Original Article

Decision Making in the Management of Obscure-Overt Gastrointestinal Bleeding in Emergency Settings

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Key Words
Obscure gastrointestinal bleeding;
Angiography;
Endoscopy;
Computed tomography

Purpose. Despite the popularity of endoscopy as the standard diagnostic tool for gastrointestinal bleeding, in 5-10% of cases the origin of bleeding is not obvious; this is referred to as obscure gastrointestinal bleeding. Despite affecting only a small number of patients, there is a disproportionate requirement for medical resources by these individuals and many patients require surgical management. We reviewed our experience with such patients during the diagnostic and decision making process, particularly in emergency settings.
Methods. Between August 1995 and June 2010, we enrolled 31 patients presenting with hematemesis, blood per nasogastric tube, melena, or hematochezia and who had negative findings by first-line endoscopy. All patients underwent surgery due to shock or refractory bleeding. Medical records were retrospectively reviewed for preoperative investigation, treatment, and outcome.
Results. Accurate preoperative localization of the source of bleeding was achieved by various diagnostic tools in 14 patients. Among the remainder, the diagnosis was made either by exploration or by endoscopy intra-operatively. Vascular lesions were the most common cause of bleeding, followed by ulcers and diverticula. Nine patients began bleeding again despite surgical intervention. There were 17 patients with morbidities and there were 12 mortalities.
Conclusion. Angiography and enhanced computed tomography aid diagnosis when patients are relatively stable. Once available diagnostic approaches are exhausted, surgical exploration with the aid of intraoperative endoscopy remains an effective diagnostic and therapeutic measure.
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Obscure gastrointestinal (GI) bleeding is defined as bleeding of unknown origin that persists or recurs after negative initial upper or lower GI endoscopy.[1] Obscure GI bleeding accounts for 5-10% of all GI bleeding.[2] Depending on the speed and amount of bleeding, obscure GI bleeding can be further divided into two clinical forms: occult or overt. Obscure-occult GI bleeding refers to persistent blood loss leading to iron deficiency anemia or positive stool occult blood without visible bleeding. On the other

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hand, obscure-overt GI bleeding refers to visible bleeding such as melena, hematochezia, or hematemesis, where the origin of the bleeding is not demonstrated by first-line endoscopy. Compared with obscure-occult GI bleeding, patients with obscure-overt GI bleeding are more likely to have an organic lesion that is associated with more severe complications and subsequently these patients suffer higher levels of morbidity and mortality.[3]

Despite the small number of patients who suffer from obscure-overt GI bleeding, a disproportionate amount of medical resources are needed to properly manage these patients, including diagnostic work-up, surgical intervention, and perioperative care. It has been believed that an accurate preoperative localization will lead to a definitive diagnosis and thus prompt definitive treatment, which would in turn improve the treatment outcome.[4] Currently, there are a variety of diagnostic tools available for localizing the source of obscure GI bleeding, such as angiography, tagged red blood cell (RBC) scan, contrast-enhanced computed tomography (CT), enteroclysis, push enteroscopy, and capsular endoscopy, all of which can be used before resorting to surgical exploration and intraoperative endoscopy.[5] However, the availability of the necessary instruments and professional expertise varies significantly among countries and institutions. For instance, at Western institutions where medical resources are more available, patients with obscure GI bleeding frequently undergo a series of investigations to delineate the source of bleeding before there is a definitive surgical intervention.[6,7] On the other hand, developing countries limit investigational efforts before embarking on surgical exploration.[6,8] This issue is even more complicated when treating an obscure-overt GI bleeding event that requires emergency surgical intervention, because a thorough investigation is not always possible and thus a prompt decision to move on to surgical intervention is frequently made without knowing the exact origin of the bleeding.

Herein we review our experience during the surgical management of obscure-overt GI bleeding, mostly in emergency settings, placing special emphasis on the role of preoperative investigation including surgical exploration, in order to aid in clinical decision making when dealing with these patients.

