Hemorrhagic angiodysplasia of the digestive tract: pathogenesis, diagnosis, and management
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GI angiodysplasia (GIA) is an acquired vascular superficial lesion, which presents typically as a bright red, irregular, round, slightly elevated lesion. GIAs are often seen in patients aged >60 years and are mostly located in the colon (cecum and ascending colon). The cause and mechanisms of GIA have yet to be completely understood. Small-bowel GIAs often are diagnosed in the setting of obscure GI bleeding. In some cases, GIAs are associated with aortic stenosis, von Willebrand’s disease, chronic renal disease, and liver disease. Endoscopic examinations are used as first-line diagnostic examinations. Video capsule endoscopy (VCE) is useful in patients with persistent obscure GI bleeding with negative gastroscopy and colonoscopy results. Enteroscopy also is used because it has cleansing and therapeutic abilities. Imaging techniques may be useful for diagnostic purposes, in cases of active overt GIA-related bleeding.

Argon plasma coagulation (APC) is the reference standard treatment measure. Bipolar electrocautery probes seem to have similar efficacy. Endoclips and cryotherapy also may be used. As far as pharmacologic treatment is concerned, hormonal therapy has been tested, but studies are inconclusive. Somatostatin analogues such as octreotide may be useful in patients with chronic GIA-related bleeding when endoscopic treatment has failed. Anti-angiogenic drugs (thalidomide, lenalidomide) are being tested and seem promising. Percutaneous embolization is best suited for cases of active bleeding, if prior endoscopic treatment has failed.

In summary, GIA is the most common vascular malformation of the digestive tract. Endoscopy is the cornerstone of diagnostic and therapeutic management. Some pharmacologic treatments have shown promising results.

INTRODUCTION

GIA is an acquired superficial vascular lesion and is the most common vascular malformation of the GI tract. The clinical significance of GIAs is rooted in their inherent risk of bleeding, causing GI bleeding.

This review focuses on the description of the epidemiology, pathogenesis, and clinical presentation of GIAs. Diagnostic methods and management are addressed, comprising new and upcoming pharmacologic treatments. Hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu syndrome), an inherited vascular condition manifesting GI telangiectasia, also will be reviewed.

We searched through the National Center for Biotechnology Information/PubMed system database by using individual free word or medical subject headings gastrointestinal angiodysplasia cross-references with other relevant terms as well as a manual search and review of reference lists, up to March 2017.

DEFINITION AND EPIDEMIOLOGY

Definition
GI vascular malformations were first described in 1839. Vascular malformations are aberrations in the structure of the affected arteries, veins, or capillaries. In 1974, the term gastrointestinal angiodysplasia was used to describe unique or multiple acquired vascular superficial lesions originating from the GI mucosa and/or submucosa that are not associated with a skin or visceral angiomaticous lesion. Today, these lesions are commonly named arteriovenous malformation, telangiectasia, angiectasia, or vascular ectasia.

A GIA typically presents as a bright red, round, small (diameter <10 mm), slightly elevated lesion with irregular contours (Fig. 1). A pale halo of the surrounding mucosa may be seen. Histologic assessment shows small vascular dilatations affecting the GI submucosal veins and mucosal venules and capillaries. The affected ectatic
vessels are lined by endothelium only, with little or no smooth muscle.\textsuperscript{4}

The differential diagnosis includes other GI vascular malformations such as benign vascular tumors (hemangiomas), malignant vascular tumors (angiosarcomas), hereditary hemorrhagic telangiectasia, and other acquired malformations: gastric antral vascular ectasia, post-radiation vascular ectasia, and Dieulafoy’s lesion. In a study by Yano et al.,\textsuperscript{5} small-bowel vascular lesions observed on endoscopy were classified in 6 groups based on their appearance. The objective was to distinguish venous (GIA) and arterial (Dieulafoy’s lesion and other vascular malformations) lesions to help select the appropriate treatment. Lesions were classified as follows: type 1a, punctuate erythema (<1 mm) with or without oozing; type 1b, patchy erythema (a few millimeters) with or without oozing (GIA); type 2a, punctuate lesions (<1 mm) with pulsatile bleeding; type 2b, pulsatile red protrusions without surrounding venous dilatation (Dieulafoy’s lesions); type 3, pulsatile red protrusions with surrounding venous dilatation (arteriovenous malformation); type 4, none of the above.\textsuperscript{5}

Epidemiology

The detection rate of GIAs has increased because of better diagnostic test performances, such as recent developments in endoscopy (high-definition endoscopy, small-bowel video capsule endoscopy). GIAs affect both sexes equally, and the prevalence is increased in patients aged >60 years\textsuperscript{6} and in patients with certain predisposing conditions including aortic stenosis, chronic renal failure, and von Willebrand’s disease.\textsuperscript{7,10}

GIAs account for 4% of all causes of upper GI bleeding\textsuperscript{11} and usually are located in the stomach and/or the duodenum. Upper digestive tract GIAs can be predictive of jejunal small-bowel GIAs on video capsule endoscopy.\textsuperscript{12} In patients with obscure GI bleeding, that is with non-contributive esogastroduodenal endoscopy and colonoscopy (5% of patients with GI bleeding), small-bowel GIAs are found in 40% to 60% of cases.\textsuperscript{13} GIAs are located mainly in the colon, predominantly in the cecum and ascending colon (over 50% of colon lesions).\textsuperscript{14,15} In a 1990 study analyzing endoscopic data of healthy asymptomatic adults aged 50 years or older, the prevalence of colon GIA was 0.83% (8/964).\textsuperscript{16} Multiple lesions are found in 40% to 60% of patients.\textsuperscript{17} Although GIAs often are localized proximally to one another, about 20% of synchronous lesions are seen in other portions of the digestive tract.\textsuperscript{18}

Spontaneous resolution of bleeding GIAs occurs in about 40% to 45% of cases of proven bleeding (by endoscopy or angiography). Resolution is assessed by the number of bleeding episodes and transfusion requirements during follow-up after an initial bleeding episode.\textsuperscript{19,20} However, multiple studies have shown elevated rates of bleeding recurrence after endoscopic therapy, ranging from 20% to 25%. This risk is higher in studies with a long follow-up. Also, recurrence of iron-deficiency anemia and/or need for transfusions has been reported in 16% to 64% of cases when follow-up was assessed at 1 and 3 years.\textsuperscript{21-23} Of note, in a recent retrospective study comprising 56 patients with small-bowel GIAs, bleeding recurrence occurred in 80% of cases. Multiple lesions (P = .048) and valvular heart disease (P = .034) were predictive of repeat bleeding.\textsuperscript{24}

