in the reporting of this outcome. This could be due simply to poor reporting of results by the investigators, or to the investigators not wishing to indicate the precise success achieved by the procedure in reducing symptoms.

The biopsy/diagnostic yield achieved varied across the studies examined. This could be explained by variation in the operators performing the procedure across the studies, and

may highlight the need for evaluation of the small bowel by capsule endoscopy prior to performing this procedure.

Transfusion requirement was poorly reported in the studies examined and little can be concluded from the one small study which reported on this outcome.

The secondary effectiveness outcomes of insertion length, examination time and the ability to examine the whole small bowel were also assessed with a body of evidence that is considered to be of low methodological value. These outcomes are greatly influenced by the location of lesions within the small bowel, as in most cases the procedure was stopped after a lesion had been found. The value of the results is therefore limited. The ability to examine the entire small bowel (when attempted) varied among the studies. This may be an indication of the different skill levels of the endoscopist as it is accepted that a learning curve is associated with performing this procedure.

Only one incidence of technical failure associated with use of the DBE system was reported in the evidence base. This involved the loss of a cap at the tip of the scope; however, it was successfully retrieved and extracted. This indicates that few technical problems arise with the use of this system.

In conclusion, on the basis of low level evidence, DBE appears to be an effective procedure for delivering therapeutic interventions to the small bowel. However, the complete absence of evidence comparing the procedure against the more invasive comparator does not allow any conclusions to be drawn in regard to the effectiveness of DBE against laparotomy with or without intra-operative enteroscopy.

Economic considerations

The financial incidence analysis estimates that a total cost of between $254,234 and $760,296 for DBE with therapy would be incurred by the Commonwealth relative to laparotomy with or without intra-operative enteroscopy for 802 procedures performed in the private sector annually.

This does not reflect the total cost to the Australian healthcare system overall, which would also include copayments, costs of disposables, hospital services and capital equipment costs. The total cost to the Australian healthcare system for DBE is estimated to range from $2,873,235 to $3,408,884 depending on whether a therapeutic intervention is carried out during the procedure. This is in contrast to costs of the comparator to the healthcare system, which would see an expenditure of between $4,551,296 and $5,273,906 for procedures carried out in the private sector. This is largely a consequence of the post-surgery hospital stay.

Recommendation

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 intra-operative enteroscopy.

While there is no direct comparative data, DBE is likely to be safer to perform than the alternative, intra-operative enteroscopy.

DBE is effective in allowing enteroscopic assessment and some treatment of the entire small intestine.

Although more costly to Medicare than intra-operative enteroscopy, DBE is potentially cost saving for the entire health funding system.

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

The Minister for Health and Ageing accepted this recommendation on 5 February 2007.

Appendix A MSAC terms of reference and membership

The MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Kwun Fong	thoracic medicine
Dr David Gillespie	gastroenterology
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Samantha Robertson	Department of Health and Ageing representative
Dr Terri Jackson	health economics
Professor Frederick Khafagi	nuclear medicine
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Ewa Piejko	general practice

Ms Sheila Rimmer	consumer health issues
Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Dr Mary Turner	Australian Health Ministers Advisory Council
Dr David Wood	orthopaedic surgery

Appendix B Advisory panel

Advisory panel for MSAC Application 1102 – Double-balloon enteroscopy

A/Prof Donald Perry-Keene (Chair) MBBS, FRACP Endocrinologist and Clinical Associate Professor, Department of Medicine, University of Queensland	MSAC member
Dr Stephen Blamey MBBS (Hons), FACS, FRACS Head of Surgery, Monash Medical Centre Chair of the MSAC	MSAC member
Dr David Gillespie MBBS, DCH (Lond), DA (UK), FRACP CEO, Hastings Day Surgery Gastroenterologist, consulting physician	MSAC member
Dr Mark Appleyard MD, FRACP, MRCP Director of Endoscopic Services, Royal Brisbane and Women's Hospital, Brisbane Associate lecturer, University of Queensland	GESA nominee
Mr Barry Cahill BBus, MHA Chief Executive Officer, Continence Foundation of Australia Parkville, Victoria	Consumers' Health Forum of Australia nominee
A/Prof Graham Newstead MB BS, FRACS, FRCS(Eng), FACS, FASCRS Hon FRSM, Hon FACP (GB&I) Conjoint Associate Professor, University NSW Head, Colorectal Surgery, Prince of Wales Hospitals Executive Director, Colorectal Surgical Society of Australasia Chairman, The Colorectal Foundation Chairman, The CSSA Foundation Chairman	RACS nominee
A/Prof Warwick Selby MBBS, MD, FRACP Senior Visiting Gastroenterologist and Director of Endoscopic Services, Royal Prince Alfred Hospital, Sydney Clinical Associate Professor, The University of Sydney	GESA nominee

Appendix C Search strategies

Bibliographic databases used to identify literature on the safety and effectiveness of double-balloon enteroscopy

Electronic database	Time period
AustHealth	2001–5/2006
Cinahl	2001–5/2006
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	2001–5/2006
Current Contents	2001–5/2006
Embase.com (including Embase and Medline)	2001–5/2006
Pre-Medline	5/2006
ProceedingsFirst	2001–5/2006
Web of Science – Science Citation Index Expanded	2001–5/2006
EconLit	2001–5/2006

Other sources of evidence (2001–5/2006)

Source	Location
Internet	
NHMRC–National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
Australian Department of Health and Ageing	http://www.health.gov.au/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
Health Technology Assessment International (HTAi)	http://www.htai.org/
International Network for Agencies for Health Technology Assessment	http://www.inahta.org/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
National Library of Medicine Locator Plus database	http://locatorplus.gov
UK National Research Register	http://www.update-software.com/National/
Google scholar	http://scholar.google.com/
Websites of Health Technology Agencies	See Appendix A
Websites of Specialty Organisations	See Appendix B
Hand searching (journals 2004–05)	
Gastrointestinal Endoscopy	Barr Smith Library or electronic access
Gastroenterology Clinics of North America	Barr Smith Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	MSAC Advisory Panel
Pearling	
All included articles will have reference lists searched for additional relevant source material	

Search terms used

Area of inquiry	Search terms
Prevalence of obscure gastrointestinal bleeding	(**'obscure gastrointestinal bleeding'** OR '**gastrointestinal hemorrhage**'/exp OR '**enteropathy**'/exp) AND ((**small** AND **'bowel'**/exp OR **intestin***) OR **'small intestine'**/exp) AND ('**prevalence**'/exp OR **rate**) AND **(cross-sectional stud*** OR **survey)** **Limit** English Human **[**1990-2006]/py
Safety, effectiveness and cost-effectiveness of intervention	(**double-balloon** OR **push-and-pull**) AND (**'gastrointestinal tract examination'**/exp OR **'intestine examination'**/exp OR **'intestine endoscopy'**/exp OR **'abdominal surgery'**/exp OR ((**enteroscop*** OR **endoscop***)) AND (**small** AND **'bowel'**/exp OR **intestin***) OR **'small intestine'**/exp **Limits** Human [2001-2006]/py
Safety of comparator techniques	((**small** AND (**bowel** OR **intestin***)) OR **'small intestine'**/exp) AND (**'laparoscopy'**/exp OR **laparoscop*** OR '**laparotomy**'/exp OR '**laparotomy**'/exp OR '**endoscopy**'/exp OR **endoscop*** OR **enteroscop*** OR '**intra-operative endoscopy**') AND ('**perioperative** AND **complication**' OR **complication*** OR '**perforation**'/exp OR '**perforation**'/exp OR '**bacterial** AND **infection**' OR '**wound** AND **infection**' OR '**sepsis**'/exp OR **'ileus'**/exp OR '**abscess**'/exp OR '**intestine** AND **hematoma**' OR '**gastrointestinal** AND **hemorrhage**' OR '**intestine** AND **intussusception**' OR **'death'**/exp OR '**pain**'/exp) AND ('**randomized controlled trial**'/exp OR '**cohort analysis**'/exp OR '**systematic review**'/exp) **Limits** English Human [1990-2006]/py