Materials and Methods

Between August 1995 and December 2010, patients presenting with hematemesis, blood per nasogastric tube, melena, or hematochezia, where the initial first-line endoscopy failed to identify the source of bleeding, were selected from the database at our institution. For clarity, according to the patient's initial presentation, we define hematemesis or blood per nasogastric tube as an upper GI presentation, while hematochezia or melena are defined as a lower GI presentation. After a negative esophagogastroscopy and/or colonoscopy, the patients underwent a series of examinations at the discretion of the attending physician, including a contrast-enhanced CT, angiography, or nuclear scan to further evaluate the origin of the bleeding.

Among these 31 patients, surgical intervention was performed because of refractory bleeding or a life-threatening condition such as hypovolemic shock (defined by a systolic blood pressure less than 90 mmHg or a mean blood pressure less than 70 mmHg). In patients with inconclusive preoperative studies or with hemodynamic instability that precluded further examination, an emergency laparotomy in preparation for intraoperative enteroscopy (IOE) was considered. IOE was performed by inserting the endoscope via both ends of the alimentary tract or via multiple enterotomies.

All patients underwent their operation with informed consent. The medical records of these 31 patients were reviewed paying special attention to their history of bleeding, preoperative transfusion requirements, underlying medical conditions, and the results of any preoperative studies. In patients undergoing multiple examinations, the tentative localization was ascribed to the most informative investigation regarding the site of bleeding. Complications and deaths that occurred within 30 days of the operation were considered morbidity and mortality. The positive predictive value (PPV) of a diagnostic test was defined as the percentage of true positive results among all positive results. The morbidity and mortality rates between patients with and without an underlying comorbidity, such as diabetes, heart disease, liver cirrhosis, or end-stage renal disease, were compared by

Fisher's exact test. The morbidity, mortality, and rebleeding rates between patients with or without a definite preoperative localization were also compared by Fisher's exact test. A p value < 0.05 was considered statistically significant.

Results

Demographics

Among the 31 patients enrolled, 20 were men and 11 were women. The mean ± SD age was 64 ± 16.2 years (range 6-87). Seven patients had upper GI presentations, while twenty patients had lower GI presentations, and the remaining 4 patients presented with both of the above. Twelve of the patients had been hospitalized previously due to GI bleeding and these ranged from 1 to 8 hospitalizations. All of the patients received operations due to hypovolemic shock or refractory bleeding. The preoperative transfusion requirement for packed RBC was 7.71 ± 3.15 U (range 4~14 U).

Preoperative investigations

A tentative localization was obtained via preoperative investigations in 18 (58.1%) patients. The results of the preoperative investigations are listed in Table 1. A contrast-enhanced CT was used for 10 patients. Of these 10 patients, 5 (50%) had an examination that was positive and the PPV was 100%. An angiography was used for 18 patients. Of these 18 patients, the examination was diagnostic for 7 (38.9%) of them; 5 of these patients were bleeding from a vascular lesion and one was bleeding from a gastrointestinal stromal tumor. For the remaining patient, the positive angiography was misleading and this resulted in the need for a second operation, which brought the PPV down to 85.7%. Among the 11 patients with a negative angiography, the bleeding was from a vascular lesion in 5 patients according to the operative or pathological findings. A tagged RBC scan was used for 11 patients and 7 showed a positive finding. However, these findings helped to localize the lesion in only 3 patients, giving a PPV of only 42.9%.

A Meckel's scan was used with one 6-year-old boy and this helped to localize the lesion. An abdominal ultrasound was performed on 4 patients and helped to find a jejunal gastrointestinal stromal tumor. One patient underwent capsular endoscopy; however, the bleeding was not localized. Enteroclysis and a double-contrast barium enema were also used with some patients and these cases are included in Table 1.

