

Received: 2019.10.08  
Accepted: 2019.12.03  
Available online: 2020.01.22  
Published: 2020.02.26

# Emergent Double Balloon Enteroscopy in Overt Suspected Small Bowel Bleeding: Diagnosis and Therapy

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**Source of support:** Departmental sources

**Background:** Double balloon enteroscopy (DBE) is a diagnosis and therapy method for suspected small bowel bleeding (SSBB). The data for emergent DBE is limited in overt SSBB cases. The aim of this study was to investigate the role of diagnosis and therapy of emergent DBE in patients with overt SSBB.





**Material/Methods:** The clinical and endoscopic data for patients with overt SSBB undergoing DBE in a single center from January 2010 to December 2017 were collected and analyzed. Emergent DBE was defined as DBE performed less than 3 days of last bleeding onset.

**Results:** A total of 265 DBEs in 265 patients with overt SSBB were enrolled (mean age, 44.7±17.3 years; 66.8% males). The patients were divided into 3 groups according to the timing of DBE: less than 3 days (n=32), more than 3 days and less than 7 days (n=146), and more than 7 days (n=87) (first group was the emergent group, the latter 2 groups were the non-emergent groups). The diagnosis yield for the emergent group was significantly higher than the non-emergent groups (84.4% versus 65.1% or 59.8%, respectively,  $P<0.05$ ), but was not different between the 2 non-emergent groups ( $P>0.05$ ). The top 3 diagnoses were angioectasias (19.6%), diverticulum (16.2%), and tumor (12.1%). For therapy yield, there was a remarkable reducing trend in the emergent group (<3 days), and the 2 non-emergent groups (3 to 7 days group and >7 days group: 78.1%, 58.2% and 39.1%, respectively,  $P<0.05$ ). The top 3 endoscopic treatments were hemostatic clips (21.9%), argon plasma coagulation (15.8%), and epinephrine injection (14.0%).

**Conclusions:** The emergent DBE had the highest yields for diagnosis and therapy. The study finding showed a pivotal role of emergent DBE in overt SSBB.

**MeSH Keywords:** **Bleeding Time • Diagnosis • Double-Balloon Enteroscopy • Endoscopy • Intestine, Small**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/920555>

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## Background

Obscure gastrointestinal bleeding (OGIB) is defined as occult or overt GI bleeding of an uncertain etiology that persists or recurs after the negative outcomes of esophagogastroduodenoscopy (EGD), colonoscopy, or small bowel evaluation [1]. OGIB accounts for about 5% to 10% of all GI bleeding [2,3]. Studies report that 40% to 75% of OGIBs are located in the small intestine because of the development of new technologies such as video capsule endoscopy (VCE), balloon-assisted enteroscopy (BAE), and multiphase computed tomography (CT) scanning [4–7]. As such, the diagnosis of OGIB may be replaced with “suspected small bowel bleeding” (SSBB) after a negative EGD and colonoscopy [1].

It was a huge challenge to gastroenterologists who used traditional endoscopy and radiologic techniques to inspect the small bowel before development of VCE and BAE. BAE is normally divided into DBE (double balloon enteroscopy) and SBE (single balloon enteroscopy). VCE and BAE have similar diagnostic yields in patients with SSBB, a technique that offers direct visual imaging of the entire small intestine [8–10]. Compared to VCE, BAE has the advantage of analyzing tissue histology from a biopsy and can provide therapeutic effects of an endoscopy to contain active bleeding.

Early VCE have been reported to show a higher diagnostic yield and result in better clinical outcomes compared to delayed VCE [11–13]. It has been recommended that VCE should be performed as soon as possible after the bleeding is revealed in an overt OGIB [4]. However, currently there is no agreement on the timing of emergent BAE in overt SSBB and related data are limited [14–18]. Therefore, the object of this research was to compare the yields of diagnosis and therapy of different timing of DBE in overt SSBB.

