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Technique and clinical applications of double balloon enteroscopy for the  
evaluation of small bowel diseases

## **Dissertation**

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### Summary

*Background:* The small intestinal mucosa is the most difficult area of the hollow gastrointestinal (GI) tract to evaluate using endoscopic methods. Double-balloon enteroscopy (DBE) is one of the major endoscopic breakthroughs of this century. DBE for the first time enabled endoscopists to practically observe the entire small intestine, take biopsies and provide treatment

*Aim:* We sought to evaluate various aspects on the technical and clinical utility of DBE.

*Methods:* Prospective and retrospective cohort studies of patients undergoing DBE at our medical center. In addition, technical reviews on the utility, present and future utilizations of this endoscopic method. *Results:* 1) There was a significant improvement in DBE performance over time, including increased depth of insertion, decline in procedural time, “speed of insertion” and decreased used of fluoroscopy for both oral and anal DBE procedures. These parameters improved significantly after the initial 10 oral (15 anal) cases. 2) DBE was useful to reach a new diagnosis in 33% and to confirm the diagnosis in two thirds of patients investigated for suspected small bowel malabsorption. 3) The frequency of lesions within reach of conventional upper and lower endoscopes definitely explaining the source of GI bleeding in patients referred for DBE was 24.3%. 4) DBE with virtual chromoendoscopy is a helpful advanced endoscopic method for the evaluation and characterization of small bowel polyps in patients with familial adenomatous polyposis, in the characterization of angiodysplasias and the definition of the submucosal capillary network, but not for patients with Peutz-Jeghers polyps, pseudopolyps, celiac disease and erosive jejunitis. *Conclusions:* 1) DBE is not only time consuming but also is a challenging procedure which requires training and follows a learning curve. 2) DBE had fair diagnostic yield in a selected group of patients with malabsorption a repeat 3) Due to the significant amount of lesions potentially explaining the cause of obscure GI bleeding, repeat EGD and ileocolonoscopy should be performed in patients referred for DBE. 4) Virtual chromoendoscopy is a promising technique to potentially improve the characterization of small bowel diseases.

**Key words:** enteroscopy, double balloon enteroscopy, single balloon enteroscopy, small bowel, angiodysplasias, small bowel polyps,

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## I. Abbreviations

CE	Capsule Endoscopy
GI	Gastrointestinal
DAE	Device-assisted enteroscopy
DBE	Double balloon enteroscopy
SBE	Single balloon enteroscopy
NBI	Narrow band imaging
FICE	Fujinon intelligent color enhancement
OGIB	Obscure gastrointestinal bleeding
EGD	Esophagogastroduodenoscopy
EATL	Enteropathy-associated T-cell lymphoma
CT	Computed tomography
MRT	Magnetic resonance tomography
WL	White light
NSAID	Non steroidal anti-inflammatory drugs
FAP	Familial adenomatous polyp syndrome
PJS	Peutz-Jeghers syndrome
NLH	Nodular lymphoid hyperplasia
HGIN	High-grade intraepithelial dysplasia
GIB	Gastrointestinal bleeding
GAVE	Gastric antral vascular ectasias
CO <sub>2</sub>	Carbon dioxide
BAE	Balloon-assisted enteroscopy
MAC	Monitored anesthesia care
FIT	Fecal immunochemical tests
SBFT	Small-bowel follow-through
RCD	Refractory celiac disease
CVID	Common variable immunodeficiency disorder
NET	Neuroendocrine tumors
EUS	Endoscopic ultrasound
PET	Positron emission tomography
APC	Argon-plasma-coagulation
DPEJ	Direct percutaneous endoscopic jejunostomy

## II. Chapter 1

### Introduction

This thesis is about the technical and clinical aspects of double-balloon enteroscopy. The small intestinal mucosa is the most difficult area of the hollow gastrointestinal (GI) tract to evaluate using endoscopic methods. The introduction of capsule endoscopy (CE) into clinical practice a decade ago resulted a major breakthrough in endoscopic imaging of the small bowel, for the first time permitting a detailed view of the entire mucosal surface (1,2). Despite the multiple advantages of CE as a “non-invasive” endoscopic method, it still holds several limitations, which include inability to obtain tissue for diagnosis or to provide endoscopic intervention such as polyp removal, dilation of strictures or cauterization of angiodysplasias, or to actively evaluate a lesion, washing the fluids or stop at a specific place to observe the lesion (3). Thus, when tissue for diagnosis is essential or carrying out an endoscopic therapeutic intervention is mandatory, traditional endoscopic methods are essential. But until fairly recently the only endoscopic method available to investigate and treat luminal disorders of the small bowel was push enteroscopy (PE) (4). However, PE has major limitations regarding depth of inspection. Fortunately new methods of endoscopic investigation and therapy such as double- and single-balloon and spiral-enteroscopy were developed and introduced into clinical practice (3, 5-7). Double balloon enteroscopy (DBE) for the first time enabled endoscopists to practically observe the entire small intestine, take biopsies and provide treatment (5, 6) (Figure 1).

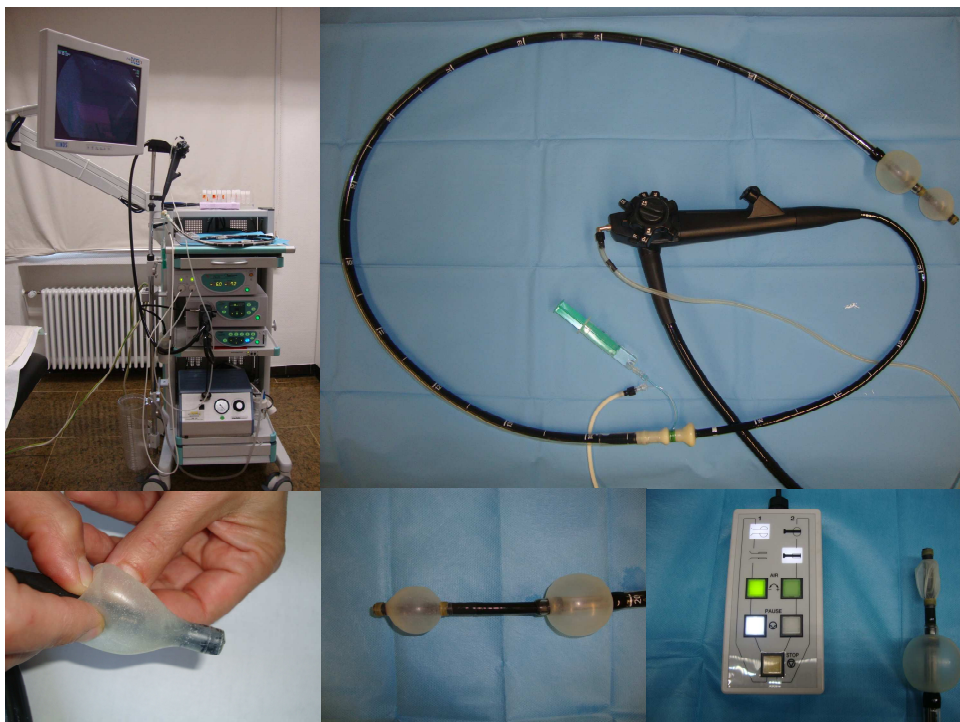


Figure 1. Double balloon enteroscope

In 2007, Tsujikawa et al introduced single-balloon enteroscopy (SBE) (7). Because both methods use a balloon on the overtube as a major mechanism for performing the procedure, the term “balloon-assisted-enteroscopy (BAE) was coined by Mönkemüller et al (8). Spiral enteroscopy (SE) was introduced in 2008 by Ackerman et al, thereby increasing the endoscopic possibilities to investigate and treat disorders of the small bowel (9). However, BAE methods remain the most widely used (10). BAE is regarded as one of the major endoscopic breakthroughs of the new century. Its addition to capsule endoscopy revolutionized the approach to the diagnosis and treatment of small bowel disorders.

In this thesis we will focus on the use of DBE. We first provide introduction into the technique of DBE. Then we evaluate the learning curve of DBE. In the next study we focus on determining the clinical applicability and utility of DBE for small bowel malabsorption states. In a large study we critically evaluate the role DBE in patients with obscure gastrointestinal bleeding and provide the Magdeburg algorithm for evaluation and treatment of obscure gastrointestinal bleeding. And finally, we explore the possibilities of advanced small bowel imaging using deep enteroscopy techniques. First we studied for the first time the utility of virtual chromoendoscopy for the diagnosis and characterization of various small bowel disorders and then we provide a state-of-the-art approach to small bowel imaging, focusing on current methods and future trends.

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### **III. Chapter 2**

#### **OUTLINE OF THE THESIS**

Our medical center was a pioneer institution utilizing double-balloon enteroscopy. Thus, we had the opportunity to investigate early on the technical aspects and clinical utility of double balloon enteroscopy. As with every new technique, many questions were raised after the first experiences with double-balloon enteroscopy. In this thesis, some of these clinical and technical issues will be addressed. For this thesis our steadily growing, prospectively collected, institutional review board-approved database of balloon-enteroscopy initiated in 2004, was used.

**Chapter three** provides a brief introduction and overview of double-balloon enteroscopy. It explains the technique of DBE. It also explains how choose the route of inspection. Furthermore, the indications and contraindications as well as complications are presented.

In **chapter four** we investigate the learning curve of DBE (1). DBE is a time consuming technique, which requires expertise in an effort to evaluate as much as possible length of the small bowel. There is scant data on the number of cases needed to acquire the skills necessary to perform DBE. Knowledge of this technical data may be helpful for endoscopists planning to perform DBE, to plan the caseload in individual endoscopy units and for establishing baselines for DBE skill certification.

In **chapter five** we evaluate the diagnostic value of DBE in patients with malabsorption of unclear origin (2). Malabsorption can be due to a wide range of processes including luminal, mucosal or submucosal etiologies. In most patients with malabsorption the diagnosis can be reached using standard methods but occasionally a specific diagnosis which includes direct visualization of the mucosa and tissue samples would be necessary to reach a diagnosis. In addition, there are malabsorptive diseases that follow a patchy small bowel distribution, thus mandating a deep enteroscopic evaluation. In this study, we investigate for the first time whether DBE detects mucosal lesions in malabsorption patients in segments of the small bowel that are usually not accessible to standard endoscopy.

In **chapter six** we critically evaluate the role of DBE in patients with obscure gastrointestinal bleeding (OGIB) (3). The most common indication for performing double balloon enteroscopy (DBE) is OGIB. OGIB is currently defined as bleeding from the GI tract that persists or recurs without an obvious etiology after a negative initial EGD and colonoscopy, and can be categorized



into obscure overt and obscure occult bleeding based on the presence or absence of clinically evident bleeding. Because most OGIB originate in the small bowel, distal to the papilla of Vater and proximal to the ileocecal valve, OGIB is also rightly called mid-GI or mid-gut bleeding. Mid-gut bleeding is currently evaluated using either capsule endoscopy (CE) and/or balloon-enteroscopy. However, bleeding sources within reach of conventional upper and lower endoscopes can be missed because of inadequate endoscopic investigation, small size, atypical location and non-active bleeding. One of the most frustrating experiences for a double balloon or capsule endoscopist is to find lesions outside the small bowel, such as gastric or colonic angiodysplasias, given that usually upper and lower endoscopies have been performed prior to the DBE procedure. In addition, missing these lesions may result in prolonged diagnostic evaluation, patient inconvenience and increased costs. The magnitude of the problem of finding abnormalities outside the small bowel on DBE is not well known. Therefore, in this study we aimed to determine the incidence of lesions outside the small bowel potentially responsible for GI bleed in patients undergoing DBE for the indication of OGIB. By doing so we also aimed at creating a useful and modern algorithm for the evaluation of patients with OGIB.

In **chapter seven** we examine the role of advanced imaging methods such as virtual chromoendoscopy (Fujinon enhanced color enhancement, FICE) to characterize various small bowel disorders (4). The direct observation of the small bowel mucosa reached with DBE could be improved using techniques, which enhance the villous details of the gastrointestinal (GI) mucosa using “virtual chromoendoscopy” or “dye-less” techniques. The current dye-less chromoendoscopy techniques include optical chromoendoscopy such as narrow band imaging (NBI; Olympus, Tokyo, Japan) and virtual chromoendoscopy including i-scan (Pentax, Tokyo, Japan) and Fujinon intelligent color enhancement (FICE; Fujifilm, Tokyo, Japan). While NBI is based on optical filters within the light source of the endoscope which narrow the bandwidth of spectral transmittance, thereby enhancing the visualization of blood vessels, i-scan and FICE use digital postprocessing for computed spectral estimation for better tissue contrast. Both methods are based on narrowing of the bandwidth of the conventional endoscopic image. Because this computer is located within the processor, FICE is not dependent on the presence of optical filters inside of the videoendoscope. Our study is the first to systematically evaluate advanced imaging methods for small bowel pathologies.

In **chapter eight** we provide a state-of-the-art review of advanced imaging methods for the small bowel (5). Standard white light endoscopes permit gross examination of the small bowel mucosa

permitting the recognition of minor and major defects such as erosions, ulcers, lymphangiectasias or abnormal duodenal folds. The water immersion technique increases our ability to inspect the small bowel villi by magnifying the view as well as providing a soluble medium where the villi and other superficial structures appear bigger and “move” inside the water. This technique can be very helpful when investigating conditions associated with villous atrophy such as celiac disease and other malabsorption syndromes. Magnification or zoom endoscopy further increases our ability to analyze the mucosal detail. Applying dyes and using magnification endoscopy can elucidate further architectural details of the mucosa. New dye-less or virtual chromoendoscopy techniques such as narrow band imaging (NBI), i-scan and Fujinon intelligent color enhancement (FICE) have further enhanced our optical capabilities for the evaluation of enteric mucosal and submucosal lesions. When using confocal laser endoscopy the targeted structure is magnified in such a way that a virtual histology image (“*in vivo* histology”) is achieved. We believe that in the near future confocal endomicroscopy may further help characterize and diagnose diseases affecting the small bowel such as celiac disease, Crohn’s disease, infections, vasculitis, mesenteric ischemia and angiodysplasias, among others.

In **chapter nine** we evaluate the current and future trends in small bowel endoscopy (6). Here we summarize the latest advances in deep enteroscopy as presented in last year’s Digestive Diseases Week, which is the premier worldwide meeting in gastroenterology. In doing this review we want to demonstrate that deep enteroscopy has now become an established area of gastrointestinal endoscopy and that there is still a lot to learn about the small bowel.

In **chapter ten** results of the thesis are summarized and discussed.

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## **IV. Chapter 3**

### **Overview of double-balloon enteroscopy**

Technical aspects of DBE:

Currently there are two major types of double balloon enteroscopes available for investigation of the small bowel (1-3). The working length of both EN-450P5 and EN-450T5 is 200 cm. The external diameter of the therapeutic DBE is 9.4 mm, whereas the diagnostic DBE has a diameter of 8.5 mm. The diameter of the working channel of the therapeutic DBE is 2,8 mm whereas the diagnostic one is 2,2 mm wide. Knowledge of these details is important in order to choose the appropriate accessory materials such as biopsy forceps, snares and needles. Both channels allow for the passage of the standard biopsy forceps, snare, injection needle standard biliary catheter and the thin argon plasma catheter. The working channel of the “therapeutic” (“T-scope”) allows for introduction of snares, baskets, needles and any other therapeutic accessories. The EN-450T5 is used with a 145-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm. The diagnostic scope is used with a 105-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm.

### **Technique:**

The use of the DBE in the pig- and the Erlangen training model increased our understanding of the mechanics and handling of the DBE (4). The major advantage of the DBE system is the presence of the balloons on both the overtube and endoscope, which help anchor the scope and/or the overtube in difficult positions, providing further stability during the procedure (5, 6). By stabilization of the intestine through gripping of the intestinal wall with a balloon attached to the distal end of a flexible overtube it is possible to advance the enteroscope deeper while the overtube prevents further bending or looping of the intestine. Furthermore, the balloon attached to the endoscopic tip anchors the endoscope during the advancement of the overtube, thus preventing the intestine to slide back while the overtube is advanced towards the enteroscope (1-3, 5, 6). The endoscope moves forward using two balloons in sequence while folding and shortening the long intestine onto the overtube and making a concentric circle with its shaft.

DBE is a complex examination and should thus only be carried out by experienced endoscopists who are well versed with the various pathologies of the small bowel. Skilled interventional endoscopists will also have the advantage of being able to utilize the enteroscope for biliary procedures, investigate the excluded stomach in patients with gastric bypass operations or to perform colonoscopies in patients with previously failed colonoscopy (7-11). Before attempting this procedure a thorough review of the basic principles of DBE is mandatory. Some experts

advocate the participation in workshops using the Erlangen or animal models. However, as with most endoscopic procedures, there is no better substitute than one-on-one training with an experienced endoscopist.

The standard approach to perform DBE requires two persons, operator and assistant. In the standard DBE method, an assistant constantly holds the overtube, while an operator handles the enteroscope, and both assistant and operator perform the two movements of the push-and-pull maneuver. Araki et al described a single endoscopist method where these two movements are performed only using the right hand of one operator, catching the proximal end of the overtube with the thumb and the forefinger, and gripping the endoscope with the little and the third fingers and the posterior part of the palm (12). The right hand of the operator is also used to insert the endoscope through the overtube. The operator's left hand is used to pull back the endoscope and hold the endoscope handle. It appears that this method is equivalent to the “two-endoscopists” approach. However, we believe that the single-operator DBE method should be used in situations where general anesthesia is used because when conscious sedation is utilized, generally there is patient movement during the procedure and the additional physicians in the room assist not only to assist for the procedure, but aid in patient monitoring.

### **Technical aspects of SBE**

The main difference when using SBE is the absence of a balloon on the tip of the enteroscope (13). The method also uses an overtube with a balloon on its tip. The push-and-pull maneuvers used to perform SBE are in essence the same as for DBE. In addition, most experts also advocate performing SBE with two operators. Recently DBE and SBE were compared in three prospective randomized studies (13-15). In the first study the rate of complete enteroscopy with DBE was three times higher than with SBE (14). DBE was also associated with a higher diagnostic yield. The second study was terminated because the total enteroscopy rate was 0% in the SBE group versus 57% in the DBE group (15). There was no difference in the diagnostic rate and the therapeutic outcome between the SBE and DBE group. The third study showed no difference in total enteroscopy between SBE and DBE (13). Thus, the final verdict on which method reaches deeper is not out yet.

### **Determination of the primary route of insertion (oral or antegrade versus anal or retrograde)**

The choice of either the oral or the anal route depends on the suspected location of the lesions within the small bowel based on the clinical manifestations, results of laboratory, radiological and CE examinations (1-3, 16, 17). For obscure gastrointestinal bleeding (OGIB) CE is currently the

main instrument used to indicate the preferential endoscope insertion route for DBE. Two studies have evaluated the “CE-directed approach” (18, 19). Pennazio et al. used this approach in a group of 44 patients and found that a one-sided procedure (oral or anal) was sufficient to reach the lesion of interest in almost 90% of the DBE examinations (18). Gay et al. reported on similar high yields (19). In cases of obscure GI bleeding the stool color can also help to direct the DBE route: the oral route in the case of melena and the anal route in the case of hematochezia. However, this approach has not been validated. In general, total enteroscopy by DBE is not required in the majority of the patients with OGIB, as the potential bleeding source can be generally identified without entire small bowel visualization. Nonetheless, about one third of patients will require two separate DBEs to make diagnosis.

In most other situations the route of investigation depends on previous clinical and radiologic findings. For example, in patients with suspected Crohn’s disease using the retrograde approach makes more sense, as the terminal ileum is a major site of involvement in this disease. Patients with Peutz-Jeghers syndrome are usually evaluated using the antegrade approach first followed by the retrograde approach.

