INTRODUCTION

Refractory, difficult-to-localize, episodic gastrointestinal (GI) bleeding continues to present a significant challenge to gastroenterologists, interventional radiologists, and surgeons. Some have termed it “obscure gastrointestinal hemorrhage” (OGH) or obscure overt bleeding. Potential sources of GI bleeding are summarized in Figure 1. Beyond the significant health-care resources, including critical care services and often multiple invasive procedures, such bleeding takes a significant toll on patients and their families alike. In addition, the associated provider fatigue and frustration may further complicate the already complex clinical picture.

DIAGNOSTIC CONSIDERATIONS

Successful bleeding localization and subsequent targeted approaches can lead to permanent resolution in most cases of GI bleeding. For patients with unstable brisk bleeding, the mainstay of such testing includes upper endoscopy and colonoscopy, tagged red blood cell scintigraphy, and visceral angiography. For patients with stable overt or occult bleeding, capsule endoscopy is the next best diagnostic test if a source is not found during upper endoscopy or colonoscopy. Capsule endoscopy is more sensitive in the detection of OGH with 72% yield as compared to 56% with angiography and 24% with computed tomographic (CT) angiography. CT enterography (CTE) is a newer technique with comparable diagnostic yield to capsule endoscopy in obscure overt bleeding. CTE uses oral contrast and multiphase intravenous (IV) contrast to differentiate between inflammatory, vascular, and neoplastic lesions.

When a small bowel bleeding source is found during capsule endoscopy or CTE, we now have a variety of “deep enteroscopy” (also known as “device-assisted enteroscopy”) options to reach the lesion and perform definitive endoscopic treatment. These options include single-balloon enteroscopy, double-balloon enteroscopy, and spiral enteroscopy. At times, surgical approaches are required including intraoperative enteroscopy or operative resection. Despite modern diagnostic and therapeutic advances, however, some cases of OGH continue to be notoriously difficult to localize because of the often episodic nature which requires “catching the bleeding when it is active” or “provoking it” using a variety of chiefly pharmacologic techniques.

DEALING WITH FAILURE OF STANDARD APPROACHES

When all of the diagnostic and therapeutic approaches have failed, the treating physician may be left with few options, including a limited number of secondary and/or less effective means of controlling the bleeding. Abnormal blood vessels (often called arteriovenous malformations [AVMs], angioectasias, or angiodysplasias) are a frequent cause of OGH. For this reason, if a bleeding source is not found during the diagnostic workup, we often use empiric medical therapy for AVMs as the next step in management.

Among these “secondary options” are hormonal therapies (e.g., exogenous estrogen-progesterone supplementation or EEPS), thalidomide, octreotide acetate administration, as well as other management adjuncts, designed to optimize systemic recovery from anemia and reduce transfusion requirements (e.g., iron supplementation and erythropoietic stimuliants).
Although EEPS may be of some therapeutic value, its prothrombotic properties may be problematic in patients who have experienced previous thrombotic events or have known thrombotic tendencies. Thalidomide, an angiogenesis inhibitor, has been used to treat patients with refractory GI bleeding associated with vascular malformations. In a controlled trial, 55 patients were randomized to receive either thalidomide 100 mg daily or iron 400 mg daily for 4 months. The rate of response was 71.4% in the thalidomide group but only 3.7% in the iron (control) group. Although there were no severe adverse effects in this trial, thalidomide is a known teratogen and has been associated with liver toxicity, peripheral neuropathy, and venous thrombosis, so it should be used with caution.

**OCTREOTIDE: POTENTIALLY VALUABLE SECONDARY THERAPEUTIC OPTION**

Given the above-mentioned risk–benefit profiles of various secondary therapies for OGH, octreotide administration may be the most viable therapeutic option in an otherwise dismal situation. Clinical approaches to obscure GI bleeding are schematically shown in Figure 2, with the recurrent yet diagnostically “negative” scenarios being most appropriate for therapeutic use of octreotide (the “green zone” as highlighted in the figure). Somatostatin is a cyclic peptide secreted in the GI tract. It can reduce bleeding by increasing platelet aggregation, decreasing splanchnic blood flow, downregulating vascular endothelial growth factor, and increasing vascular bed resistance. Octreotide is an analog of somatostatin. Although the clinical experience using octreotide in the setting of OGH is limited, there is reasonable evidence to suggest that the overall safety profile of this intervention may be favorable and that its efficacy is well defined. A meta-analysis found that octreotide reduced the need for blood transfusions in a significant number of patients, and a prospective study showed that this benefit persisted even up to 2 years.

Unfortunately, octreotide has typically been given as a daily IV or subcutaneous injection which can be very cumbersome and affect patient compliance. However, octreotide is now available in a long-acting release formulation that can be given as an intramuscular injection once every 4 weeks. In a small study, 69% of patients did not need iron supplementation or blood transfusions after taking long-acting octreotide 10 mg intramuscularly monthly for 1 year. Another prospective study demonstrated a reduction of the number of transfusions (median 2 vs. 10), higher overall hemoglobin level (median 10 vs. 7), and lower percentage of patients who experienced bleeding (20% vs. 73%) under active treatment. An additional added benefit of long-acting octreotide is the potential cost savings to the health-care system as a whole. In another retrospective study of 19 patients, 7 of them (37%) had a complete response, 7 (37%) had a partial response with the remaining

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**Figure 2:** Generalized approach to obscure gastrointestinal bleeding. Octreotide may be most appropriate in cases of bleeding that is diagnostically “negative” yet recurs during clinical observation periods (highlighted in green)
5 patients (26%) still requiring continued readmissions to the hospital and further care with additional blood transfusions and/or endoscopic procedures. There was a significant reduction in the number of inpatient hospital days spent for these patients after they were commenced on long-acting octreotide (23 days vs. 2 days, \( P < 0.0001 \)). In their hospital system, this led to a reduction in costs of over 61\%.[26]

The side effect profile of long-acting octreotide appears to be overall favorable.[27] A recent meta-analysis showed that of all the current treatment modalities for OGH used including endoscopic approaches and medical therapies, there was either insufficient or low-quality evidence demonstrating effectiveness. Given this, the addition of long-acting octreotide as an adjunct to the treatment armamentarium for OGH is reasonable, especially when a physician is taking care of an individual patient who has had recurrent OGH suspected to be due to AVMs as it may work, may decrease cost, and appears to be safe.[24,27] Future prospective studies are warranted.

CONCLUSIONS

Sufficient evidence exists to support the use of octreotide in selected cases of OGH. Factors limiting the application of octreotide include its high cost, lack of definitive guidelines, and limited reported clinical experience. It is, also, unclear when octreotide can be safely stopped, especially in the setting of a positive clinical response. Since octreotide is usually used in conjunction with other therapies for OGH, the attributable therapeutic benefit can be difficult to quantify. Furthermore, adverse events such as thrombocytopenia (reverses with withdrawal of therapy), gallstone formation, and local skin reaction at the injection site have been reported in up to 30% of patients, but this is significantly lower than up to 71% complication rate reported with thalidomide.[19]

The management of OGH can be very challenging, but fortunately, octreotide seems to be a viable option when endoscopic or other interventional management approaches are not successful.

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