Origin, presentation, and management

All the patients received operations and the etiologies were confirmed (Table 2). The source of bleeding was located in the stomach of 6 patients (19.4%) and in the duodenum of 4 patients (12.9%). Thirteen patients, the majority, bled from the small bowel (41.9%), while 11 patients (35.5%) bled from the jejunum, and 2 patients (6.5%) bled from the ileum. The remaining 8 patients bled from the colorectal region (25.8%). In terms of the nature of the lesions, the

Table 1. Results of the preoperative investigations

	No.	Positive	Negative	Localization	
				Tentative	Definite
CT	10	5	5	5	5
Angiography	18	7	11	5	4
RBC scan	11	7	4	6	3
Meckel's scan	1	1	0	1	1
Ultrasound	4	1	3	0	0
Enteroclysis	2	1	1	1	1
DCBE	1	0	1	0	0
Capsular endoscopy	1	0	1	0	0

No.: number of investigations; CT: computed tomography; RBC: red blood cell; DCBE: double-contrast barium enema.

majority were caused by a vascular lesion, such as angiodysplasia, which occurred in 12 individuals (38.7%). Six patients (19.4%) bled from ulcers and 5 patients (16.1%) bled from diverticular disease.

Most patients with lesions in the stomach and duodenum showed an association with an upper GI presentations (90%, Table 2); nevertheless, four of these patients (44.4%) had a concomitant lower GI presentation. Similarly, most patients with lesions located distal to the ligament of Treitz were associated with a lower GI presentation (19/21, 90.5%). Therefore, the sensitivity of upper and lower GI presentation in predicting the site of the bleeder was 90% and 90.5%, respectively. On the other hand, 5 patients (50%) with lesions in the stomach and duodenum were not associated with a lower GI presentation, while 19 patients (90.5%) with lesions located distal to the ligament of Treitz were not associated with an upper GI presentation. Therefore, the specificity of the upper and lower GI presentation in predicting the site of the bleeder was 90.5% and 50%, respectively. The surgical procedure used was determined by the location and nature of the lesion and therefore a segmental resection of the involved bowel was performed in most cases (Table 2).

The methods and results of the definite localization of the lesion are listed in Table 3. Among the 18 patients with tentative preoperative localization, the bleeders were demonstrated accurately by preoperative investigations in 14 individuals. Among the patients with lesions located in the stomach or duodenum, only 3 (30%) out of 10 underwent enhanced CT or angiography to help with the preoperative localization of their identified lesions. The other patients were brought directly to the operating room for surgical exploration because their hemodynamic instability precluded further investigation. In contrast, among the patients with lesions in the small and large

Table 2. Origin, presentation, and management of overt obscure GI bleeding

Etiology	No.	Presentation	No.	Procedure
Stomach	6			
Vascular lesion	3	U	1	Suture ligation
		U+L	2	Suture ligation
Ulcer	2	U	1	Resection
		U+L	1	Resection
Emphysematous gastritis	1	U	1	Resection
Duodenum	4			
Ulcer	2	U	1	Resection
		U+L	1	Suture ligation
Diverticulum	1	L	1	Resection
Aortoduodenal fistula	1	U	1	Resection
Jejunum	11			
Vascular lesion	4	L	4	Resection
GIST	2	L	2	
Polyarteritis nodosa	1	L	1	Resection
Diverticulosis	3	U	2	Resection
		L	1	
Adenocarcinoma	1	L	1	Bypass
Ileum	2			
Meckel's diverticulum	1	L	1	Resection
Chronic ileitis	1	L	1	Resection
Colon and rectum	8			
Vascular lesion	5	L	5	Resection
Ulcer	2	L	2	Resection
Ischemic colitis	1	L	1	Resection

No.: number of patients; GI: gastrointestinal; GIST: gastrointestinal stromal tumor; U: upper gastrointestinal presentation; L: lower gastrointestinal presentation.

intestine, 11 (52.4%) lesions were identified preoperatively. Both contrast-enhanced CT and angiography demonstrated 3 lesions (14.3%), respectively. A tagged RBC scan was able to localized 3 lesions (14.3%), all within the colorectal region. The lesions of 10 patients (47.6%) were not identified until after the surgical intervention, with 6 of them being in the small bowel and 4 of them being in the colon.

