



Crohn's disease presenting as acute gastrointestinal hemorrhage

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Abstract

Severe gastrointestinal (GI) hemorrhage is a rare complication of Crohn's disease (CD). Although several surgical and non-surgical approaches have been described over the last 2 decades this complication still

poses significant diagnostic and therapeutic challenges. Given the relative infrequency of severe bleeding in CD, available medical literature on this topic is mostly in the form of retrospective case series and reports. In this article we review the risk factors, diagnostic modalities and treatment options for the management of CD presenting as GI hemorrhage.

Key words: Crohn's disease; Recurrence; Gastrointestinal hemorrhage; Biologic agents; Risk factors

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Core tip: Severe gastrointestinal (GI) hemorrhage is a rare complication of Crohn's disease (CD). With the relative infrequency of severe bleeding in CD, available medical literature on this topic is mostly in the form of retrospective case series and reports. In this article we reviewed the available medical literature and summarized the risk factors, diagnostic modalities and treatment options for the management of CD presenting as GI hemorrhage.

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INTRODUCTION

Although Crohn's disease (CD) is often associated with mild gastrointestinal (GI) bleeding, severe GI hemorrhage is a rare complication. The first case of hemorrhage due to regional enteritis was described in 1941^[1]. Since then, multiple case reports and case series of severe bleeding in CD have been published

with reported incidence ranging from 0.6%-4%^[2-7]. This presentation poses significant diagnostic and therapeutic challenges for the following reasons: (1) difficulty accurately identifying the origin of the bleed primarily due to presence of multiple areas of inflammation; (2) presence of other complications such as stricturing CD that can compromise endoscopic evaluation; and (3) increased risk of recurrent bleed^[3].

Limitations on available clinical data has made it difficult to formulate a consensus on the definitive diagnostic and treatment modalities for this condition. We will review the current working definition of GI hemorrhage in CD, its pathogenesis, epidemiologic factors, diagnostic and therapeutic options.

DEFINITION OF GI HEMORRHAGE IN PATIENTS WITH CD

The definition of GI hemorrhage in CD has changed over the years. Homan *et al.*^[8] in 1976 defined it as profuse rectal bleeding that required blood transfusions to maintain normal vital signs. Since then the definition has varied ranging from rectal bleeding requiring more than 4 units of blood over a period of 2 wk^[5] to 2-5 units in 24 h^[2,7]. In a recent case series the definition was again modified to a drop in hemoglobin (Hb) of 2 g/dL below the baseline +/- hemodynamic instability or an abrupt fall in Hb to less than 9^[3,4].

Source and location of bleed

In most patients a definitive bleeding site, defined as a lesion that is either actively bleeding or possesses an adherent clot, is not identified and the bleeding source is attributed to diffuse areas of active inflammation^[4]. When found, the source of bleeding is more commonly described as a deep ulcer eroding into a blood vessel^[9]. On rare occasions, a large pseudopolyp in the ileum or colon has been identified as the source of bleeding^[2,10]. The majority of bleeds originate from the ileum and colon as visualized on pathology after surgery, endoscopy or imaging studies. Only a small number of episodes have been attributed to a jejunal or upper GI source. Isolated colonic bleeding accounts for 3%-50% of hemorrhagic CD, diffuse ileo-colonic lesions for 22.7%-68.5%, and 19%-66% originate from the small bowel^[2-5,7]. Although it may seem logical to assume that the presence of significant disease activity and symptomatic CD would result in a higher incidence of acute lower GI bleeding, two series have shown 65%-78% of patients had quiescent CD at the time of bleeding^[2,3].

Epidemiology

The incidence of severe lower GI bleeding in CD has ranged from 0.6%-4%. Cirocco *et al.*^[7] reported an incidence of 0.6% in their 631 patients diagnosed with CD while Kim *et al.*^[3] reported an incidence of 4% in their study of 1731 patients. Other large series

reported incidences from 1.3%-1.6%^[4,5]. Some studies describe a similar incidence in males and females^[2,5] whereas others have found a higher incidence in males^[3,4,7]. The average age of presentation has been around 30 years ranging from 27-45 years^[2-5,7]. Since the peak age for the diagnosis of CD is in the 20's, it is possible that patients present with severe bleeding after having the disease for some years.