Appendix D Internet sites searched

Websites of health technology assessment groups

AUSTRALIA

- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/open/asernip-s.htm
- Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
- Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au

AUSTRIA

- Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm

CANADA

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/
- Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html
- Canadian Coordinating Office for Health Technology Assessment (CCOHTA) http://www.ccohta.ca/entry_e.html
- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca
- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

DENMARK

- Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
- Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html

FINLAND

- FINOHTA http://www.stakes.fi/finohta/e/

FRANCE

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/

GERMANY

- German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/en/hta/index.html

THE NETHERLANDS

- Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php

NEW ZEALAND

- New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/

NORWAY

- Norwegian Centre for Health Technology Assessment (SMM) http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm

SPAIN

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/aets/

- Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN

- Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/admin/index.asp

- Center for Medical Health Technology Assessment http://www.cmt.liu.se/English/Engstartsida.html

SWITZERLAND

- Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM

- Health Technology Board for Scotland http://www.htbs.org.uk/

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/index.htm

UNITED STATES

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.hsph.harvard.edu/cearegistry/

- U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/consumertec/index.html

Specialty websites

- American Society for Gastrointestinal Endoscopy (ASGE) http://www.asge.org/
- British Society for Gastroenterology Care of Patients with Gastrointestinal Disorders in the United Kingdom: http://www.bsg.org.uk/
- Canadian Association of Gastroenterology http://www.cag-acg.org/
- Canadian Society of Gasteroenterology Nurses and Associates http://www.csgna.com/
- Colorectal Surgical Society of Australasia http://www.cssa.org.au/
- Conjoint Committee for Recognition of Training in Gastrointestinal Endoscopy (Australia) http://conjoint.gesa.org.au/
- European Endoscopy Training Center (Italy) http://www.eetc.it/index_eng.html
- European Society of Gastrointestinal Endoscopy www.esge.com
- Gastroenterological Society of Australia http://www.gesa.org.au/
- Gastrohep.com www.gastrohep.com
- Joint Advisory Group on GI Endoscopy – JAG (UK) http://www.thejag.org.uk/
- MASTER Unit & Mersey School of Endoscopy UK http://www.masterunit.co.uk/index.htm
- National Endoscopy Training Programme (UK) http://www.stgeorges.nhs.uk/endoskills.asp
- New Zealand Standards of Practice for Gastroenterology and Endoscopy Nurses http://www.nzno.org.nz/Site/Sections/Sections/Gastroenterology/Standards.aspx
- NHS Endoscopy Programme http://www.endoscopy.nhs-uk.org/View.aspx?page=/default.html
- Organisation of an Endoscopy Service and How to Improve Global Rating Scale Scores http://www.grs.nhs.uk/documents/GRS%20getting%20started%20-%20monitoring%20meetings.pdf
- Primary Care Society of Gastroenterology UK http://www.pcsg.org.uk/

Appendix E Critical appraisal checklist

Checklist for the critical appraisal of case series

Source: [Young and Ward 1999 #19]

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Score: ***/3***

1. Was the study conducted prospectively? ***/1***

- Were the key outcomes measured before and after the intervention, using clear criteria defined *a priori*?

2. Was the method of selection of cases identified and appropriate? **/1**

- Were patients selected consecutively or in an unbiased manner?
- Was there evidence that the characteristics of the included cases were not significantly different from those of the treated population?

3. **Was the duration and completeness of follow-up reported and was it adequate?**

- Are the number and characteristics of losses to follow-up presented? [#] **/0.5**
- Are losses to follow-up managed by performing sensitivity analysis and/or including them in the final analysis? **/0.5**

[#] Losses to follow-up >20% are unacceptable, particularly if unaccounted for.

Appendix F Studies included in the review

Study Location	Location	Level of evidence (interventional) Quality	Study design	Study participants	Inclusion/exclusion criteria	Procedure	Outcomes assessed	Length of follow-up
(Attar et al 2005))	Not stated	N/A	Case report	47-year-old woman with chronic and obscure gastrointestinal bleeding	N/A	DBE with electrocoagulation	*Safety* • Safety data	5 months
(Di Caro et al 2005)	Gemelli Hospital, Catholic University, Rome, Italy Teaching hospital of the University of Mainz, Wiesbaden, Germany Georges Pompidou European Hospital, Paris, France Free University Medical Centre, Amsterdam, Holland	Level IV Quality: 1.5/3 Retrospective	Uncontrolled post-test case series	No. of patients =62 Race=Caucasian Mean age=52 ± 35 years Gender=M: 43, F: 19 OGIB=33 Chronic diarrhoea=5 IDA and positive FOBT=5 Refractory or suspected celiac disease with negative gastroscopy=4 Abdominal pain=3 FAP=3 Impaired clinical conditions in Crohn's disease=3 Follow-up of GI tumours=3 Peutz-Jeghers syndrome=2 Gardner's syndrome=1	*Inclusion* Small bowel disease previously documented by radiologic investigation or VCE; or suspected small bowel disease after negative upper and lower endoscopy, and radiographic or angiographic evaluation of the GI tract *Exclusion* Not stated	Approach: Oral route=26 Anal route=9 Oral and anal route=27	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield Secondary: • Examination time • Insertion length	Not stated
(Ell et al 2005)	Gemelli Hospital, Catholic University, Rome, Italy Teaching Hospital of the University of Mainz, Wiesbaden, Germany Georges Pompidou European Hospital, Paris, France	Level IV Quality: 3/3	Uncontrolled post-test case series	No. of patients=100 Mean age=56±16 years (range 13–90 years) GI bleeding=64 Polyposis=8 Abdominal pain=7 Suspected Crohn's	*Inclusion* *Not stated* *Exclusion* Not stated	Approach: Oral route=122 Anal route=35	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield • Therapeutic interventions	Not stated

				disease=7 Chronic diarrhoea=7 Other=7			Secondary: • Examination time • Insertion length • Completion of procedure	
(Fukumoto et al 2005)	Not stated	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=14 OGIB=7 Abnormal findings of other modalities=7	*Inclusion* *Not stated* *Exclusion* Not stated	DBE with endoscopic ultrasound	*Effectiveness* Primary: • Diagnostic yield	Not stated
(Gasbarrini et al 2005)	Not stated	N/A	Case report	No. of patients=1 Abdominal pain, GI bleeding and syncope=1	N/A	DBE (orally and anally)	*Safety* • Safety data	48 hours
(Gay et al 2006)	Not stated	Level IV Quality: 3/3	Uncontrolled post-test case series	No. of patients=42 Suspicion of tumour=13 Celiac disease=4 Crohn's disease=3 AVM=10 Obscure GI bleeding=3 Obstructive symptoms=4 Other=5	*Inclusion* Intestinal lesion found at CE which required further investigation or treatment. Also, if suspected intestinal stenosis *Exclusion* Pregnancy, diabetes with known visceral neuropathy, cardiac pacemaker, and other known contraindications to DBE	Approach was determined by lesion seen at CE, and performed under general anaesthesia. Alternate route was undertaken within 48 hours if lesion not reached initially.	*Safety* Safety data *Effectiveness* Primary: • Diagnostic yield • Therapeutic intervention Secondary: • Examination time • Completion of procedure	3,6,9 or 12 months
(Gay et al 2005)	Not stated	Level IV Quality: N/A **Abstract** These patients are possibly included in	Uncontrolled post-test case series	No. of patients=26 Mean age=60 ± 12 years Gender=M: 15, F: 11 Suspicion of intestinal	*Inclusion:* *Not stated* *Exclusion* Not stated	Anaesthesia: General Approach: Orally unless suspected	*Safety* • Safety data *Effectiveness*	Not stated

