A prospective comparative study of push and wireless-capsule enteroscopy in patients with obscure digestive bleeding

André Van Gossum, Axel Hittelet, Alain Schmit, Erik Francois, Jacques Devière

Department of Gastroenterology and Hepatopancreatology, Hôpital Erasme, Université Libre de Bruxelles.

Abstract

Objectives : **To prospectively compare the global and specific diagnostic yields of push and wireless videocapsule enteroscopy for small bowel lesions in patients with obscure digestive bleeding after esogastroduodenoscopy and colonoscopy.**

Methods : **The patients studied had unexplained chronic iron-deficient anemia or digestive blood loss after routine investigations. Small bowel investigation was performed first with the wireless-capsule (M2A, Given Imaging) and then with the push-enteroscope (Olympus SIF100).**

Results : **Twenty-one patients were included in the protocol (14 females and 7 males), whose mean age was 60 years (range : 18 to 81). All patients had iron-deficient anemia with occult bleeding (n = 16) or overt bleeding (n = 5). A digestive lesion was observed in 14 of 21 cases (66%). Lesions were : esophageal varices (n = 2), reflux esophagitis (n = 1), upper gastrointestinal tract ulcerations (n = 9), intestinal angioectasia (n = 4), ileal varices (n = 1), cecal angioectasia (n = 1) and tumor-like angioma in the jejunum (n = 1). These 19 lesions were discovered by both methods in 10 cases (52%), by push-enteroscopy only in 6 (31%) and by wireless-capsule endoscopy only in 3 (17%). The global diagnostic yield was therefore slightly but not significantly higher for push wireless-capsule enteroscopy (61 vs 52% ; NS) and the specific diagnostic yield was similar (20%). Interobserver agreement on the wireless-capsule recordings reached 85% for detection of findings.**

Conclusions : **In patients with obscure digestive bleeding, no significant difference in diagnostic yield was evidenced between push and wireless-capsule endoscopy. The main advantage of the latter method versus the former was the detection of distal lesions in the small bowel. Wireless-capsule enteroscopy is mandatory for patients with active unexplained bleeding and negative push-enteroscopy, or for defining the extension of a disease involving, for instance, the presence of angioectasia.** (Acta gastroenterol. belg., **2003**, 66, **199-205**).

Key words : obscure bleeding, small intestine, enteroscopy, wireless capsule, angioectasia.

Introduction

The source of gastrointestinal bleeding can be rapidly determined by conventional diagnostic procedures such as endoscopy or barium examinations in most of cases. Only 5% of patients bleed, chronically or intermittently, from an unidentified source (1). Obscure digestive bleeding is defined as recurrent bleeding for which no definite source has been identified by routine endoscopic or radiologic procedures (2). The management of these patients is a frustrating challenge that can consume enormous medical resources, because they often require multiple hospitalizations and blood transfusions, in addition to a diagnostic work-up that usually includes esogastroduodenoscopy, colonoscopy, barium examinations, radionuclide scans and abdominal computed tomography (CT) scan.

In most of these cases the source of bleeding is located in the small bowel, between the second portion of the duodenum and the ileocecal valve. The various radiologic procedures, including enteroclysis, visceral angiography, CT scan as well as radioisotope bleeding scans have limitations in case of obscure gastrointestinal (GI) bleeding, particularly in case of angioectasia (also named arterio-venous malformation), the most frequent lesion found in this setting.

Endoscopic techniques likely to visualize the small bowel mucosa include push-enteroscopy, sonde-enteroscopy, and intraoperative enteroscopy. Push-enteroscopy is currently the most widely used method for examining the small bowel. For obscure digestive bleeding, its diagnostic yield ranges from 35 to 70% (3,4).

A new method using a wireless capsule (M2A, Given Imaging, Is), which allows visualization of the entire small bowel in human subjects, has recently been reported (5) and tested in animals (6). Preliminary results suggest that it can detect small bowel lesions with great accuracy (7).

However, its place in the diagnostic work-up of obscure bleeding remains to be determined, particularly in comparison with push-enteroscopy for patients referred after previous upper and lower GI work-up.