A study to evaluate risk factors for acute hemorrhage in CD showed that patients on corticosteroids had a higher rate of bleeding when compared to a control group of CD patients with no bleeding but this was not confirmed on multivariate analysis^[3]. The same study showed that Azathioprine/6-Mercaptopurine (6-MP) could actually have a role in preventing severe hemorrhage in CD OR = 0.53 (95%CI: 0.30-0.91).

DIAGNOSIS

Available diagnostic modalities include: upper and lower endoscopy, radionuclide bleeding scan, mesenteric angiography, computed tomography (CT) enterography and capsule endoscopy. The following sections describe the utility of these tests.

Endoscopy

Only 2 case series studies have utilized upper endoscopy (EGD) for diagnosis^[3,4]. Kim *et al.*^[3] analyzed 30 patients who underwent an EGD with no diagnostic yield. In the second study, EGD was performed in patients with suspected upper GI bleed or with a negative colonoscopy, and the source of bleeding was identified in 2 patients but there was no mention of the total number of patients undergoing EGD.

There are 3 large case series that have utilized colonoscopy for diagnosis producing variable results as demonstrated in Table 1. Pardi was the first to evaluate the role of colonoscopy in the diagnosis and treatment of hemorrhagic CD. Patients included in this study underwent colonoscopy within 24 h of presentation and the source of bleeding was identified in 78%. Only 3 patients were treated endoscopically with no subsequent recurrence of bleeding^[4]. Belaiche *et al.*^[2] found the yield of colonoscopy in identifying the bleeding site at 60% (18/30). Ulcers located in left and sigmoid colon were recognized as the cause of bleeding in 95% cases while one patient bled from a pseudopolyp. In contrast to the previous two studies, the diagnostic yield for colonoscopy was only 10.6% in a Korean case series. Some of the factors that may have led to a lower yield of colonoscopy in this study include a delay in colonoscopy examination, as its timing was not specified^[3], and location of the bleeding site as in most cases in this study the bleeding site originated from the small bowel. As demonstrated in these case series, colonoscopy was not only useful in determining the site of bleeding but also could be used therapeutically.

Table 1 Identification of the bleeding site in case series *n* (%)

| Ref. | Study type | <i>n</i> | Identification of origin of bleeding | Location | Colonoscopy | Mesenteric angiography | Radionuclide bleeding scan | CT enterography | EGD |
|---|----------------------------------|----------|--------------------------------------|--|--------------|------------------------|----------------------------|-----------------|----------|
| Kim <i>et al</i> ^[3] (2012) | Retrospective review | 70 | 22 (31.4) | Small bowel 19 Large bowel 3 | 5/47 (10.6) | 5/19 (26.3) | 8/27 (29.6) | 9/46 (19.6) | 0/30 (0) |
| Pardi <i>et al</i> ^[4] (1999) | Retrospective review (1989-1996) | 31 | 31 (100.0) | NA | 25/31 (78.0) | 1/3 (33.0) | 3/4 (75.0) | NA | 2 |
| Belaiche <i>et al</i> ^[2] (1999) | | 34 | 22 (65.0) | Colon (85%) Isolate small bowel (15%) | 18/30 (60.0) | 3/4 (75.0) | 0/2 | NA | NA |
| Robert <i>et al</i> ^[5] (1991) | Retrospective review (1960-1986) | 21 | 2 (10.0) | NA | NA | 2/5 (40.0) | NA | NA | NA |

CT: Computed tomography; EGD: Esophagogastroduodenoscopy.

Radionuclide bleeding scan and mesenteric angiography

There is very limited literature demonstrating the utility of angiography and radionuclide scan with variable results, success ranging from 26% to 75% for angiography and 0% to 75%^[2-4] for radionuclide bleeding scan (Table 1). These modalities do not ascertain if the site of bleeding is resulting from CD but in some instances a presumptive diagnosis can be established based on angiographic signs that have been associated with CD. These signs include the presence of mesenteric neovascularity, an increased contrast staining of bowel loops, early and prominent venous return, skip lesions, and the "zoning" sign^[11-13]. The zoning sign refers to a double-layer appearance of the bowel wall with a densely staining inner wall representing a hypervascular submucosa and mucosa and a thick but relatively avascular outer muscle layer.