		the paper (Gay et al 2006)		tumour=12 Coeliac disease with chronic bleeding=5 Arteriovenous malformation=9		lesion not reached, then anally	Primary: • Therapeutic intervention for AVM Secondary: • Examination time • Hospital stay	
(Groenen et al 2006)	Erasmus Medical Center, Rotterdam, The Netherlands	Level IV Quality: 1/3	Uncontrolled post-test case series	No. of patients=2 Anaemia and melaena=1 Anaemia=1	*Inclusion* *Not stated* *Exclusion* Not stated	*DBE* Oral route=2	*Safety* • Safety data	20 days – 6 months
(Heine et al 2006)	Medical Center, Free University of Amsterdam Erasmus Medical Center, Rotterdam	Level IV Quality: 2.5/3 Prospective study except for first 30 patients	Uncontrolled post-test case series	No. of patients=275 Mean age=57 years (range 17–89) Gender=M: 144, F: 131 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 Protein-losing enteropathy=3 Pre-operative evaluation and tattoo=2 Radiation enteritis=2	*Inclusion* Not stated *Exclusion* Not stated	Anaesthesia: Midazolam Approach: Oral and anal if required	*Safety* • Safety data *Effectiveness* Primary: • Therapeutic intervention • Diagnostic yield Secondary: • Insertion length • Examination time	At least 2 hours and up to 1 month after treatment
(Honda et al 2006)	Not stated	N/A	Case report	58-year-old man with tarry stool and severe anaemia	N/A	DBE	*Safety* • Safety data	30 days

(Iwamoto et al 2004)	Jichi Medical School, Tochigi, Japan	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=12 Median age=64.5 years (range 41–85) Gender=M: 8, F: 4 Rectal bleeding=5 Anaemia=5 Diarrhoea=1 Palpable abdominal mass=1	*Inclusion* Small bowel tumour *Exclusion* Not stated	DBE	*Safety* • Safety data *Effectiveness* Primary: • Biopsy/diagnostic yield • Therapeutic intervention	Not stated
(Kaffes et al 2006)	Sydney, Australia.	Level IV Quality: 3/3	Uncontrolled post-test case series	No. of patients=40 Mean age=58 years (range 14–89) Gender=M: 17, F: 23 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	*Inclusion* Not stated *Exclusion* Not stated	Initial Approach: Oral route=31 Anal route=9 Second alternate approach=19 Repeat initial approach=3	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield • Therapeutic intervention	16 weeks
(Li et al 2005)	Not stated	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=61	*Inclusion* Not stated *Exclusion* Not stated	Approach: Oral route=39 Anal route=38 Oral and anal route=16	*Effectiveness* Primary: • Diagnostic yield • Therapeutic intervention	Not stated
(May et al 2005a)	Not stated	Level IV Quality: 3/3 First two patients were retrospective	Uncontrolled post-test case series	No. of patients=137 Mean age=56.6 ± 17.8 years (range 20–90) Gender=M: 77, F: 60	*Inclusion* Not stated *Exclusion*	Approach: Oral route=50 Anal route=7 Oral and anal route=80	*Safety* • Safety data *Effectiveness* Primary:	Not stated

		and therefore not included in analysis of procedural time and insertion depth		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 Others=5	Not stated		• Diagnostic yield Secondary: • Examination time • Insertion length • Technical / equipment success/failure	
(Mitsui et al 2005)	Nippon Medical School Hospital, Tokyo, Japan	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=65 Mean age=57.2 years (range 19–82) Gender=M: 40, F: 25 OGIB=27 FOBT positive iron deficiency anaemia=13 IBD=7 Ileus=5 Tumour=4 Investigation of surgically altered gastrointestinal tract=3 Miscellaneous=6	*Inclusion* Not stated *Exclusion* Not stated	Not stated	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield Secondary: • Examination time	Not stated
(Mönkemüller et al 2006)	Not stated	Level IV Quality: 2/3	Uncontrolled post-test case series	No. of patients=53 Mean age=60 years (range 24–80) Gender=M: 34, F: 19 GI bleeding=29 Suspected Crohn's	*Inclusion* Not stated *Exclusion* Not stated	Approach: Oral route=46 Anal route=24	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield	Mean= 4 months and 18 days

				disease=6 Abdominal pain=4 Polyp removal or evaluation=6 Chronic diarrhoea=4 Surveillance or tumour search=4			• Therapeutic intervention Secondary: • Examination time	
(Ohmiya et al 2005b)	Not stated	Level IV Quality: 3/3	Uncontrolled post-test case series	No. of patients=2 Peutz-Jeghers syndrome=2	*Inclusion* Not stated *Exclusion* Not stated	DBE to resection Peutz-Jeghers polyps	*Safety* • Safety data	2–6 days
(Ohmiya et al 2005a)	Not stated	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=100 OGIB=50 Ileus=24 SI tumours/polyps=14 Abdominal pain=7 Chronic diarrhoea=5	*Inclusion* Not stated *Exclusion* Not stated	Approach: Oral route=62 Anal route=105	*Effectiveness* Primary: • Therapeutic intervention • Diagnostic yield	Not stated
(Su et al 2005)	Taiwan	Level IV Quality: 3/3	Uncontrolled post-test case series	No. of patients=10 Mean age=57 ± 9.9 years (range 43–76) Gender=M: 4, F: 6 Chronic or recurrent gastrointestinal bleeding=5 Acute gastrointestinal bleeding=5	*Inclusion* Not stated *Exclusion* Not stated	Approach: Oral route=6 Anal route=2 Oral and anal route=2	*Effectiveness* Primary: • Reduction in gastrointestinal bleeding • Biopsy yield	Not stated
(Sunada et al 2005b)	Jichi Medical School, Tochigi, Japan	Level IV Quality: 3/3	Uncontrolled post-test case series -retrospective	No. of patients=17 Mean age=45.0 years (range 23–68) Gender=M: 9, F: 8 Bowel obstruction=12	*Inclusion* Strictures of the small intestine *Exclusion* Not stated	Approach: Oral route=8 Anal route=7 Oral and anal route=2	*Safety* • Safety data *Effectiveness* Primary:	Not stated