The primary end-point of this prospective pilot study was to compare the diagnostic yield of these two methods in patients with an obscure digestive bleeding. Secondary end-points of this study included the evaluation of the safety and tolerance of each method.

Methods

Patients

The protocol was accepted by the Ethical Committee of our hospital and all the patients signed an informed consent form.

The results of this study were presented during the Digestive Disease Week, San Francisco, May 2002.

Address for correspondence : André Van Gossum, M.D., Ph.D., Department of Gastroenterology and Hepatopancreatology, Hôpital Erasme, Université Libre de Bruxelles, Route de Lennik, 808, B-1070 Brussels, Belgium. E-mail : Andre.Van.Gossum@ulb.ac.be.

Twenty-one patients (mean age : 60 ; range 18-80 years) with obscure GI bleeding were included in this study. Obscure GI bleeding was defined either as recurrent overt bleeding (rectal discharge of blood) or chronic iron-deficient anemia (the serum hemoglobin level at least below 10 g/l) with positive blood research on stools, for which no source had been identified after at least esogastroduodenoscopy and total colonoscopy. Any gynecologic problem was excluded in all the females patients.

The results of other gastrointestinal investigations, the need for blood transfusion and the use of nonsteroidal anti-inflammatory drugs (NSAIDS) within the previous 6 months were also recorded.

Exclusion criteria included pregnancy ; known or suspected stenosis of the small bowel ; previous abdominal surgery ; swallowing disorder ; clinically unstable or uncontrolled clinical conditions ; presence of a cardiac pacemaker or other implanted electromedical devices and the need to undergo magnetic resonance imaging (MRI) before the elimination of the enteroscopic wireless-capsule.

Study design

All patients underwent wireless-capsule enteroscopy first, and then, within one week, push-enteroscopy in a single endoscopic unit at Erasme hospital. The latter was performed after wireless-capsule enteroscopy to allow biopsy sampling or therapeutic intervention when indicated. The two procedures were performed blindly by two independent operators and interobserver agreement was assessed for the wireless-capsule recordings. The global and specific diagnostic yields were defined as follows : the global diagnostic yield included all lesions detected in the upper GI tract and the visualized gut, and the specific diagnostic yield only included those lesions located beyond the reach of routine esogastroduodenoscopy. We only took into account significant lesions that could explain a chronic digestive bleeding. For statistical analysis, Fisher's exact test was used to compare the results of wireless-capsule and push-enteroscopy.

Complications were recorded. Tolerance of the procedures was assessed from patient's answers to a questionnaire (including nine questions with a scoring system from 0 to 5).

Special attention was given to all features likely to hamper good visualization of the mucosa. The time required for gastric release of the capsule (i.e. for passage through the pylorus) and the time taken by the capsule to reach the cecum were determined for each patient.

The wireless videocapsule

We used the M2A® videocapsule system designed by Given Imaging Ltd (Yogneam, Israel) (5).

Briefly, the capsule includes a complementary metal oxide silicon imaging chip, a miniature processor, a white-light emitting diode, a lens with a short focal length, a miniature transmitter and an antenna powered by silver oxide batteries. The video images are transmitted by a radiofrequency signal (about 410 MHz), at a rate of two frames per second, to an array of 8 aerials attached to the abdominal wall that allow image capture. The images are stored on a portable recorder carried on a belt, and can subsequently be downloaded in a specifically designed workstation.

The capsule is ingested in the morning (between 8 and 9.30 am) at least 12 hours after the last meal, without any special preparation. Patients are allowed to drink and eat one hour and 3 hours after capsule ingestion, respectively.

Push-enteroscopy

We used the Olympus XSIF-100 push-enteroscope. This device has a working length of 240 cm and a diameter of 11.3 mm. It has a flexible distal tip and an operating channel. The push-enteroscope is introduced orally after intravenous premedication with 2-6 mg midazolam and topical oropharyngeal anesthesia using a xylocaine spray and gel.

Anxious patients are sedated with propofol, administered by an anesthesiologist. The overtube was only used when the progression of the tube was limited by intragastric looping. Fluoroscopy was not used. The length of small intestine investigated was assessed endoscopically during the withdrawal of the scope. The upper GI (UGI) tract was always carefully examined before the scope was pushed into the jejunum.