## Material and Methods

### Definitions

Overt SSBB was described as observable GI hemorrhage of suspected small bowel that continued with or without recurrence when initial EGD and colonoscopy was performed. Emergent DBE was described as DBE performed less than 3 days of identified bleeding onset. The timing of DBE operation was according to the clinical symptom and/or other actual signs including previous medical history, appointment of admission and DBE.

The source of bleeding was categorized as ulcer (more than 1.0 cm in diameter) and vascular lesion by Yano et al. [19]. Tumors/polyp with ulcer/erosion, and diverticulum with ulcer/vessel were described by Shinozaki et al. [20] and

Fujita et al. [21]. Tumors larger than 2.0 centimeter with or without ulcers were regarded to be bleeding sources. Angiodysplasia (less than 1.0 mm) without bleeding mark was not considered to be a bleeding origin.

### Patients

From January 2010 to December 2017, there were 702 patients with 1264 DBEs performed because of suspected small bowel disease. Of these cases, 367 patients had 661 DBEs for SSBB, and 312 patients had 562 DBEs for overt SSBB. Patients who had prior positive findings on VCE and radiographic imaging were excluded. Our key interesting was whether DBEs were performed without prior diagnosis information of the small intestine. DBEs with positive CTE finding performed for biopsy outcomes was also not considered for the purpose of our study. In multiple DBEs, we selected the DBE with the earliest procedure timing if all DBEs were negative, and the DBE that produced a positive diagnosis.

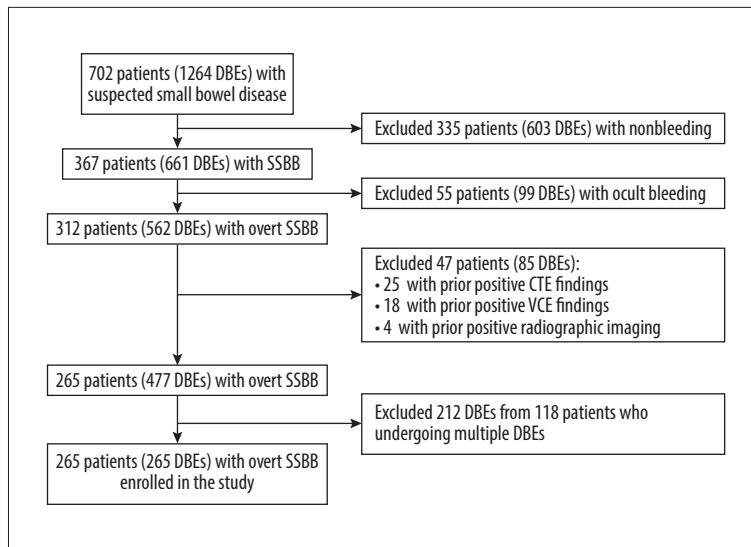
Demographic data, and data on diagnostic yields and therapeutic yields were collected and analyzed. According to the definition of overt SSBB, at least one EGD and colonoscopy had to have been finished in all patients before DBE, of which the outcomes were negative for a bleeding origin. Informed consent was obtained from all patients before enrollment in this study. This study was performed in conformity with the Declaration of Helsinki.

### Double balloon enteroscopy procedure

General anesthesia (intravenous propofol, 2 to 3 mg/kg per hour) was performed under cardiorespiratory monitoring during the procedure. In the current study, all DBEs were performed with Fujifilm EN-530T enteroscopy system. The initial insertion route was directly determined on clinical information and/or previous medical history. All patients were told to fast for at least 12 hours before their DBE procedure. Bowel preparation was not mandatory for an antegrade route. Bowel cleaning (polyethylene glycol electrolyte mixed with 2000 mL water was taken about 4 hours before the DBE) was needed if the procedure was to be performed via a retrograde route. The DBE procedures were manipulated by at least 2 endoscopists with experience of at least 100 DBE examinations, according to the principles and techniques described by the innovator Yamamoto et al. [22]. Carbon dioxide insufflation was used during DBE procedures without x-ray fluoroscopy guidance.