The mortality rate of bleeding GIAs is low. In a study by Cappell and Gupta,\textsuperscript{25} the in-hospital mortality rate was 2.1%. In that study, including 56 patients with small-bowel GIAs, a mortality rate of 3.5% was found. Two patients in the study died as a direct consequence of GI bleeding, and both were anticoagulated for metallic heart valves.\textsuperscript{24}

PATHOGENESIS, CLINICAL ASPECTS, AND DIAGNOSTIC TOOLS

Pathogenesis

The etiology and mechanisms leading to the constitution of GIAs are yet to be completely understood. One
potential age-related mechanism, described by Boley and Brandt,\(^6\) is a partial obstruction of submucosal veins, secondary to increased contractility of the muscular layer of the colon wall. This chronic obstruction causes a weakening of the pre-capillary sphincters, creating congestion. Ultimately, failure of pre-capillary sphincters causes an arteriovenous communication to develop, termed collateral vessel. In another described mechanism, mucosal ischemia due to chronic hypoxia and/or chronically decreased blood flow in the setting of cardiac and respiratory diseases has a central role.\(^{26}\) It is believed that mucosal ischemia impairs the balance between proangiogenic factors (vascular endothelial growth factor [VEGF], basic fibroblast growth factor), and angiogenesis inhibitors, resulting in the fabrication of neo-veins.\(^{27}\) Most recently, the role of von Willebrand’s factor (vWF), known to be implicated in angiogenesis regulation, has been studied. It was shown in vitro that the inhibition of the secretion by endothelial cells of vWF causes up-regulation of angiogenesis and VEGF-dependent cellular proliferation.\(^{28}\) Numerous mechanisms implicated in the genesis of GIA lesions are yet to be explored and understood.

**Clinical aspects**

GIAs can be asymptomatic or may present with signs and symptoms of GI bleeding, which range from chronic, well-compensated (majority of patients) to acute, life-threatening bleeding. GIAs often are diagnosed in the setting of obscure GI bleeding that is with non-contributive esogastroduodenal endoscopy and colonoscopy, whether it be occult or overt bleeding. Finally, GIAs can be associated with several conditions such as aortic stenosis, von Willebrand’s disease, left ventricular assist devices in patients with end-stage heart failure, chronic renal failure, chronic liver disease, and hereditary hemorrhagic telangiectasia (HHT).

**Aortic stenosis.** In 1958, Heyde et al were the first to describe the association between hemorrhagic GIAs and aortic stenosis (Heyde’s syndrome). In a retrospective study including 1443 patients, the incidence of aortic stenosis in patients with unexplained digestive bleeding and GIAs was significantly higher than that of the control group (25% vs 4%; \(P < .05\)).\(^7\) These results were confirmed in later studies such as an epidemiologic study published in 2004.\(^{29}\) Furthermore, valve replacement seems to reduce the risk of bleeding, and in some cases GIA lesions disappear.\(^{30}\) The mechanisms of this association remain unclear. Elevated shear stress due to a heart valve disease (aortic stenosis), causing linear elongation of vWF and exposure of hidden cleavage sites to the proteolytic enzyme ADAMTS13, thus causing proteolysis and resulting in an acquired vWF deficiency, may account for this association.\(^{31}\)

**von Willebrand’s disease.** von Willebrand’s disease is characterized by a quantitative or qualitative deficiency of vWF, either acquired (aortic stenosis) or inherited (type IIa), a large, multimeric glycoprotein involved in hemostasis. vWF is essential to platelet adhesion and aggregation at the site of vascular injury because of its action as a bridge between platelet receptors and the collagen of the subendothelium as well as between platelets themselves.\(^{32}\) The first association between von Willebrand’s disease and GIAs was described in 1967.\(^{33}\) Since then, this association has been confirmed multiple times.\(^8,9\) Patients with GIAs have a higher risk of GI bleeding in this setting.\(^{34,35}\)

**Left ventricular assist devices in patients with end-stage heart failure.** Left ventricular assist devices (LVADs) are an increasingly prevalent form of mechanical support for patients with end-stage heart failure. LVADs are associated with GI bleeding in approximately 20% to 30% of cases\(^{36}\) and with recurrent bleeding in 30% to 40% of cases.\(^{37}\) GIAs and gastroduodenal erosive disease are the predominant causes of bleeding.\(^{38}\) Overt, upper GI bleeding is the most common presentation, with 50% of patients reporting melena.\(^9\) Bleeding is likely multifactorial. A described mechanism is narrowed arterial pulse pressure with decreased aortic valve opening and relative hypoperfusion of the gut in patients with LVADs.\(^{40}\) This mechanism closely mimics what is seen in aortic stenosis, a condition associated with Heyde’s syndrome. Heyde’s syndrome is associated with a higher prevalence of GIA than is found in the general population (see earlier text). Of note, patients who have LVADs can have cessation of GI bleeding after cardiac transplantation.\(^{40,41}\) Another mechanism described is the loss of high molecular weight multimers and reduced vWF functional activity in patients with LVADs.\(^{42}\) It may be caused by shear forces created by the LVAD causing proteolysis of the multimers, thereby entailing acquired von Willebrand’s disease.\(^{43}\) Although this has not been proven to be solely responsible for GI bleeding, it may contribute to an increased propensity to bleed.\(^{44}\) Finally, patients with LVADs have impaired ability of both plasma and platelet factors to mediate ristocetin-induced platelet aggregation. This impaired platelet aggregation has been suggested as a contributing mechanism in the association with GI bleeding.\(^{45}\) Finally, a recently published, cross-sectional study showed that in patients presenting with GI bleeding, LVADs are not associated with a higher mortality (despite therapeutic anticoagulation, increased comorbidities, and comparatively delayed endoscopy) compared with a control group.\(^{46}\)