Results

Diagnostic yield

Twenty-one patients (14 females, 7 males, mean age 60 (range 18 to 81) years were included in the study. All patients had iron-deficient anemia with either occult bleeding (n = 16) or overt bleeding (n = 5). The 5 patients with overt bleeding had lower GI bleeding but no hematemasis. Patients had had the following examinations before the study : esogastroduodenoscopy (n = 44), colonoscopy (n = 21) and ileoscopy (n = 191), small bowel X-ray (n = 14), abdominal CT scan (n = 8), mesenteric angiography (n = 6), nuclide scan (n = 7). During the previous 6 months, 15 of the 21 patients required a blood transfusion. The mean number of blood units was 2.1 (range : 1 to 12). At baseline evaluation, the mean level of hemoglobin was 9.8 g/dl (5.2 to 11.2 g/dl). All patients had received iron supplementation, either orally (n = 16) or parenterally (n = 5). Three patients had taken oral NSAID's medications within the previous 6 months. Nineteen out of the 21 patients were referred to our center from other hospitals. Routine endoscopic examinations were not repeated in our center.

After wireless-capsule and then push-enteroscopy, a digestive lesion was observed in 14 of the 21 cases

(66%). Amongst the 5 patients with overt bleeding, a lesion was detected in 4 of them. In this series, the lesions included : esophageal varices (n = 2), reflux esophagitis (n = 1), UGI ulcerations (n = 9), intestinal angioectasia (n = 4), ileal varices (n = 1), cecal angioectasia (n = 1), and tumor-like angioma in the jejunum (n = 1) (Figs. 1-4). A small bowel lesion was only detected in 6 patients (28%). The small bowel angioectasia were multiple but not spontaneously bleeding at the time of evaluation ; only some of them bled during coagulation. In two patients, the capsule discovered angioectasia that were detected by push-enteroscopy but also vascular lesions that were located beyond the reach of enteroscopy. These 19 lesions (Table) were discovered by both methods in 10 cases (52%), only by push-enteroscopy in 6 (31%) and only by wireless-capsule endoscopy in 3 (17%). The three lesions detected only by the wireless-capsule were located in the distal small intestine (n = 2) and cecum (n = 1). Therefore, in terms of patients, the global diagnostic yield was slightly but not significantly higher for push-enteroscopy than for the wireless-capsule method (61 vs 52% ; NS) and the specific diagnostic yield was similar in each case (20%). The lesions of the UGI were missed (n = 9) or underestimated (n = 4) at the initial esogastroduodenoscopy. The two patients who had a lesion located in the terminal ileum had undergone an endoscopic ileoscopy.

In two patients with negative findings, a lesion was subsequently diagnosed. One of them was a 51 year-old female (patient 11) with persistent iron-deficient anemia, in whom a cecal tumor was discovered during a second colonoscopy. The first colonoscopy only reached the hepatic flexure and the barium enema was considered normal. A second reading of the radiography did reveal the lesion. In this patient, the capsule failed to show the cecum because of slow intestinal transit. The other patient, was a 64 years old man (patient 13) in whom laparotomy revealed a varice located in the terminal ileum. Repeated reading of the wireless-capsule recording did not allow the visualization of this lesion.

Safety and tolerance

No complications were observed with either procedure. Push-enteroscopy was performed under sedation with midazolam in all but one patient, who asked for general anesthesia.

The overtube had to be used in 3 out of 21 patients.

Oral swallowing of the capsule was easy in all cases. Its elimination in the stools was spontaneous and easy in all but one patient, whose capsule was blocked in an appendiceal stump. This problem was suspected when analyzing the recording of the wireless-capsule and was confirmed by plain X-rays of the abdomen (Fig. 5). In this patient, the capsule was retrieved by a snare, through colonoscopy (Figs. 6-7).

Subjective tolerance of both procedures was good for all patients. However, all of them preferred the wireless capsule method to the endoscopic method.