### Endoscopic therapy

Enteroscopic hemostasis included argon plasma coagulation (APC) (ERBE, Tubingen, Germany) for electrocoagulation, and Resolution Clip Device (Boston Scientific, MA, USA) and



**Figure 1.** Flowchart for the process of identifying the study cohort. DBE – double balloon enteroscopy; SSBB – suspected small bowel bleeding; CTE – computed tomography enterography; VCE – video capsule endoscopy.

QuickClip 2 (Olympus, Tokyo, Japan) for clipping. Adrenaline injection of submucosa was operated before APC and clipping if needed. Enteroscopic resection of sessile polyps was done according to the previous description [23]. Any kind of endoscopic therapy was considered for therapy yield analysis.

### Statistical analysis

Continuous variables were expressed as mean±standard deviation. For comparison of categorical variables, chi-square test and/or Fisher's exact test were used when appropriate. Differences were considered significant with *P* value of <0.05. Statistical analysis was performed using the IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Characteristics of clinic

There were 562 DBEs (312 patients) performed because of overt SSBB. Of these, 85 DBEs (47 patients) were ruled out because of prior positive findings on CTE (25 patients), VCE (18 patients), or radiographic imaging (4 patients). And 212 DBEs from 118 patients undergoing multiple DBEs were also excluded. Therefore, 265 DBEs (265 patients) with overt SSBB were enrolled in this retrospective study (Figure 1). The mean age was 44.7±17.3 years, the range of age was 14 to 84 years, and 66.8% patients were male. The most common clinical presentations were hematochezia (62.7%), followed by melena (22.3%) and mixed bloody stool (15.0%). The mean hemoglobin was 7.6±2.1 g/dl; 81.5% of patients required transfusion. We found that 42.6% of patients had comorbidities, and 26.8% of patients were taking anticoagulant and/or non-steroid anti-inflammatory drug (NSAIDs) that may have potential bleeding side effects (Table 1).

**Table 1.** Baseline characteristics of the study patients.

Number of patients	265
Age (mean±SD) (range) (years)	(44.7±17.3) (14–84)
Gender (male) [n (%)]	177 (66.8)
Clinical symptom	
Hematochezia [n (%)]	166 (62.7)
Melena [n (%)]	59 (22.3)
Mixed [n (%)]	40 (15.0)
Hemoglobin (mean±SD) (g/dl)	7.6±2.1
Blood transfusion [n (%)]	216 (81.5)
Comorbidity [n (%)]	113 (42.6)
Anticoagulant and/or NSAIDs [n (%)]	71 (26.8)
PPIs (proton pump inhibitors) [n (%)]	168 (63.4)

SD – standard deviation; NSAIDs – non-steroid anti-inflammatory drug.

### Characteristics of DBEs

Of the 265 DBEs, 32 patients (12.1%) had received emergent DBE, 146 patients (55.1%) had DBE within 3 to 7 days of bleeding onset, 87 patients (32.8%) had DBEs after 7 days (Table 2). The mean number of DBEs per patient was 1.5±0.7, the maximum number was 5, and the number of first-time enteroscopy was 172 (64.9%). The insertion route was retrograde in 71.3% of DBEs, and anterograde in 28.7%. In insertion of depth, the most common area was the middle ileum (55.6%) using the retrograde route, distal jejunum and deeper (63.1%) using the anterograde route. The average procedure time was 141.6±28.1 minutes for retrograde DBE, and 35.8±16.7 minutes for anterograde DBE. Major adverse events occurred in