				Abdominal tumour=2 Anaemia=1 Hematochezia=1 Low protein=1			• Biopsy yield • Therapeutic intervention	
(Sunada et al 2005a)	Jichi Medical School, Tochigi, Japan	Level IV Quality: N/A **Abstract**	Uncontrolled post-test case series	No. of patients=9 Mean age=49.1 years (range 30–89) Gender=M: 3, F: 6 Crohn's disease=3 NSAIDs enteritis=1 Post-traumatic stricture=1 Post-incarcerated inguinal hernia stricture=1 Non-specific multiple ulcers=1 Strictures of unknown aetiology=2	*Inclusion* Strictures of the small intestine *Exclusion* Not stated	DBE	*Safety* • Safety data	12 months
(Sunada et al 2004)	Jichi Medical School, Tochigi, Japan	N/A	Case report	No. of patients=1 Crohn's disease with jejunal strictures=1	N/A	DBE with balloon dilatation	*Safety* • Safety data	7 months
(Yamamoto et al 2004a)	Jichi Medical School, Tochigi, Japan	Level IV Quality: 2/3	Uncontrolled post-test case series -retrospective	No. of patients=123 Median age=60 years (range 8–88) Gender=M: 70, F: 53 OGIB=66 Obstructive symptoms=22 Suspicion of intestinal tumour=11 Other=32	*Inclusion* Not stated *Exclusion* Not stated	Anaesthesia: conscious sedation Approach: Oral route=89 Anal route=89	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield • Therapeutic intervention Secondary: • Insertion length • Examination time	Not stated
(Yamamoto et al 2004b)		Level IV Quality: N/A	Uncontrolled post-test case	No. of patients=99	*Inclusion* Not stated	Approach: Oral route=73	*Safety* • Safety data	Not stated

		Abstract There may be some overlap between this population and that of the paper by Yamamoto et al 2004a	series		*Exclusion* Not stated	Anal route=67	*Effectiveness* Primary: • Diagnostic yield • Therapeutic intervention Secondary: • Insertion length	
(Yamamoto et al 2001)	Jichi Medical School, Tochigi, Japan	Level IV Quality: 2.5/3	Uncontrolled post-test case series	No. of patients=4	*Inclusion* Not stated *Exclusion* Not stated	DBE	*Safety* • Safety data	Not stated
(Zhi et al 2005)		Level IV Quality: 2/3	Uncontrolled post-test case series	No. of patients=57 Mean age=36.3 years (range 6–71) Gender=M: 38, F: 19 Clinically suspicious intestinal haemorrhage=57	*Inclusion* Not stated *Exclusion* Not stated	Approach: Oral route=22 Anal route=20 Oral and anal route=15	*Safety* • Safety data *Effectiveness* Primary: • Diagnostic yield Secondary: • Examination time	Not stated

DBE=double-balloon enteroscopy; EATL=enteropathy-associated T-cell lymphoma; FAP=familial adenomatous polyposis; IDA=iron deficiency anaemia; FOBT=faecal occult blood test; OGIB=obscure gastrointestinal bleeding; IBD=inflammatory bowel disease; NSAIDs=non-steroidal anti-inflammatory drugs; CE=capsule endoscopy

Appendix G Excluded studies

Not a study

Carey, E.J. and Fleischer, D.E. (2005). 'Investigation of the small bowel in gastrointestinal bleeding - Enteroscopy and capsule endoscopy' *Gastroenterology Clinics Of North America,* 34 (4), 719–734.

Gay, G. and Delvaux, M. (2006). 'Small-bowel endoscopy', *Endoscopy,* 38 (1), 22–26.

Gerson, L.B. (2005). 'Double-balloon enteroscopy: the new gold standard for small-bowel imaging?', *Gastrointestinal Endoscopy,* 62 (1), 71–75.

Gerson, L.B. & Van Dam, J. (2004). 'Wireless capsule endoscopy and double-balloon enteroscopy for the diagnosis of obscure gastrointestinal bleeding', *Techniques in Vascular and Interventional Radiology,* 7 (3), 130–135.

Keuchel, M. & Hagenmuller, F. (2005). 'Small bowel endoscopy', *Endoscopy,* 37 (2), 122–132.

Kita, H. & Yamamoto, H. (2006). 'Double-balloon endoscopy for the diagnosis and treatment of small intestinal disease', *Best Practice and Research in Clinical Gastroenterology,* 20 (1), 179–194.

Leighton, J.A. & Loftus, E.V.Jr. (2005). 'Evolving diagnostic modalities in inflammatory bowel disease', *Current Gastroenterology Reports,* 7 (6), 467–474.

Lin, S. & Rockey, D.C. (2005). 'Obscure gastrointestinal bleeding', *Gastroenterology Clinics Of North America,* 34 (4), 679–698.

Marek, T. A. (2005). 'Gastrointestinal bleeding', *Endoscopy,* 37 (11), 1098–1104.

Pennazio, M. (2004).'Small-bowel endoscopy', *Endoscopy,* (1), 32.

Pennazio, M. (2005). 'Capsule endoscopy', *Endoscopy,* 37 (11), 1073–1078.

Rockey, D.C. (2005). 'Occult gastrointestinal bleeding', *Gastroenterology Clinics of North America,* 34 (4), 699–718.

Yamamoto, H. (2005). 'Double-balloon endoscopy.' *Clinical Gastroenterology and Hepatology,* 3 (7 SUPPL), S27–S29.

Yamamoto, H. & Kita, H. (2005a). 'Double-balloon endoscopy', *Current Opinion In Gastroenterology,* 21 (5), 573–577.

Yamamoto, H. & Kita, H. (2005b). 'Enteroscopy', *Journal Of Gastroenterology,* 40 (6), 555–562.

Yamamoto, H. & Sugano, K. (2003). 'A new method of enteroscopy - The double-balloon method', *Canadian Journal Of Gastroenterology,* 17 (4), 273–274.

Incorrect study design

Al-Toma, A., Hadithi, M. et al, (2005). 'Retrieval of a video capsule endoscope by using a double-balloon endoscope', *Gastrointestinal Endoscopy,* 62 (4), 613.

Chan, A.O.O. & Lai, K.C. (2006). 'A patient with long-standing iron-deficient anemia', *Nature Clinical Practice Gastroenterology & Hepatology,* 3 (2), 112–116.

Chen, Y.Y., Su, W.W. et al, (2006). 'Eosinophilic jejunitis presenting with acute abdomen: the usefulness of double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 63 (3), 532–534.

Chen, Y.Y., Yen, H.H. et al, (2005). 'Intestinal pseudo-obstruction as the initial presentation of systemic lupus erythematosus: the need for enteroscopic evaluation', *Gastrointestinal Endoscopy,* 62 (6), 984–987.

Hashimoto, A., Yano, T. et al, (2003). 'A case of malignant lymphoma of the small intestine with successful endoscopic hemostasis using double-balloon enteroscopy', *Progress of digestive endoscopy,* 62 (2), 104–105.

Hayashi, Y., Yamamoto, H. et al, (2005). 'Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy', *World Journal of Gastroenterology,* 11 (31), 4861–4864.

Hiyama, S., Komori, M. et al, (2005). 'A case of mantle cell lymphoma of the small intestine with multiple tumor formation diagnosed by double-balloon enteroscopy', *Gastroenterological Endoscopy,* 47 (9), 2178–2184.

Iwamoto, M., Yamamoto, H. et al, (2005). 'Double-balloon endoscopy for ileal GI stromal tumor', *Gastrointestinal Endoscopy,* 62 (3), 440–441.

Ji, J.S., Choi, H. et al, (2005). 'Two cases of GI involvement of Gorham's disease diagnosed by double-balloon enteroscopy: case report and review of the literature', *Gastrointestinal Endoscopy,* 62 (2), 312–315.

Kita, H., Yamamoto, H. et al, (2005). 'Bleeding polyp in the mid small intestine identified by capsule endoscopy and treated by double-balloon endoscopy', *Gastrointestinal Endoscopy,* 61 (4), 628–-629.