Methodologic features of the wireless capsule

Mean recording time was 6 hours 7 min (range : 5 h 53 to 7 h 26). The number of frames showing a low

Table. — **Lesions that were observed by push-enteroscopy and wireless-capsule in a series of 21 patients with obscure digestive bleeding**

No.	Sex	Age	Type of bleeding	Push	VCE
1	Male	78	Overt	UGI	–
2	Male	79	Overt	Esophageal varices UGI	Ileal varice Caecal angioectasia
3	Female	66	Occult	UGI	–
4	Female	42	Occult	–	–
5	Female	75	Occult (NSAIDs)	UGI	UGI
6	Female	44	Occult	–	–
7	Female	47	Overt	UGI/esophagitis	UGI/esophagitis
8	Female	71	Overt (NSAIDs)	UGI	UGI
9	Male	60	Occult	UGI	UGI
10	Female	60	Occult	S.B. angioectasia	S.B. angioectasia+
11	Female	51	Occult	–**	–**
12	Male	81	Occult (NSAIDs)	UGI	UGI
13	Male	64	Overt	–*	–*
14	Male	78	Occult	S.B. angioectasia	S.B. angioectasia+
15	Female	18	Occult	–	–
16	Female	32	Occult	–	–
17	Male	70	Occult	UGI Esophageal varices	UGI Esophageal varices
18	Female	80	Occult	S.B. angioectasia	–
19	Female	63	Occult	S.B. angioectasia	–
20	Female	22	Occult	–	–
21	Female	77	Occult	–	Jejunal tumor-like angioma

*ileal varices discovered at laparotomy ; **caecal cancer ; +beyond the reach of push-enteroscopy.
UGI = upper GI peptic lesions ; S.B. = small bowel.

Fig. 1. — Gastric erosions

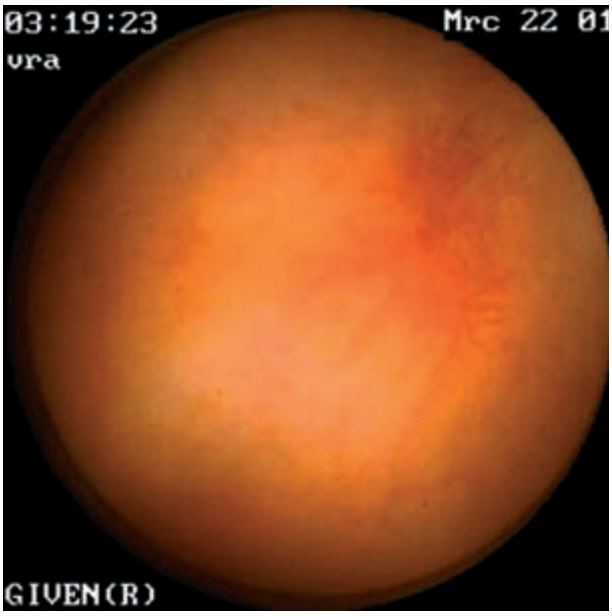

Fig. 3. — Cecal angioectasia that was initially missed at colonoscopy.

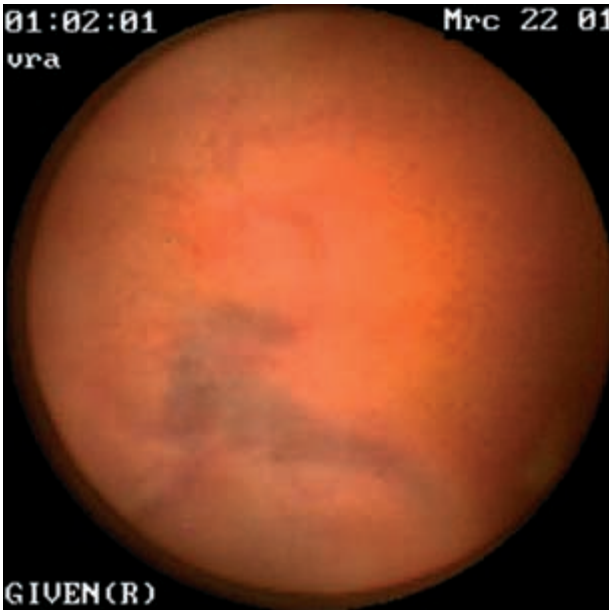

Fig. 2. — Dilated vein located into the distal ileum in a patients with portal hypertension.