**Chronic renal failure.** The prevalence of GIAs is higher in patients with chronic renal failure. The risk of developing GIAs rises with time and in end-stage renal disease.\(^{10}\) The underlying mechanisms of this association are unclear. Mucosal ischemia, described earlier as a potential mechanism of GIA, may be exacerbated in patients with chronic renal failure, often because of associated comorbidities such as diabetic microangiopathy and atherosclerotic peripheral vascular disease.\(^{47}\)
Identification of a heterozygous pathogenic gene variant establishes the diagnosis if clinical features are inconclusive.\textsuperscript{55,56} Arteriovenous malformations occur most commonly in the lungs (30%-50%), liver (74%), and brain (10%).\textsuperscript{57,58} Although endoscopy or capsule endoscopy show gastric or small-intestine telangiectasias in 80% of patients,\textsuperscript{59} only 25% to 30% of patients will develop symptomatic GI bleeding, which usually does not present until the fifth or sixth decade of life.\textsuperscript{60,61} GI bleeding usually is slow, chronic, and intermittent. Patients become symptomatic because of iron deficiency anemia. However, acute GI bleeding also can be seen.\textsuperscript{62} Gastric and duodenal telangiectasia are more common than colon telangiectasia.\textsuperscript{66}

**Diagnostic tools**

Methods used to diagnose GIA lesions vary, depending on the clinical presentation and the severity of the GI bleeding.

**Endoscopy.** Endoscopic procedures are first-line examinations. Techniques and image resolution have evolved, allowing better diagnostic performances. Upper and lower digestive tract GIAIs are accessible via high-definition upper esogastroduodenal endoscopy and colonoscopy. Overt or occult bleeding of the colon is caused by a GIA lesion with certainty, only if active bleeding is witnessed on endoscopy. When lesions are located in the small bowel, VCE and device-assisted enteroscopy (single-balloon enteroscopy), double-balloon enteroscopy, and spiral enteroscopy are used for diagnostic purposes. On the other hand, push enteroscopy is easily available because it does not require specialized equipment or training and may be used for investigation of proximal small-bowel lesions.\textsuperscript{63} However, comparison of double-balloon enteroscopy and push enteroscopy indicates a superior diagnostic yield with double-balloon enteroscopy.\textsuperscript{64} Intraoperative enteroscopy is now rarely performed because it is time-consuming, logistically difficult, and has higher rates of adverse events,\textsuperscript{65} but also because of recent advances in noninvasive imaging and device-assisted enteroscopy.

Today, VCE has an established role in patients with obscure GI bleeding (Fig. 2). American Society for Gastrointestinal Endoscopy guidelines recommend that in patients with overt GI bleeding, a repeat EGD or colonoscopy should be performed in case of a clinical presentation suggestive of upper or lower GI bleeding, respectively, before small-bowel evaluation.\textsuperscript{66} Similar recommendations are made in the setting of occult obscure GI bleeding with a high clinical suspicion for an upper or lower GI lesion\textsuperscript{66} because there is a relatively high miss rate of lesions reported.\textsuperscript{67} However, studies have shown that a systematic second-look endoscopy in these patients does not seem to be cost effective.\textsuperscript{68,69} In the absence of localizing signs or symptoms, small-bowel evaluation is recommended.\textsuperscript{66} Small-bowel VCE is a
noninvasive procedure with a high rate of complete small-bowel exploration (>90%) and high diagnostic performances (>60%). 70,71 It is useful in assessing the size and number of GIAs. Small-bowel VCE is the preferred method of small-bowel evaluation because of higher or at least equivalent diagnostic performance, compared with other, more invasive techniques, like push enteroscopy, mesenteric angiography, and intraoperative enteroscopy. 70,72 However, small-bowel VCE has several limitations. Lesion localization is estimated according to the transit time and the use of the pylorus and cecum as landmarks, but these lack precision. 73 In a study published by Plum et al., 74 push enteroscopy, small-bowel VCE, ileoscopy, and enteroclysis were compared in 25 patients with familial adenomatous polyposis, showing that small-bowel VCE does not allow precise localization of small-bowel lesions. Several localization systems have been tested such as capsules with odometer capabilities, magnetic field or electromagnetic wave–emitting capsules, allowing 3-dimensional localization, but their accuracy remains suboptimal. 75,76 Nonetheless, small-bowel VCE can help in deciding the best insertion route for enteroscopy if that examination is considered (upper or lower). Based on previously published studies, a lower enteroscopy is indicated if the capsule transit time from ingestion to arrival at the lesion is equal to or over 75% of the total transit time (from ingestion to arrival at the cecum). 77,78

Another limitation is that the visibility of the distal ileum may be hindered by the presence of digestive liquid, which is more abundant in this part of the small bowel. Finally, this procedure lacks therapeutic abilities. All in all, small-bowel VCE is the preferred first-line investigation in the setting of obscure GI bleeding once upper and lower sources have been ruled out, and second-look endoscopy has been considered.

Three types of device-assisted enteroscopy (double-balloon enteroscopy, single-balloon enteroscopy, and spiral enteroscopy) are used in practice. They all have similar diagnostic and therapeutic abilities as well as the same adverse event rates. 79,80 However, double-balloon enteroscopy is the most evaluated technique, and 2 randomized trials showed that the complete examination rate was significantly higher with double-balloon enteroscopy than single-balloon enteroscopy (57%-66% vs 0%-22%; P < .03), although the diagnostic yield was similar. 81,82 Enteroscopy has cleansing abilities (using water), allowing a better visualization of the mucosa, contrary to that of small-bowel VCE. Furthermore, biopsies can be performed as well as treatment procedures. GIAs can be missed by enteroscopy when lesions are located behind a mucosal fold or in a very mobile part of the small bowel. Thus, if GIAs are strongly suspected, repeat procedures may be needed. 83 Two approaches can be considered for enteroscopy: anterograde and retrograde (for which colonoscopy preparation is required). Also, a complete enteroscopy (evaluation of the entire small bowel) can be performed with a single approach or by combining anterograde and retrograde approaches. Of note, the clinical impact of complete small-bowel visualization, which is highest with double-balloon enteroscopy, is controversial because diagnosis and therapy often can be accomplished without the need for complete enteroscopy. 84,85 The depth of insertion and mean procedure time are higher with the anterograde approach compared with the retrograde approach during double-balloon enteroscopy and single-balloon enteroscopy. 86,87 The anterograde approach is easier because of the difficulty in intubating the terminal ileum via the retrograde approach (double-balloon enteroscopy and single-balloon enteroscopy alike). All in all, the usefulness of complete enteroscopy is not clear, and the choice of approach for enteroscopy should be specific to each case, depending on the suspected localization of the lesions to treat (often determined with the help of small-bowel VCE).