Lee, B.I., Choi, H. et al, (2005). 'Retrieval of a retained capsule endoscope by double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 62 (3), 463–465.

May, A., Nachbar, L. et al, (2005). 'Extraction of entrapped capsules from the small bowel by means of push-and-pull enteroscopy with the double-balloon technique', *Endoscopy,* 37 (6), 591–593.

Miyata, T., Yamamoto, H. et al, (2004). 'A case of inflammatory fibroid polyp causing small-bowel intussusception in which retrograde double-balloon enteroscopy was useful for the preoperative diagnosis', *Endoscopy,* 36 (4), 344–347.

Nosho, K., Endo, T. et al, (2005). 'Diaphragm disease of small intestine diagnosed by double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 62 (1), 187–189.

Ohmiya, N., Taguchi, A. et al, (2004). 'Usefulness of double-balloon total enteroscopy for diagnosis and treatment of small intestinal diseases', *Gastrointestinal Endoscopy,* 59 (5), AB156.

Scherubl, H., Faiss, S. et al, (2005). 'Double-balloon enteroscopy for the detection of midgut carcinoids [4] (multiple lettres)', *Gastrointestinal Endoscopy,* 62 (6), 994–995.

Shinozaki, S., Yamamoto, H. et al, (2004). 'Case report: Direct observation with double-balloon enteroscopy of an intestinal intramural hematoma resulting in Anticoagulant Ileus', *Digestive Diseases And Sciences,* 49 (6), 902–905.

Yamaguchi, T., Manabe, N. et al, (2005). 'Multiple carcinoid tumors of the ileum preoperatively diagnosed by enteroscopy with the double-balloon technique', *Gastrointestinal Endoscopy,* 62 (2), 315–318.

Yano, T., Yamamoto, H. et al, (2002). 'Enteroscopy using a double-balloon method for blind loop syndrome with small intestinal ulcers: Report of two cases', *Gastrointestinal Endoscopy,* 55 (5), AB148.

Yen, H. H., Chen, Y.Y. et al, (2006). 'Nonsteroidal anti-inflammatory drug-associated ileal ulcers: An evaluation by double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 63 (2), 328.

Yoshida, N., Wakabayashi, N. et al, (2004). 'Ileal mucosa-associated lymphoid tissue lymphoma showing several ulcer scars detected using double-balloon endoscopy', *Endoscopy,* 36 (11), 1022–1024.

Not a higher level of evidence than available in English

Fath, R. (2005). 'Double-balloon enteroscopy brings light into the small bowel', *Deutsche Medizinische Wochenschrift,* 130 (8), 376.

Hiyama, S., Komori, M. et al, (2005). 'A case of mantle cell lymphoma of the small intestine with multiple tumor formation diagnosed by double-balloon enteroscopy', *Gastroenterological Endoscopy,* 47 (9), 2178–2184.

Yabiku, T., Yao, K. et al, (2005). 'A case of diaphragm disease of the small intestine associated with nonsteroidal anti-inflammatory drugs: The diagnosis with double-balloon enteroscopy', *Gastroenterological Endoscopy,* 47(9), 2172–2177.

Incorrect comparator technique

Hadithi, M., Heine, G.D.N. et al, (2006). 'A prospective study comparing video capsule endoscopy with double-balloon enteroscopy in patients with obscure gastrointestinal bleeding.' *American Journal Of Gastroenterology* 101(1), 52–57.

Matsumoto, T., Moriyama, T. et al, (2005). 'Performance of antegrade double-balloon enteroscopy: comparison with push enteroscopy', *Gastrointestinal Endoscopy,* 62 (3), 392–398.

May, A., Nachbar, L. et al, (2005). 'Prospective trial comparing push-enteroscopy and push-and-pull enteroscopy using double-balloon technique in patients with small bowel diseases', *Gastrointestinal Endoscopy,* 61 (5), AB175.

Nakamura, M., Niwa, Y. et al, (2006). 'Preliminary comparison of capsule endoscopy and double-balloon enteroscopy in patients with suspected small-bowel bleeding', *Endoscopy,* 38 (1), 59–66.

Zhong, J., Zhang, C. et al, (2005). 'Etiological diagnosis of 34 patients with suspected obscure small intestinal bleeding - A comparative study of double-balloon push enteroscopy and enteroclysis', *Chinese Journal of Gastroenterology,* 10 (1), 15–19.

Duplication of results

Ehara, A., Tanaka, S. et al, (2005). 'Double-balloon endoscopy for diagnoses of small bowel tumors', *Gastrointestinal Endoscopy,* 61 (5), AB163.

Ell, C., May, A. et al, (2005). 'Prospective European multicenter trial for evaluation of push-and-pull enteroscopy in patients with small bowel diseases', *Gastrointestinal Endoscopy,* 61 (5), AB105.

Hayashi, Y., Yamamoto, H. et al, (2004). 'Clinical features of small intestinal ulcers induced by the nonsteroidal anti-inflammatory drugs identified by the double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 59 (5), AB156.

Hayashi, Y., Yamamoto, H. et al, (2005). 'Endoscopic resection of elevated lesions in the small bowel by using double-balloon endoscopy', *Gastrointestinal Endoscopy,* 61 (5), AB166.

Heine, D.G., Hadithi, M. et al, (2005). 'Double balloon enteroscopy: The Dutch one year experience indications, yield, and complications in a series of 125 cases', *Gastrointestinal Endoscopy* 61 (5), AB166.

Kita, H., Yamamoto, H. et al, (2005). 'Diagnostic yields and outcomes of treatment in patients with obscure gastrointestinal bleeding using double-balloon endoscopy', *Gastrointestinal Endoscopy,* 64 (5), AB105.

May, A., Nachbar, L. et al, (2005). 'Prospective evaluation of push-and-pull enteroscopy in patients with small bowel disorders', *Gastrointestinal Endoscopy,* 61 (5), AB105.

Sato, H., Yamamoto, H. et al, (2004). 'Analysis of the clinical features and endoscopic treatment of small intestinal angiodysplasia identified by using double-balloon enteroscopy', *Gastrointestinal Endoscopy,* 59 (5), AB156.

Sunada, K., Yamamoto, H. et al, (2004). 'Accessibility of the double-balloon endoscopy to the anatomically altered gastrointestinal tract by surgical procedures', *Gastrointestinal Endoscopy,* 59 (5), P157.

Incorrect population

Daperno, M., Sostegni, R. et al, (2004). 'The role of endoscopy in inflammatory bowel disease', *European Review for Medical and Pharmacological Sciences,* 8 (5), 209–214.

Di, Z. H., Shin, J. H. et al, (2005). 'Colorectal anastomotic strictures: Treatment by fluoroscopic double balloon dilation', *Journal of Vascular and Interventional Radiology,* 16 (1), 75–80.

Kuno, A., Yamamoto, H. et al, (2004). 'Double-balloon enteroscopy through a Roux-en-Y anastomosis for EMR of an early carcinoma in the afferent duodenal limb', *Gastrointestinal Endoscopy,* 60 (6), 1032–1034.

May, A., Nachbar, I. et al, (2006). 'Push-and-pull enteroscopy using a single-balloon technique for difficult colonoscopy', *Endoscopy,* 38 (4), 395.

Raju, G. S. & Gomez, G, (2005). 'Endoloop ligation of a large colonic lipoma: a novel technique', *Gastrointestinal Endoscopy,* 62 (6), 988–990.