Fig. 4. — Small bowel angioectasia

esophagus was 0 for 5 patients, 1-3 for 12, and > 3 for four. The median time to gastric release of the capsule was 12 min (range : 58 sec to 210 min). The median time required for the capsule to reach the cecum was 3h32 min (range : 1 h 38 to 5 h 33) (n = 16). The cecum was not reached in 5 of 21 cases. Visualization of the gastrointestinal mucosa in some segments was hampered by the presence of air bubbles (n = 8), a small amount of intestinal fluid (n = 12), a large amount of fluid (n = 4), blood (n = 1), an undigested residues (n = 2), no expansion of the intestinal lumen (n = 2), and/or hyperperistaltism (n = 8). There was a gastric food residue in 2 patients (gastric release times : 67 and 210 min). The image window remained clear throughout the entire transmission period in all 21 patients. The mean time taken required to analyze the recordings was 1 h 12 min (range : 55 min to 1 h 35 min).

Interobserver agreement for the wireless-capsule recordings reached 85% for the detection of findings. For the remaining 15%, this agreement could not been reached. Most of these "uninterpretable" findings corresponded to erythematous lesions that only appeared on

Fig. 5. — Plain X-rays showing the capsule remaining in the right quadrant.

one or two frames. In this case, it was not considered to be a lesion.

Discussion

In this group of 21 patients, the global diagnostic yield of push-enteroscopy (61%) was in the range of that previously reported for large series (35 to 62%) (8-11). However, the specific diagnostic yield of 20% was lower than in other series, including our own initial experience (33 to 49%) (8). This might be because this series included more patients presenting with chronic iron-deficient anemia than with overt bleeding. Nevertheless, this small series of patients corresponds to the patients who are referred to our center in routine practice for evaluation of a so-called obscure bleeding (8). The global and specific diagnostic yields of push-enteroscopy indeed appear to be lower for occult than overt bleeding. In a French series, Landi et al reported a global diagnostic yield of 20% and a specific yield of 6% in patients with chronic anemia but without blood extravasation (12). In a recent series of 180 patients with overt bleeding characterized by melena or hematochezia, the global and specific diagnostic yields were 43 and 30%, respectively (13).

The present results confirm the high percentage of "missed" or underestimated UGI lesions after the initial endoscopic procedures (8,9). Thus, a cecal adenocarcinoma was subsequently discovered in one patient with an initially negative work-up. Unfortunately, in this particular case, the capsule failed to show the cecum because of slow gastric release.

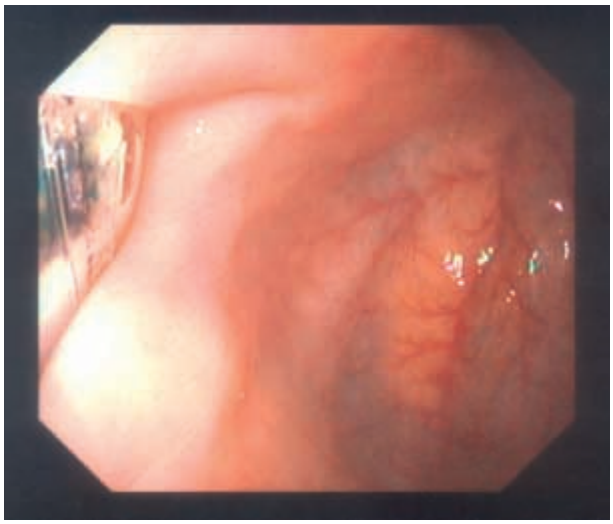

Fig. 6. — Video-capsule that was blocked in an appendiceal stump.

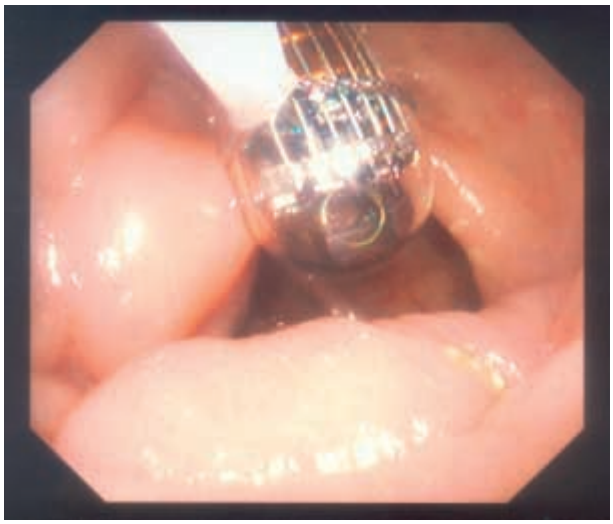

Fig. 7. — Endoscopic withdrawal of the capsule with a snare.