CT enterography

CT enterography of the small bowel was introduced in 1997 and was found helpful in assessing the extent and severity of CD^[14]. The underlying principle was the combination of neutral (low-density) oral contrast with "enteric phase" CT to enhance contrast resolution between mucosa and lumen to better characterize small bowel abnormalities. CT enterography has been utilized in detecting obscure GI bleed^[14]. Its utility to detect hemorrhage in patients with CD was demonstrated only in one series where CT enterography diagnosed the site of bleeding in 9/46 (19.6%)^[3].

Capsule endoscopy

The role of capsule endoscopy has not been studied in patients with hemorrhagic CD likely due to concern of capsule retention secondary to strictures or previous surgeries^[15]. The role of capsule endoscopy has been limited to diagnosing obscure GI bleeds in patients with CD. In these cases capsule endoscopy has been found to be superior to push enteroscopy and small bowel radiography^[16].

TREATMENT

In an early case series, 3/21 (14.3%) patients presenting with GI hemorrhage due to CD died from bleeding or associated complications^[5]. Later case series have demonstrated decreased mortality in patients with severe hemorrhage from CD with either no mortality in 34 patients^[2] or 1/32 (3.1%)^[4]. Initial management should always include primary resuscitation with IV fluids and blood transfusion as in any patient with a significant GI bleed. If the patient continues to be hemodynamically unstable the surgical team should be involved early in the course while continuing resuscitation. Treatment consists of medical management, minimally invasive interventions and surgical management.

Medical management

Treatment of CD has evolved over the years. In the early 1990's the most common strategy for the management of CD with hemorrhage was surgery. However beginning in the late 1990's there has been a paradigm shift in the management with a tendency to avoid surgery and instead utilize medical management^[2,4]. Besides blood transfusions, medical management consists of medications used to treat CD including corticosteroids, mesalamine, antibiotics and continuation of 6-MP^[2,4,17]. Belaiche *et al*^[18] successfully achieved hemostasis with the use of infliximab in non-surgical candidates presenting with GI hemorrhage and attributed this success to the high rates of mucosal healing with this medication. Since then, additional case reports and case series have reported the effectiveness of infliximab in cessation of GI hemorrhage^[19,20]. Aniwani *et al*^[21] recently published a case series in which bleeding was controlled within 24 h in 6/7 patients who received infliximab. No rebleeding episodes were reported after 30 d of follow up and surgery was avoided in all patients. The potential advantage of infliximab in the treatment of patients

with unclear site of bleeding was described. There are at least 11 additional reports of patients presenting with CD related GIB treated with infliximab with successful control of bleeding in all the cases^[18,21-25]. Patients selected for treatment with infliximab in these case reports included poor surgical candidates and those who developed recurrent bleeding after undergoing surgery.

There is only one comparative study evaluating medical therapy for CD presenting with severe bleeding in the era of biologics consisting of 70 cases^[3]. All patients were initially managed with 5-ASA, azathioprine/ 6-MP or corticosteroids. Eleven patients required additional intervention including embolization, endoscopic management, surgery or infliximab (5 patients) to treat the index bleeding. A total of eleven patients underwent treatment with infliximab (5 first bleeding and 6 rebleeding) and only 1 patient had further bleeding episodes requiring surgery. The benefits of infliximab therapy did not reach statistical significance when compared to patients undergoing other treatments because of the small sample size. The study suggests that medical treatment can have better outcomes than what has been previously reported and surgery could be reserved for patients who fail initial medical treatment or exhibit recurrent bleeding.

There was one case report utilizing recombinant factor VIIa in the management of GI hemorrhage secondary to CD. Recombinant factor VIIa improves hemostasis and has been shown to be effective in treating hemorrhage in patients with hemophilia A or B. The standard dose for these conditions is 90 to 110 µg/kg every 2 to 3 h for two to three doses^[26]. In this case report they used 2 doses of 120 µg/kg three hours apart with cessation of bleeding over the next 12 h.