Riemann, J. F., Hartmann, D. et al, (2006). 'Frequency of small bowel polyps in patients with duodenal adenoma but without familial adenomatous polyposis', *Zeitschrift Fur Gastroenterologie,* 44 (3), 235.

Sakai, P., Kuga, R. et al, (2005). 'Is it feasible to reach the bypassed stomach after Roux-en-Y gastric bypass for morbid obesity? - The use of the double-balloon enteroscope', *Endoscopy,* 37 (6), 566–569.

Yano, T., Yamamoto, H. et al, (2004). 'Application of double-balloon endoscopy for technically difficult cases with conventional colonoscopy', *Gastrointestinal Endoscopy,* 59 (5), P266.

Yano, T., Yamamoto, H. et al, (2005). 'Technical modification of the double-balloon endoscopy to access to the proximal side of the stenosis in the distal colon', *Gastrointestinal Endoscopy,* 62 (2), 302–304.

Incorrect intervention

Eliakim, A.R. (2006). 'Video capsule endoscopy of the small bowel (PillCam SB)', *Current Opinion In Gastroenterology,* 22 (2), 124.

Jakobs, R., Hartmann, D. et al, (2006). 'Diagnosis of obscure gastrointestinal bleeding by intra-operative enteroscopy in 81 consecutive patients', *World Journal of Gastroenterology,* 12 (2), 313–316.

Marmo, R., Rotondano, G. et al, (2005). 'Meta-analysis: capsule enteroscopy vs. conventional modalities in diagnosis of small bowel diseases', *Alimentary Pharmacology & Therapeutics,* 22 (7), 595–604.

Scapa, E., Jacob, H. et al, (2002). 'Initial experience of wireless-capsule endoscopy for evaluating occult gastrointestinal bleeding and suspected small bowel pathology', *The American Journal of Gastroenterology,* 97 (11), 2776–2779.

Schulmann, K., Hollerbach, S. et al, (2005). 'Feasibility and diagnostic utility of video capsule endoscopy for the detection of small bowel polyps in patients with hereditary polyposis syndromes', *The American Journal of Gastroenterology,* 100 (1), 27–37.

Swain, P. & Fritscher-Ravens, A. (2004). 'Role of video endoscopy in managing small bowel disease', *Gut,* 53 (12), 1866–1875.

Appendix H DBE safety and effectiveness data in conference abstracts

Table 22 Major complications resulting from double-balloon enteroscopy (conference abstracts)

Study	Level and quality	Population	Major complications per procedure
(Ohmiya et al 2005a)	Level IV: Uncontrolled post-test case series	100 patients	0/167 procedures
(Yamamoto et al 2004b)	Level IV: Uncontrolled post-test case series Note: There may be some overlap with the population described in the paper by Yamamoto et al 2004a	99 patients	1/140 (0.07%) procedures: 1 case perforation
(Mitsui et al 2005)	Level IV: Uncontrolled post-test case series	65 patients OGIB=27 FOBT positive iron deficiency anaemia=13 IBD=7 Ileus=5 Tumour=4 Investigation of surgically altered gastrointestinal tract=3 Miscellaneous=6	0/90 procedures
(Gay et al 2005)	Level IV: Uncontrolled post-test case series	26 patients	0/29 procedures
(Iwamoto et al 2004)	Level IV: Uncontrolled post-test case series	12 patients 12 cases suspected small bowel tumours	0/12 procedures
(Sunada et al 2005a)	Level IV: Uncontrolled post-test case series	9 patients	0/9 procedures

Table 23 Minor complications of double-balloon enteroscopy (conference abstracts)

Study	Level and quality	Population	Minor complications per procedure
(Ohmiya et al 2005a)	Level IV: Uncontrolled post-test case series	100 patients	0/167 procedures
(Yamamoto et al 2004b)	Level IV: Uncontrolled post-test case series	99 patients	1/140 (0.07%) procedures: 1 case abdominal pain and fever
(Mitsui et al 2005)	Level IV: Uncontrolled post-test case series	65 patients	0/90 procedures
(Gay et al	Level IV: Uncontrolled post-	26 patients	0/29 procedures

Study	Level and quality	Population	Minor complications per procedure
2005)	test case series		
(Iwamoto et al 2004)	Level IV: Uncontrolled post-test case series	12 patients	0/12 procedures
(Sunada et al 2005a)	Level IV: Uncontrolled post-test case series	9 patients	0/9 procedures

Table 24 Reduction of symptoms after therapeutic intervention by double-balloon enteroscopy (conference abstracts)

Study	Level and quality	Population	Therapeutic intervention	Successful intervention / reduction of symptoms [a]
(Ohmiya et al 2005a)	Level IV: Uncontrolled post-test case series	100 patients	Overall=26 Angiodysplasia=14 Dieulafoy's ulcer=1 Balloon dilation=6 EMR=1 Polypectomy=3 Enteroscopic resection=1	Overall=26 (100%)
(Yamamoto et al 2004b)	Level IV: Uncontrolled post-test case series	99 patients	Overall=16 Electrocoagulation=12 Polypectomy=1 Balloon dilation=3	Overall=16 (100%)
(Li et al 2005)	Level IV: Uncontrolled post-test case series	61 patients	Overall=2 Epinephrine injection=2	Overall=2 (100%)
(Gay et al 2005)	Level IV: Uncontrolled post-test case series	26 patients	Overall=9 Argon plasma coagulation=9	Overall=9 (100%)
(Iwamoto et al 2004)	Level IV: Uncontrolled post-test case series	12 patients	Overall=1 Endoscopic resection	Overall=1 (100%)

EMR=endoscopic mucosal resection; [a] Patients with successful therapeutic intervention/reduction of symptoms (% treated successfully)

Table 25 Biopsy yield / diagnostic yield of double-balloon enteroscopy (conference abstracts)

Study	Level and quality	Population	Biopsy yield / diagnostic yield
(Ohmiya et al 2005a)	Level IV: Uncontrolled post-test case series	100 patients	Overall 77/100 (77%) GI bleeding 34/50 Ileus 24/24 Tumours or polyps 14/14 Abdominal pain 3/7 Chronic diarrhoea 1/5
(Yamamoto et al 2004b)	Level IV: Uncontrolled post-test case series	99 patients	Overall 64/79 (85%) GI bleeding 39/51 (76%) Suspected strictures 18/20 (90%)

Study	Level and quality	Population	Biopsy yield / diagnostic yield
			Suspected small intestine tumours 7/8 (88%)
(Mitsui et al 2005)	Level IV: Uncontrolled post-test case series	65 patients	Overall 37/65 (57%)
(Li et al 2005)	Level IV: Uncontrolled post-test case series	61 patients	Intestinal haemorrhage 27/36 (75%) Abdominal pain 6/14 (43%) Diarrhoea 4/6 (67%) Vomiting 2/2 (100%) Intestinal obstruction 1/4 (25%)
(Fukumoto et al 2005)	Level IV: Uncontrolled post-test case series	14 patients	Overall 9/14 (64%)
(Iwamoto et al 2004)	Level IV: Uncontrolled post-test case series	12 patients	Biopsy 12/12 (100%)

GI=gastrointestinal

Table 26 Examination time of double-balloon enteroscopy (conference abstracts)

Study	Level and quality	Population	Mean examination time (minutes) by approach	Number of approaches used per patient
(Mitsui et al 2005)	Level IV: Uncontrolled post-test case series	65 patients	Oral=73 (range 10–150) Anal=70 (range 20–80)	Not stated
(Li et al 2005)	Level IV: Uncontrolled post-test case series	61 patients	Not stated	Single approach=45/61 (74%) Both approaches=16/61 (26%)
(Gay et al 2005)	Level IV: Uncontrolled post-test case series	26 patients	Oral=55 ± 21 Anal=61 ± 24	Not stated