**Imaging techniques.** In the setting of active overt GIA-related bleeding, imaging techniques are useful for diagnostic purposes and for localizing the culprit lesion. Techniques used include radionuclide scanning, multi-phasic cross-sectional imaging, and catheter angiography.

Technetium-99m–labeled red cell scintigraphy (a radionuclide scanning technique) can localize GI bleeding when the blood flow is over 0.1 mL/minute. It is a noninvasive test, with a sensitivity ranging between 25% and 90%. However, its localization accuracy is low, and it does not allow therapeutic intervention. 88,89 Given these limitations, this technique is used for diagnostic purposes only 90,90 and is not widely used in the acute setting. 91

CT enterography and magnetic resonance enterography are cross-sectional imaging techniques that are optimized for imaging of the small bowel. These techniques are minimally invasive but have no therapeutic ability. CT enterography has a higher spatial resolution that can improve detection of small lesions (masses and vascular abnormalities), is widely available, and allows imaging of the entire abdomen in 1 breath hold, leading to better tolerance with less motion artifact. Repeat CT, however, entails a radiation risk. Magnetic resonance enterography, on the other hand, allows imaging of the small bowel without radiation exposure, has superior soft tissue contrast, and is more informative than CT enterography when intravenous contrast material cannot be administered. 92 Both methods require ingestion of large volumes (900-1500 mL) of neutral enteric contrast agents to distend the bowel. In the setting of occult GI bleeding, a thorough examination of the small bowel is indicated. CT enterography or magnetic resonance enterography can be used to identify the specific cause of slow or intermittent bleeding. These techniques do not allow localization of an active extravasation, contrary to cases of overt GI bleeding. CT enterography can be complementary to small-bowel VCE and may identify vascular abnormalities missed on capsule endoscopy. 95
However, small-bowel VCE remains the preferred initial study. GIAs appear on CT enterography as focal punctate or discoid areas of enhancement <5 mm in size or bulbous swelling of the intramural small-bowel vessels. Of note, whether these bulbous lesions represent normal vessels or asymptomatic GIAs is unknown. Enhancement of GIAs is brightest during the enteric phase and fades during the delayed phase. GIAs do not enhance during the arterial phase, as opposed to arterial lesions. Enlarged feeding arteries and early draining veins usually are not seen. Lesion characterization by multiphase CT enterography allows triaging of patients to an adapted treatment such as catheter embolization for arterial lesions and endoscopy for GIAs. The effect of lesion characterization by multiphase CT enterography on treatment strategies needs further evaluation. Overall, multiphase CT enterography is complementary to small-bowel VCE and is better at detecting small-bowel tumors. In the setting of overt GI bleeding, multiphase CT angiography without the need for oral contrast material can be performed, allowing detection of bleeding rates of 0.3 mL/minute. CT angiography can accurately localize the site of bleeding, allowing triaging of patients to colonoscopy, enteroscopy, or angiography. In a prospective study including 26 patients with suspected bleeding from colon GIAs, sensitivity, specificity, and positive predictive value of CT angiography were 70%, 100%, and 100%, respectively. In a recent meta-analysis, CT angiography had a pooled sensitivity of 89% and specificity of 85% for detecting active bleeding.

Traditional indications for catheter angiography in the small bowel have been replaced by CT enterography and CT angiography. A prospective randomized study published in 2012 showed that its diagnostic performances are inferior than that of VCE in patients with overt GI bleeding (20% vs 53%; P = .016). Currently, catheter angiography is used as a therapeutic method only, for catheter-directed interventions. This procedure is indicated in patients presenting an active, abundant bleeding and hemodynamic instability. It is useful in this setting because it allows accurate localization and therapeutic selective embolization at the same time. The definitive sign of bleeding is extravasation of contrast material into an extravascular location, which may be the small-bowel lumen. GIAs are characterized by an abnormal vascular tangle, early opacification of a draining vein, and simultaneous filling of the feeding artery and the draining vein. In order to be identified, the bleeding rate must be of about 1.0 mL/minute or greater. However, most episodes of GI bleeding are intermittent, which accounts for the poor diagnostic performances (see earlier text). The challenge resides in the timing of the angiography. However, GI bleeding is likely to recur, so repeat angiography may be necessary. Repeat angiography can be performed with provocative techniques aimed at inducing active bleeding and thus identifying the source and allowing definitive treatment. Bleeding can be induced by using different protocols, which typically include intra-arterial administration of a combination of vasodilators, anticoagulants, and thrombolytics. This method can be considered in selected cases of recurrent hemodynamically significant or chronic indolent bleeding, with normal or non-localizing endoscopic and imaging findings (including angiography). Prior consulting with a surgical team and assessment of contraindications to administration of anticoagulants or thrombolytic agents are mandatory. In a case series by Kim et al, including 34 patients with occult lower GI bleeding, provocative mesenteric angiography was safe and effective for eliciting the source of bleeding, leading to definitive therapy in about 1 third of patients.

Management

The choice of treatment depends on the clinical presentation. The aim of the treatment is to stop the bleeding but also to prevent further episodes from occurring. This treatment is based on the destruction of each potential bleeding GIA lesion. In the setting of GIAs presenting as occult or overt obscure GI bleeding, treatment of these lesions is indicated after all other causes of bleeding have been ruled out. Decision to treat and modalities of treatment depend on the size, site, and number of lesions as well as the clinical severity of anemia and blood loss. On the other hand, asymptomatic, incidentally diagnosed, non-bleeding GIAs do not require preventive treatment and should not be treated because the risk of future bleeding is low, and most patients remain asymptomatic. A management algorithm is proposed (Fig. 3) for bleeding GIAs.

Endoscopic treatment

APC. APC is a non-contact thermal method of hemostasis involving the use of a jet of ionized argon gas (plasma) that is directed through a probe passed through the endoscope. The probe is placed at some distance from the bleeding lesion (3-5 mm). A high-voltage spark is delivered at the tip of the probe, which ionizes the argon gas as it is sprayed from the probe tip in the direction of the target tissue. The depth of coagulation ranges from 0.5 to 3 mm (superficial mucosa). APC is the reference standard treatment measure in the setting of any GIA. The intensity of the thermal effect is managed by using the power setting (watts), the gas flow (liters per minute), and the duration of the application. All of these can be adjusted, depending on the site and the size (diameter, depth, elevation) of the area being treated.
settings used are based on expert opinion: 0.8 L/minute and 50 W in the stomach; 0.6 L/minute and 40 W in the esophagus, duodenum, small bowel, ascending colon, and cecum; and 0.8 to 1 L/minute and 50 W in the descending colon.