### **Indications**

The most common indications for DBE are OGIB and evaluation of suspected Crohn’s disease (1-3, 5, 6, 20, 21). Table 1 compiles the current indications for deep enteroscopy.

**Table 1.** Indications and potential therapeutic interventions using the double balloon enteroscope

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Small bowel bleeding:
Hemostasis
Argon plasma coagulation
Injection of Epinephrine
Injection of Hisytoacryl
Placement of clips
Crohn’s disease
Stricture dilation
Celiac disease (surveillance)
Polyposis syndromes (surveillance)
Polypectomy
Endoscopic mucosal resection
NSAID enteropathy
Balloon dilation of strictures
Tumors (adenocarcinoma, search for neuroendocrine tumors)
Submucosal injection with India ink
Small bowel and colonic stent placement
Removal of foreign body
PEG in altered bowel anatomy (gastric bypass, roux-Y)
Biliary interventions: ERCP

### Complications of DBE:

Besides post-polypectomy bleeding and perforation, several unique complications related to DBE have been reported such as pancreatitis, intestinal necrosis from an epinephrine injection, intramural hematoma and paralytic ileus (22-24). Two large studies have reported on the complications associated DBE (23, 24). A large multicenter, international complication survey was presented by Mensink et al (23). A total of 10 centers across four continents participated in the study and reported on a total of 40 complications in 2362 DBE procedures, 13 in 1728 diagnostic DBE (0.8 %) and 27 during 634 therapeutic procedures (4.3 %). The complications were rated minor in 21 (0.9 %), moderate in 6 (0.3 %) and severe in 13 procedures (0.6 %). No fatal complications were reported. Seven cases of pancreatitis were reported, six after diagnostic (0.3 %) and one after therapeutic (0.2 %) DBE (40). Therefore pancreatitis should always be considered in patients with persistent abdominal complaints after DBE. In another study Moeschler et al contacted all endoscopic units using DBE in Germany and collected data during a 3-year period (24). 64 of 85 endoscopic centers responded to the questionnaire. Of a total 3894 reported DBE-examinations (2685 using the oral route, 1209 using the anal route), including 1086 therapeutic interventions (857 APC-therapy, 177 polypectomies, 26 dilatations and 26 other) a total of 48 complications were reported (1,2%). The most common complications were acute pancreatitis in 9 patients (0,34%) with 1 lethality, perforation in 8 cases (6 post-polypectomy), major bleeding in 6 patients (4 in the context of polypectomy and 2 after biopsy) (24). All patients received endoscopic treatment and recovered from this complication.

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**V. Chapter 4**

**Learning curve of double balloon enteroscopy**

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**Abstract:**

DBE is a time consuming procedure. Although prospective research on the learning curve for this procedure are lacking, there is data from prospective cohorts that have evaluated the learning curve of DBE. It is evident that a significant amount of time and a minimum of 10-15 procedures are required to acquire the skills necessary to perform DBE. Knowledge of this technical data may be helpful for endoscopists planning to perform DBE, to plan the case load in individual endoscopy units and for establishing baselines for DBE skill certification.

**Introduction:**

The double balloon enteroscope (DBE) has been employed since 2001 for evaluation of small disorders (1-5). There is still considerable clinical and research interest in evaluating the technical issues regarding DBE (6-10). DBE is a time consuming procedure. Although prospective research on the learning curve for this procedure are lacking, there is data from prospectively cohorts that have evaluated the learning curve of DBE. At the time of submission of this manuscript there were two abstracts and one article published on the learning curve of DBE (11,12). We will discuss the available information in this article.

**Technical aspects:****Instruments and Materials:**

Currently there are two types of double balloon enteroscopes available for investigation of the small bowel. The working length of both EN-450P5 and EN-450T5 is 200 cm. The external diameter of the therapeutic DBE is 9.4 mm, whereas the diagnostic DBE has a diameter of 8.5 mm. The diameter of the working channel of the therapeutic DBE is 2,8 mm whereas the diagnostic one is 2,2 mm wide. Both channels allow for the passage of the standard biopsy forceps, snare, injection needle standard biliary catheter and the thin argon plasma catheter (APC catheter 20132-212, Erbe, Tübingen, Germany). EN-450T5 is used with a 145-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm. EC-450BI5 is used with a 105-cm overtube that has an external diameter of 13.2 mm and an internal diameter of 11 mm.

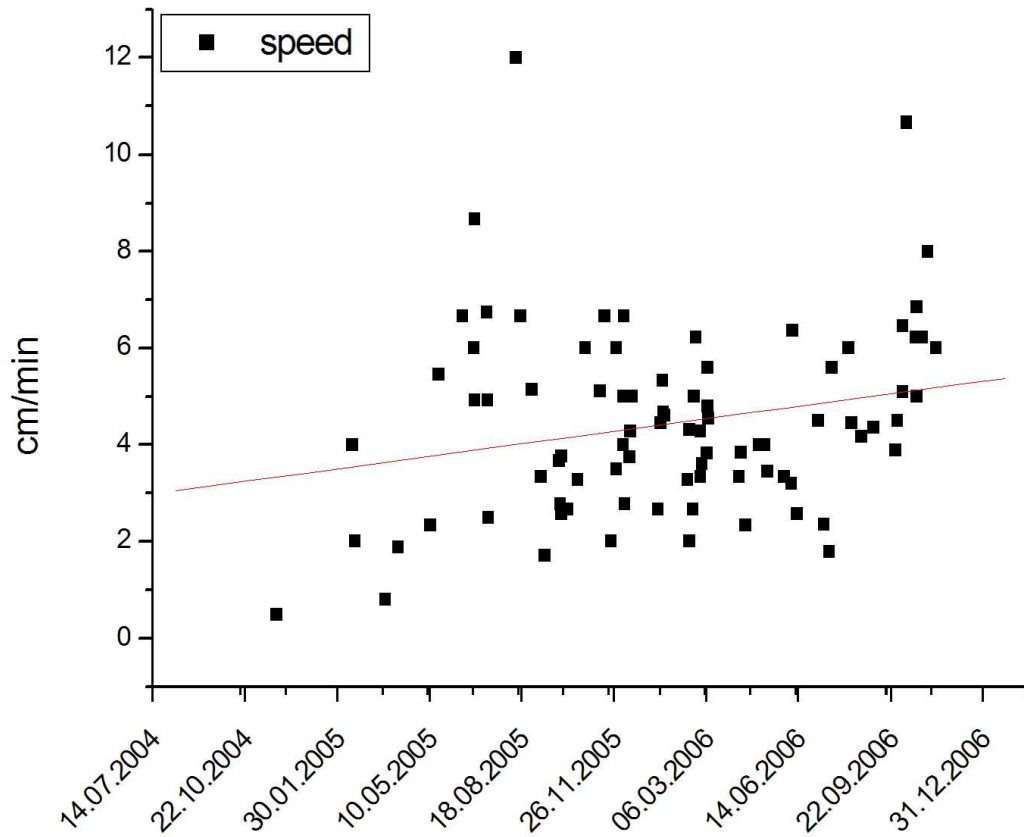
Most initial experience with DBE was obtained with the diagnostic DBE. Many small bowel units, including ours, have currently both types of scopes available. Based on our experience and that of others, it appears that a faster and deeper small insertion is reached when using the therapeutic enteroscope, with exception of patients with previous abdominal surgery. As far as we know there are no comparisons published to date regarding technical handling issues between both scopes. Data evaluating the learning curves of DBE were mainly based on the diagnostic DBE.

## **Outcomes:**

We evaluated the learning curve of DBE in 140 patients undergoing 168 DBE by a single endoscopist during a 2-year period in a prospective cohort study (10). The following performance parameters were documented prospectively: depth of insertion, duration of the procedure, fluoroscopy use, endoscopic findings and therapeutic interventions. All procedures were performed using the diagnostic DBE. The performance parameters from the endoscopist's initial 10, 15 and 20 cases were compared to the subsequent examinations. The procedure duration was studied in relation to procedure date. In addition, the "speed of insertion" was also investigated (cm per minute).

A total of 126 oral DBE and 42 anal DBE were performed. The mean ( $\pm$ SD) duration for both oral and rectal DBE were:  $92.3 \pm 38.6$  minutes for the first 10 cases,  $84.1 \pm 35.5$  minutes for the first 20 cases ( $P < .005$ ), and  $64.1 \pm 31.2$  for the subsequent cases. Both rectal and oral DBE were performed significantly faster over time. The mean depth of insertion increased and the mean fluoroscopy exposure declined significantly over time. For oral DBE the mean insertion was  $150.4 \pm 15$  cm for the first 10 cases,  $170.4 \pm 25.2$  cm for the first 15 cases and  $245 \pm 22.4$  for the subsequent cases (Figure). The mean ileal insertion for anal DBE was  $30.5 \pm 15.8$  for the first 15 cases and  $95.5 \pm 22.3$  for the subsequent cases ( $p < 0,022$ ). Deep ileal intubation via the anal route failed in 7 (17%) cases (40% of the initial 10 cases, versus 6% of the subsequent cases). There was a significant negative correlation between the procedure duration and the number of days from the endoscopist's first procedure for both oral and anal procedures ( $p < 0,001$ ). The depth of insertion and the "speed of insertion" correlated positively between the initial days of the procedure and subsequent days.

Diagnostic or therapeutic interventions were performed in 86% of cases; DBE led to a diagnosis or therapeutic intervention in 111 (79%) patients. Only 8% of patients had prior capsule endoscopy. A total of three complications occurred (none severe): bleeding after polypectomy ( $n=1$ ), ileus ( $n=1$ ) and respiratory depression ( $n=1$ ).



**Figure 1.** Over the time, the mean duration of DBE decreased while the reached distance in the small bowel increased. Expressed together in the term of insertion depth per time ([cm/min](speed)), the examination improved significantly ( $r=0,226$ ;  $p=0.037$ ).

**Discussion:**

We have demonstrated that there was a significant improvement in DBE performance over time, including increased depth of insertion, decline in procedural time, “speed of insertion” and decreased used of fluoroscopy for both oral and anal DBE procedures. These parameters improved significantly after the initial 10 oral (15 anal) cases. In a multicenter study involving six U.S. tertiary centers with a total of 188 subjects undergoing 237 procedures, Mehdizadeh et al investigated the technical details the learning curve associated with DBE (11). The performance parameters from each center's initial 10 cases were compared to the subsequent examinations. The main outcome measurements were exam duration, depth of insertion, and findings on DBE examination. DBE was introduced by mouth in 149 (63%) cases, by rectum in 77 (33%) cases. The mean ( $\pm$ SD) duration was  $109.1 \pm 44.6$  minutes for the first 10 cases and  $92.4 \pm 37.6$  minutes for subsequent cases ( $P = .005$ ) but did not change for rectal DBE procedures. There was no change in mean depth of insertion, but the mean fluoroscopy time declined significantly ( $P = .025$ ). Diagnostic or therapeutic maneuvers were performed in 64% of cases; DBE led to a diagnosis in 81 (43%) patients. One perforation occurred (0.4%). Per-rectal cases failed to reach the small bowel in 24 (31%) cases (11). The authors concluded that there was a significant decline in overall procedural time and fluoroscopy time after the initial 10 DBE cases. There was no improvement in performance parameters when DBE was performed via the rectal approach despite increased, but limited, operator experience (11). Although more data of additional centers are needed, we believe that knowledge of this technical data may be helpful for endoscopists planning to perform DBE, to plan the caseload in individual endoscopy units and for establishing baselines for DBE skill certification. Future studies using the therapeutic DBE and comparing the learning curve using both types of endoscopy may improve our knowledge on the learning curve of DBE. Nonetheless, it appears that a significant amount of time and a minimum of 10-15 procedures are required to acquire the skills necessary to perform DBE.

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**VI. Chapter 5.**

Utility of double-balloon enteroscopy  
for the evaluation of malabsorption

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**Abstract:**

**Introduction:** Occasionally, patients with malabsorption represent a diagnostic challenge. Double-balloon enteroscopy (DBE) allows deep and detailed examination of the small bowel.

**Aim:** The aim of this study was to determine the diagnostic value of DBE in patients with malabsorption of unclear origin.

**Methods:** DBE was performed in a total of 12 patients with clinical malabsorption. Biopsy specimens were taken from macroscopic lesions or from examined small bowel at three different levels of scope insertion depth. Tissue specimens were evaluated with standard hematoxylin and eosin, the modified Marsh classification and, when indicated, special stains for amyloidosis.

**Results:** Fifteen DBE were successfully performed in 12 patients without complications. DBE with small bowel biopsies yielded a diagnosis in 8 patients (67%). A new diagnosis was reached in 4 patients (33%). The new diagnoses included: Crohn's disease, primary intestinal lymphagiectasia and jejunal amyloidosis. In none of these 4 patients did the duodenal biopsies yield a diagnosis. Also, DBE excluded enteropathy-associated T-cell lymphoma (EATL) and/or ulcerative jejunitis in symptomatic celiac disease patients.

**Conclusions:** DBE had a diagnostic value of 42% in patients with malabsorption of unclear origin. In addition DBE was useful to rule out complications of long-standing celiac disease such as ulcerative jejunitis or EATL. DBE should be reserved for patients with unexplained malabsorption. DBE with jejunal and ileal biopsies appears to have a diagnostic value in patients with malabsorption, even when duodenal biopsies are histologically normal.

**Introduction:**

Malabsorption can be due to a wide range of processes including luminal, mucosal or submucosal etiologies (1-3). Although a diagnosis can be reached in most patients with malabsorption, occasionally there are patients in whom a specific diagnosis cannot be reached using standard methods. Both, capsule endoscopy (CE) and double balloon endoscopy (DBE) have improved our ability to visualize the mucosa of the small bowel (4-7). CE was recently proposed as another potential diagnostic method for the evaluation of patients with malabsorption and celiac disease, refractory Whipple's disease or graft-versus-host disease (8-10). However, using CE, lesions may only be depicted without the ability to obtain samples for histological examination. DBE allows for a detailed examination of the small bowel mucosa, obtain biopsies, and perform endoscopic interventions. In the present study, we investigated for the first time whether DBE detects mucosal lesions in malabsorption patients in segments of the small bowel that are usually not accessible to standard endoscopy. Therefore, the aim of this study was to determine the diagnostic value of DBE in patients with malabsorption of unclear origin.

## Patients and Methods

Twelve patients who were evaluated for malabsorption of small bowel origin at the Magdeburg University Medical Center (Otto von Guericke University, Magdeburg, Germany) were included. Exclusion criteria comprised pregnancy, clinical suspicion of bowel obstruction and inability to provide informed consent. The study was conducted and carried out in accordance to the Helsinki Declaration. The patients provided written informed consent to undergo endoscopy with the DBE after the endoscopist and attending physician had explained the procedure in detail to them. DBE was performed using Fujinon intestinoscopes (Fujinon EN-450 P5 and EN-450 T5, Fujinon Corporation, Saitama City, Japan). The technical details of DBE using this DBE have been presented in detail elsewhere (11). Depth of intestinoscope insertion into the small bowel was calculated based on the method described by May et al (12). Patients underwent small bowel cleansing on the day before the procedure using 4 Lt of a standard colon lavage solution (Kleanprep, Germany) and underwent the procedure after an overnight fast. All procedures were performed using conscious sedation with midazolam and disoprivan. An additional physician administered the sedatives.

Before DBE, all patients had undergone a previous thorough diagnostic workup, which included laboratory tests (hemoglobin, hematocrit, white blood count, differential, blood chemistries, liver function tests, iron studies, vitamin B12 and folate levels, albumin, kidney function tests), serological tests for celiac disease (anti-tissue transglutaminase, anti endomysial antibodies and anti gliadin antibodies), D-xylose test, stool fat estimation, as well as esophagogastroduodenoscopy (EGD) with duodenal biopsies and ileocolonoscopy with terminal ileum biopsies. All patients also underwent abdominal ultrasonography. In selected cases the following radiological imaging was performed: CT scan, MRT enterography. Two patients also underwent capsule endoscopy (CE) (Note: CE just recently became available in our institution). Malabsorption was defined on clinical and laboratory basis which included: lower extremity edema, alopecia, anemia, hypoalbuminemia, positive D-xylose test, prolonged prothrombin time, deficit of vitamins A, E, B12 and/or folic acid. During DBE the small bowel mucosa was assessed macroscopically and with the water immersion technique for *a priori* defined lesions which included: thinning or flattening of villi, scalloping, mosaicism, nodular appearance of the mucosal surface, presence of submucosal vessels, erosions, ulcers and tumors. An erosion was defined as a superficial defect of the mucosal surface less than 3 mm. An aphtha was defined as a raised erosion surrounded by a red halo. Ulcers were defined as deep mucosal defects larger than 3 mm in diameter. The shapes of erosions and ulcers were: round, with heaped up borders, stellate, linear or punched out lesions. Endoscopic findings were considered jejunal if they were found in the proximal 3-4 meters. The proximal ileum was defined

as the small bowel located 4 meters distal to the pylorus. The terminal ileum was defined as the distal 50 cm of the small bowel. A successful anal DBE was defined as intubation and inspection of at least 25 cm of terminal ileum. Biopsies were obtained using a forceps designed for use with the DBE (Fujinon Europe, Germany).

**Histological assesment:**

Small bowel biopsy specimens were fixed and preserved in 10% formalin for histopathological and immunohistochemical evaluation. In patients with suspicion of sprue, besides hematoxylin-eosin staining, anti-CD3 (DakoCytomation, Glostrup, Denmark) staining was performed for optimal assessment of the number of intraepithelial lymphocytes. Duodenal and small bowel biopsies were evaluated according to the modified Marsh criteria.

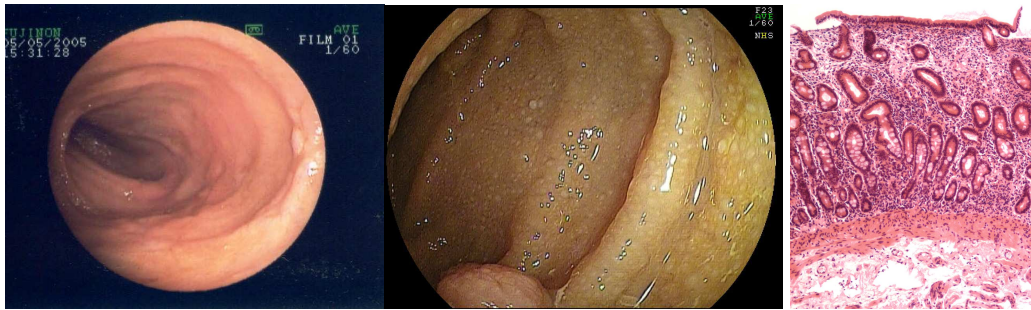
In lymphangiectasia immunohistochemical evaluation included staining with anti-CD3, anti CD-31 and anti-CD34 to distinguish between blood vessel and lymphatic capillars. Congo red-staining in polarized light, anti-amyloid P-component antibody and anti-lambda light chain-antibody were performed in one case, after histology revealed small amounts of amyloid deposits in the jejunum.

## Results

The demographic, clinical and laboratory characteristics of the 12 patients with malabsorption who underwent DBE between February 2005 and July 2007 are summarized in Table 1. All patients were symptomatic and were suffering from chronic diarrhea and had clinical symptoms of malabsorption. Fifteen DBE were successfully performed in 12 patients, (2 patients anal and oral DBE, 10 oral DBE in 9 patients, and one anal DBE in one patient) without procedure-related complications. The median-depth of insertion of the intestinoscope was 225 cm (range 80-550 cm) beyond the pylorus and of 35 cm from ileo-cecal valve in the patient with anal approach (range 25-80 cm). A total small bowel examination was possible in two patients: in one patient the cecum was reached twice from the oral route. In both cases examined using both the oral and anal route, approximately 80-90% of small bowel could be examined. The mean duration of the procedure was 48 min (range 35–70 min). Conscious sedation with midazolam low dose (2-3 mg) followed by disoprivan 280 to 470 mg was performed in 11 patients, the 4-year old patient received general anesthesia.