Outcome

The outcomes of the patients are listed in Table 4. Despite aggressive surgical treatment, 9 patients (29%) had rebleeding events. Five of these were due to vascular lesions such as angiodysplasia (55.6%). In one patient, the initial angiography misled the surgeons into perform a right hemicolectomy under suspicion of bleeding from the right upper quadrant. Further exploration showed that the bleeding originated from a duodenal diverticulum. The patient survived, but the postoperative course was complicated by wound dehiscence. In another patient with multiple colonic ulcers, a right hemicolectomy was performed initially. Recurrent bleeding eventually resulted in a need for a total colectomy. Five rebleeding events happened in patients who had a preoperative tentative localization, while the other four were in those without any preoperative investigation. Fisher's exact test showed no difference in the rebleeding rate whether the lesion was localized preoperatively or intraoperatively ($p = 1$).

Table 3. Methods and results of definite localization

Localization	No.	Localization method	No.
Stomach	6	Exploration ± IOE	4
		Enhanced CT	1
		Angiography	1
Duodenum	4	Exploration ± IOE	3
		Enhanced CT	1
Jejunum	11	Exploration ± IOE	6
		Enhanced CT	2
		Angiography	2
		Enteroclysis	1
Ileum	2	Meckel's scan	1
		Enhanced CT	1
Colon and rectum	8	Exploration ± IOE	4
		RBC scan	3
		Angiography	1

No.: number of patients; IOE: intraoperative endoscopy; CT: computed tomography; RBC: red blood cell.

There were 18 morbidities occurring among 17 patients (54.8%) in this series. These included 3 pulmonary infections, 2 anastomotic leaks, 3 wound dehiscences, one peripheral arterial occlusion, one cerebral vascular event, and 8 multiple organ failures. In the 18 patients with a tentative preoperative localization, morbidity occurred in 11 patients (61.1%). On the other hand, morbidities occurred in 6 of the 13 patients whose lesions were identified intraoperatively (46.2%). Fisher's exact test showed no difference in morbidity whether the lesion was localized preoperatively or not ($p = 0.48$). Thirteen of these patients had underlying comorbidities, while four did not. Fisher's exact test showed a marginally higher morbidity rate among patients with an underlying comorbidity ($p = 0.07$).

All 12 mortalities (38.7%) resulted from postoperative septic complications, and 11 of the patients had underlying comorbidities. Seven of these patients had a preoperative tentative localization while 5 patients did not. Fisher's exact test showed no difference in the mortality rate whether the lesion was localized preoperatively or during the operation ($p = 1$). In contrast, the Fisher's exact test did show a significant differences in the mortality rate between patients with and without underlying comorbidities, ($p = 0.008$).

For 7 out of the 31 (22.6%) patients, the bleeding could not be localized without using IOE. Four of these patients (57.1%) subsequently died, and 6 patients (85.7%) had morbidities including wound

Table 4. Surgical outcomes of obscure-overt GI bleeding

	No. (%)	With/without preoperative localization	*p*	With/without comorbidities	*p*
Rebleeding	9 (29)	5/4	1	7/2	0.43
Morbidity	17 (54.8)	11/6	0.48	13/4	0.07
Mortality	12 (38.7)	7/5	1	11/1	0.008

No.: number of patients; *p*: *p* value by Fisher's exact test.

infection, multi-organ failure, and anastomotic leakage. Three patients (42.9%) had rebleeding even after IOE.

Discussion

In this study, we reviewed our experience during the surgical management of obscure-overt GI bleeding, mostly in emergency settings. The most common etiology in this series was vascular lesions such as angiodysplasia and the most common location of the lesion was in the small bowel. In patients with an upper GI presentation, the management was more straightforward as the range distribution of the possible bleeding sites was relatively limited. However, the brisk nature of the bleeding also often precluded a detailed examination of the patients. In patients with a lower GI presentation, preoperative CT and angiography of the relatively stable patients seems to have aided the localization and helped the surgical planning.