The global diagnostic yield for wireless-capsule enteroscopy was slightly but not significantly lower than for push-enteroscopy. This was partly because the capsule failed to detect some lesions, mainly those located in the esophagus and upper fundus. However, visualization of the antrum and prepyloric area was extremely good.

Although, the specific diagnostic yield of wireless-capsule enteroscopy was the same as that of push-enteroscopy (20%), each technique detected different lesions. Some lesions located in the duodenum and upper jejunum were missed by the capsule, probably due to either intestinal hyperperistaltis or the presence of intestinal fluid in the lumen. However, the capsule detected more of the lesions distally located in the

jejunum than push-enteroscopy, because the jejunum was beyond the reach of the push-enteroscope.

In an animal model, Appleyard et al compared the diagnostic yields of push and wireless-capsule enteroscopy for the detection of beats that had been surgically placed in the small bowel of dogs (6). In this model, the diagnostic yield of wireless-capsule enteroscopy was larger than that of push-enteroscopy. This was mainly due to the detection by the capsule of lesions which were distally located, beyond the reach of the endoscope. However, the authors mentioned that the capsule failed to detect some of the beats that had been placed in the duodenum.

In an initial series of patients with obscure bleeding, B. Lewis reported diagnostic yields of 60% and 47% for wireless-capsule and push-enteroscopy respectively (14). However, in this study, the authors considered in 4 patients the presence of fresh blood in the intestinal lumen without visible lesion as a positive finding. On the other hand, they didn't include in the positive finding the Cameron's ulcerations that the push-enteroscopy discovered in 2 patients. Ell et al reported a series of 32 patients with chronic digestive bleeding, who required a mean of 17 ± 18 blood units. In this population, a definite source of bleeding was discovered in 28% of patients with the push-enteroscopy and in 68% of the patients with the wireless capsule ($p < 0.001$) (15).

The difference with the present series could be partially due to the selection of patient with more severe or more overt bleeding.

Visualization of the intestinal mucosa was altered by several factors, including hyperperistaltis, residual intestinal liquid or food residues, and in 2 patients, the absence of expansion in some segments of the lumen. In the latter patients, this absence of lumen was not considered pathologic.

Further studies are necessary to establish whether or not polyethylene glycol or simethicone administration or prokinetics limit the interaction of these factors.

The gastric release time varies greatly from one patient to another. Slow release might shorten the time available for visualization of the small intestine. However, since the images are not analyzed in real time, it seems difficult to interfere with GI motility. The gastric and intestinal release times of the capsule can also provide interesting informations. Data acquired by wireless-capsule enteroscopy about GI motility should be compared to those acquired by other methods of assessing GI motility, such as isotope scans or manometry. The fact that the caecum was not visualized in 5 out of 21 patients is due to the lifetime of the batteries and a slow intestinal transit time. This percentage is similar to the data from other series (14,15). The lifetime of batteries of the capsules of the new generation is now longer.

Here, tolerance was good for both the techniques tested, but tolerance was better for wireless-capsule than push-enteroscopy.

In this series, one capsule was trapped in an appendiceal stump but did not give rise to provoking any symptom. This, as far as we know, is the first reported case of such a pug. Nevertheless, one should bear in mind that the capsule can be blocked by any stricture or diverticulum. Caution must therefore be exercised when patients display clinical signs of intestinal occlusion or have a history of abdominal surgery advisability of using wireless-capsules in indications other than obscure GI bleeding, such as Crohn's disease, celiac disease, malabsorption, polyposis, etc., should be carefully assessed in prospective comparative studies. In a series of 21 patients, Costamagna et al showed that the video-capsule examination was more effective than the small-bowel follow-through in patients with suspected intestinal disease (16).