Endoscopic findings included: flattening or disappearance of the villi, loss of folds and scalloping, easy visualization of submucosal vessels, aphtae, erosions, ulcers, pseudopolyps and lymphangiectasias. The endoscopic findings for each patient are depicted in Table 1. DBE with small bowel biopsies yielded a diagnosis in 8 patients (67%), this was new in 5 cases (42%) (lymphangiectasia, Crohn's disease and amyloidosis) and confirmed in 3 patients (25%). The new diagnosis included: Crohn's disease, primary intestinal lymphangiectasia and jejunal amyloidosis. The most striking findings were in patients with amyloidosis, refractory celiac disease, Crohn's disease and primary lymphangiectasia (Figure 1). The patient with amyloidosis showed a localized, 4 x 5 cm segment of edematous mucosa and plump ulcerated folds in the proximal jejunum (Figure 2). These ulcers were irregular, deep, with heaped up borders and stellate-shaped, similar to Crohn's disease, with the exception of a bluish-red discoloration. The patient with Crohn's disease showed erosions and ulcers localized to the terminal ileum. The patient suffering from Cronkhite Canada-syndrome had giant fold gastritis and pseudopolyps of the colon. Interestingly, the duodenum and jejunum were characterized by severe atrophic changes (Figure 3). In the jejunum the villi were not only atrophic but they were also elongated, with finger-like projections. In this patient, histology demonstrated classic findings of celiac disease (Marsh 3), but repeated celiac antibody testing remained negative. The clinical and histological features of this patient improved on steroids and magnesium supplementation. In Case 3 a diagnosis of Crohn's disease was finally reached after histopathological study of a full thickness ileal resection obtained laparoscopically. Histology revealed non-caseating granulomas. This patient underwent two DBE with multiple

biopsies, which were always interpreted as “non-specific” inflammation. This was in marked contrast with the severe endoscopic appearance of the ileum, which prompted us to include a lymphoma in the differential diagnosis, which was the reason why she underwent a laparoscopy. Overall, histology confirmed endoscopic findings in 8 patients, but interestingly, in three patients with clear endoscopic features of mucosal atrophy the biopsy was negative and in one patient with intestinal lymphangiectasias demonstrated by CE and DBE, the histology was also negative. Histological findings of the duodenum were normal in four patients with isolated deep small bowel disease: Crohn’s disease of the ileum, primary lymphangiectasia and jejunal amyloidosis. In the remaining patients the duodenal findings correlated with the jejunal pathology.



**Figure 1.** Amyloidosis

**Figure 2.** Lymphangiectasia

**Figure 3.** Celiac disease

**Table 1:** Demographic, clinical and laboratory characteristics of the patients with malabsorption

N°	Age	Sex	Indication	Endoscopic findings	Histology/ Diagnosis	Alb	Ca	Hb	MCV
1	54	f	Alopecia, dysgeusia, weight loss, crural edema, hypoalbuminemia, deficit of vit. B12	complete villous atrophy	Increased intraepithelial lymphocytes, Marsh type IIIc/ Cronkhite Canada Syndrome	27,1	2,00	7,2	97
2	57	m	weight loss, anemia, abdominal pain, recurrent vomiting	Edematous and ulcerated mucosa, ulcerative jejunitis	mucosal and submucosal AL-amyloid deposits/ Amyloidosis	33,5	N	7,4	N
3	78	f	Abdominal pain, intestinal obstruction, diarrhea, hypoalbuminemia, anemia	Ulcerative ileitis, pseudopolyps, lymphangiectasia, erosions, aphthae	Chronic inflammation, fibrosis, non-caseating granulomas (laparoscopy)/ Crohn's disease	32	2,14	6,7	N
4	37	m	Perianal fistulas, diarrhea, hypoalbuminemia,	villous atrophy	Histology: normal Final diagnosis: Hyper-IgE-syndrome	24,7	2,07	5,7	96
5	4	m	diarrhea, hypoalbuminemia	Lymphangiectasias, exsuding of white fluid after biopsy, diffuse edema of folds, plump villi, pseudopolyps,	Lymphangiectasias/ Primary lymphangiectasias	25,5	N	N	73
6	65	f	Diarrhea, hypoalbuminemia, anemia	Mucosal edema of distal jejunum and mild scalloping of folds, lymphangiectasia	Normal Final diagnosis: unknown	28	N	5,7	90
7	72	m	Refractory celiac disease, hypoalbuminemia	Villous atrophy, scalloping folds, lymphangiectasia	subtotal atrophy, increased intraepithelial T-lymphocytes (>40/100 epithelial cells)/CD	32	1,5	N	98
8	42	f	Hypocalcemia, abdominal pain, diarrhea, intolerance to milk products	Villous atrophy, scalloping folds, edematous mucosa, micronodularity	Atrophy of folds, crypts hyperplastic, increased intraepithelial lymphocytes, Marsh type IIIc/CD	35,8	1,59	N	100
9	32	f	Refractory celiac disease, hypoalbuminemia	plump and diminished folds, scalloping of folds, lymphangiectasia, exuding of white fluid after biopsy	Subtotal/ total atrophy, increased intraepithelial T-lymphocytes, celiac disease Marsh type I/CD	28	2	N	N
10	23	f	Hypoalbuminemia, recurrent crural edema	Lymphangiectasias, diffuse edema of folds, plump villi	Primary intestinal lymphangiectasia	20,9	1,84	N	N
11	59	m	Chronic diarrhea, chronic hepatitis B, lower abdominal pain, anemia	mucosal atrophy, plump folds	Normal	34,9	2,07	6,2	N
12	65	m	Diarrhea, hypoalbuminemia	Villous atrophy, plump folds	Unspecific inflammation, flattened villi	28,3	N	N	N

Alb=Albumin: normal value 35-52 g/l; Ca: Calcium: normal value 2,15 – 2,55 mmol/L; MCV: mean corpuscular volume 80-95 fl; Hb: haemoglobin 7,4-10 mmol/l; N: normal; CD: celiac disease; m=male; f=female



## **Discussion:**

This is the first study investigating the utility of DBE in patients with malabsorption of small bowel origin. We found that DBE had a high diagnostic yield in a selected group of patients with malabsorption in whom previous extensive investigations had been negative. DBE was useful to reach a new diagnosis in 33% and to confirm the diagnosis in two thirds of patients investigated. This high yield does not mean that DBE should be used as a primary tool in patients with malabsorption. Our study rather demonstrates that malabsorptive diseases with primary small bowel mucosal involvement could be adequately evaluated with DBE. In our study, DBE allowed for a detailed characterization of the morphology of the small bowel mucosa, permitting a proper localization and extent of small bowel involvement. In addition, small bowel biopsies were obtained for histological analysis. This was most helpful in the patients with lymphangiectasias and jejunal amyloidosis. Nonetheless, despite the ability to analyze the mucosa with histological methods a diagnosis could not be reached in up to one third of patients. Three patients had clear endoscopic abnormalities but the histology was entirely normal. In addition, in one patient with high suspicion of Crohn's disease based on her clinical and endoscopic findings, the histology was repeatedly negative, and it was not until a full-thickness small bowel specimen was obtained via laparoscopy that a final diagnosis was reached.

Our case series confirms that reaching a diagnosis in patients with malabsorption of small bowel origin can be a challenge, and that DBE might be a useful method in this setting. Nevertheless, it is clear that the investigation of malabsorption should follow standardized algorithms (13). DBE appears to be useful when there is a high suspicion that the mucosal phase of absorption is affected. Although our series is small, it provides information on the potential place of DBE in the diagnostic algorithm of these patients. DBE appears to have its greater value in patients in whom standard upper and lower endoscopy have been negative, as well as in patients in whom it is important to rule out complications of long-standing or severe celiac disease. This latter issue was elegantly addressed by Mulder's group in Amsterdam (14). Hadithi et al prospectively assessed the value of DBE in patients with refractory celiac disease. Twenty-four procedures were successfully performed in 21 patients. Enteropathy-associated T-cell lymphoma (EATL) was found in five patients (24%) as circumferential, discrete, or confluent ulcerations. Furthermore, DBE could exclude the presence of EATL in four patients that was suggested by abdominal computerized tomography. This study demonstrated that complications of refractory celiac disease like ulcerative jejunitis or EATL could efficiently be detected or excluded by DBE (14).

Although we are presenting the first study using DBE to investigate malabsorption, there is one previous study evaluating the use of push enteroscopy in patients with chronic diarrhea and

biological signs of intestinal malabsorption but no evidence of celiac disease. In that study Cuillerier et al. found that push enteroscopy had a diagnostic value of only 12% (15). In that study in none of the patients with normal duodenal biopsies did jejunal biopsies add any new diagnosis (15). We believe that our diagnostic yield was higher because DBE allowed for deeper inspection of the small bowel. The study of Hadithi et al. in patients with long-standing celiac disease and EATL further confirms the utility of DBE for investigating more extensive parts of the small bowel (14). The superiority of DBE over push enteroscopy in terms of depth of visualization of small bowel has also clearly demonstrated by Matsumoto et al. (7).

Although small our study is the largest series of patients with malabsorption being investigated by DBE. Potential limitation of the study are: a) the relatively limited number of patients and b) the patient selection bias in a referral center like ours. However, our patients reflect the population seen at similar tertiary centers throughout the world. In addition, our patients were carefully evaluated before undergoing DBE, following accepted algorithms for the work-up of malabsorption.

In summary, DBE had diagnostic value of 67% in patients with malabsorption of unclear origin. DBE with jejunal and/or ileal biopsies provided a new diagnosis in 33% of patients with malabsorption, even when duodenal biopsies were histologically normal. In addition DBE was useful to rule out complications of long-standing celiac disease such as ulcerative jejunitis or EATL. DBE should not be used in the initial stages of the work-up of malabsorption, but rather be employed in patients in whom an extensive work-up has been conducted and mucosal disease is a likely cause of malabsorption.

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**VII. Chapter 6.**

Incidence of bleeding lesions within reach of conventional upper  
and lower endoscopes in patients undergoing double balloon  
enteroscopy for obscure GI bleeding

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## **Abstract**

**Background and Aims:** Double balloon enteroscopy (DBE) is a useful method for evaluation of obscure gastrointestinal bleeding (OGIB). The study aim was to determine the incidence of lesions within reach of conventional upper and lower endoscopes as the cause of OGIB in patients referred for DBE.

**Methods:** All patients undergoing DBE for OGIB at a university hospital were studied. OGIB was defined according to AGA guidelines.

**Results:** 143 DBEs were performed in 107 patients for obscure overt (n=85) and obscure occult (n=22) GIB. Lesions outside the SB as possible sources of GIB were found in 51 patients (47.6%) and a definite source of bleeding outside the small bowel (SB) was detected in 26 patients (23.4%). Lesions considered to explain a definite source of GIB were: gastric ulcer (n=3), duodenal ulcer (n=3), Cameron's lesions (n=2), gastric antral vascular ectasias (n=4), radiation proctitis (n=1), radiation ileitis (n=2), colon angiodysplasias (n=3), and others (n=7).

**Conclusions:** The frequency of non-small bowel lesions definitely explaining the source of GI bleeding in patients referred for DBE was 24.2%. Therefore, repeat EGD and ileocolonoscopy should be taken into consideration before DBE.

**Introduction:**

The most common indication for performing double balloon enteroscopy (DBE) is obscure gastrointestinal bleeding (OGIB) (1-4). OGIB accounts for approximately 5% of all GI bleeds, and is currently defined as bleeding from the GI tract that persists or recurs without an obvious etiology after a negative initial EGD and colonoscopy, and can be categorized into obscure overt and obscure occult bleeding based on the presence or absence of clinically evident bleeding (5). Because most OGIB originate in the small bowel, distal to the papilla of Vater and proximal to the ileocecal valve, OGIB is also rightly called mid-GI or mid-gut bleeding (5,6). Midgut bleeding is currently evaluated using either capsule endoscopy (CE) and/or balloon-enteroscopy (2,4,7,8). However, bleeding sources within reach of conventional upper and lower endoscopes can be missed because of inadequate endoscopic investigation, small size, atypical location and non active bleeding. One of the most frustrating experiences for a double balloon or capsule endoscopist is to find lesions outside the small bowel, such as gastric or colonic angiodysplasias, given that usually upper and lower endoscopies have been performed prior to the DBE procedure. In addition, missing these lesions may result in prolonged diagnostic evaluation, patient inconvenience and increased costs. The magnitude of the problem of finding abnormalities outside the small bowel on DBE is not well known.

The aim of this study was to determine the incidence of lesions outside the small bowel potentially responsible for GI bleed in patients undergoing DBE for the indication of OGIB.

## **Patients and Methods:**

Consecutive patients who were evaluated for OGIB between October 2004 and August 2008 at University of Magdeburg Medical Center (Universitätsklinikum Magdeburg, Otto von Guericke University, Magdeburg, Germany) were included and their data recorded in a prospectively collected database. The study was approved by the ethics committee of the University of Magdeburg and conducted out in accordance to the Helsinki Declaration.

All patients provided written informed consent to undergo DBE, including endoscopic therapy. Data abstracted for analysis from the prospectively collected database included patient's demographics, past medical history, laboratory values, indication for endoscopy, history of comorbid illnesses, social history, medications, reports of prior endoscopies, results of endoscopic biopsies (if any), and technical and endoscopic findings on DBE. OGIB was defined according to AGA guidelines (5). Thus, all patients underwent EGD and colonoscopy prior to DBE. These endoscopies were performed within one week of DBE.

DBE was performed using Fujinon enteroscopes (Fujinon FN 450P 5/20, EN-450T5, Fuji, Fujinon Corp., Saitama, Japan). From October 2004 to February 2006 all DBE were performed using the diagnostic DBE (FN 450P) and from February 2006 onwards all DBE for OGIB were performed using the therapeutic DBE (EN-450T5). With the availability of both DBEs, it is the policy in our unit to perform all DBE that have potential therapeutic consequences with the EN-450T5 scope. The characteristics of the DBE have been presented in detail elsewhere (2,9). Depth of enteroscope insertion into the small bowel was calculated based on the method of May et al (10). The DBE was considered of limited technical success if <20 cm of small bowel were visualized. All patients underwent small bowel cleansing before the procedure using a standard colon lavage solution (Kleanprep®, Norgine, Marburg, Germany) and underwent the procedure after an overnight fast. All the DBE were performed in our endoscopy suite dedicated for fluoroscopic procedures. Fluoroscopy was performed using a Philips C-arm (Philips®, Best, Holland). All procedures were performed using conscious sedation with propofol (Lipuro®, Braun, Melsungen, Germany, which was administered by one physician.

Any mucosal lesion not located in the small bowel, distal to the papilla of Vater and proximal to the ileocecal valve was considered "outside the small bowel" (i.e. outside the reach of a gastroscope and colonoscope). The terminal ileum was not included in this definition as a 100% ileal intubation is not always achievable. We used a clinical classification to categorize bleeding lesions (8). Nakamura classifies GI lesions based on the clinical action taken to treat them into 1) A1: immediate haemostatic measures required, and 2) A2: close observation required). If patients had more than one diagnosis the likely cause of bleeding was defined based on endoscopic and



clinical findings. For example if the patient with melaena was found to have varices with stigmata of bleeding and few small bowel erosions or portal jejunoenteropathy, the varices were considered to be the cause of GIB. Similarly, if the patient had occult obscure GIB and during endoscopy colonic diverticuli were found, but the patient also had multiple angiodysplasias of the small bowel, the latter were considered the likely cause of bleeding. Furthermore, lesions were defined as “possible” or “definite” source of bleeding, based on clinical criteria. If the patient had overt GI bleeding (melena or hematochezia) none of the following lesions were considered as “definite” cause of acute GI bleed: erosive esophagitis grade A or B, small esophageal varices without stigmata of bleeding or red whale signs, non-specific duodenitis, minimal gastric antral vascular ectasias, single colonic angiodysplasias, hemorrhoids without stigmata of bleeding. If the patient presented with occult GI bleeding any lesion was categorized as “possible”, except colon diverticulosis, esophageal varices and hemorrhoids.

#### **Determination of the primary route of insertion (oral or antegrade versus anal or retrograde)**

The choice of either the oral or the anal route depended on the suspected location of the lesions within the small bowel based on the clinical manifestations (e.g. melena or hematochezia), results of laboratory, radiological and previous endoscopic examinations. In cases of obscure overt GIB the route of insertion was dictated by the color of the stool; in cases of melena the oral approach was preferred, whereas in the presence of hematochezia the anal approach was used first. If a patient had undergone CE, we used the results of this test to guide the insertion route. CE was not available at our institution until the latter part of 2006. A combined oral and anal approach was employed if no source of bleeding could be identified using the initial route, i.e. if one DBE route did not yield any diagnosis the opposite route was used for the second investigation. To confirm total enteroscopy India ink marking of the small bowel was performed. Total enteroscopy was also confirmed if the cecum or colon could be visualized when using the oral approach. Complications of DBE were defined according to standard criteria (11). Descriptive statistics were employed to describe the patient’s demographics and clinical characteristics, presenting means and ranges.

#### **Results:**

We performed 143 DBE procedures in 107 patients. The type of OGIB was obscure overt (n=85) and obscure occult (n=22). The characteristics of the study group are presented in Table 1. The route for DBE was oral (n=108), anal (n=35). The mean duration of the procedure was 75 minutes, (range 25-150). The mean radiation exposure was 185 dGy/cm<sup>2</sup> (range 0-1462). The mean small bowel insertion was 300 (range 30–540 cm, excluding cases with limited technical success, see

below and table 2). The depth of insertion was deeper when performing per oral DBE (mean 224 cm, range 30 to 540), as compared with anal DBE (mean 55 cm, range: 0 to 120 cm) ( $p < 0.01$ ). In 10 patients (9.3%) it was possible to evaluate the entire small bowel (in 7 patients using both oral and anal routes, and in 3 patients it was possible to intubate the cecum via the oral route). There were a total of 6 DBEs with limited technical success (5 anal, 1 oral) (Table 2). In 5 anal DBE it was either impossible to intubate the ileum or less 20 cm of ileum were visualized. In the oral DBE with limited technical success the efferent limb could only be intubated 40 cm distal to the anastomosis. Further advancement was impossible due to adhesions that resulted from previous surgery.

A potential small bowel etiology of GI-bleeding was found in 69 patients (64.5%). Findings included angioectasias/angiodysplasias (n=34), erosive and NSAID-induced small bowel injury or jejunal ulcers (n=12), small bowel tumors (n=6), Dieulafoy's lesion (n=3), portal-hypertensive jejunopathy (n=3), Crohn's disease (n=3), jejunal varices (n=2) and others (n=6) (Table 3).

Lesions within reach of conventional upper and lower endoscopes either as definite or possible sources of GI bleeding were found in a total of 51 patients (47.6%). Findings within reach of conventional upper and lower endoscopes included colonic diverticulosis (n=11), gastric or duodenal ulcers (n=6), colonic angiodysplasias (n=5), gastric antral vascular ectasias (n=5), Cameron's lesions, (n=2), hemorrhoids (n=1), esophageal varices (n=1), gastritis (n=4), and others (n=16) (Table 4).

A definite source of bleeding within reach of conventional upper and lower endoscopes was detected in 26 patients (24.3%). Lesions considered to explain a definite source of GI blood loss were: gastric ulcer (n=3), duodenal ulcer (n=3), Cameron's lesions (n=2), gastric antral vascular ectasias (prominent) (n=4), radiation proctitis (friable and bleeding on minor touch) (n=1), radiation ileitis (n=2), duodenal angiodysplasias (active bleeding) (n=1), hemorrhoids with stigmata of recent bleed (n=1), colon angiodysplasias (multiple cecal angiodysplasias) (n=3), colon diverticulosis (in patients with hematochezia and in the absence of blood in the small bowel) (n=3), colonic Crohn's disease (n=1), anastomotic ulcers (n=1) (friable mucosa, spontaneous bleeding) (Table 4).