The use of APC in the small bowel is simple, efficacious, and cost effective. However, there is very little data concerning the follow-up of patients treated with APC during double-balloon enteroscopy. In a single-center, retrospective study of 50 patients, May et al. showed a significantly reduced blood transfusion requirement after APC. However, after a mean follow-up of 4.5 years, small-bowel bleeding recurred in 21 patients (42%). Gerson et al. showed a similar rate of recurrence (45%) after a mean follow-up of 30 months. In another retrospective study including 261 patients presenting with unexplained GI bleeding explored by double-balloon enteroscopy, 50% had small-bowel angiodysplasia, most of which were treated with APC. The bleeding recurrence rate after 3 years of follow-up was 46%. The predictive factors of recurrence included a high number of lesions and a history of heart rhythm disorder and/or heart valve disease. The bleeding recurrence after APC treatment of colon lesions ranges from 7% to 15% after a mean follow-up of 6 to 20 months.

Adverse event rates vary between 1.7% and 7%. Colon perforation is a rare (<0.5%) albeit serious adverse event. Perforation usually occurs in the cecum because its wall is thinner. Submucosal saline solution injection (with or without epinephrine) to elevate the lesion area before applying APC has been suggested by some studies. This technique may prevent perforation, specifically in the cecum, in lesions >1 cm. Cecum diastatic perforation (because of pneumatic forces within the lumen, leading to over-distension of the wall) because of excessive gas insufflation may be avoided by repeat exsufflation during the procedure. Finally, colon gas explosion, although rare, is a described iatrogenic adverse event occurring during colonoscopy with electrocautery. This adverse event is the result of an accumulation of colon gases to explosive concentrations, but it may be prevented by meticulous bowel preparation. Guidelines recommend bowel preparation before APC.

Heater probe and bipolar electrocautery. GIA coagulation by heater probe was the standard of care in the 1980s, but it is no longer used because of an elevated risk of perforation (5%), especially in the cecum, as well as an elevated recurrence rate (>50% after 3 years of follow-up).

Bipolar electrocautery, by using probes such as the Gold Probe (Boston Scientific, Natick, Mass), deliver thermal energy by completion of an electrical circuit between 2 electrodes at the tip of the probe, as current flows through non-desiccated tissue. Three to 4 electric impulses are
delivered within a few seconds. The diameter of the sheath is either 7F or 10F. The standard power output setting is 10 to 20 W. As the targeted tissue desiccates, there is a decrease in electrical conductivity, limiting the maximum temperature (100°C) and depth and breadth of tissue injury. Pressure is applied to the target tissue during coagulation (force perpendicular to the wall) to ensure coaptation. The efficacy and adverse event rate of bipolar electrocautery in the setting of GIAs are comparable with that of APC. To this day, there is no prospective randomized study comparing these techniques. Efficacy and safety data regarding APC are much more extensive. Heater probes and bipolar electrocautery disposable probes are more expensive than APC non-reusable catheters. Thus, APC is the preferred first line of treatment (expert opinion).

Laser photocoagulation. Argon and neodymium-YAG (yttrium-aluminum-garnet) laser photocoagulation is a technique that is being abandoned, given the lack of available data, a high perforation rate (2%-3%), and a high cost.

Endoscopic clipping devices. Endoclips have shown their efficacy in treating colon angiodysplasia in specific cases such as large isolated bleeding GIAs with a visible feeding arteriole and in patients with a high risk of recurrence (ie, antiplatelet therapy and/or blood thinners, coagulation defect). Endoclips can be used alone or in combination with thermal destruction techniques (APC, bipolar electrocautery).

Endoscopic cryotherapy. Cryotherapy allows mucosal destruction by using cryogenic refrigerants (such as nitrous oxide). Nitrous oxide is forced through the endoscope under pressure and, when it has escaped at the distal tip, the change in pressure causes a sudden, massive drop in temperature (~89.5°C). The standard flow is set to 25 to 30 mL/minute. This technique is being evaluated, and there are little data available. In a pilot study of 26 patients, 7 of whom had gastric and duodenal arteriovenous malformations, cryotherapy was shown to be an efficient (86%) and safe (no adverse event reported) treatment.

Other endoscopic techniques. Other endoscopic techniques have been tested in this setting, but available data and number of cases are limited. Endoscopic band ligation allowing vascular obstruction by strangulation has shown immediate hemostatic efficacy in gastric angiodysplasia. A recent study showed a bleeding recurrence rate of 43%, after a mean follow-up of 18 months, in small-bowel angiodysplasia. Sclerotherapy is seldom used for GIA, although 2 studies showed promising results. This technique achieved complete destruction of gastroduodenal IAs by injection of sodium tetradecyl sulfate 1.5% or ethanolamine, with no adverse events reported.

Pharmacologic therapy

Although endoscopic techniques are performed more often, GIAs have a complex physiopathology, and endoscopic treatment may be insufficient. Bleeding can recur, especially in the small bowel. Multiple and extensive lesions of the GI tract may account for a higher recurrence risk. In these cases, pharmacologic therapy is of interest with regard to preventing recurrence.

Hormonal therapy. The use of hormonal therapy was extrapolated from anecdotal reports of use for nasal bleeding in patients with hereditary hemorrhagic telangiectasia. The efficacy of this treatment, in the setting of bleeding GIAs, has been assessed in 5 studies. Three of these studies showed the beneficial properties of hormonal therapy but lacked a control group. The 2 other studies included a larger number of patients and compared hormonal therapy with placebo. Lewis et al published the first of these 2 studies in 1992. They did not show a significant difference in terms of GI bleeding occurrence and transfusion requirements between patients receiving hormonal therapy (norethynodrel either with mestranol or with conjugated estrogens) and placebo, with a mean follow-up of 16 months. In 2001, Junquera et al published a large randomized clinical trial in which 72 patients with bleeding GIAs were randomized to receive hormonal therapy (ethinylestradiol and norethisterone) or placebo for a minimum period of 1 year. Failure of treatment occurred in 39% of patients in the treatment group and 46% of patients in the placebo group (P = .6). No significant difference was found between the 2 groups in terms of the number of bleeding episodes and transfusion requirements. The main results of these studies are summarized in Table 1. All in all, hormonal therapy is not recommended for overt or occult bleeding caused by a GIA lesion.