Despite the advances in diagnostic endoscopy, surgeons regularly still have to manage patients with obscure-overt GI bleeding in an emergency setting from time to time. Any lesions from the oral cavity to the anal canal may cause GI bleeding. A lesion may escape detection because it bleeds slowly or because it bleeds intermittently and it may even stop bleeding spontaneously. In addition, anemia, hypovolemia, or poor bowel preparation may make the lesions less obvious.[9,5,10] Based on previous studies, approximately 58-75% of obscure GI bleeding cases are found to be small bowel lesions.[5,11,12] In another series, small bowel angiectasias were detected in 30-60% of the examinations for obscure-overt GI bleeding.[13] Our results are comparable with these previous series in that most of the lesions were located in the small bowel (41.9%) and because vascular lesions such as angiodysplasia were responsible for most of the bleeding (38.7%).

The majority of our patients with upper GI presentation did not receive a second endoscopy or another examination. According to a previous series, it was likely that obscure bleeding is not truly obscure in patients with upper GI presentations. Instead, up to half of the lesions seem to be overlooked. Repeat endoscopy is able to reveal various previously missed lesions, such as Cameron's lesions, Dieulafoy's lesions, angiodysplasias, and peptic ulcers.[14,15] However, if the patients' condition does not permit repeated endoscopic examination, the strategy for management is more straightforward; this is because the anatomical distribution of possible lesions is relatively limited. Surgical exploration is justified and further investigations are not necessary. The high sensitivity (90%) and specificity (90.5%) of upper GI presentation in predicting the bleeding site in this series supported such a management strategy.

On the other hand, the diagnosis and management of obscure GI bleeding in patients with lower GI presentation is more ambiguous. Of the 20 patients whose presentation was limited to hematochezia or melena, only 6 (30%) were operated on because of shock, indicating that there may be sufficient time for further localization studies.[16] The low specificity of lower GI presentations found in our study also warrants carrying out more detailed investigations if the conditions permitted. Previous studies have recommended push enteroscopy or capsular endoscopy for relatively stable patients. These examinations are, however, technique-dependent and time-consuming. For example, a complete capsular endoscopic examination may take 24 to 48 hours, so it is not time-efficient in emergency settings.[17] The diagnostic yield has also been shown to vary considerably across a number of studies, ranging from 35% to 76%.[5] The diagnostic yield of push enteroscopy is operator-dependent and also varies significantly among series (3% to 70%).[5] Complications associated with the use of an overtube in the procedure have also been reported.[18]

In our series, both enhanced CT and angiography were associated with high PPVs and helped to localize the bleeder in 25.8% of patients. By demonstrating the extravasation of the contrast media, an enhanced CT is able to identify the bleeding source easier and faster than other investigational modalities. CT also has the advantage of detecting unexpected lesions,[19] such as emphysematous gastritis and mass lesions in our series. Angiography may demonstrate bleeders with bleeding velocity greater than 0.5 ml/min,[20] and also allows the identification of nonbleeding lesions such as vascular ectasias, tumors, and inflammatory lesions.[21] Another advantage of angiography is that it is a therapeutic intervention when there is active arterial bleeding. The disadvantages of angiography are, however, catheter-related complications and a limited ability to detecting lesions that are bleeding intermittently or are venous in origin. The extensive territory supplied by the superior and inferior mesenteric arteries may also limit the techniques ability to precisely localize a lesion even when bleeding is confirmed. As a result, additional measures, such as surgical exploration or intraoperative endoscopy, may must be considered.

Tagged RBC scan is the most sensitive technique for detecting active GI bleeding. Bleeders with a rate of 0.1 mL/min are able to be detected.[22,23] This approach also has the advantage of being noninvasive, allowing the detection of both arterial and venous bleeders, and being useful when trying to detect intermittent bleeding.[21] In our series, a tagged RBC scan was used on 11 patients and accurately localized the lesion in 3 cases (27.3%), which is comparable to that reported in previous series (27%).[5,6] The low localization ability and diagnostic yield resulted mainly from poor anatomical resolution. Tagged RBC scans are also time-consuming to perform, and the nuclear scan is not therapeutic in itself.[21] These disadvantages limit the use of tagged RBC scans in emergency settings.