A possible source of bleeding within reach of conventional upper and lower endoscopes was found in 25 patients (23.4%) (Table 4). In 20 patients (18,7%) a definite bleeding source could neither be identified by DBE nor by EGD and colonoscopy.

**Table 1. Demographic and clinical characteristics of the study group.**

<b>Total</b>	<b>n = 107 patients</b>	
<b>Age (mean ± SEM)</b>	<b>64 ±10.9</b>	<b>(range 19 - 88)</b>
<b>Sex</b>	<b>Female</b>	<b>40 (37.4%)</b>
<b>DBE, total</b>	<b>n = 143</b>	
<b>Oral DBE only</b>	<b>n=87</b>	
<b>Anal DBE</b>	<b>n=14</b>	
<b>Oral and anal DBE</b>	<b>n=21</b>	
<b>Indications</b>	<b>Obscure overt GIB</b>	<b>85</b>
	<b>Obscure occult GIB</b>	<b>22</b>

**DBE, double-balloon enteroscopy; GIB=gastrointestinal bleeding;**

**Table 2.****DBE of limited technical success: Clinical, technical, endoscopic aspects and final diagnosis**

<b>Route</b>	<b>Indication</b>	<b>Endoscopic/technical aspects</b>	<b>Finding</b>	<b>Final diagnosis</b>
<b>Oral</b>	<b>hematochezia</b>	<b>partial gastric resection and Billroth II anastomosis</b>	<b>Active bleeding from anastomosis</b>	<b>Anastomotic ulcers</b>
<b>Anal</b>	<b>hematochezia</b>	<b>Oral DBE was normal</b>	<b>Massive diverticulosis and fresh blood in the colon</b>	<b>Colon diverticulosis</b>
<b>Anal</b>	<b>hematochezia</b>	<b>Intubation up to 15 cm of ileum normal</b>	<b>Hemorrhoids with active bleeding</b>	<b>Hemorrhoids</b>
<b>Anal</b>	<b>hematochezia</b>	<b>Failed ileum intubation</b>	<b>Multiple cecal angiodysplasias</b>	<b>Cecal angiodysplasias</b>
<b>Anal</b>	<b>Hemoccult + anemia</b>	<b>Normal oral DBE (350 cm of small bowel visualized)</b>	<b>Failure to intubate ileum</b>	<b>No diagnosis</b>
<b>Anal</b>	<b>Hemoccult + anemia</b>	<b>Oral DBE: multiple jejunum angiodysplasias</b>	<b>Failed ileal intubation</b>	<b>SB angiodysplasias</b>

DBE=double balloon enteroscopy;

\* Efferent limb could only be intubated 40 cm distal to the anastomosis. Further advancement was impossible due to adhesions that resulted from previous surgery.

**Table 3. Small bowel diagnosis in the study cohort.**

	Total
<b>Angioectasias / angiodysplasias</b>	<b>34</b>
<b>NSAID-induced small bowel injury</b>	<b>10</b>
<b>Small bowel tumors*</b>	<b>6</b>
<b>Dieulafoy's lesion</b>	<b>3</b>
<b>Portal hypertensive jejunopathy</b>	<b>3</b>
<b>Crohn's disease</b>	<b>3</b>
<b>Undiagnosed ulcers</b>	<b>2</b>
<b>Jejunal varices</b>	<b>2</b>
<b>Polyps**</b>	<b>2</b>
<b>Small bowel diverticulum</b>	<b>1</b>
<b>Giant arteriovenous malformation</b>	<b>1</b>
<b>Ischemic jejunitis</b>	<b>1</b>
<b>Leucocytoclastic vasculitis (Henoch-Schönlein purpura)</b>	<b>1</b>

A potential small bowel etiology of GI bleeding was found in 69 patients (64.5%).

\*Tumors included 3 adenocarcinomas, 2 neuroendocrine tumors and 1 metastasis from testicular cancer

\*\*Ulcerated lipoma, inflammatory polyp

**Table 4. GI bleeding sources within the reach of conventional endoscopes**

	Possible		Definite		Total
	Obscure occult	Obscure overt	Obscure occult	Obscure overt	
Colon diverticulosis	5	3	0	3	11
Colon angiodysplasias	1	1	1	2	5
Haemorrhoids	0	0	0	1	1
Portal hypertensive colonopathy	1	0	0	0	1
Segmental colitis (colonic Crohn's disease or ischemic colitis)	1	0	0	2	3
Radiation proctitis	0	0	0	1	1
Radiation ileitis	0	0	2	0	2
Unspecific ileitis	1	1	0	0	2
Gastric or duodenal ulcers	0	0	2	4	6
GAVE	1	0	3	1	5
Cameron's lesions	0	0	1	1	2
Duodenitis	3	0	0	0	3
Esophageal varices	0	1	0	0	1
Erosive esophagitis	2	0	0	0	2
Gastritis	4	0	0	0	4
Duodenal angiodysplasias	0	0	1	0	1
Anastomotic ulcer	0	0	0	1	1
<b>Total (% of study cohort, n=107)</b>	<b>19</b>	<b>6</b>	<b>10</b>	<b>16</b>	<b>51</b>
	<b>(17,8%)</b>	<b>(5,6%)</b>	<b>(9,3%)</b>	<b>(14,9%)</b>	<b>(47,6%)</b>
<b>Total</b>	<b>25 (23,4%)</b>		<b>26 (24,2%)</b>		<b>51 (47,6%)</b>

GI=gastrointestinal; GAVE: gastric antral vascular ectasias

Some lesions were not considered as neither definite nor possible cause of GIB (please refer to text, materials and methods).

**Discussion:**

In this large study we found that in patients investigated for OGIB with DBE it is common to find lesions within reach of conventional upper and lower endoscopes that could explain the obscure GI blood loss either as a primary or associated cause. Lesions within reach of conventional upper and lower endoscopes were found in more than half the patients investigated and these were present in both the upper and lower GI tract. Although not all these lesions could explain the GI blood loss in patients with OGIB, such as colon diverticulosis, duodenitis and haemorrhoids, it is evident that many definite bleeding lesions were missed during EGD and colonoscopy performed before DBE. These lesions included peptic ulcers, colonic angiodysplasias, Cameron's lesions and radiation proctitis. Lesions such as these can be considered a definite source of GI blood and were found in one 24.3% of patients undergoing DBE for suspected small bowel bleeding. Although similar data regarding the yield of push enteroscopy were published more than a decade ago, our study has the advantage of having investigated both proximal and distal lesions (12, 13). In the push enteroscopy studies only missed upper GI lesions were evaluated. Because push enteroscopy is performed only via the oral route there are no data available regarding missed lesions in the lower GI tract. Furthermore, data from previous push enteroscopy studies cannot just be extrapolated to DBE. It is now clear that the depth of insertion of push enteroscopy is less than that of double balloon enteroscopy. Thus, DBE permits a better appreciation of small bowel lesions than other invasive endoscopic methods and is thus considered the current gold standard to diagnose and treat a large variety of small bowel disorders. Therefore, we believe that our study has several potential relevant clinical implications. Firstly, performing an unnecessary DBE will result in patient inconvenience. DBE is an invasive procedure which can result in complications, which albeit low, are associated with significant morbidity. DBE complications are either directly related to the procedure (i.e. perforation and pancreatitis) or due to sedation (i.e. arrhythmias, hypotension, respiratory failure) (11, 14-16). Pancreatitis is a complication which appears to be uniquely associated with balloon enteroscopy (11, 14-16). Secondly, DBE is a demanding and time consuming procedure. Thus, performing an unnecessary investigation adds a strain on the utilization of endoscopic human and material resources. And lastly, in patients with OGIB DBE should be used judiciously and repeat EGD and ileocolonoscopy should be taken into consideration before performing DBE. In addition, performing a capsule endoscopy (CE) may also be helpful. If no lesions are found, CE may obviate the need for an invasive DBE, and if a lesion is detected it would point to the diseased segment to be investigated with the DBE. Therefore, CE and DBE should be viewed as tests complementing each other. Even though performing a CE or repeating EGD and ileocolonoscopy can add to the total costs of care, their use can lead to a specific diagnosis in a significant percentage of patients.

Repeating EGD and colonoscopy in patients with OGIB probably also applies to patients that are referred for CE. In a recent study, Elijah et al. also found that up to 38.8% of patients undergoing CE for OGIB had significant lesions of the upper GI tract such as GAVE, gastric ulcers and Cameron's lesions (17).

Per definition, the vast majority of OGIB should originate from the small bowel, distal to the papilla of Vater and proximal to the ileocecal valve, and thus are called mid-GI or mid-gut bleeding (6). However, the etiology of OGIB may vary depending on various factors including the quality of clinical and endoscopic investigation. As shown in our study, from one fourth to one half of the episodes OGIB may have originated within reach of conventional upper and lower endoscopes. In our cohort, however, not all the lesions within reach of conventional upper and lower endoscopes (e.g. colon diverticulosis) could be considered as the primary culprits of OGIB. Nevertheless, evident lesions such as GAVE, Cameron's lesions and gastroduodenal ulcers can be certainly considered as a definite source of "obscure" overt or occult GI bleeding. In patients with more than one lesion it is difficult to exactly pinpoint the bleeding source. However, by using the Nakamura classification as well as clinical and endoscopic findings we believe that we were able to classify most lesions in the best possible way.

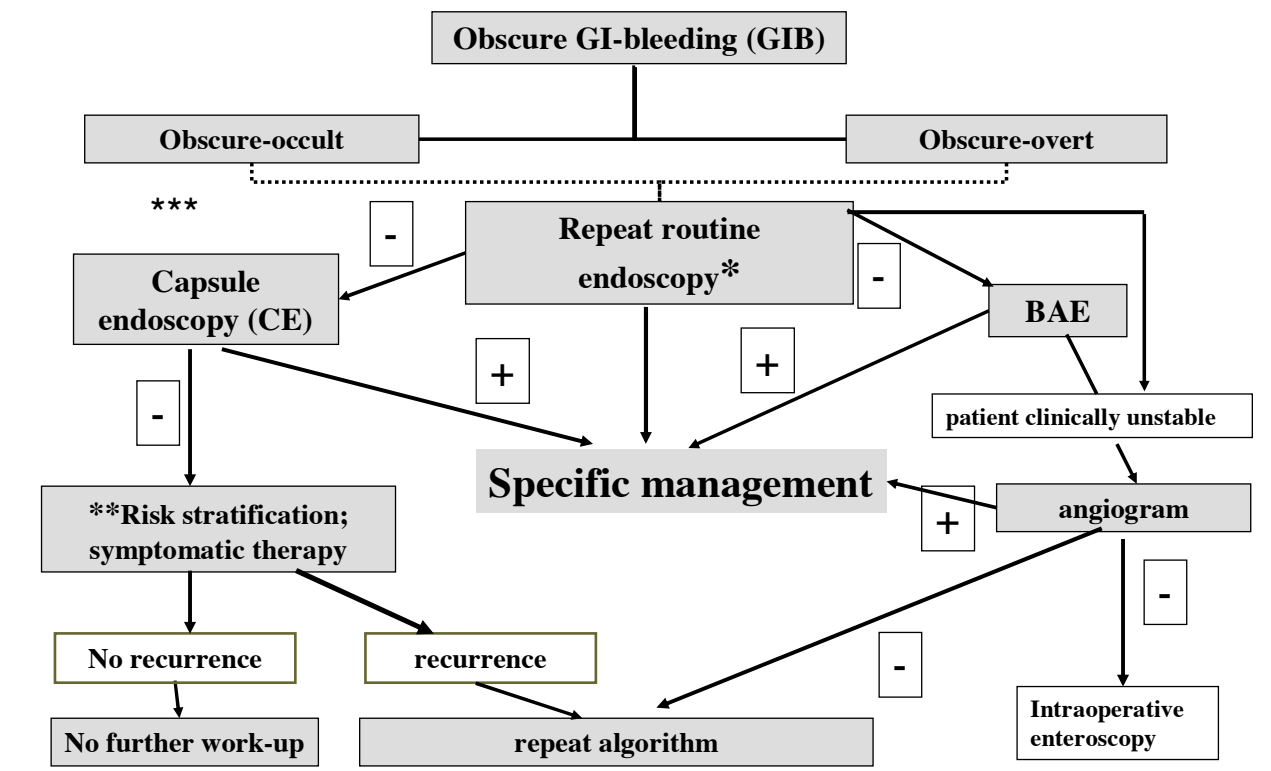
There are various possible explanations of why lesions can be missed. Occasionally their size or location such as Dieulafoy's ulcer or Cameron's lesion precludes their proper visualization. Sometimes a sub-standard colon preparation may impede visualization of cecal angiodysplasias. Furthermore, failure to intubate the terminal ileum may hamper the discovery of ileal ulcers, radiation enteritis or blood emanating from the small bowel. However, we believe that in the current era of video- and high definition endoscopy, these obvious lesions should not be missed. We suspect that several of the "obvious" gastroduodenal ulcers, varices of portal gastropathy were either missed because of operator's inexperience or the performance of a "quick" and/or "superficial" EGD or colonoscopy. Too often we have seen endoscopists in endoscopy units around the world, including ours, perform a "quick" EGD, not even taking enough time for a proper retroflexion. One could argue that by using the oral approach an "EGD" is also performed during DBE. Thus, some endoscopist may feel secure that a DBE will follow when either the EGD or colonoscopy were negative. This is true, and in fact, a thorough DBE should always include an inspection of the upper GI tract. However, the time planning and use of resources is much larger when performing DBE. The AGA guidelines define obscure GI bleeding as bleeding from the GI tract that persists or recurs without any obvious etiology after EGD and colonoscopy (5). The AGA guidelines recommend to repeat EGD or colonoscopy if there is a suspicion of an overlooked lesion (5). However, based on our findings it appears that a routine second look upper and lower



endoscopy is indicated before proceeding with further investigations such as CE and/or DBE (see algorithm, Figure 1). Although it is possible that any operator can miss lesions, a rule of thumb is to definitely repeat the EGD and/or colonoscopy if the endoscopist who performed the initial endoscopy either used suboptimal equipment, has less endoscopic experience, there was inadequate mucosal visualization due to poor colon preparation or there is no clear documentation of the landmarks seen.

We want to acknowledge potential limitations of our study. First, the study was not designed prospectively. However, at our institution we have a prospectively collected database containing the clinical and laboratory information of all patients undergoing DBE. Second, we are a tertiary center, and the pathologies observed here may differ from other settings. Nonetheless, our diagnosis mirrored those of other studies using DBE (1-4). Third, our definition of “possible” and “definite” source of GIB would need confirmation by others. However, this definition is a potential advantage of our study, specially because it is based on commonly applied clinical criteria. In addition, most previous studies did not use any exacter definition for GIB, some even considered gastritis as a bleeding source (12-14, 17).

In summary, we found that the frequency of within reach of conventional upper and lower endoscopes definitely explaining the source of GI bleeding in patients referred for DBE was 24.3%. Therefore, a repeat EGD and ileocolonoscopy should be considered before DBE. And these examinations should be performed thoroughly. At times of limited endoscopic capacities DBE should be employed judiciously in order to reduce patient inconvenience and to better allocate endoscopist, nurses and material resources in the endoscopy unit. Further studies focusing on the clinical and laboratory factors that can predict the etiology of small bowel pathologies in the setting of OGIB are warranted.



\*In your institution (even if EGD and colonoscopy have been performed previously; BAE = balloon assisted enteroscopy;  
 \*\* risk stratification: if high risk continue searching for source of anemia;  
 \*\*\*There is no solid scientific evidence on when to perform CE. Based on the published literature and clinical experience it is recommended to perform CE in patients with obscure occult GIB, followed by DBE if the CE was positive, and to perform DBE if the type of obscure GIB is overt. However, currently, the use of CE will mostly depend on local possibilities.

**Figure 1.** University of Magdeburg Algorithm for the investigation of obscure gastrointestinal bleeding

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VIII. Chapter 7.

Double Balloon enteroscopy assisted virtual chromoendoscopy  
for small bowel disorders- a case series

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**Abstract**

Fujinon intelligent color enhancement (FICE) system is a new, virtual chromoendoscopy technique that enhances mucosal visibility. The objective of this study was to assess the utility of double-balloon enteroscopy (DBE) with FICE-technology (EPX-4400 processor, Japan) for the characterization of various small bowel diseases. Overall, a total of 574 endoscopic pictures were obtained and analyzed. FICE was found to be a helpful method for the evaluation of adenomatous small bowel polyps and angiodysplasias. Its use for the characterization of celiac and Crohn's disease appears to be limited. Overall, FICE may become a useful method that aids in the characterization and provides new insights of small bowel pathologies.

**Introduction:**

Standard dye-based chromoendoscopy techniques enhance the villous details of the gastrointestinal (GI) mucosa (1-3). Currently, two imaging techniques that enhance the mucosal surface without the use of dyes exist (“virtual chromoendoscopy”) (4-7). Both methods are based on narrowing of the bandwidth of the conventional endoscopic image. Whereas with Olympus technology narrow band imaging (NBI) is based on the presence optical filters within the light source of the endoscope which constrain the bandwidth of spectral transmittance, with FICE (Fujinon intelligent color enhancement) the bandwidth of the conventional endoscopic image is narrowed down arithmetically using a computerized spectral estimation technology (4-7). Because this computer is located within the processor, FICE is not dependent on the presence of optical filters inside of the videoendoscope (4, 7).

Whereas different studies have focused on the use of virtual chromoendoscopy in the upper and lower gastrointestinal (GI) tract no data are available for this method in the small bowel (4, 7-9). Here, we assessed the application possibilities and the value of FICE in different small bowel pathologies.

**Case series:**

17 patients (10 female, 7 male; mean age 40 years, range 4-78) underwent double balloon enteroscopy (DBE) assisted virtual chromoendoscopy using FICE (Fuji EN-450 T5/20, (EPX-4400 processor, Fuji Saitama, Japan) (4). All patients or respectively their legal representatives provided informed consent before endoscopy. The study was conducted according to the guidelines of Helsinki and approved by the ethics committee of our institution. Conscious sedation was performed using a combination of intravenous midazolam and propofol.

Similar to the NBI technology of Olympus endoscopes, the digital processing system of FICE is able to switch over between an ordinary image and a virtual image immediately, at any time of the procedure, by a simple push of a button on the handle of the endoscope (4,7). The wavelengths of the various types of FICE were chosen based on previously published data (4). These settings can be also used to evaluate the esophagus, stomach and colon (7). The chosen sets were as follows: set A [or 1]: red (R) 520 nm, green (G) 450 nm and blue (B) 400 nm; set B [or 2] R 500 nm, G 445 nm, B 415 nm,; set C [or 3] R 500 nm, G 470 nm, B 420 nm; set D [or 4], R 500 nm, G 480 nm, and B 420 nm; set E [or 5] R 580 nm, G 520 nm, B 460 nm; and set F [or 6] R 550 nm, G 500 nm, B 470 nm (4). We simplified the letter (or number) classification by focusing on the predominant virtual chromoendoscopy color obtained for four sets: for set A [1] the predominant color is red, for set D [4] the predominant color is blue, for set E [5] the predominant color is orange and for set F [6] the predominant color is green. Figure 1 exemplifies this classification.