**Table 2.** The 265 DBEs in patients with overt SSBB.

Timing of DBEs [n (%)]		Procedure time (mean±SD) (minutes)	
<3 days (emergent)	32 (12.1)	Retrograde	141.6±28.1
3–7 days	146 (55.1)	Anterograde	35.8±16.7
>7 days	87 (32.8)	Complications [n (%)]	
DBE procedures/patient (mean±SD, max)	1.5±0.7, 5	Hyperamylasemia and/or acute pancreatitis	13 (4.9)
First-time enteroscopy [n (%)]	172 (64.9)	Perforation	4 (1.5)
Route of insertion [n (%)]		Total diagnostic yield [n (%)]	174 (65.7)
Retrograde	189 (71.3)	Angioectasias	52 (19.6)
Anterograde	76 (28.7)	Diverticulum	43 (16.2)
Insertion of depth [n (%)]		Tumor	32 (12.2)
Retrograde (n=189)		Ulcer/erosion	29 (10.9)
Distal ileum	29 (15.3)	Polyp	9 (3.4)
Middle ileum	105 (55.6)	Others	9 (3.4)
Proximal ileum and deeper	55 (29.1)	Total therapeutic yield [n (%)]	144 (54.3)
Anterograde (n=76)		Hemostatic clip	58 (21.9)
Proximal jejunum	5 (6.6)	Epinephrine injection	37 (14.0)
Middle jejunum	23 (30.3)	APC	42 (15.8)
Distal jejunum and deeper	48 (63.1)	Polypectomy	7 (2.6)

DBE – double balloon enteroscopy; SSBB – suspected small bowel bleeding; APC – argon plasma coagulation.

13 patients (4.9%) with hyperamylasemia and/or acute pancreatitis, 4 patients (1.5%) with perforation (Table 2).

### Diagnostic findings and diagnosis yield

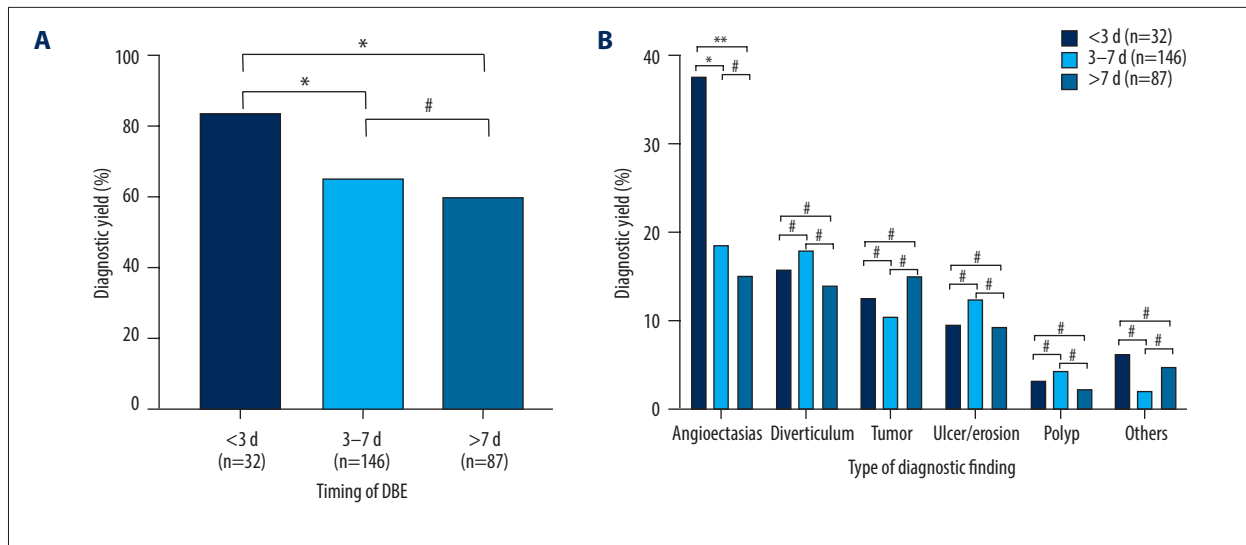
The total diagnosis yield rate was 65.7%. The most common positive diagnosis was angioectasias (19.6%), followed by diverticulum (16.2%), tumors (12.2%), ulcer/erosion (10.9%), polyp (3.4%), and “others” (3.4%) (Table 2). “Others” included portal hypertensive enteropathy, cryptogenic multifocal ulcerous stenosing enteritis, unspecified ileitis, Mallory-Weiss tear, Crohn’s disease, and ancylostomiasis. There was a significant difference in general yield of diagnosis between emergent group and 3 to 7 day non-emergent group and the >7 day non-emergent group (84.4% versus 65.1% or 59.8%;  $P=0.03$  or  $P=0.01$ , respectively), but not difference between the 3 to 7 days group and the >7 days group (65.1% versus 59.8%,  $P=0.42$ ) (Figure 2A). There was a significant difference in diagnosis yield of angioectasias between the emergent group and the 3 to 7 days group or the >7 days group (37.5% versus 18.5% or 14.9%;  $P=0.02$  or  $P=0.01$ , respectively), but no difference between the 2 non-emergent groups ( $P=0.49$ ). The diagnostic

yield of other types of endoscopic findings were not different in any 2 groups (Figure 2B).