In the present study, we showed that the wireless-capsule is easily swallowed and well tolerated. The main advantage of wireless-capsule versus push-enteroscopy is that the capsule detects distal lesions which are beyond the reach of the enteroscope. This series also confirmed the high percentage of missed or underestimated lesions of the UGI tract in patients with what is known as obscure digestive bleeding. This suggests that wireless-capsule method should be used for patients with obscure bleeding after performing a push-enteroscopy or at least, in referred patients, after repeating careful esogastroduodenoscopy. A larger series should confirm the cost-effectiveness of this policy compared to first-line capsule enteroscopy.

Acknowledgments

The video-capsules have been kindly provided by Given Imaging“ (Israel).

References

1. ROCKALL T., LOGAN R., DEVLIN H. *et al.* Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. *Br. Med. J.*, 1995, **311** : 222-224.
2. VAN GOSSUM A. Obscure digestive bleeding. *Best Practice and Research Clin. Gastroenterol.*, 2001, **15** : 155-174.
3. WAY J. Small-intestinal endoscopy. *Endoscopy*, 2001, **33** : 24-30.
4. ROSSINI F., PENNAZIO M. Small-bowel endoscopy. *Endoscopy*, 2002, **34** : 13-20.
5. IDDAN G., MERON G., GLUKHOVSKY A. *et al.* Wireless-capsule endoscopy. *Nature*, 2000, **405** : 417.
6. APPLEYARD M., FIREMAN Z., GLUKHOVSKY A. *et al.* A randomized trial comparing wireless-capsule endoscopy with push-enteroscopy for the detection of small bowel lesions. *Gastroenterology*, 2000, **119** : 1431-1438.
7. APPLEYARD M., GLUKHOVSKY A., SWAIN P. Wireless-capsule diagnostic endoscopy for recurrent small bowel bleeding. *N. Engl. J. Med.*, 2001, **344** : 232-233.
8. DESCAMPS C., SCHMIT A., VAN GOSSUM A. “Missed” upper gastrointestinal tract lesions may explain “occult” bleeding. *Endoscopy*, 1999, **31** : 452-455.
9. ZAMAN A., KATON R. Push enteroscopy for obscure gastrointestinal bleeding yields a high incidence of proximal lesions within reach of a standard endoscope. *Gastrointestinal Endoscopy*, 1998, **47** : 372-376.
10. CHAK A., KOELHER M., SUNDAAM S. *et al.* Diagnostic and therapeutic impact of push-enteroscopy. *Gastrointestinal Endoscopy*, 1998, **47** : 18-22.
11. HAYAT M., AXON A., O'MAHONY S. Diagnostic yield and effect on clinical outcomes of push enteroscopy in suspected small-bowel bleeding. *Endoscopy*, 2000, **32** : 369-372.

12. LANDI B., TKOUB M., GAUDRIC M. *et al.* Diagnostic yield of push-enteroscopy in relation to indication. *Gut*, 1998, **42** : 421-425.
13. LEPERE C., CUILLERIER E., SCHMIT A. *et al.* Are there any predictive factors of diagnostic yield of upper push enteroscopy in patients with unexplained gastrointestinal bleeding ? *Acta Gastroenterol. Belg*., 2001, **64** : D33 (abstract).
14. LEWIS B., SWAIN P. Capsule endoscopy in the evaluation of patients with suspected small intestinal bleeding : the results of the first clinical trial. *Gastrointestinal Endoscopy*, 2002, **56** : 349-353.
15. ELL C., REMKE S., MAY A. *et al.* The first prospective controlled trial comparing wireless capsule endoscopy with push enteroscopy in chronic gastrointestinal bleeding. *Endoscopy*, 2002, **34** : 685-689.
16. COSTAMAGNA G., SHAH S., RICCIONI M., FOSCHIA F., MUTIGNANI M., PERRI V., VECCHIOLI A., BRIZI M., PICCIOCCHI A., MARANO P. A prospective trial comparing small bowel radiographs and video-capsule endoscopy for suspected small bowel disease. *Gastroenterology*, 2002, **123** : 909-1005.