*Image Evaluation*

The targeted lesion was observed with standard white light (WL) settings and with FICE. First, two index pictures were obtained using WL. Then at least 2-4 pictures of the same lesion were sequentially obtained using the aforementioned FICE-settings. A total of 574 images were obtained. The following pathologies were evaluated (images are indicated in parenthesis): angiodysplasias n=4 (144); Crohn's disease n=3 (78); NSAIDs enteropathy n=1 (38); malabsorption syndromes: celiac disease n=2 (76); primary small bowel lymphangiectasia n=1 (24), Whipple's disease n=1 (36); polyposis n=5: familial adenomatous polyp syndrome (FAP) n=2 (58), Peutz-Jeghers n=1 (60), B-cell lymphoma n=1 (32), nodular lymphoid hyperplasia (NLH) n=1 (30).

Endoscopic images were stored electronically in \*.tiff format (300 dpi) and randomly allocated to two blinded readers (KM, LCF). No video recordings were stored routinely or evaluated for this study.

*Findings:*



All four FICE spectral modes allowed the visualization and characterization of angiodysplasias (Table 1). However, only the blue mode (R 500 nm, G 480 nm, B 420 nm) permitted an improved characterization of angiodysplasias (Figures 1 A and B). We were able to define various types of angiodysplasias. Whereas the classic simple-shaped angiodysplasias were found most commonly, there were other small bowel angiodysplasias, too, which merely involved a few villi and appeared as a tiny conglomerate of microvessels. However, FICE did not improve the further sub-classification of these vessels. In contrast, erosions had a heterogeneous appearance and acquired a white color upon switching to FICE (Figure 2). However, a true differentiation of angiodysplasias and erosions could not be proven because, for obvious reasons, we did not have a histological gold standard. Small bowel vessels could also be well defined at hepaticojejunostomy using white light and FICE.

The detection or delineation of ulcers and erosions due to Crohn's disease was not improved by FICE. WL was sufficient to locate and define these lesions.

FAP polyps were flat, slightly raised, with irregular borders (Figure 3 A and B). The polyp surface had a cerebriform pit pattern. FICE clearly accentuated the surface contrast, thus enhancing the margin evaluation of FAP polyps. In patients with FAP, FICE aided in the detection of additional polyps (Figures 4 A and B). The whitish surface of these polyps seen during WL endoscopy was markedly enhanced using any FICE setting. In one patient some of the polyps were flat and only visible with FICE (biopsy confirmed adenomas).

Polyps associated with PJS were sessile or pedunculated, with a regular mucosal surface, and a serrated, thickened villous pattern (Figures 5 A-C). The use of FICE did not improve either the characterization or the additional detection of any PJS polyps as compared to standard WL.

The patient with NLH had hundreds of small bowel pseudopolyps (Figure 6 A and B). These pseudopolyps resembled small hamartomatous polyps of PJS. However, the mucosal surface was smoother, non-distorted, with a regular pit pattern and similar in hue to the adjacent tissue, clearly different than the adenomatous polyps seen in FAP.

#### *Celiac disease*

The endoscopic findings in celiac disease included serrated folds, villous atrophy and mosaicism of the mucosa. No erosions or ulcers were found using either white light or FICE. In the presence of mucosal atrophy the submucosal capillary network became more visible. However, FICE did not improve the detection of any mucosal characteristic in CD. The classic endoscopic features of CD were seen similarly using WL or FICE. However, due to its color contrast capabilities and the addition of endoscopic magnification, the characteristics of small bowel villi can be studied nicely using FICE (Figures 7 A-C).

The small bowel mucosa of the patient with Whipple’s disease was edematous, with slightly engorged villi and with multiple white ring-like structures within the mucosa. FICE enhanced the white color of these rings, but it did not lead to the discovery of more such structures or additional lesions or mucosal characteristics not seen on white light endoscopy.

In the patient with primary intestinal lymphangiectasia, the mucosal changes could be better appreciated using FICE but did not reveal any additional findings when compared with standard white light endoscopy (Figures 8A and B). In the patient with B-cell lymphoma the jejunal mucosa was normal with patchy areas of edema, which was more pronounced in proximity to several submucosal tumors. Here the villi were engorged and filled with whitish material.

The inter- and intraobserver variabilities for the classification of small bowel polyps were assessed for each of the polyps (adenomatous versus non-adenomatous). There was excellent intraobserver and interobserver agreement for both white light and FICE (white light [ $\kappa= 0.94$ ], FICE [ $\kappa= 0.96$ ]) and excellent interobserver agreement (white light [ $\kappa= 0.91$ ], FICE [ $\kappa= 0.96$ ]).

**Table 1: Utility of FICE for the evaluation of various small bowel pathologies.**

Condition	FICE		
	worse	same	improved
Angiodysplasias			+
Adenomatous polyp			+
Peutz-Jeghers polyp		+	
Celiac disease		+	
Erosion		+	
Villous pattern of the mucosa		+*	
Crohn’s disease		+	
Whipple’s disease		+	
Primary intestinal lymphangiectasia		+**	

FICE= Fujinon intelligent color enhancement. The evaluation of whether FICE had any influence on the qualitative evaluation of the lesion as compared to white light endoscopy and was divided into three groups: *worse*, *same* or *improved*. ‘*Worse*’ was defined as poor visualization of targeted lesion. ‘*same*’ was defined as no change in visual characterisation and ‘*improved*’ was defined as the ability to better characterize a lesion. Better characterisation could be achieved by either a better definition or delineation (i.e. demarcation) of the targeted lesion.

\* FICE allowed for the visualization of the tiny intravillous capillaries and enhances the submucosal capillary network.

\*\* The villous lymphatics were more visible with FICE.



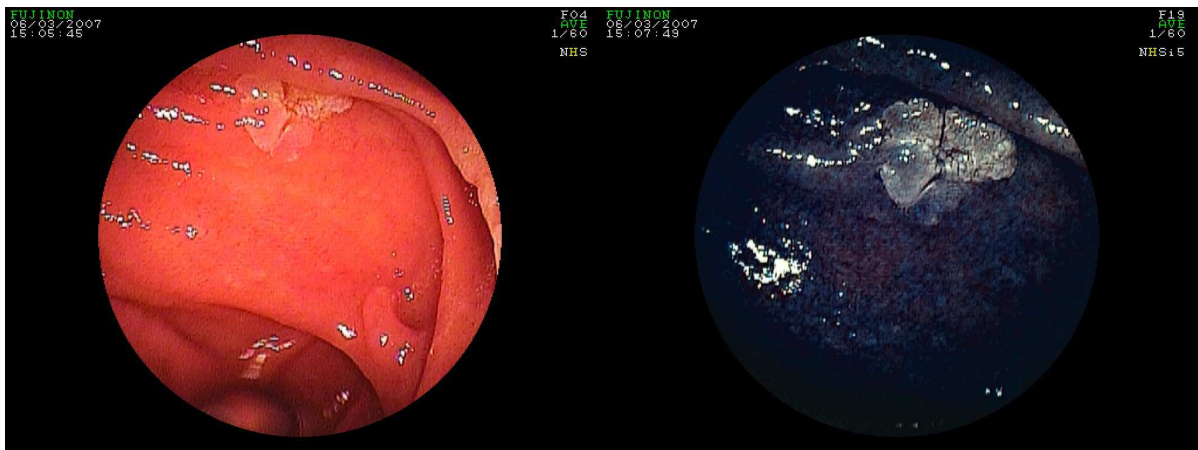
**Figure 1 A**

**Figure 1 B**

**Figure 2**

**Figure 1 A and B: Visualization of angiodyplasias in using FICE.** Panel A shows standard white light endoscopy of an angiodyplasia. With the blue mode (B) the angioectasia can be clearly demarcated from the surrounding mucosa and appears as an homogenous spot within the mucosa. The actual theoretical advantage of FICE is that due to the vast amount of possible “wavelength mixes” that can be obtained, it is possible to evaluate the mucosa with various virtual “dyes”. In contrast, NBI from Olympus has only one set of filters, which currently cannot be easily manipulated to create more colors. However, we are not sure of whether having more options result in a better characterize of the mucosa or mucosal lesions. In essence, the major aspects that need to be considered when using any virtual methods is: a) capability to enhance the visualization of the mucosal surface and hence, improve pit pattern characterization, and b) augment the visibility of the submucosal capillary network.

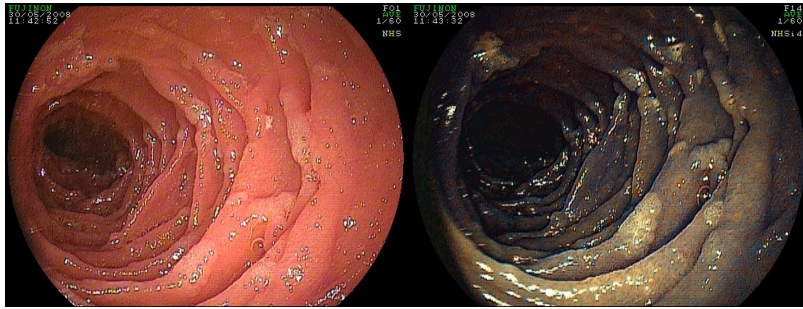
**Figure 2: Jejunal erosion.** With FICE the erosion is clearly seen as a white filling defect of the mucosa. The other spotty mucosal findings seen on the right side represent detritus and small bowel fluids.



**Figure 3 A**

**Figure 3 B**

**Figure 3: Adenomatous polyps associated with FAP.** Panel A demonstrates an adenomatous FAP polyp of the proximal jejunum. Note the white color of the polyp as well as its clear demarcation from normal mucosa using FICE (B). The pit pattern of adenomatous polyps resembles that of colon polyps. However, neither previous studies using FICE in the colon nor we could define whether FICE is useful for differentiation of low from high grade dysplasia. Thus, the quest continues to evaluate whether any of the virtual or standard chromoendoscopy techniques can replace histology.



**Figure 4 A**

**Figure 4 B**

**Figure 4 : Adenomatous polyps associated with FAP.** Panel A shows multiple small bowel polyps using standard white light endoscopy. With FICE it was possible to better delineate these polyps and due to the contrast enhancement it is possible to detect more lesions (panel B). However, despite having increased the visualization of diminutive adenomatous polyps in FAP, FICE did not result in new diagnosis or changes in therapy. In addition it is possible to observe that white reflections tend to increase during the FICE mode, potentially interfering with the image.



**Figure 5 A**

**Figure 5 B**

**Figure 5 C**

**Visualization and characterization of Peutz-Jeghers hamartomatous polyps using different FICE-settings.**

(A) Standard white light; (B) blue; (C) green. Although FICE did not improve the mucosal and villous evaluability of PJS polyps, the submucosal capillary pattern was enhanced. One might be confused by the fact that the predominant color for setting D is blue, when setting E (orange) and setting F (green) have higher components of blue. This effect might be related to the “mixture” resulting from the individual wavelengths which in turn leads to a predominant color. Interestingly, in NBI (Olympus) the predominant color is dark brown-grey, despite having high components of blue. If the bandwidths would be further manipulated, it would be possible observe different predominant colors in Olympus NBI as well.



**Figure 6 A**

**Figure 6 B**

**Figure 6. Nodular lymphoid hyperplasia (NLH).** White light (A) and FICE (B) were equivalent for the definition of the mucosal characteristics and delineation of the pseudopolyps in NLH.





**Figure 7 A**

**Figure 7 B**

**Figure 7 C**

**Figure 7: Jejunal villous architecture using white light (A) and FICE.** Due to its color contrast capabilities and the addition of endoscopic magnification, the characteristics of small bowel villi can be studied nicely using FICE. In addition to allowing for the inspection of the villous structure, FICE permits the view of the intravillous capillary system (B). However, with the exception of the duodenal bulb, FICE did not allow us to differentiate the various parts (i.e. upper, middle or lower) of the normal small bowel mucosa. It is possible that using magnification endoscopy or the immersion technique that a better characterization of the villi can be achieved, and thus differentiate whether the mucosa is jejunum or ileum. The classic endoscopic features of CD were seen similarly using WL or FICE. However, due to its color contrast capabilities and the addition of endoscopic magnification, the characteristics of small bowel villi can be studied nicely using FICE (Figures 7 A-C).



**Figure 8 A**

**Figure 8 B**

**Figure 8. Primary intestinal lymphangiectasia.** White light endoscopy revealed engorged mucosal villi and lymphangiectasias (A). This could be better appreciated using FICE (B).

**Discussion:**

In this study we found that FICE is a feasible virtual chromoendoscopy technique, which enhances the surface visualization of the small bowel mucosa. DBE with FICE technology was found to be a helpful method for the evaluation of small bowel polyps in patients with FAP, in the characterization of angiodysplasias and the definition of the submucosal capillary network.

Data regarding the usefulness of FICE in identifying gastrointestinal vascular ectasias, colon polyps and intestinal metaplasia in the esophagus have been promising (4,7-9). In a pilot study FICE appeared to be as accurate as conventional chromoendoscopy in the detection of HGIN or early cancer and may therefore be appropriate for surveillance of Barrett's esophagus (7). In another pilot study, Pohl et al. compared the feasibility of FICE, standard colonoscopy and conventional chromoendoscopy with indigo carmine for determination of colonic polyps and found that FICE not only identified morphological details that efficiently predict adenomatous histology, but that it was also superior to standard colonoscopy and equivalent to conventional chromoendoscopy (7). In our study FICE was useful for the characterization of small bowel polyps and pseudopolyps. Whereas FICE did not improve the definition of Peutz-Jeghers syndrome-polyps, it was quite useful for defining adenomatous polyps associated with FAP and differentiating them from non-neoplastic polyps. FICE was useful to better delineate the margin of adenomatous polyps from healthy surrounding mucosa and was of further assistance for the detection of small jejunal polyps missed by conventional white light. In addition, margin evaluation may be useful when resecting polyps using snare or mucosectomy technique or ablating them with argon plasma. Thus, margin evaluation may permit a better delineation before resection and may allow confirmation of complete eradication.

In a previous study using dye-based (indigo carmine) DBE-assisted chromoendoscopy, we showed that standard chromoendoscopy was useful for the characterization and detection of small bowel polyps in patients with FAP (10). Given the easier handling of FICE, this method may prove more useful for the screening and surveillance of these patients. Recently, Ringold et al. described two cases in which high contrast imaging with FICE improved the visibility of normal mucosal vessels and aided in the detection of vascular ectasias that were not easily seen by routine endoscopy (11). In our study, which included a larger number of patients, we reached similar observations.

In summary, this is the first report on the potential utility of DBE with FICE to evaluate a broad spectrum of small bowel diseases. So it sets the basis for further prospective studies evaluating the usefulness of FICE for the differentiation and characterization of specific small-bowel pathologies such as polyps and angioectasias.

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**IX. Chapter 8.**

**Enteroscopy:  
Advances in Diagnostic Imaging**

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**Abstract:**

Routine endoscopic imaging of the small bowel is performed with videoendoscopic white light technology. However, currently there are many new methods that improve our visual acuity when evaluating the small bowel mucosa. These methods are collectively called “advanced endoscopic imaging”. These imaging methods include high-definition white light endoscopy, standard and dyeless or “virtual” chromoendoscopy, magnification endoscopy and confocal endomicroscopy. Regardless of the method used to image the small bowel the endoscopist needs to pay attention to detail and focus on three essential aspects: a) the shape of the lesion, b) the superficial mucosal detail (i.e. “pit pattern”) and c) the submucosal vessel pattern. This review describes advances in the endoscopic imaging methods to study the small bowel.

**Introduction:**

The main aim of luminal endoscopic visualization of the luminal gastrointestinal tract is to detect mucosal pathologies by studying the composition and distribution of folds, studying the mucosal detail (i.e. appearance of the villi) and viewing of the submucosal vessel pattern (1-3). All endoscopic imaging techniques further increase our ability to describe, delineate and characterize abnormal structures and lesions in great detail (3-5). Standard white light endoscopes permit gross examination of the small bowel mucosa permitting the recognition of minor and major defects such as erosions, ulcers, lymphangiectasias or abnormal duodenal folds. The water immersion technique increases our ability to inspect the small bowel villi by magnifying the view as well as providing a soluble medium where the villi and other superficial structures appear bigger and “move” inside the water (6-8). This technique can be very helpful when investigating conditions associated with villous atrophy such as celiac disease and other malabsorption syndromes (6, 7). Magnification or zoom endoscopy further increases our ability to analyze the mucosal detail (9, 10). By applying dyes and magnifying the mucosa (magnification chromoendoscopy) further architectural detail of the mucosa can be elucidated (10, 11). New dyeless or virtual chromoendoscopy techniques such as narrow band imaging (NBI), i-scan and Fujinon intelligent color enhancement (FICE) have further enhanced our optical capabilities for the evaluation of enteric mucosal and submucosal lesions (5, 12-14). Endocytoscopy and confocal laser endomicroscopy are currently the most advanced endoscopic techniques (3, 15-18). When using confocal laser endoscopy the targeted structure is magnified in such a way that a virtual histology image (“*in vivo* histology”) is achieved (16-18). We believe that in the near future confocal endomicroscopy may further help characterize and diagnose diseases affecting the small bowel such as celiac disease, Crohn’s disease, infections, vasculitis, mesenteric ischemia and angiodysplasias, among others. Table 1 shows a list of diseases resulting in destruction of the mucosa and submucosa of the small bowel. This review describes advances in the endoscopic imaging methods to study the small bowel.

**Principles of endoscopic inspection:**

The basic concept behind endoscopic imaging is the visualization and characterization of the lesion’s shape and its mucosal and submucosal architecture (1, 2). All benign or malignant mucosal and submucosal lesions will “stand out” from its surroundings by virtue of various characteristics such as growth, excavation, protrusion, villous destruction, villous flattening and submucosal vessel architecture (2).

**Mucosal analysis:**

In the small bowel the main “player” is the villus, of which there exist several billion (Figure 1 A and B). Each villus is a unique “unit” that has a layer or coat of various types of cells, which have different functions and degrees of maturation from base to tip. Inside the villi there is a fine venocapillary and lymphatic network that is responsible for homeostasis, bringing oxygen to the cells and transporting absorbed elements (Figure 2). During inflammatory, neoplastic, angiogenic and infiltrative processes this minute vessels become deranged and this can be observed at varying degrees with existing endoscopic imaging methods. In addition, any mucosal or submucosal lesion will have a superficial epithelial “pattern” (e.g. “pit pattern”) and characteristic borders which result from absorbance, reflection and shadowing of light. The surface changes result commonly from processes that are inflammatory, infiltrative, angioproliferative, destructive or which lead to uncontrolled growth of neoplastic cells.

**Submucosal capillary analysis:**

Submucosal inspection (or submucosal surface analysis) is focused on visualizing the underlying vascular pattern of a given lesion (1-5). As angiogenesis is a major marker and promoter of malignancy, the endoscopically observed submucosal capillary network of a small bowel polyp can provide us with a clue regarding its neoplastic degree. The submucosal vascular pattern can be described based on the vascular pattern intensity and individual vessel characteristics (2-4). Thus, vessels are characterized endoscopically based on their amount, length, convolutions, elongations, tortuosity, looping and proliferative patterns (1,2).

**Mucosal vessel derangement:**

In addition to angiogenesis as a result of neoplasia often there are malformations and proliferation of the arteriovenous system. These vascular lesions are commonly called arteriovascular malformations (AVMs) or angiodysplasias. However, the term angiodysplasia is controversial as it implies “neoplastic” changes. Some endoscopists prefer to use the term angioectasia. In addition, a clear distinction should be made of venous and arterial malformations. A classic example of a “venous” malformation are small bowel varices or veins present in the blue-rubber bleb syndrome (Fig. 3).

**The concept of multimodal, advanced small bowel imaging:**

Advanced endoscopic image refers to the utilization of tools that enhance mucosal and submucosal visualization. In essence, the characteristics of the mucosal surface and subsurface are accentuated

or even made visible. Advanced endoscopic imaging comprises techniques such as high definition white light, standard white light with chromoendoscopy, virtual chromoendoscopy, magnification as well as endomicroscopy for the evaluation of the gastrointestinal mucosa (1-5). The concept of using more than one imaging method when performing endoscopy is currently called multimodal endoscopy (3). For example, using a combination of standard white light and chromoendoscopy is an example of bimodal endoscopy. When using three methods the terminology changes to advanced trimodal imaging and so forth (4, 6).