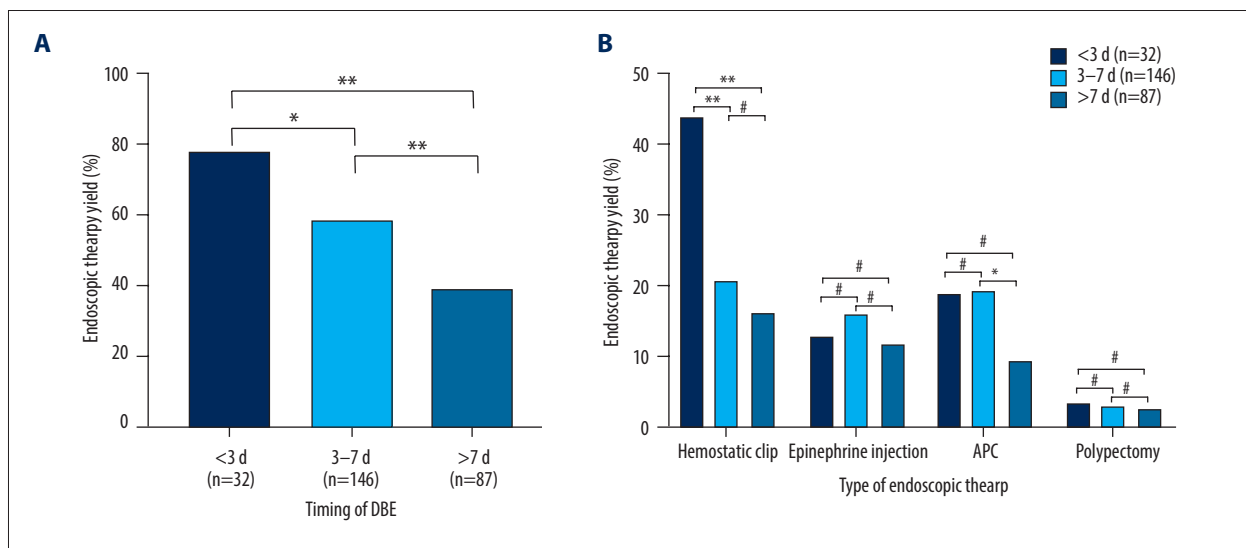
### Endoscopic therapies and therapy yield

The overall endoscopic therapy yield rate was 54.3%. The most common endoscopic therapy type was hemostatic clip (21.9%), followed by APC (15.8%), epinephrine injection (14.0%), and polypectomy (2.6%) (Table 2).

There was a significant difference in general yield of endoscopic therapy in any 2 groups (78.1%, 58.2%, or 39.1%, respectively) (Figure 3A). And there was a significant difference in endoscopic therapy yield of hemostatic clip between emergent group and the 3 to 7 days group or the >7 days group (43.8% versus 20.5% or 16.1%;  $P=0.01$  or  $P\leq 0.01$ , respectively), but no difference in non-emergent groups ( $P=0.40$ ). The endoscopic therapy yield of other types of endoscopic therapy were not different between the 2 groups, but APC was different in the non-emergent groups ( $P=0.04$ ) (Figure 3B).



**Figure 2.** Diagnostic yield of different timing of DBE (A) and different type of diagnostic finding (B). DBE – double balloon enteroscopy. \*  $P < 0.05$ , \*\*  $P < 0.01$ , #  $P > 0.05$ .