Table 27 Completion of double-balloon enteroscopy procedures (conference abstracts)

Study	Level and quality	Population	Mean length of insertion (mean ± SD cm)	Total enteroscopy	Termination of DBE procedure
(Yamamoto et al 2004b)	Level IV: Uncontrolled post-test case series	99 patients	Not adequately stated	16/19 (oral and anal)	Not stated

Glossary and abbreviations

Adenoma	Benign tumour originating in a gland
Anaemia	Deficiency in red blood cells and/or haemoglobin
Angiography	The radiographic (x-ray) study of blood vessels using a radio-opaque substance or contrast medium to allow visualisation
Capsule endoscopy	A small pill which includes its own light source and lens, and emits a radio frequency to allow a continuous movie of the gastrointestinal tract
Crohn's disease	Chronic inflammatory disease of the gastrointestinal tract, often involving the small and large intestine
DBE	Double-balloon enteroscopy
Endoscopy	The use of a flexible lighted instrument to examine the inside of the body, in general through the mouth or the anus
Enteroscopy	The use of a flexible instrument to examine the small intestine
Gastrointestinal stromal tumour	Tumours that originate in the stroma, the connective tissue that supports the organs involved in digestion
Haematemesis	Vomiting of either bright red blood or blood with coffee-grounds appearance
Ileus	Obstruction of the intestine, due to inactivity, causing constipation and bloating
Intra-operative	Medical procedure for the complete evaluation of small bowel endoscopy
Intussusceptions	The folding of one part of the intestines into another, leading to a blockage
Laparotomy	Surgical incision into the abdominal wall
Laparoscopy	Surgical procedure used to examine the interior of the abdominal or pelvic cavities by means of a fibre optic instrument (a laparoscope)
Leiomyoma	Benign soft-tissue neoplasm that arises from smooth muscle
Leiomyosarcoma	A malignant sarcoma arising from smooth muscle
Lymphoma	A cancer of the lymphatic system
Melaena	Blood coating or mixed in the stool

MSAC	Medical Services Advisory Committee
MBS	Medicare Benefits Schedule
Neoplasm	New abnormal growth of tissue
NHMRC	National Health and Medical Research Council
NHS	National Health Service (United Kingdom)
OECD	Organisation for Economic Cooperation and Development
OGIB	Obscure gastrointestinal bleeding
Polyp	A mass of tissue that builds up inside a hollow organ (such as the small intestine) – it may be benign, premalignant or malignant
Radio-labelled red blood cell nuclear scanning	Diagnostic technique used to identify the site of possible gastrointestinal disorder – red blood cells are labelled with a radioactive substance (such as Technetium 99m), then the patient's body is scanned
RR	Relative risk or rate ratio
Sarcoma	Malignant tumour of connective tissue
Small bowel series	A series of x-rays taken after the ingestion of a barium suspension – performed to examine the small intestine
Ulcer	Open sore of the skin, eyes or mucous membrane, generally maintained by an inflammation and/or infection

References

Aprahamian, C. & Wittmann, D.H. (1991). 'Operative management of intraabdominal infection', *Infection,* 19 (6), 453–455.

Attar, A., Maissiat, E. et al, (2005). 'First case of paralytic intestinal ileus after double balloon enteroscopy', *Gut,* 54 (12), 1823–1824.

Becker, J.M. & Stucchi, A.F. (2004). 'Intra-abdominal adhesion prevention: are we getting any closer?', *Annals of Surgery,* 240 (2), 202–204.

Beckmann, E C. (2006). 'CT scanning the early days', *British Journal of Radiology,* 79 (937), 5–8.

Bernstein, C.N., Greenberg, H. et al, (2005). 'A prospective comparison study of MRI versus small bowel follow-through in recurrent Crohn's disease', *American Journal of Gastroenterology,* 100 (11), 2493–2502.

Brown, J. (2004). *Medline Plus Medical Encyclopedia* [internet], U.S. National Library of Medicine and the National Institute of Health, available from: http://www.nlm.nih.gov/medlineplus/ency/article/003816.htm [accessed 12 May 2006].

Carey, E.J. & Fleischer, D.E. (2005). 'Investigation of the small bowel in gastrointestinal bleeding – enteroscopy and capsule endoscopy', *Gastroenterology Clinics of North America,* 34 (4), 719–734.

Cheadle, W.G. & Spain, D.A. (2003). 'The continuing challenge of intra-abdominal infection', *American Journal of Surgery,* 186 (5A), 15S–22S; discussion 31S–34S.

Department of Health and Ageing (2005). *Private hospital data bureau annual report (2004–2005)* [internet], available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/97A7E248A331C070CA257077001ABB83/$File/PHDB%20Annual%20Report%20-%202004-05.pdf [accessed 25 July 2006].

Department of Human Services (2000). *Better Health Channel - Laparotomy* [internet], Department of Human Services, Victoria, Australia, available from: http://www.betterhealth.vic.gov.au/bhcv2/bhcpdf.nsf/ByPDF/Laparotomy/$File/Laparotomy.pdf [accessed 7 February2006].

Di Caro, S., May, A. et al, (2005). 'The European experience with double-balloon enteroscopy: indications, methodology, safety, and clinical impact', *Gastrointestinal Endoscopy,* 62 (4), 545–550.

Downs, S.H. & Black, N. (1998). 'The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions', *Journal of Epidemiology and Community Health,* 52 (6), 377–384.

Ell, C., May, A. et al, (2005). 'Push-and-pull enteroscopy in the small bowel using the double-balloon technique: Results of a prospective European Multicenter study', *Endoscopy,* 37 (7), 613–616.

Fujinon Australia (2005). *MSAC Application No. 1102 - Double Balloon Electronic Enteroscopy System.*

Fukumoto, A., Manabe, N. et al, (2005). 'Usefulness of endoscopic ultrasonography with double-balloon enteroscopy for diagnosis of small bowel diseases', *Gastrointestinal Endoscopy,* 61 (5), AB278.

Gasbarrini, A., Di Caro, S. et al, (2005). 'Double-balloon enteroscopy for diagnosis of a Meckel's diverticulum in a patient with GI bleeding of obscure origin', *Gastrointestinal Endoscopy,* 61 (6), 779–781.

Gay, G., Delvaux, M. et al, (2005). 'Does double balloon enteroscopy examine the entire small bowel?', *Gastrointestinal Endoscopy,* 61 (5), AB164.

Gay, G., Delvaux, M. et al, (2006). 'Outcome of capsule endoscopy in determining indication and route for push-and-pull enteroscopy', *Endoscopy,* 38 (1), 49–58.

Gerson, L.B. & Van Dam, J. (2004). 'Wireless capsule endoscopy and double-balloon enteroscopy for the diagnosis of obscure gastrointestinal bleeding', *Techniques in Vascular and Interventional Radiology,* 7 (3), 130–135.

Given Imaging (2005). *PillCam Capsule Endoscopy Register.*

Gourtsoyiannis, N.C., Papanikolaou, N. et al, (2006). 'Magnetic resonance imaging evaluation of small intestinal Crohn's disease', *Best Practice & Research Clinical Gastroenterology,* 20 (1), 137–156.

Gray, H. (1977). *Gray's anatomy*, Bounty Books, New York.