### **White light endoscopy:**

The current standard to investigate the small bowel mucosa is white light or high-definition white light endoscopy. Indeed, most of the published literature on small bowel diseases has based their results on white light observations.

### **Water immersion technique:**

The water immersion technique is a relatively simple adjunct to endoscopy (7, 8). The basic principle of the water immersion technique consists of viewing the mucosa under water (6-8). The endoscopist flushes water through the working channel of the endoscope and inundates the field of view. The mucosal villi appear larger and can be very well characterized (Figure 1B). In essence, this method is a “magnifying” technique. In the presence of mucosal atrophy the villi appear blunted or may even disappear (Figure 4). The immersion technique has been most widely studied by Cammarota et al from Rome (6, 7). In several studies he and his group were able to demonstrate a high specificity and sensitivity to diagnose celiac disease. In one such study evaluating patients with serologically and histologically proven celiac disease the endoscopic appearance of the duodenum with air insufflation alone had a positive predictive value for the diagnosis of celiac disease of 84% and a specificity of 87% (6). Visualization of villi with the water immersion technique had a higher positive predictive value (99%) and specificity (99%) (7). In a study designed to monitor the celiac patient’s response to a gluten-free diet the immersion technique was as good as biopsy to detect villous blunting (7). Their data supports the concept of an endoscopy-based approach that avoids the need for biopsy when monitoring the dietary adherence and/or response of patients with an initial diagnosis of celiac disease (8). A biopsy remains standard for the initial diagnosis of celiac disease but when evaluating these patients on follow-up (i.e. surveillance), a good immersion technique investigation of the small bowel mucosa may suffice to detect active disease (i.e. villous blunting and atrophy).

### **Dye-based-Chromoendoscopy:**

Chromoscopic endoscopy relies on the instillation of a dye (e.g. indigo carmine or methylene blue) to highlight the superficial details and improve visualization of the mucosa. The contrast enhancement of the mucosal surface often results in an improved detection of subtle lesions. The various dye agents used for chromoendoscopy are divided in a) absorptive agents (Lugol, methylene blue, toluidine blue, cresyl violet), b) contrast agents (indigo carmine, acetic acid) and c) reactive staining agents (congo red, phenol red). Dye agents are mostly applied via standard spraying or plain biliary catheters.

Patients with celiac disease have a 28-fold increased risk of developing enteropathy-associated T-cell lymphoma compared with the general population. Hadithi et al from Amsterdam described the chromoendoscopic appearances of jejunal enteropathy-associated T-cell lymphoma, before and after indigo carmine spraying, in a patient who was undergoing a double-balloon endoscopy (19). Scalloping or loss of folds, a mosaic appearance of the jejunal mucosa, and round or circumferential ulcers (10±90mm along their longitudinal axis) were detected with standard video endoscopy, but the villi were easier to recognize after indigo carmine staining of scalloped jejunal folds

In a case series of patients with familial adenomatous polyposis syndrome we assessed the usefulness of double-balloon enteroscopy (DBE) assisted chromoendoscopy for the detection and characterization of small bowel polyps (11). In this prospective evaluation of patients with clinical and genetically proven FAP who were enrolled in endoscopic surveillance program DBE-assisted chromoendoscopy was performed with indigo carmin. Small bowel polyps (including papillary adenoma) were detected in 7/9 (88%) (Figure 5). Jejunal polyps were detected in 6/9 (67%) patients. Chromoendoscopy aided in the detection of additional polyps in two patients. In one patient the polyps were flat and only visible with chromoendoscopy (biopsy confirmed adenomas). Thus, DBE-assisted chromoendoscopy was assistance for the delineation and detection of jejunal polyps (11).

### **Dye-less chromoendoscopy (“virtual” chromoendoscopy):**

Dye-less chromoendoscopy is divided into optical chromoendoscopy including narrow band imaging (NBI; Olympus, Tokyo, Japan) and virtual chromoendoscopy including i-scan (Pentax, Tokyo, Japan) and Fujinon intelligent color enhancement (FICE; Fujinon, Tokyo, Japan). While NBI is based on optical filters within the light source of the endoscope which narrow the bandwidth of spectral transmittance, thereby enhancing the visualization of blood vessels, i-scan and FICE use digital postprocessing for computed spectral estimation for better tissue contrast (1-

3, 5, 12). Because these methods do not use dye but rely on either color filters or computerized color changes of the image, they are called “virtual chromoendoscopy” or dye-less chromoendoscopy. FICE is also called CVC (computed virtual chromoendoscopy), OBI (optical band image) or spectral estimation technology (SET) (1-3, 5, 12). The activation of the filter is simply done by pushing a button on the handle of the scope (1-3, 5). Similar to the NBI technology, the digital processing system of FICE or i-scan is able to switch over between an ordinary image and a virtual image immediately, at any time of the procedure, by a simple push of a button on the handle of the endoscope (1-3, 5, 12). A practical difference between NBI and FICE or i-scan needs to be emphasized. NBI was developed to study the submucosal vessel pattern whereas FICE and i-scan are more useful to evaluate the shape, contour and structure of the mucosal surface.

In a small case series evaluating three follicular lymphomas Chowdhury et al described the enteroscopic characteristics of this tumor using FICE (13). On white light endoscopy multiple nodular lesions and elevated white patches, multiple polypoid lesions, and scattered white polypoid and nodular lesions in the duodenum and small intestine were seen. FICE demonstrated small, whitish nodules, with a coiled, elongated vascular pattern within the elevated lesions (13).

In the largest study published to date we evaluated the potential usefulness of FICE for characterizing various small bowel disease. A total of 574 images from 17 with the various pathologies including angiodysplasias, Crohn’s disease, NSAIDs enteropathy, celiac disease, primary small bowel lymphangiectasia, Whipple’s disease, familial adenomatous polyp syndrome, Peutz-Jeghers, B-cell lymphoma and nodular lymphoid hyperplasia were studied (12). We found that all four FICE spectral modes allowed the visualization and characterization of angiodysplasias. However, only the blue mode (R 500 nm, G 480 nm, B 420 nm) permitted an improved characterization of angiodysplasias. However, angiodysplasias can always be clearly visualized using plain white light (Figure 6). The detection or delineation of ulcers and erosions due to Crohn’s disease was not improved by FICE. WL was sufficient to locate and define these lesions. FAP polyps were flat, slightly raised, with irregular borders (Figure 7). The polyp surface had a cerebriform pit pattern. FICE clearly accentuated the surface contrast, thus enhancing the margin evaluation of FAP polyps. The whitish surface of these polyps seen during WL endoscopy was markedly enhanced using any FICE setting.

We are not aware of any studies evaluating the usefulness of i-scan for detection and characterization of small bowel pathology. Banerjee and Reddy from Hyderabad, India have briefly reported on the potential use of high-resolution NBI with magnification for the detection and characterization of

celiac disease (14). Using this approach the authors were able to clearly visualize areas of patchy defects in celiac disease.

### **Magnification endoscopy:**

Magnification endoscopy uses videoendoscopes with the capability to image magnification in a variable continuous range (up to 150 x) by using a movable lens controlled by the endoscopist (9, 10, 20) (Figure 1). In a study aimed at finding villous atrophy Lo et al used the combination of enhanced magnification endoscopy with 3% acetic acid instillation in patients with celiac disease and tropical sprue (9). Using this method the authors were able to describe four different mucosal pit patterns: I, normal; II, stubbed; III, ridged; and IV, foveolar. Three of the 4 patterns were strongly associated with the presence of villous atrophy (pattern I, 1/18 [5.5%]; II, 16/17 [94%]; III, 12/12 [100%]; and IV, 5/5 [100%]). EME was more sensitive than standard endoscopy for detecting villous atrophy, 100% versus 58% in celiac disease and 93% versus 20% in tropical sprue. Furthermore, EME identified patchy areas of partial villous atrophy in 16 patients (5 CD and 11 TS) in whom standard endoscopy was normal (9). We have also studied the characteristics of Whipple's disease and other malabsorptive states using magnification endoscopy (20) (Figure 8).

### **Endocytoscopy:**

Endocytoscopy is a novel diagnostic technique allowing in vivo real-time visualization of mucosa under x 450 magnification (15, 16). Matysiak-Budnik et al studied sixteen patients with documented celiac disease and seven controls without celiac disease. Endocytoscopic images obtained from several fields were compared in a blinded fashion to standard histology. Endocytoscopy showed three different patterns of in vivo histology: (1) the presence of normal-appearing, long, thin villi; (2) the presence of thick, shortened villi, reflecting partial villous atrophy; and (3) the total absence of villi and the presence of enlarged crypt orifices, reflecting total villous atrophy. Good concordance between endocytoscopy and standard histology was found in all 16 patients with celiac disease. This preliminary study shows that endocytoscopy allows in vivo, real-time, noninvasive visualization and characterization of villous architecture and may be a promising method for in vivo evaluation of duodenal mucosa in celiac disease (15).

In another study evaluating the usefulness of endocytoscopy for the diagnosis of celiac disease Heiko Pohl et al prospectively studied 166 endocytoscopy recordings of forty patients with established (n = 32) or suspected (n = 8) celiac disease (16). Of the 166 duodenal biopsy sites, 23% were classified as Marsh III (moderate to severe), 10% as Marsh I (mild), and 67% as Marsh 0 (normal). Using the 450x magnification, we found that identification of crypts was diagnostic for

celiac pathology. Four criteria were significant predictors of Marsh III pathology when adjusted by multivariate analysis: low number of villi per visual field (<3), confluence of villi, irregular epithelial lining, and inability to delineate loop capillaries. However, none was a good predictor of Marsh I pathology (16).

### **Confocal laser endomicroscopy:**

Confocal laser endomicroscopy (CLE) was introduced in 2004 and has rapidly emerged as a promising imaging method to obtain real time *in vivo* histology during ongoing endoscopy. The magnification equates that of white light microscopy, with image increases up to 1000 times (17, 18). The technique is based on tissue illumination with a blue laser light after the topical (acriflavin, tetracycline, cresyl violet) or systemic (fluorescein sodium) application of fluorescence agents. Multiple images are then recorded at different depths of the the mucosal layer. The resolution of CLE ranges from 0.7 to 1  $\mu\text{m}$  and a depth of 7  $\mu\text{m}$ . The field of view is around 600  $\mu\text{m}$  (17, 18). CLE can be performed in two ways: a) a probe with bundled fibers which is advanced through the working channel of the endoscope, which is called probe-based CLE (*pCLE*) (Cellvizio, Mauna Kea technologies, Paris, France) or a miniature confocal scanner microscope which integrated into the tip of the endoscope (endoscope CLE or *eCLE* (Pentax®, Ft. Wayne, NJ, USA) (3, 35). The probe-based method is the most feasible for deep enteroscopy as it permits the advancement of the probe through the enteroscope. Currently there is not enteroscope available with an integrated scanner microscope on its tip. Nevertheless, the endoscope-based probe can also be used to study the mucosal detail of the duodenum, upper jejunum and terminal ileum (Figure 9). In an elegant study evaluating patients with suspected celiac disease Rupert Leong et al from Australia found that confocal laser endomicroscopy equates histology in its diagnostic accuracy. The accuracy of CEM in diagnosing CD was excellent (receiver operator characteristics area under the curve, 0.946; sensitivity, 94%, specificity, 92%) and correlated well with the Marsh grading (R-squared, 0.756) (18).

### **Summary:**

High-definition white light endoscopy is the standard imaging method to visualize the small bowel. New imaging methods are being investigated and offer fascinating possibilities to improve the detection and characterization of small bowel diseases. Every endoscopist interested in small bowel imaging should master the concept of multimodal and advanced imaging.



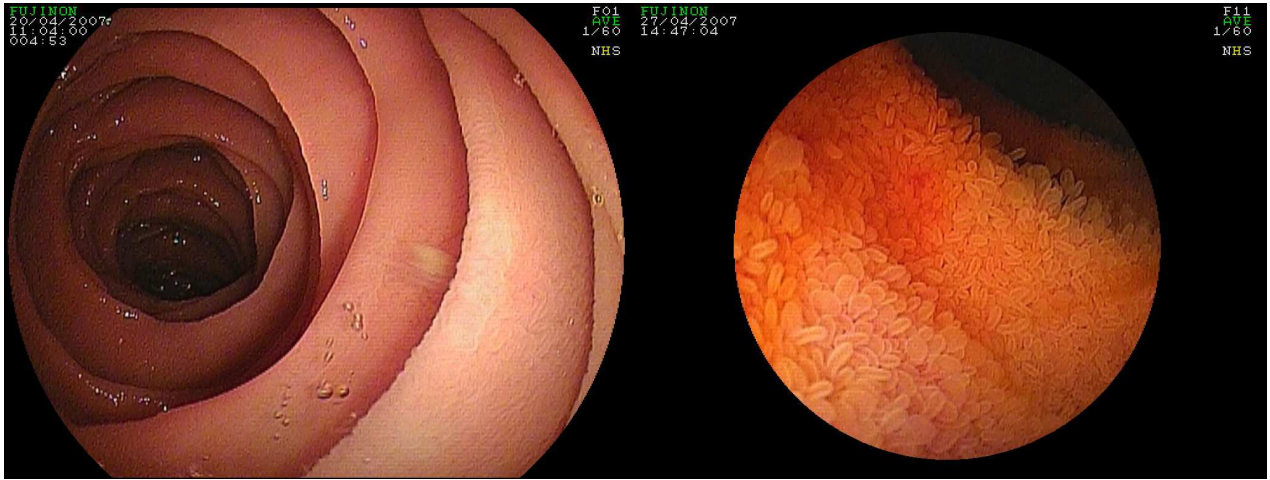


Figure 1A

Figure 1B

**Figures 1 A and B.** White light photos of the normal small bowel. Figure A is a standard white light image, figure B shows the water immersion technique (the villi are observed under water).

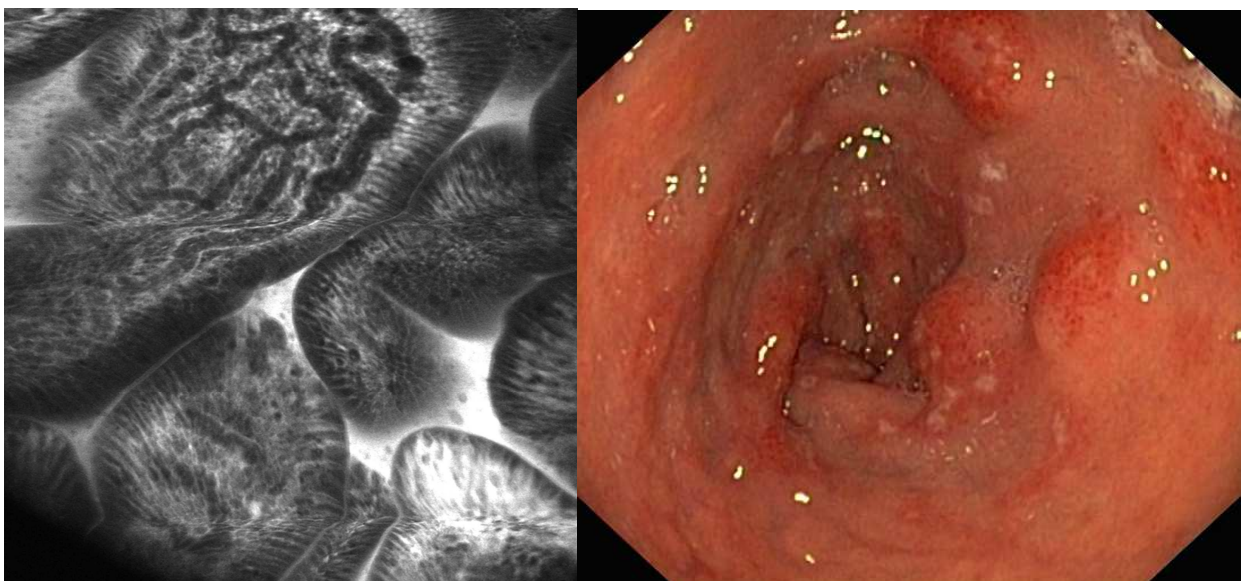


Figure 2

Figure 3

**Figure 2.** Inside the villi there is a fine vascular network which can be clearly observed using confocal laser endomicroscopy imaging.

**Figure 3.** Classic arteriovenous malformations should be clearly distinguished from varicosities of the small bowel.



Figures 4 A-C

**Figures 4 A-C.** Celiac disease. A. Serrated folds. B. Blunting and flattening of the villi (“mosaic pattern”). C. Water immersion view of flattened villi.



Figure 5

Figure 6

Figure 7

**Figure 5.** Small bowel adenomas in patients with familial adenomatous polyposis (FAP) syndrome appear as protruded, whitish mucosal lesions (chromoendoscopy with indigo carmin).

**Figure 6.** Small bowel angiodysplasias. A. Appearance with high-definition white light imaging.

**Figure 7.** FAP polyps are flat, slightly raised, with irregular borders and a white surface (FICE).

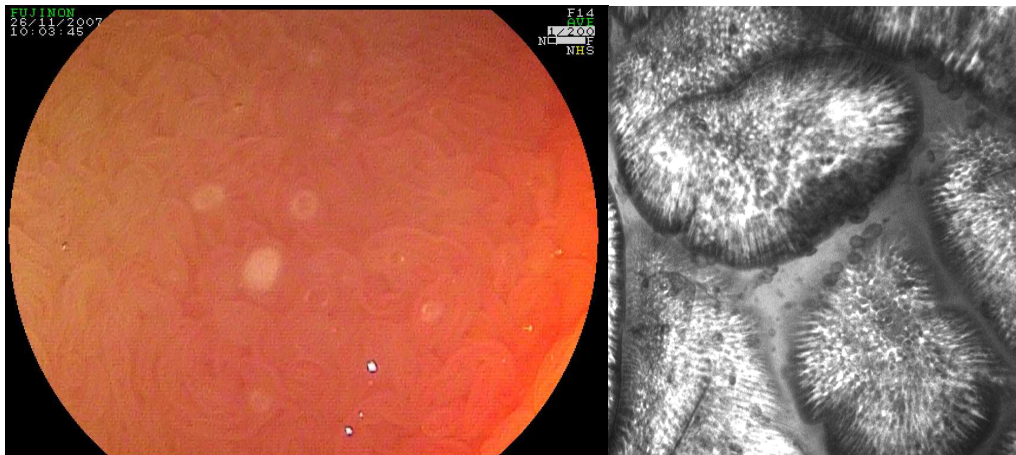


Figure 8

Figure 9

**Figure 8.** Magnification endoscopic view of Whipple’s disease. Note the characteristic white rings appear inside of the mucosal villi.

**Figure 9.** Confocal laser endomicroscopy of a patient with Crohn’s disease. The photo could well represent a histologic image.

**Table 1. Examples of various diseases resulting in small bowel mucosal and submucosal abnormalities**

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*Luminal or mucosal destruction*

Ulcerative, inflammatory and/or autoimmune diseases

Crohn's disease

Ulcerative jejunitis

Eosinophilic gastroenteritis

Vasculitis: Churg-Strauss, polyarteritis nodosa

Celiac disease

Tropical sprue

Giardia lamblia

Strongyloides stecoralis

*Infiltrative or submucosal destruction*

Mastocytosis

Whipple's disease

Neoplastic or proliferative (lymphoma, metastasis)

Adenomas

Peutz-Jeghers syndrome

Cronkhite Canada syndrome

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**X. Chapter 9.**

## Small Bowel Endoscopy

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## **Introduction**

Small-bowel endoscopy is now an essential tool for the investigation of patients with suspected small-bowel disorders. The current endoscopic methods to investigate the small-bowel lumen are: video capsule endoscopy (VCE) and device-assisted enteroscopy (DAE). DAE comprises single balloon, double balloon, and spiral enteroscopy. The interest in small-bowel diseases and methods to diagnose and treat them endoscopically continues to increase, as reflected by the contributions to this year's Digestive Disease Week (7–10 May 2011; Chicago, Illinois, USA).