MINIMALLY INVASIVE INTERVENTIONS

Minimally invasive management consists of endoscopic treatment or embolization. Endoscopy may not be feasible in patients with strictures but when possible thermocoagulation alone or combination of epinephrine injection and bipolar coagulation have been described. Application of hemoclips may be compromised in the presence of inflamed and friable mucosa^[15,27]. Endoscopic treatment of bleeding lesions was successful in 5/7 cases in one series and 3 (2 upper EGD and 1 colonoscopy) patients in another report underwent therapeutic endoscopy with no recurrent bleeding^[2,4].

Superselective embolization can present with complications such as intestinal infarction but recent advances in interventional radiology (microcatheters, embolic agents and microcoils) have reduced the rate of complications^[28]. Success rate with this treatment modality ranges from 81% to 93%, with a mortality rate between 0% and 7%^[29].

In addition to superselective embolization, there are

isolated case reports on the use of arterial vasopressin therapy to control bleeding in cases with diffuse lesions or when superselective catheterization is not technically possible^[30]. In these, vasopressin infusion either successfully controlled or reduced the rate of bleeding to stabilize patients before surgery^[29-31]. However, vasopressin infusion can result in complications including hypertension, vasoconstriction, cardiac arrhythmia and bowel ischemia^[32]. In summary, superselective angiographic embolization has become the standard in treating angiogram positive GI bleeding. In cases where embolization is difficult to perform either because of diffuse pathology or absence of adequate collateralization, vasopressin infusion is an alternative^[29].

SURGICAL MANAGEMENT

Papi *et al*^[22] summarized 5 series published from 1991-2001^[2,4-7]. Of the 101 patients included in this study 37 (36.6%) underwent surgery during the first episode of bleeding and 64 (63.4%) underwent non-operative management. Although the mortality in the medical group was not reported, the mortality in the surgical group was 6.9%. Recurrence of bleeding was noted to be higher in patients who did not undergo surgery (38.5% vs 5.7%)^[22]. The major challenges they reported with surgery were accurate identification of the bleeding site and the risk of short gut syndrome^[33-35].

REBLEEDING

The recurrence rates of severe bleeding have been reported from 19%-41%^[2-5] underscoring the high recurrence rate of this complication. An early case series published in 1991 followed 21 patients after GI hemorrhage from Crohn's and found a rate of rebleeding of 4/21 (19%). The rate of rebleeding after medical therapy was 3/10 (30%) compared with 1/11 (9%) in those that received surgical treatment^[5]. In another series of 25 patients with a median follow up of 2 years there was a recurrence of bleeding in 35% of patients who were managed with non-operative measures as opposed to no recurrence in surgically managed patients^[2].

Kim *et al*^[3] reported a total of 64 rebleeding episodes. The rates of rebleeding were 51% in patients treated medically, 50% in those treated endoscopically and 57% in those after embolization. There is limited but promising evidence to support the role of infliximab in prevention of rebleeding. Cumulative probability of rebleeding for 11 patients on infliximab was 9.1% after 1-5 years^[3] but the study does not provide information about characteristics of these patients on biologics such as how were these patients selected for infliximab therapy. Based on the available evidence it is prudent to say that the recurrence of bleeding is high and after the management of the initial episode of GI hemorrhage, patients should be

subsequently started on immunomodulator therapy or anti-TNF therapy.

CONCLUSION

CD with acute hemorrhage is a challenging medical condition with evidence for management limited to case reports and few case series. The site of bleeding commonly follows the distribution of disease and is best localized with angiography or endoscopy. Endoscopic or angiographic therapy may be attempted when a source of bleeding is identified. Surgery should be recommended in patients with massive bleeding not stabilized by multiple transfusion (> 4 PRBC/24 h), those who fail medical management or with recurrent massive hemorrhage. Use of infliximab for control of acute hemorrhage is encouraging as limited evidence has demonstrated resolution of bleeding in most patients but additional studies are required to better assess its role.

Recurrent hemorrhage is not unusual and occurs more commonly in non-surgically treated patients. After control of the index bleed, patients should be placed on anti-TNF or immuno-modulator therapy to prevent recurrence.

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