**Figure 3.** Endoscopic therapy yield of different timing of DBE (A) and different type of endoscopic therapy (B). DBE – double balloon enteroscopy; APC – argon plasma coagulation. \*  $P < 0.05$ , \*\*  $P < 0.01$ , #  $P > 0.05$ .

## Discussion

GI bleeding is a common indication for hospital admission of Gastroenterology Department. After upper and lower GI bleeding etiology are excluded by EGD and colonoscopy, appropriate decision-making of inspection method to small bowel which still need much more attention. In overt SSBB, there is no agreement on the timing and the role for emergent BAE. A diagnosis yield of 90% and emergency BAE within 24 hours was practicable and helpful to the patients with overt SSBB [15]. Pinto-Pais et al. had a similar conclusion that emergency SBE within 24 hours which was helpful to diagnosis bleeding etiology in patients with active overt OGIB [16]. However,

Nelson et al. found that there were no significant differences in the yields of diagnosis and therapy of BAE, which were performed within 24 hours or later in occult and overt OGIB [24].

In this study, diagnosis yield in the emergent group (84.4%) was significantly higher than in the 3 to 7 days group or the >7 days group (65.1% and 59.8%, respectively), which was in accordance with previous data [14,17]. In order to apply this approach to clinical practice, the time of emergent DBE was defined within 3 days when it was performed from the last visible GI bleeding or continued bleeding. In our hospital, 3 days would be appropriate before emergent DBE because some patients need to have a repeat EGD and/or colonoscopy, or

complete relevant examinations after admission. And the appointment time for hospitalization and DBE which would also need to be considered.

The previous study showed that a high proportion of patients that were regarded as SSBB were found to have missed bleeding etiology within reach of conventional EGD and/or colonoscopy, which included the diagnosis yield ranging from 2% to 25% in patients undergoing repeat EGD and 6% to 23% on repeat colonoscopy [7]. The similar conclusion had also been confirmed by using DBE and VCE in more recent research [25,26]. We consider that some of overt SSBB that should be assessed first with a second-look procedure to exclude upper and lower bleeding in a standard endoscope. In this study, a colonic angiodysplasia was found when using emergent DBE in the retrograde routes. In order to reach hemostasis, we finished the endoscopic therapy by using hemostatic clips in a colonoscopy.

Now more and more endoscopic therapies have been used in the process of examinations for patients with SSBB. There has been agreement that an earlier timing of an enteroscopy could augment the possibility of treatment in the BAE [14,15,17]. In this study, the endoscopic therapy yield in the emergent group (78.1%) was significantly higher than it in the 3 to 7 day group or the >7 day group (58.2% and 39.1%,  $P<0.05$  and  $P<0.01$ , respectively), which was consistent with previous research reports [14]. And endoscopic therapy yield was also different between the non-emergent groups ( $P<0.01$ ). The data showed that the shorter the timing of DBE, the higher the endoscopic therapy yield. We considered that when DBE was performed earlier, lesion identifying become easier, especially in the presence of marked bleeding, which resulted in a greater need of endoscopic therapy.

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## Study limitations

Some limitation of the study must be acknowledged. First, it was a single center retrospective study with a relatively small sample size. Possible bias might have existed in evaluating the value of this study. The study data might not be consistent with the actual situation. Second, although we believed that 3 days used for emergent DBE better reflects what happens in clinical practice, including different time points, such as 24 hours and/or 48 hours, should be included in future research. In addition, follow-up was not considered in this study because it was not main point of study, although the rebleeding rate is one of the major limitations of the endoscopic therapy in the small bowel [27–29].

## Conclusions

This study underlines the use of DBE for diagnosis and therapy of overt SSBB. We found that the diagnostic yield and therapeutic yield were higher in the emergent group. The data showed a crucial role for emergent DBE in overt SSBB. In our opinion, DBE should also be one of the first-line methods in overt SSBB and should be performed as soon as possible. Prospective studies with cost-effectiveness, rebleeding rate, and more samples are needed to further explore the impact of diagnosis and therapy of emergent DBE in the patients with overt SSBB.

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