We also reported a 6-year-old boy whose bleeding was from a Meckel's diverticulum, which was detected by a Meckel's scan. From an epidemiological point of view, a Meckel's scan can be considered for the localization of GI bleeders in patients younger than 40 years old.[21] However, a positive Meckel's scan shows the presence of ectopic gastric mucosa, but not necessarily the definitive source of the bleeding.[24]

Although the diagnostic yield of IOE has been reported to be 58-88% and has been advocated by some as the standard diagnostic tool for obscure GI bleeding,[25] a significant percentage of the bleeders may be missed and rebleeding occurs in up to 60% of patients.[25] Moreover, IOE is associated with significant morbidity and a high mortality rate of up to 17%.[5] In our series, the use of IOE was associated with high mortality, high morbidity, and a high rebleeding rate. The multiple enterotomies and manipulation during IOE prolong the operation time and aggravate bowel content contamination, which may increase the risk of wound infection, anastomotic leakage, ileus, and pneumonia.

In this series the morbidity, mortality, and rebleeding rates were significantly higher than those reported in previous series.[6] One possible explanation is that most of our patients were operated on in emergency settings and had unstable hemodynamics. Another possible reason is that a high proportion of our patients had underlying comorbidities, which is supported by the fact that our results showed a significantly higher mortality rate among patients with an underlying comorbidity. Previous studies have also demonstrated that preoperative comorbidity is associated with increased morbidity and mortality.[26] Another possible reason for the high morbidity and mortality rates in our series are that 13 patients had to be operated on without preoperative localization, and IOE had to be used with 7 of these patients to localize the bleeders. Previous studies have reported that if the bleeding site can not be localized and a blind limited resection is performed, the mortality rate can reach 30-57%.[27,10] On the other hand, if angiography successfully localizes a lower GI bleeding site and a limited resection is carried out, this results in a significantly lower morbidity rate than among patients without angiographic localization (8.6% vs. 37%).[4] In our series, however, the morbidity, mortality, and rebleeding rates were not significantly different between the groups of patients where preoperative localization was successful and those where it was not. The retrospective nature of the study, the lack of a well-structured diagnostic algorithm, and the quality of the preoperative investigations might be an origin of bias in this context.

Conclusion

In summary, the use of diagnostic tools and timing of surgery should be dictated by the presentation and condition of the patient. In patients with lower GI presentation and relative stable hemodynamic status, enhanced CT and angiography may be arranged for more precise localization. In unstable patients, surgical exploration is still a reasonable course of action.

Further prospective study design and a definite algorithm are necessary for the optimal management of obscure-overt GI bleeding.

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原　著

緊急情況下針對明顯之不明原因消化道出血評估與臨床決斷

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背景　儘管內視鏡檢查廣泛而常規的使用於消化道出血之診療，但有 5-10% 的病人仍無法確認出血位置，是為不明原因消化道出血。雖然這類病人比例較少，但是更需要使用大量醫療資源。本文中我們回顧本院在緊急狀況下，對合併大量出血的此類病人進行診斷及臨床決策之經驗。

材料與方法　從 1995 年 8 月至 2010 年 1 月，從本院資料庫中搜尋到 31 位病人，合併明顯出血之病人如吐血，鼻胃管中有血，血便，或是瀝青便，經由初步之上消化道內視鏡及大腸鏡無法定位之出血。所有病人皆因休克或大量出血而接受手術。我們針對病歷回顧並分析術前檢查，治療以及結果。

結果　共有 14 位病人可經由術前檢查準確定位出血位置。其餘病人仍需靠手術探查，甚至合併術中內視鏡檢查方能準確定位。血管病灶為最常見出血原因，其次是潰瘍與憩室。有 9 名病人術後再出血，並有 17 例發生合併症及 12 例死亡。

結論　儘管檢查工具進步，在緊急情況下，明顯之不明原因消化道出血的診斷與處置仍是實務上一大挑戰。血管攝影和注射顯影劑之電腦斷層掃描，可以在相對穩定的病人使用。在緊急狀況下，手術探查與術中內視鏡仍不失為一有效的診斷與治療方法。

關鍵詞　不明原因消化道出血、血管攝影、內視鏡檢查、電腦斷層掃描。