## **Device-assisted enteroscopy: technical aspects and sedation**

Air insufflation is vital to allow us to investigate the small-bowel lumen and its mucosal detail. However, hyperinsufflation results in patient discomfort. In addition, as a result of looping and bowel dilation, the ability of the endoscopist to advance the enteroscope is limited, thus decreasing intubation depth. Carbon dioxide (CO<sub>2</sub>) is rapidly absorbed from the bowel lumen and prevents distension of the abdomen during the endoscopic procedure. Thus, CO<sub>2</sub> appears to be an ideal substitute for air in DAE. In a large retrospective study involving 178 patients, Landaeta et al. showed that CO<sub>2</sub> insufflation improved the depth of enteroscopy and resulted in less abdominal distension and pain compared with standard air insufflation (1). The main limitation of the study was its retrospective design. Nonetheless, there are already data published in the literature showing the advantages of CO<sub>2</sub> for complex endoscopic investigations. Thus, CO<sub>2</sub> should be considered a standard insufflation method for DAE.

Current spiral enteroscopy requires an overtube with a raised spiral at the distal end. Akerman et al. presented their initial experience using a “motorized” spiral enteroscope (2). The motor is in the handle and drives the spiral rotation using foot pedal control, which has variable speed and torque and is electronically limited. The spiral segment is 5.5 mm high, 45-Fr in size, and is positioned 20–41 cm from the end of the endoscope. The authors were able to observe an average of 400 cm in the first 18 patients studied. Amazingly, the procedure lasted, on average, slightly less than half an hour. If this equipment is not too expensive and further studies confirm these findings, we believe that the motorized spiral scope can become the next hit in small-bowel endoscopy.

Balloon-assisted enteroscopy (BAE) is an advanced endoscopic method that can be both strenuous for the patient and the team performing the procedure. The procedure can be performed using sedation or general anesthesia. Sedation with propofol should always be administered by trained medical staff. In some countries propofol is only administered by anesthesia personnel (monitored anesthesia care [MAC]), whereas in some European countries (e.g. Germany, Switzerland) nurse-assisted propofol sedation is widely and safely practiced. In The USA and many other countries

(e.g. Argentina, Brazil, France) general anesthesia is used to perform double balloon endoscopy (DBE). The main argument for using general anesthesia is assumed patient safety, possible better procedure tolerance, improved endoscopist satisfaction, and lower risk of complications. Interestingly, this issue has not been widely studied. Stephen et al. retrospectively studied the safety and efficacy of DBE performed under moderate conscious sedation and MAC/general anesthesia in a cohort comprising more than 200 patients (3). Although the average depth of insertion for DBE was 458 cm for general anesthesia compared with 358 cm for moderate sedation ( $P = 0.0814$ ), the rate of complications was similar for both groups. The procedure was terminated early in three patients under moderate sedation due to increased agitation, and two patients under general anesthesia experienced anesthesia-related complications. This study is an important first step in this field and should prompt the performance of a prospective, multicenter study evaluating this issue.

### **Capsule endoscopy: technical aspects**

The technical capabilities of VCE continue to increase and include increased capture time due to longer-lasting battery power, smaller size, improved photographic detail, and increased number of images shot. Standard capsule endoscopes capture two images/second (2/s). The SB2/4 capsule (Given Imaging, Yoqneam, Israel) is capable of capturing four images/second. In a clever study, Delvaux et al. evaluated whether 4/s resulted in a diagnostic increment compared with 2/s in a study involving 100 patients (4). The investigators were able to reach a diagnosis in 70 patients from the 4/s group, 69 from the 2/s group, 61 patients from the 4QV (4/s QuickView; Given Imaging), and 57 patients from the 4+2/s recordings, respectively. In 62 patients with multiple lesions, the number of lesions was significantly higher on the 4/s and 4QV recordings compared with the 2/s and 4+2/s recordings ( $P < 0.01$ ). In summary, a higher frame rate at 4/s does not significantly increase the diagnostic yield of the small-bowel capsule, compared with the usual 2/s capsule. However, the 4/s capsule seemed to detect more individual lesions, during both normal and QuickView readings.

### **Gastrointestinal bleeding**

Although the guaiac and fecal immunochemical tests (FIT) were mainly designed to screen for colorectal tumors, it is not known whether or not small-bowel lesions can also lead to a positive test. Levi et al. investigated whether gastroduodenal or small-bowel lesions found through VCE examination could result in positive FIT in 56 consecutive patients undergoing VCE for obscure occult gastrointestinal bleeding (OGIB) (5). Of the 26 patients (46.4%) with small-bowel lesions classified as a probable or suspected cause of bleeding, 12 patients (46.1%) had a positive FIT. In



contrast, only two out of 30 patients (6.6%) with normal small bowel had a positive FIT ( $P = 0.008$ ). The sensitivity, specificity, and positive predictive value of FIT for small-bowel lesions classified as a probable or suspected source of bleeding were 46.2%, 93.3%, and 85.7%, respectively. Interestingly, none of the seven patients with gastroduodenal lesions classified as a probable or suspected source of bleeding had a positive FIT. These preliminary data suggests that the specificity of FIT for small-bowel lesions classified as a probable or suspected source of bleeding is acceptable. It seems reasonable to perform a small-bowel endoscopy in patients with negative colonoscopy with occult blood in stool. Of further interest, even in patients with upper gastrointestinal pathology findings that might explain the OGIB, a small-bowel endoscopy should still be considered (Figs. 1 and 2).

Several studies have shown that BAE is useful for patients with OGIB. Safatle-Ribeiro et al. from São Paulo, Brazil, went a step further and classified the patients with OGIB into four groups: current overt (within 1 month after the last episode of overt bleeding), previous overt (more than 1 month after the last episode of overt bleeding), current occult (anemia with positive fecal occult blood test within 1 month after the last episode of bleeding), and previous occult (chronic anemia) (6). In their prospective study comprising 130 patients, the authors identified a small-bowel bleeding etiology in 65.4% of patients. There was an association between the OGIB classification and the presence of the lesions in the small bowel: current overt (positive findings in 43.5%), previous occult (12.9%), current OGIB (overt or occult, 62.4%), and previous OGIB (overt or occult, 37.6%). In summary, we agree with the author's recommendation to use BAE as an initial test in patients with current overt and occult gastrointestinal bleeding, reserving VCE for patients with previous overt and occult gastrointestinal bleeding.

### **Crohn's disease**

The diagnosis of Crohn's disease, especially in cases of isolated small-bowel involvement, remains challenging (Figs. 3 and 4). Despite its known limitations small-bowel follow-through (SBFT) remains a standard test for detecting small-bowel Crohn's disease. In a prospective, blinded, multicenter study, Ian Gralnek et al. determined the incremental diagnostic yield of VCE and compared this with that for ileocolonoscopy and SBFT in the diagnosis of small-bowel involvement in 50 patients with "suspected Crohn's disease" (7). Interestingly, the incremental diagnostic yield of VCE (28.6%) compared with SBFT (18.4%) was not statistically significant. However, the combination of VCE and ileocolonoscopy (35.0%) had a trend toward higher diagnostic yield for detecting pathology in patients with suspected small-bowel Crohn's disease compared with SBFT plus ileocolonoscopy (28.6%). Based on its enhanced ability to show the

mucosal detail we would have anticipated a clear-cut advantage of VCE over SBFT. These results underscore the need for using multiple imaging tests to diagnose Crohn's disease.

Nevertheless, the use of multiple tests is not always convenient, neither for the patient nor the physician. Thus, the order and timing of imaging tests for the diagnosis of suspected Crohn's disease needs to be re-evaluated. In another prospective, multicenter, blinded cohort study, Leighton et al. evaluated whether VCE prior to ileocolonoscopy and SBFT impacts disease management in 74 patients with suspected Crohn's disease (8). The physicians reported that VCE altered disease management in 24/74 patients (32%), ileocolonoscopy altered disease management in 17/73 patients (23%), and SBFT altered disease management in 10/70 patients (14%). This study supports the concept of a "step-wise, top-down" diagnostic approach for the diagnosis of suspected Crohn's disease, which may revolutionize the way we approach diagnostics in Crohn's disease.

The diagnostic superiority of VCE compared with radiological tests was further confirmed in a large retrospective experience from the same group at the Mayo Clinic (Scottsdale, USA) (9). In a study comprising 114 patients, Boroff et al. found that VCE had a higher diagnostic yield and resulted in management change in a greater proportion of patients with established Crohn's disease compared with patients with suspected Crohn's disease. The authors also found that abnormal radiology testing did not correlate with abnormal VCE. However, because there was no clear "gold standard" to define small-bowel Crohn's disease we do not know whether VCE missed these radiological lesions or whether these were true radiological false positives. Despite all these exciting data we need to remember that there are still no standardized and clearly validated criteria for capsule endoscopy in Crohn's disease that are specific and sensitive for its diagnosis. Thus, we need studies evaluating these imaging methods using an accepted Crohn's disease "gold standard".

### **Celiac disease and other malabsorptive states**

Despite the great improvement in serological testing, diagnosing celiac disease still requires duodenal biopsy coupled with a positive response to a gluten-free diet (Figs. 5–7). Nevertheless, the histological pattern of celiac disease is often patchy, with the risk of missed diagnoses. To evaluate the patchiness of the histological lesions along the small bowel, Di Nardo et al. performed push enteroscopy instead of conventional upper gastrointestinal endoscopy in 20 consecutive pediatric patients with suspected celiac disease (positive anti-transglutaminase and anti-endomysial antibodies) (10). Standard biopsies were taken from five different sites: bulb, second duodenum, fourth duodenum, proximal jejunum, and distal jejunum. A homogeneous pattern of histological damage was found in 10 patients (50%); five patients (25%) had a patchy pattern of lesions, whereas minor lesion variability among different sites was shown in nine patients (45%). The second and fourth duodenum were involved in 18 patients (90%). In one patient who lacked lesions

in the bulb and duodenum, the diagnosis of celiac disease could only be confirmed by proximal jejunal biopsies. This study confirms that celiac disease presents in a patchy pattern. Although most patients have involvement of the duodenum, a small but significant percentage only have jejunal disease. Never rule out celiac disease based solely on normal duodenum histology.

Patients with celiac disease who do not respond to a gluten-free diet should undergo small-bowel imaging studies to identify refractory celiac disease (RCD) or enteropathy-associated T-cell lymphoma (EATL). Even though VCE has been used in this setting it is still unclear whether specific VCE parameters are associated with these conditions. Van Weyenberg et al. from Amsterdam aimed to identify parameters that discriminate between RCD type I and type II, and to identify features associated with RCD type II or EATL (11). In a retrospective, blinded evaluation of VCE studies on 52 patients with suspected RCD, a multivariate analysis showed that none of the proposed endoscopic findings could reliably help to distinguish RCD type I from RCD type II. However, the presence of proximal focal erythema and absence of progression of the capsule to the distal intestine were independently associated with the presence of RCD type II or EATL. Whereas only one of the 29 patients (3.4%) with none of these two features died during follow-up, six of seven patients (85.7%) with both features died during follow-up. This study shows that the endoscopic appearance of RCD is wide and that it is almost impossible to distinguish RCD type I from II based on these features. However, proximal focal erythema and absence of progression of the capsule to the distal intestine were strongly associated with RCD II and EATL making VCE a possible risk-stratification tool to predict survival in these patients.

Common variable immunodeficiency disorder (CVID) is one of the most common immunodeficiency states in adults. Patients with CVID are prone to intestinal and extra-intestinal infections and malignancy, especially lymphomas. Few case reports and series have reported on the endoscopic findings of this disease. The most common finding reported in CVID is nodular lymphoid hyperplasia (NLH). Moneghini et al. studied the endoscopic findings in six patients with this immunoglobulin deficiency (median age 42 years) using VCE (12). The lesions described included normal mucosa, villous blunting, celiac-like atrophy, ileal mucosal erythema, aphthous ulcers, and NLH. Two patients had diffuse B-cell lymphoma of the small bowel. An important finding of this study was that the lesions were present in only part of the small bowel in most patients. Of note, the small-bowel ulcers were reminiscent of Crohn's disease (see Figs. 3 and 4). Remember this clinical pearl: always think of CVID in patients with chronic diarrhea.

The role of enteroscopy in the evaluation of malabsorptive disorders has not been widely studied. In a single-center, retrospective study, Ohmiya et al. studied 25 consecutive patients with protein-losing enteropathy using VCE, DBE, and fluoroscopic enteroclysis (13). The diagnostic yield of

DBE was higher (100%) than that of fluoroscopic enteroclysis (60%) in 15 patients who underwent both tests, but not significantly different from VCE in 17 patients (DBE 82% vs. VCE 77%). The following diagnoses were made: intestinal lymphangiectasia, chronic nonspecific multiple ulcers of the small intestine unrelated to nonsteroidal anti-inflammatory drugs, intestinal amyloidosis, small-bowel tumors, extragastrointestinal diseases, strongyloidiasis, Crohn's disease, and small-bowel ulcers due to polyarteritis nodosa. It remains to be clarified how VCE had such a high diagnostic yield when tissue for diagnosis cannot be obtained using this method. This study shows that protein-losing enteropathy can be caused by a large number of pathologies and emphasizes the need for multiple imaging tests.

### **Small-bowel polyps and tumors**

Until now there have only been three large studies published on the role of DBE for the diagnosis and treatment of small-bowel tumors. Dinesen et al. from Sydney, Australia, prospectively assessed the diagnostic and therapeutic impact of DBE in patients with suspected or documented small-bowel neoplasia seen on VCE or computed tomography (CT) scan (14). Over a 6-year period, a total of 580 DBE procedures were carried out. A total of 48 patients were found to have neoplastic disease/masses. A total of 35 tumors were detected prior to DBE (33 by VCE and two by CT), nine were suspected at VCE but only found at DBE, and two cases were missed by VCE altogether. The final pathology was: nine small submucosal lesions with normal biopsy (normal histology), four adenomas, three lymphomas, three lymphangitic cysts, two adenocarcinomas, one Meckels diverticulum, one hamartoma, one lymphoid hyperplasia, one lipoma, and one metastatic melanoma. Whereas four tumors could be managed endoscopically and three were resected surgically, 18 patients were followed clinically and three underwent chemotherapy for lymphoma. This large study supports the utility of DBE for the management of small-bowel tumors.

In another study on the topic of small-bowel tumors, Mann et al. searched for a primary tumor site in 39 patients with metastatic neuroendocrine tumors (NET) using VCE, DBE, endoscopic ultrasound (EUS), octreotide scan, and positron emission tomography (PET)-CT (15). Although none of the imaging tests alone found all of the tumors, a primary NET was identified in 30 patients (77%) with various combinations of VCE, DBE, and EUS. Of interest, octreotide scan, which is typically considered the gold standard, had a sensitivity of only 59%. PET-CT scans were done on four patients and all were negative. This interesting study shows the necessity of utilizing various imaging methods for the diagnosis of primary NET in patients with metastatic disease. We look forward to seeing the full publication as we hope the authors will propose an algorithm for the stepwise use of the various tests.

## **Therapeutic small-bowel enteroscopy**

The advent of DAE has not only revolutionized the way we observe the small bowel but has also brought means to treat various small-bowel pathologies. In a large retrospective, three-center study, Jovanovic et al. analyzed the results of therapeutic small-bowel endoscopy in a large cohort of patients (16). A total of 534 patients underwent 614 DBE over a 5-year period. A therapeutic small-bowel endoscopy was performed in 121 patients (22%). Therapeutic procedures included argon-plasma-coagulation (APC) of vascular lesions (n = 73), polypectomy (n = 49; the range of polyps resected in each patient with Peutz–Jeghers syndrome [PJS] and familial adenomatous polyposis was 1–15, mean 4), mucosectomy (n = 5), stricture dilation (n = 7), foreign body extraction (n = 7; capsule endoscopy, needles, coins), injection of fibrin glue (n = 10), and clip placement (n = 5). There were a total of five complications (0.9%; paralytic ileus [n = 2], pancreatitis [n = 1], bleeding [n = 1]). No perforation or death occurred. This study is of interest as it shows that therapeutic small-bowel endoscopy is performed in a fifth of patients undergoing BAE. Thus, endoscopists who perform DBE should be trained in and prepared to provide therapeutic interventions for small-bowel disorders, including APC, injection, hemoclipping, polypectomy, mucosectomy, and foreign body extraction. Therapeutic small-bowel endoscopy, albeit associated with complications in about 1% of cases, can be considered a relatively safe procedure.

Kopacova et al. from Prague presented one of the largest experiences worldwide of diagnostic and therapeutic DBE for PJS (17). A total of 27 DBEs were performed in 13 patients with PJS, in whom a total of 344 polyps (1–46 hamartomas, mean of 13 per session) were removed. Although the complication rate per polypectomy was only 0.9%, the per-patient complication was 15% – one bleeding episode (treated endoscopically) and three perforations (two acute, one late). In our view, enteroscopy is the main route for the removal of polyps in PJS. We always have the surgeon on stand-by when treating these patients. If a perforation is sealed endoscopically or with immediate surgery the patient outcome is good.

And finally, we want to discuss a new therapeutic indication for DAE: placement of a direct percutaneous endoscopic jejunostomy (DPEJ). Aktas et al. from the Erasmus University Medical Center, Rotterdam, prospectively assessed the efficacy and safety of DPEJ using the single-balloon enteroscopy technique in consecutive patients referred to this academic tertiary center for jejunal tube feeding (18). During an 8-month period, 12 DPEJ procedures were performed in 11 patients. All procedures were performed under conscious sedation using midazolam and fentanyl. DPEJ was successful in 11 of the 12 procedures (92%). In one patient DPEJ was not possible because of

failure to transilluminate a satisfactory location for insertion. This study shows that single balloon endoscopy-assisted percutaneous jejunal feeding tube placement is a useful and successful approach for patients requiring long term jejunal access.



Figure 1

Figure 2

Figure 3

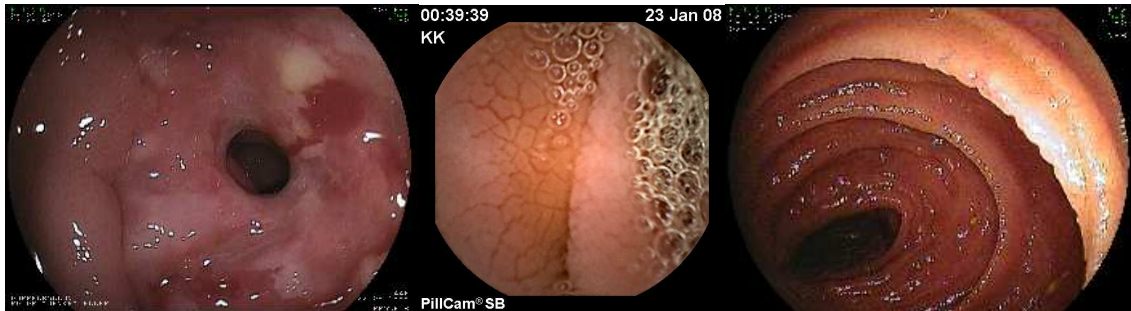


Figure 4

Figure 5

Figure 6

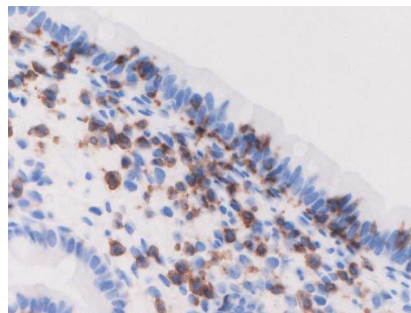


Figure 7

**Fig. 1** Multiple angioectasias in a patient with Osler–Weber–Rendu (double balloon enteroscopy).

**Fig. 2** Bleeding angioectasia in a patient with overt gastrointestinal bleeding (capsule endoscopy). It might be better to first perform device-assisted enteroscopy in such a patient as this offers the ability to perform endoscopic hemostasis.