Somatostatin analogues. There are several ways in which somatostatin analogues such as octreotide might reduce bleeding. These mechanisms include improved platelet aggregation, decreased splanchnic blood flow, increased vascular resistance, and inhibition of angiogenesis by lowered VEGF synthesis. Many prospective case series evaluating the impact of somatostatin analogs on repeat bleeding rates have been published. However, these case series differ in terms of patient baseline characteristics such as comorbidities (chronic renal failure, cardiac failure, or cirrhosis) as well as the treatment schedule. The results of these studies are summarized in Table 2. In a meta-analysis reported by Brown et al in 2010, including 3 of the studies mentioned earlier, with a total of 62 patients, the pooled clinical response rate to octreotide was 0.76 (95% confidence interval [CI], 0.64-0.85). The authors concluded that this compares favorably with data from natural history studies. In a more recent meta-analysis by Jackson and Gerson in 2014, including mostly the same studies and using cessation of bleeding as the primary outcome measure, a significant effect on bleeding cessation was shown, with a pooled odds ratio of 14.52 (95% CI, 5.9-36).
TABLE 1. Studies evaluating hormonal therapy efficacy in GI angiodysplasia

<table>
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<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Hormone therapy</th>
<th>Follow-up, mo.</th>
<th>Results</th>
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<td>Junquera et al 20</td>
<td>P, C, Rz, DB</td>
<td>72</td>
<td>Ethinylestradiol + norethisterone</td>
<td>13 (12-36)</td>
<td>Failure of treatment: 39% in treated group vs 46% in placebo group (NS). No significant difference for no. of bleeding episodes (0.7 ± 1.0 vs 0.9 ± 1.5) and transfusion requirements (0.9 ± 1.9 vs 0.7 ± 1.5).</td>
</tr>
<tr>
<td>Barkin et al 206</td>
<td>P, Ch</td>
<td>43</td>
<td>Norethynodrel + mestranol then norethindrone + mestranol</td>
<td>18 (1-51)</td>
<td>Stops rebleeding in patients with occult GI bleeding of obscure origin.</td>
</tr>
<tr>
<td>Junquera et al 137</td>
<td>R, Ch</td>
<td>18</td>
<td>Lynestrenol + mestranol</td>
<td>22 (3-60)</td>
<td>76% without evidence of hemorrhage. No. of hemorrhagic episodes and transfusion requirements per year decreased (P &lt; .05).</td>
</tr>
<tr>
<td>Lewis et al 19</td>
<td>R, CC</td>
<td>64</td>
<td>Norethynodrel mestranol or estrogens</td>
<td>15.6 (2-31)</td>
<td>50% (treated group) vs 44% (untreated group) did not require further transfusion during therapy (NS).</td>
</tr>
<tr>
<td>Van Cutsem et al 128</td>
<td>P, CO, DB</td>
<td>10</td>
<td>Ethinylestradiol + norethisterone</td>
<td>6</td>
<td>Transfusion needs decreased from 10.9 to 11 units (P &lt; .003).</td>
</tr>
</tbody>
</table>

P, Prospective; Rz, randomized; DB, double blinded; Ch, cohort; R, retrospective; CC, case control; CO, crossover.

TABLE 2. Studies evaluating octreotide efficacy in GI angiodysplasia

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Octreotide</th>
<th>Follow up, mo.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holleran et al 24</td>
<td>P, Ch</td>
<td>24</td>
<td>IM, 20 mg/mo., 3 mo. min.</td>
<td>8.8 (3-17)</td>
<td>Complete, partial, and nonresponse rates: 70%-20%-10%. Higher hemoglobin levels (9.19-11.35 g/dL).</td>
</tr>
<tr>
<td>Bon et al 234</td>
<td>P, Ch</td>
<td>15</td>
<td>IM, 20 mg/mo., 12 mo.</td>
<td>14 (10-36)</td>
<td>Reduction of transfusion need: 2 (0-14) after treatment vs 10 (6-24) before treatment (P &lt; .05).</td>
</tr>
<tr>
<td>Molina et al 233</td>
<td>P, Ch</td>
<td>11</td>
<td>IM, 20 mg/mo.</td>
<td>15 (5-48)</td>
<td>Reduction of transfusion need: 4 (0-4) after treatment vs 10 (6-24) before treatment (P &lt; .05).</td>
</tr>
<tr>
<td>Scaglione et al 232</td>
<td>P, Ch</td>
<td>13</td>
<td>IM, 10 mg/mo., 12 mo.</td>
<td>32 (12-60)</td>
<td>Discontinuation of iron intake by 69% of patients after treatment.</td>
</tr>
<tr>
<td>Junquera et al 19</td>
<td>P, Ch, C</td>
<td>32</td>
<td>SC, 50 μg/12 h, 12-24 mo.</td>
<td>13 (12-36)</td>
<td>Hemorrhagic recurrence lessened in treated group (23% vs 48%; P &lt; .04).</td>
</tr>
<tr>
<td>Nardone et al 130</td>
<td>P, Ch</td>
<td>17</td>
<td>SC, 100 μg/12 h, 6 mo.</td>
<td>12</td>
<td>Higher hemoglobin levels in treated patients.</td>
</tr>
</tbody>
</table>

P, Prospective; Ch, cohort; IM, intramuscular; min., minimum; C, controlled; SC, subcutaneous.

a proof of concept open label single-center trial by Holleran et al. 207 Twenty-four patients with refractory small-bowel angiodysplasia were treated with long-acting, extended release octreotide. The rates of complete, partial, and no response were 70%, 20%, and 10%, respectively. The average hemoglobin rates increased from 9.19 to 11.35 g/dL (95% CI, 3.5-1.1; P < .0027), and 70% of patients remained transfusion-free after a mean treatment duration of 8.8 months. All in all, although data are limited, octreotide may be useful in patients with chronic GIA-related bleeding when endoscopic treatment has failed. To this day, there is no prospective, randomized, controlled trial on the matter. The duration of treatment as well as the optimal dosing strategy are not known. This treatment appears to be well-tolerated, with no reported serious adverse events. Also, a cost-effectiveness study showed significant reduction in the length of admission per year (22.79 vs 2.01 days; P < .0001) as well as in the number of blood transfusions administered (11.19 vs 2.55/year; P = .002) and a reduction of costs of 61.5% between the year before and after treatment was started ($ 41,356.41 to $ 15,998.96 per patient and year; P = .01). 208 Finally, the use of long-acting, extended release octreotide is more convenient and could be advantageous in terms of compliance. A new, long acting somatostatin analogue, pasireotide, is being evaluated.