Groenen, M.J.M., Moreels, T.G.G. et al, (2006). 'Acute pancreatitis after double-balloon enteroscopy: An old pathogenetic theory revisited as a result of using a new endoscopic tool', *Endoscopy,* 38 (1), 82–85.

Hartmann, D., Schmidt, H. et al, (2005). 'A prospective two-center study comparing wireless capsule endoscopy with intraoperative enteroscopy in patients with obscure GI bleeding', *Gastrointestinal Endoscopy,* 61 (7), 826–832.

Heine, G.D.N., Hadithi, M. et al, (2006). 'Double-balloon enteroscopy: Indications, diagnostic yield, and complications in a series of 275 patients with suspected small-bowel disease', *Endoscopy,* 38 (1), 42–48.

Honda, K., Mizutani, T. et al, (2006). 'Acute pancreatitis associated with peroral double-balloon enteroscopy: A case report', *World Journal of Gastroenterology,* 12 (11), 1802–1804.

Iwamoto, M., Yamamoto, H. et al, (2004). 'Small-bowel tumors diagnosed and treated by double-balloon endoscopy: Report of twelve cases', *Gastrointestinal Endoscopy,* 59 (5), AB155.

Jensen, J.E. & Freese, D. (2006). *Gastrointestinal Bleeding* [internet], Colorado Center for Digestive Disorders, available from: www.gastromd.com/education/gastrointestinalbleeding.html [accessed 6 February 2006].

Juni, P., Altman, D.G. et al, (2001). 'Systematic reviews in health care: assessing the quality of controlled clinical trials', *British Medical Journal,* 323 (7303), 42–46.

Kaffes, A.J., Koo, J.H. et al, (2006). 'Double-balloon enteroscopy in the diagnosis and the management of small-bowel diseases: an initial experience in 40 patients', *Gastrointestinal Endoscopy,* 63 (1), 81–86.

Kendrick, M.L., Buttar, N.S. et al, (2001). 'Contribution of intraoperative enteroscopy in the management of obscure gastrointestinal bleeding', *Journal of Gastrointestinal Surgery,* 5 (2), 162–167.

Li, W., Yang, Y.S. et al, (2005). 'Double-balloon enteroscopy is renovating the understandings of small-intestinal disorders', *Gastroenterology,* 128 (4), A73.

May, A., Nachbar, L. et al, (2005a). 'Double-balloon enteroscopy (push-and-pull enteroscopy) of the small bowel: feasibility and diagnostic and therapeutic yield in patients with suspected small bowel disease', *Gastrointestinal Endoscopy,* 62 (1), 62–70.

May, A., Nachbar, L. et al, (2005b). 'Push-and-pull enteroscopy using the double-balloon technique: method of assessing depth of insertion and training of the enteroscopy technique using the Erlangen Endo-Trainer', *Endoscopy,* 37 (1), 66–70.

Medicare Australia (2005a). *MBS Item Reports* [internet], available from: http://www.medicareaustralia.gov.au/providers/health_statistics/statistical_reporting/medicare.htm [accessed 13 June 2006].

Medicare Australia (2005b),.*Medicare Benefits Schedule Book*, Australian Government Department of Health and Ageing.

Mitchell, S.H., Schaefer, D.C. et al, (2004). 'A new view of occult and obscure gastrointestinal bleeding', *American Family Physician,* 69 (4), 875–881.

Mitsui, K., Tanaka, S. et al, (2005). 'Perspective of double-balloon enteroscopic diagnoses of small intestinal diseases', *Gastrointestinal Endoscopy,* 61 (5), AB176.

Moher, D., Pham, B. et al, (1998). 'Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?', *Lancet,* 352 (9128), 609–613.

Mönkemüller, K., Weigt, J. et al, (2006). 'Diagnostic and therapeutic impact of double-balloon enteroscopy', *Endoscopy,* 38 (1), 67–72.

MSAC (2003). *M2A Capsule endoscopy for the evaluation of obscure gastrointestinal bleeding in Adult patients,* Medical Services Advisory Committee, Canberra.

NHMRC (2000). *How to use the evidence: assessment and application of scientific evidence,* National Health and Medical Research Council, Canberra.

NHMRC (2005). *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines* [internet], NHMRC, available from: www.health.gov.au/nhmrc/ [accessed 2 June 2005].

Ohmiya, N., Taguchi, A. et al, (2005a). 'Usefulness of double-balloon enteroscopy (DBE) for diagnosis and treatment of small intestinal diseases', *Gastrointestinal Endoscopy,* 61 (5), AB177.

Ohmiya, N., Taguchi, A. et al, (2005b). 'Endoscopic resection of Peutz-Jeghers polyps throughout the small intestine at double-balloon enteroscopy without laparotomy', *Gastrointestinal Endoscopy,* 61 (1), 140–147.

Ros, P., Huprich, J. et al (2005). *Suspected small bowel obstruction* [internet], American College of Radiology, available from: http://www.guideline.gov/summary/summary.aspx?doc_id=8595 [accessed 12 May 2006].

Schulz, K.F., Chalmers, I. et al, (1995). 'Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials', *Journal of the American Medical Association,* 273 (5), 408–412.

Su, M.Y., Liu, N.J. et al, (2005). 'Double balloon enteroscopy - The last blind-point of the gastrointestinal tract', *Digestive Diseases And Sciences,* 50 (6), 1041–1045.

Sunada, K., Yamamoto, H. et al, (2004). 'Successful treatment with balloon dilatation using a double-balloon enteroscope for a stricture in the small bowel of a patient with Crohn's disease', *Digestive Endoscopy,* 16 (3), 237–240.

Sunada, K., Yamamoto, H. et al, (2005a). 'Balloon dilatation of small-intestinal benign strictures using double-balloon endoscopy', *Gastrointestinal Endoscopy,* 61 (5), AB183.

Sunada, K., Yamamoto, H. et al, (2005b). 'Clinical outcomes of enteroscopy using the double-balloon method for strictures of the small intestine', *World Journal of Gastroenterology,* 11 (7), 1087–1089.

Taylor, J.S. & Erkek, E. (2004). 'Latex allergy: diagnosis and management', *Dermatological Therapy,* 17 (4), 289–301.

Tilson, M. & Saltzman, J.R. (2006). *Small bowel bleeding and capsule endoscopy* [internet], American College of Gastroenterology, available from: www.acg.gi.org/patients/gihealth/smallbowel.asp [accessed 6 February 2006].

Yamamoto, H. (2005). 'Double-balloon endoscopy', *Clinical Gastroenterology and Hepatology,* 3 (7 SUPPL), S27–S29.

Yamamoto, H., Kita, H. et al, (2004a). 'Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases', *Clinical Gastroenterology and Hepatology,* 2 (11), 1010–1016.

Yamamoto, H., Kita, H. et al, (2004b),. 'Endoscopic diagnosis and treatment of small intestinal diseases using the double-balloon endoscopy', *Gastrointestinal Endoscopy,* 59 (5), AB100.

Yamamoto, H., Sekine, Y. et al, (2001). 'Total enteroscopy with a nonsurgical steerable double-balloon method', *Gastrointestinal Endoscopy,* 53 (2), 216–220.

Young, J.M. & Ward, J.E. (1999). 'General practitioners' use of evidence databases.' *Medical Journal of Australia,* 170 (2), 56–58.

Zhi, F.C., Xiao, B. et al, (2005). 'Double-balloon enteroscopy in detecting small intestinal bleeding', *Chinese Medical Journal,* 118 (21), 1834–1837.