**Fig. 3** Aphthous ulcer in Crohn's disease (capsule endoscopy).

**Fig. 4** Multiple ulcers and a stenosis in a patient with Crohn's disease. The stenosis was dilated with a through-the-scope over-the-wire balloon.

**Fig. 5** Typical mosaic pattern of atrophic mucosa. In this case this is celiac disease (capsule endoscopy).

**Fig. 6** Serrated appearance of the mucosa in the presence of significant atrophy (double balloon enteroscopy, celiac disease).

**Fig. 7** Device-assisted enteroscopy allows for the retrieval of tissue for examination. Note the mucosal atrophy and the large number of intraepithelial lymphocytes in this patient with celiac disease.





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## **XI. Chapter 10      Summary/Zusammenfassung**

In this thesis we aimed to investigate on the technique and clinical applications of double-balloon enteroscopy.

In the first study (chapter four) we evaluated the learning curve of DBE. We found that DBE is not only time consuming but also is a challenging procedure. We demonstrated that there was a significant improvement in DBE performance over time, including increased depth of insertion, decline in procedural time, “speed of insertion” and decreased used of fluoroscopy for both oral and anal DBE procedures. These parameters improved significantly after the initial 10 oral (15 anal) cases. Knowledge of this technical data will be helpful for endoscopists planning to perform DBE, to plan the caseload in individual endoscopy units and for establishing baselines for DBE skill certification. Future studies using the therapeutic DBE and comparing the learning curve using various types of enteroscopy are worth conducting. In summary, it appears that a minimum of 10-15 procedures is required to acquire the skills necessary to perform DBE.

In the second study (chapter five) we performed the first study investigating the utility of DBE in patients with malabsorption of small bowel origin. We found that DBE had a high diagnostic yield in a selected group of patients with malabsorption in whom previous extensive investigations had been negative, being useful to reach a new diagnosis in 33% and to confirm the diagnosis in two thirds of patients investigated. In addition DBE was useful to rule out complications of long-standing celiac disease such as ulcerative jejunitis or EATL. This high yield does not mean that DBE should be used as a primary tool in patients with malabsorption. Our study rather demonstrates that malabsorptive diseases with primary small bowel mucosal involvement could be adequately evaluated with DBE. Our study confirms that reaching a diagnosis in patients with malabsorption of small bowel.

In the third study (chapter six) we critically investigated the role of double balloon enteroscopy in patients with obscure gastrointestinal bleeding. We found that the frequency of lesions within reach of conventional upper and lower endoscopes definitely explaining the source of GI bleeding in patients referred for DBE was 24.3%. These lesions included peptic ulcers, colonic angiodysplasias, Cameron’s lesions and radiation proctitis. Our study demonstrated that a carefully endoscopical investigation of upper and lower GI-tract can avoid unnecessary DBE which result in patient inconvenience, possible complications allowing a better allocation of endoscopist, nurses and material resources in the endoscopy unit. Therefore, a repeat EGD and ileocolonoscopy should be considered before DBE. And these examinations should be performed thoroughly. Further

studies focusing on the clinical and laboratory factors that can predict the etiology of small bowel pathologies in the setting of OGIB are warranted.

In the fourth study (chapter seven) we were the first group to investigate the feasibility of virtual chromoendoscopy techniques of the small bowel. We found that DBE with FICE technology is a helpful advanced endoscopic method for the evaluation and characterization of small bowel polyps and pseudopolyps in patients with familial adenomatous polyposis (FAP), in the characterization of angiodysplasias and the definition of the submucosal capillary network. Whereas FICE did not improve the definition of Peutz-Jeghers syndrome-polyps, it was quite useful for defining flat adenomatous polyps associated with FAP and differentiating them from non-neoplastic polyps. FICE was useful to better delineate the margin of adenomatous polyps from healthy surrounding mucosa and was of further assistance for the detection of small jejunal polyps missed by conventional white light. In addition, margin evaluation may be useful when resecting polyps using snare or mucosectomy technique or ablating them with argon plasma. Thus, margin evaluation may permit a better delineation before resection and may allow confirmation of complete eradication.

In the state-of-art review (chapter eight) we present and discuss on advanced endoscopic imaging possibilities for small bowel disorders. The standard imaging method to visualize the small bowel is the high-definition white light endoscopy. During the last years new imaging methods are being investigated, offering new possibilities to improve the endoscopic detection and characterization of small bowel diseases. With these methods the mucosal surface and subsurface are accentuated or even made visible in a new concept called multimodal and advanced imaging. Advanced endoscopic imaging comprises techniques such as high definition white light, standard white light with chromoendoscopy, virtual chromoendoscopy, magnification as well as endomicroscopy for the evaluation of the gastrointestinal mucosa. The use of more than one imaging method when performing endoscopy is currently called multimodal endoscopy. Endocytoscopy and confocal laser endomicroscopy are currently the most advanced endoscopic techniques achieving a virtual histology image (“*in vivo* histology”).

In the current review (chapter nine) we present the latest developments of DBE. Since its development in 2004 double-balloon-enteroscopy has quickly become the standard deep enteroscopy method for the investigation and treatment of small bowel disorders. Now, other uses for DBE include colonoscopy, ERCP, creation of jejunostomy and gastrostomy access in patients with bypassed stomach. Despite its advances balloon- and spiral enteroscopy methods are still time consuming, cumbersome and do not permit for a one-step total enteroscopy. Thus, further research into simplifying and improving these endoscopic methods is warranted and in progress.

## **Zusammenfassung**

Ziel dieser Dissertation ist die Untersuchung der technischen und klinischen Anwendung der Doppelballonenteroskopie.

Im ersten Teil der Studie (Kapitel vier) erfolgte die Evaluation der Lernkurve der Doppelballonenteroskopie. Hier konstatierten wir, dass die Doppelballonenteroskopie nicht nur eine zeitaufwändige, sondern auch eine anspruchsvolle Untersuchung ist. Wir demonstrierten eine signifikante Verbesserung der Untersuchungstechnik mit zunehmender Erfahrung, eine zunehmende Untersuchungstiefe, eine deutliche Verkürzung der Untersuchungszeit mit rascherem Vorschub des Endoskopes und eine verminderte Durchleuchtungszeit für die orale und anale Doppelballonenteroskopie. Diese Parameter verbesserten sich deutlich nach initialen 10 oralen beziehungsweise nach 15 analen Doppelballonenteroskopien. Kenntnisse dieser technischen Daten helfen dem Endoskopiker bei der Planung einzelner Doppelballonenteroskopie, bei der Planung der Untersuchungsfülle einzelner Endoskopieeinheiten und bei der Etablierung von Mindeststandards für die Doppelballonenteroskopie. Weitere Studien mit Vergleich unterschiedlicher Enteroskope und der jeweiligen Lernkurve sollten in Zukunft durchgeführt werden. Zusammenfassend ist festzustellen, dass ein Minimum von 10-15 Untersuchungen notwendig ist um ausreichende Fähigkeiten zur Durchführung einer Doppelballonenteroskopie zu erlangen.

Der zweite Teil der Untersuchung (Kapitel fünf) untersucht als erste Studie überhaupt die Sinnhaftigkeit der Doppelballonenteroskopie bei Patienten mit Malabsorption im Rahmen einer Dünndarmerkrankung. Die Doppelballonenteroskopie besitzt einen hohen Stellenwert bei Patienten mit Malabsorption, bei denen vorherige, umfangreiche Untersuchungen negativ ausgefallen waren. Bei 33 % der Pat. konnte eine Neudiagnose erfolgen, bei 2/3 der Patienten konnte die vorherige Verdachtsdiagnose bestätigt werden. Zusätzlich zeigte die Doppelballonenteroskopie einen Nutzen bei Diagnose von Komplikationen einer langjährigen Zöliakie, wie einer ulzerierenden Jejunitis oder einer EATL. Diese hohe diagnostische Ausbeute bedeutet natürlich nicht, dass die Doppelballonenteroskopie das diagnostische erste Mittel zur Abklärung einer Malabsorption ist. Unsere Studie demonstriert aber, dass eine malabsorptive Erkrankung mit Beteiligung der Dünndarmmukosa gut und ausreichend mit der Doppelballonenteroskopie untersucht werden kann. Der dritte Teil der Studie (Kapitel sechs) untersucht kritisch die Rolle der Doppelballonenteroskopie bei obskurer, gastrointestinaler Blutung. Bei den Patienten, die mit der Frage nach einer obskuren gastrointestinalen Blutung zur Doppelballonenteroskopie zugewiesen wurden, fanden wir eine Blutungsquelle bei 24,3 % der Patienten mittels konventioneller oberer oder unterer Endoskopie. Die gefundenen Läsionen umfassten dabei peptische Ulzera,

Angiodysplasien des Colons, Cameron Läsionen und Strahlenproktitiden. Unsere Untersuchung demonstriert, dass durch die sorgfältige Untersuchung des oberen und unteren Gastrointestinaltraktes unnötige Doppelballonenteroskopien und andere invasive Verfahren vermieden werden können. Dies verhindert einen Discomfort des Patienten, vermeidet potentielle Komplikationen und ermöglicht einen besseren und gezielteren Einsatz der Ressourcen von Endoskopikern, Pflegepersonal und Material. Deshalb sollte vor Einsatz der Doppelballonenteroskopie eine erneute ÖGD und Ileokoloskopie erwägt werden. Diese Untersuchungen sollten sorgfältigst durchgeführt werden. Weitere Studien klinischer und laborchemischer Faktoren als Prädiktoren einer mittleren, gastrointestinalen Blutung sollten in Zukunft durchgeführt werden.

Im vierten Studienteil (Kapitel sieben) berichten wir als erste Arbeitsgruppe überhaupt über die Durchführung der Technik der virtuellen Chromendoskopie des Dünndarms. Die Doppelballonenteroskopie mit FICE (engl. Fujinon image chromoenhancement) Technologie ist eine hilfreiche endoskopische Methode zur Evaluation und Charakterisierung von Dünndarmpolypen und Pseudopolypen bei Patienten mit familiärer adenomatöser Polyposis coli. Weiterhin ist sie hilfreich in der Charakterisierung von Angiodysplasien und des submukösen Kapillarnetzes. Obwohl FICE die Charakterisierung von Peutz-Jeghers Polypen nicht verbesserte, war es doch hilfreich für das Erkennen von flachen adenomatösen Polypen, die mit der FAP assoziiert sind und bei der Abgrenzung dieser von nicht neoplastischen Polypen. FICE zeigte sich außerordentlich hilfreich bei der Abgrenzung von adenomatösen Polypen zur normalen Mukosa und der Detektion von kleinen jejunalen Polypen, die in der normalen Weißlichtendoskopie nicht sichtbar waren. Die Abgrenzung zur normalen Mukosa scheint besonders sinnvoll vor Resektion eines Polypen in Schlingen- oder Mukosektomietechnik oder vor einer geplanten Argonplasmaablation.

In Kapitel acht werden die modernen endoskopischen Darstellungsmöglichkeiten für Erkrankungen des Dünndarms erläutert. die Standardmethode ist weiterhin die Weißlichtendoskopie. Während der letzten Jahre wurden mehrere Methoden vorgestellt, die neue Möglichkeiten zur Detektion und Charakterisierung von Dünndarmerkrankungen bieten. Mit diesen Methoden kann die Mukosa und Submukosa akzentuiert dargestellt werden. Neuere Darstellungstechniken wie die hochauflösende Weißlichtendoskopie, die Standardweisslichtendoskopie mit Chromendoskopie, die virtuelle Chromendoskopie, die Magnifikationsendoskopie stehen für die Untersuchung der gastrointestinalen Mukosa zur Verfügung. Der Gebrauch mehrerer dieser Techniken bei der Endoskopie wird als multimodale Endoskopie bezeichnet. Endocytoskopie und die confokale Laserendomikroskopie sind aktuell die

fortschrittlichsten Technologien und ermöglichen ein virtuelles histologisches Bild („in vivo Histologie“).

Im Kapitel neun werden die letzten Entwicklungen der Doppelballonenteroskopie präsentiert. Seit der Einführung der Doppelballonenteroskopie 2004 hat sie sich zur Standardmethode für die Untersuchung und Behandlung von Dünndarmerkrankungen entwickelt. Die Doppelballonenteroskopie wird heutzutage auch für die Durchführung schwieriger Coloskopien endoskopische retrograde Cholangiopankreatographien (ERCP), Platzierung von perkutanen endoskopischen Jejunostomien und Gastrostomien benutzt.

Trotz aller Fortschritte in der Ballon- und Spiraleroskopie sind diese Techniken weiterhin zeitaufwendig, anspruchsvoll und erlauben normalerweise nicht die totale Dünndarmendoskopie in einem Schritt. In Zukunft werden weiterhin Anstrengungen zur Vereinfachung und Verbesserung dieser Methoden notwendig sein.

## **XII. Acknowledgments**

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### **XIII. Erklärung**

Ich erkläre, dass ich in die der Medizinischen Fakultät der Otto-von-Guericke-Universität zur Promotion eingereichte Dissertation mit dem Titel

“Technique and clinical applications of double balloon enteroscopy for the evaluation of small bowel diseases”

in der Klinik für Gastroenterologie, Hepatologie und Infektiologie und im Marienhospital Bottrop mit Unterstützung durch

Prof. Dr. med. habil. Klaus Mönkemüller

ohne sonstige Hilfe durchgeführt und bei der Abfassung der Dissertation keine anderen als die dort aufgeführten Hilfsmittel benutzt habe.

Bei der Abfassung der Dissertation sind Rechte Dritter nicht verletzt worden.

Ich habe diese Dissertation bisher an keiner in- oder ausländischen Hochschule zur Promotion eingereicht. Ich übertrage der Medizinischen Fakultät das Recht, weitere Kopien meiner Dissertation herzustellen und zu vertreiben.

Magdeburg, den 16.05.2012

Dr. medicina (Univ. Montevideo) **Lucia Cecilia Fry**, FASGE (USA)

## **XIV. Curriculum vitae**

Name Lucía C. Fry, M.D, FASGE

**Born** July 11<sup>th</sup>, 1966

### **Education**

Medical Doctor, Universidad de la Republica, Montevideo, Uruguay, 6/1992

Internship, Prof. Jorge Torres, Gynecological Clinic "C" Pereira Rossell Hospital

Internal Medicine (CTI) Hospital de Clinicas and Ambulatory Clinic of Maldonado, 7/1992 to 6/1993

Fellowship in Gastroenterology: Hospital de Clinicas, Universidad de la Republica, 1/1994 to 1/1998

Endoscopy Training: Hospital de Clinicas, Montevideo and Sanatorio Casa de Galicia, Montevideo, 1/1997 to 1999

Visiting Fellowship in Gastroenterology: University of Alabama at Birmingham, May-October 2001

Visiting Fellowship in Gastroenterology: Mayo Clinic Scottsdale, Scottsdale, AZ, April 2004- Sept 2004 (David Fleischer and Jonathan Leighton).

Introduction to Clinical Research, Mayo Graduate School, 2004

Fellowship in Internal Medicine and Gastroenterology, 2004 to 2006, Otto-von-Guericke University, Magdeburg, Germany

### **Professional Memberships**

American Society of Gastrointestinal Endoscopy, FASGE

Chamber of Physicians and Surgeons, Saxony-Anhalt, Germany

Chamber of Physicians and Surgeons, Nordrhein-Westfalen, Germany

Sociedad de Gastroenterología del Uruguay

Sociedad Uruguaya de Endoscopía Digestiva

Sindicato Medico del Uruguay (Uruguay Medical Association)

### **Academic Honors and Awards**

Best Scientific Poster 2011, Nordrhein-Westfalen Gastroenterology Society, Germany, 2011

Fellow, American Society for Gastrointestinal Endoscopy (FASGE), USA, 2011

Best Scientific Poster 2010, Nordrhein-Westfalen Gastroenterology Society, Germany, 2011

*Video of distinction*, American Society of Gastrointestinal Endoscopy, DDW, Washington, 2007

Travel Grant Award for United European Gastroenterology Week, Oral presentation, London, 2009

Poster Prize, first place (Best endoscopic work: „Utility of double balloon enteroscopy for ERCP in patients with Roux-en-Y operation“, Austrian Society of Gastroenterology, Innsbruck, 2007

Travel Award for Young Gastroenterologist/Hepatologist, United European Gastroenterology Week, 2002, Geneva, Switzerland

### **Publications** (peer reviewed)

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### **Book chapters**

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- Fry LC, Dageförde J, Weigt J, Mönkemüller K, Malferteiner P. Cronkhite-Canada syndrome: alopecia and intestinal polyps. In: Mulder CJJ (ed). Atlas of double balloon endoscopy, Medconnect GmbH, Munich, Germany, 2007;20:78-79.
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Mönkemüller K, Neumann H, Fry LC. Middle gastrointestinal bleeding. In: Mönkemüller, Wilcox, Muñoz-Navas (ed), Karger, 2010.

Mönkemüller K, Neumann H, Fry LC. Principles and technique of colon polypectomy. In: Mönkemüller, Wilcox, Muñoz-Navas (ed), Karger, 2010.

### ***Ongoing Research***

Double Balloon Enteroscopy Database, prospective study: University of Magdeburg and Marienhospital Bottrop

Principal Site Investigator, RESINET, Multi-Center German Study on *H. pylori* Resistance.

Co-investigator, SUN-BRAVO Study, Evaluation of symptom response to esomeprazole with objective pH-measurement using the BRAVO capsule in patients with GERD

Principal Investigator, Capsule endoscopy and double balloon enteroscopy for small bowel disorders, Otto-von-Guericke University, Magdeburg

Co-investigator, DIAMOND Study, Utility of questionnaires for the diagnosis of reflux disease

Co-investigator, PUB Study, Peptic Ulcer Bleeding, multi-center study on the utility of esomeprazole iv in addition to endoscopic therapy, Astra Zeneca, Sweden

Co-investigator, Prospective evaluation of snare versus injection-snare for colorectal polypectomy, Otto-von-Guericke University, Magdeburg

Co-investigator, "Bundesministerium für Forschung und Technik" (01ZZ0407/PFG1 and LOMNERD): GERD and Barrett Study,

### ***Invited Lectures***

Midgut bleeding, current approach and algorithms, Congreso de Gastroenterologia, Uruguay, 2010

Advanced diagnostic imaging, Hospital de Clinicas, Montevideo, Uruguay, 2009

Gastroesophageal reflux disease: Utility of the BRAVO capsule, Hamburg, 2007

Small bowel tumors and polyposis syndromes: CE vs DBE, 10<sup>th</sup>, European Bridging Meeting, Magdeburg, Germany, November 2007

Endoscopic therapy of bleeding gastric varices using histoacryl. 9<sup>th</sup> European Bridging Meeting, Napoli, Italy, November 2006

Capsule Endoscopy, Clinica Nutricion y Digestivo, Facultad de Medicina, Montevideo, Uruguay. July 2005.

Anticoagulation and Endoscopy, Otto-von-Guericke University, Magdeburg, Germany. December, 2006.

What is new in Barrett's esophagus, 30<sup>th</sup> Guatemalan Congress of Surgery, April 9-11, 2003, Guatemala City

Update in the management of esophageal varices, 30<sup>th</sup> Guatemalan Congress of Surgery, April 9-11, 2003, Guatemala City