**Thalidomide.** Thalidomide is an immune modulator that suppresses tumor necrosis factor. Thalidomide is an angiogenesis inhibitor (VEGF and basic fibroblast growth factor mediated effect), although the exact anti-angiogenic mechanism is unknown. Initially, case reports and case series had reported its efficiency in reducing the risk of GIA-related bleeding recurrence, with the observation that a short treatment (3-4 months) exerts a lasting effect, with no recurrence for several years in some patients. A randomized controlled study published...
in 2011 confirmed these findings. In 55 patients with refractory GI bleeding, daily treatment with thalidomide (100 mg daily) was compared with placebo (400 mg oral iron supplementation). Results showed a significantly lower rate of bleeding episodes (3.7% vs 71.4%; P < .001) after a mean follow-up of 39 months.

The number of adverse effects were higher in the treated group, consisting mainly of fatigue (32%), constipation (25%), light-headedness (21%), and peripheral edema (14%). Finally, a prospective study by Garrido et al. including 12 patients with GIA-related refractory bleeding, showed a mean hemoglobin level increase (6.5-12.1 g/dL). The results of the main studies published on the efficiency of thalidomide are shown in Table 3. In a recent literature review by Boey et al., comprising 70 patients who had received thalidomide (50-400 mg per day), with a follow-up ranging from 3 to 72 months, bleeding episodes and transfusions ceased in one third of these cases. Although the efficacy of thalidomide has been shown, the duration of treatment as well as the optimal dosing strategy are not known. In terms of safety, neurotoxicity is the most relevant long-term side effect of thalidomide, and its underlying mechanism remains unclear. Early studies reported peripheral neuropathy in 1% to 25% of patients, which seemed to be dose-dependent. Regardless, the main safety concern is thalidomide’s teratogenic effect. However, in the setting of bleeding GIAS, most affected patients are aged >60 years, making it less of an issue.

Lenalidomide, an angiogenesis inhibitor that is an analogue of thalidomide, has fewer adverse effects and could present a new therapeutic asset. Bowcock and Patrick reported the case of a patient with HHT whose bleeding was better controlled by lenalidomide than thalidomide, with minimal toxicity.

### Percutaneous embolization

This treatment is best suited for cases of active GI bleeding, if prior endoscopic treatment has failed. It also can be considered as an alternative to surgery in high-risk patients. The aim is to stop the bleeding by obstruction of the vessel (or vessels) located in the area where active extravasation of arterial contrast material was detected. Super-selective transcatheter embolization, by using biodegradable gelatin sponges and microcoils, is the current preferred angiographic technique (Fig. 4). The success rate is high (about 80%-90%), and the rate of hemorrhagic recurrence is low. The adverse event rate ranges from 5% to 9% and consists mainly of hematomas, arterial dissection, thrombosis, pseudo-aneurysm, and rarely intestinal necrosis. As mentioned previously, when bleeding localization has failed, repeat angiography can be performed with provocative techniques aimed at inducing active bleeding, allowing definitive treatment.

### Surgery

Surgical management of bleeding GIAS is rarely necessary because endoscopy and radiology techniques are today effective treatment alternatives. However, in some studies, surgery was performed in up to 12% of cases. Surgery is warranted if acute and severe GI bleeding occurs, requiring packed red blood cell transfusion, with a clearly identified source, after several noninvasive treatments (endoscopic, radiologic) have failed. Per-procedure endoscopy may help in localizing the source of acute or chronic bleeding when all other strategies have failed.

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**Table 3. Studies evaluating thalidomide efficacy in GI angiodysplasia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Thalidomide</th>
<th>Follow-up, mo.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garrido et al</td>
<td>P</td>
<td>12</td>
<td>200 mg qd</td>
<td>4</td>
<td>Mean Hb increased 6.5 g/dL to 12.1 g/dL by end of therapy</td>
</tr>
<tr>
<td>Ge ZZ et al</td>
<td>P, Rz</td>
<td>53</td>
<td>100 mg qd</td>
<td>39 (8-52)</td>
<td>Lower rate of bleeding episodes (3.7% vs 71.4%; P &lt; .001)</td>
</tr>
<tr>
<td>Kamalaporn et al</td>
<td>CS</td>
<td>7</td>
<td>50 mg qd increased by 50 mg/wk until 200 mg</td>
<td>12</td>
<td>Four patients discontinued because of side effects, 3 patients with no bleeding for 6 mo., then loss of response</td>
</tr>
<tr>
<td>Dabak et al</td>
<td>CS</td>
<td>3</td>
<td>100 to 400 mg qd</td>
<td>8 (4-12)</td>
<td>Decreased need for transfusions within 12 wk in 2 patients (remained transfusion-free during follow-up)</td>
</tr>
<tr>
<td>Bauditz et al</td>
<td>CS</td>
<td>3</td>
<td>100 mg qd</td>
<td>34</td>
<td>No bleeding episode (during/after treatment) and Hb maintained at normal levels</td>
</tr>
<tr>
<td>Bauditz et al</td>
<td>CS</td>
<td>6</td>
<td>300 mg qd, 50-100 mg qd after 6-9 mo.</td>
<td>33 (22-49)</td>
<td>Bleeding stopped within 2 wk in all patients. Hb normalized without further transfusions for the whole observation period</td>
</tr>
<tr>
<td>Shurafa et al</td>
<td>CR</td>
<td>1</td>
<td>100 mg qd increased to 200 mg qd</td>
<td>3</td>
<td>Decrease in transfusion requirement by 2 wk. Requiring no more than 2 transfusions every 2 wk. Response was maintained for 13 wk.</td>
</tr>
</tbody>
</table>

P, Prospective; Hb, hemoglobin; Rz, randomized; CS, case series; CR, case report.
Therefore, it is necessary to
Finally, several single cases
Various pharmacologic agents have shown
Thus, the treatment course should
All in all, there is insuf
In the setting
There may be a role for endoscopic
Prospective controlled trials are
Finally, supplementation
This
Various intravenous iron prepa-
www.giejournal.org
and other
When
care should be dealt with, and
Coagulation defects should be dealt with, and
The transfusion requirement addressed when appropriate.
Associated measures
In most cases of GI bleeding, iron deficiency anemia is a
Therefore, it is necessary to directly treat iron deficiency anemia. The treatment goal is the normalization of hemoglobin, the replenishment of iron stores, and relief of the symptoms of anemia. There are 2 treatment approaches: oral and intravenous supplementation. Oral iron supplementation can be used if inflammation (leading to reduced intestinal iron absorption) and signs of intestinal malabsorptive disease are absent. A dose of 100 to 200 mg elemental iron (ferric salts) in 2 divided daily doses is recommended. This approach is limited by adverse effects, such as nausea, abdominal pain, and constipation and/or diarrhea. When the treatment is effective, increased erythropoiesis (increased reticulocyte counts) is seen within 3 to 10 days, and a normalization of hemoglobin levels occurs within 6 to 12 weeks. Iron stores replenishment requires an additional 12 to 16 weeks. Thus, the treatment course should last approximately 6 months. Intravenous iron treatment is used if there is prolonged inflammation, malabsorption, adverse effects, or lack of intake of oral iron and for situations in which a rapid increase in iron stores is needed, such as cases of severe anemia (hemoglobin <10 g/dL in women and <11 g/dL in men). Various intravenous iron preparations are available and are equally effective. In the setting of GIAs, conservative management, including intravenous iron therapy and transfusions, is a reasonable option in high-risk elderly patients. Prospective controlled trials are needed in this regard. This type of management may be considered in cases of overt obscure GI bleeding with a negative CT angiography result. Finally, supplementation may delay and/or prevent the development of iron deficiency anemia in patients with frequent episodes of GI bleeding. Coagulation defects should be dealt with, and the transfusion requirement addressed when appropriate.
Temporary or definitive discontinuation of treatments that increase the risk of bleeding, such as antiplatelet therapy and anticoagulants, should be discussed with the cardiologist, especially in elderly patients in whom these treatments are commonly used.
HHT
Treatment of GI bleeding in the setting of HHT is unnecessary unless aggressive iron therapy has been ineffective in maintaining hemoglobin concentration in the normal range. There may be a role for endoscopic therapy when iron replacement has failed, although there is insufficient evidence to recommend endoscopic therapy as first-line therapy in HHT-related GI bleeding. Expert opinion is that APC is the most effective method. Various pharmacologic agents have shown promise, based on case reports or small uncontrolled series. This includes hormonal therapy (estrogen/progesterone preparations or danazol), antifibrinolytics (aminocaproic acid or tranexamic acid), and other medications reported in isolated case reports (tamoxifen, interferon, thalidomide, and sirolimus). Of note, in a small, controlled, cross-over study comparing combination hormonal therapy versus placebo in 10 patients presenting with severe GI bleeding, 5 of the 6 patients with HHT had no further GI bleeding. All in all, there is insufficient evidence to recommend any medical treatment as first-line therapy in this setting. Finally, several single cases of reduction in GI bleeding after administration of bevacizumab, an anti-angiogenic drug, have been reported.

In conclusion, GIAs are the most common vascular malformation of the digestive tract. Endoscopy constitutes the cornerstone of diagnostic and therapeutic management. However, pharmacologic therapy, radiology techniques, and surgery should be considered in the management of bleeding GIAs. Recently developed techniques allowing exploration of the small bowel, such as VCE and enteroscopy, yield a more efficient treatment of GIAs, even those located in the distal part of the small bowel. However, data regarding long-term efficacy of these different treatments are still lacking, and the recurrence rate remains high. Consensus dictates that GIAs should be destroyed by using endoscopic techniques, APC being the first-line treatment.
to consider. If APC fails, pharmacologic therapy, such as somatostatin analogues, which are efficacious and well-tolerated, can be used. Novel therapies, such as antiangiogenic molecules (anti-VEGF), might be interesting alternatives to use in the near future.

REFERENCES

Hemorrhagic angiodysplasia of the digestive tract


Hemorrhagic angiodysplasia of the digestive tract


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Reprint requests: Gabriel Rahmi, MD, PhD, Gastroenterology and Endoscopy Division, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015, Paris, France.
1. A patient presents with a second episode of overt GI bleeding, the initial episode resulted in a negative EGD and colonoscopy, bleeding stopped spontaneously. The next best procedure(s) in this case should be:
   a. video capsule endoscopy
   b. EGD and colonoscopy
   c. spiral small bowel endoscopy
   d. technetium RBC scan

True or False

2. Recurrent bleeding after endoscopic therapy for GIA occurs in up to 80% of cases, valvular heart disease and multiple lesions predict rebleeding

3. A 0.7cm cecal angiodysplasia found during routine colon cancer screening colonoscopy should be ablated.

4. Complete enteroscopy is clearly superior to partial antegrade or retrograde enteroscopy in most cases

5. Hormonal therapy is not recommended for the treatment of GIA

6. GI bleeding in cases of hereditary hemorrhagic telangiectasia is usually slow and can be managed by iron replacement therapy, prior to attempting endoscopic therapy

7. Heater probe therapy should not be used to treat GIA due to higher risk of perforation

8. von Willebrand’s disease is a risk factor for GIA

9. Left ventricular assist devices are a risk factor for GIA, lower GI bleeding is the most common presenting sign.

10. Thalidomide has been shown to reduce GI bleeding from GIA, however, peripheral neuropathy and teratogenicity limits its use

11. CT angiography has replaced catheter angiography for the localization of bleeding

12. After APC therapy, bleeding from colonic GIA’s is more likely to recur than from small bowel GIA’s

13. Monopolar coagulation appears to be as effective and safe as APC ablation of GIA’s

14. Long-acting octreotide preparations may be helpful in the management of GIA’s

15. Iron deficiency from GIA bleeding should be managed with IV iron replacement as oral therapy is usually ineffective