**Systematic Reviews and Meta-Analyses**

**Medical and Endoscopic Therapies for Angiodysplasia and Gastric Antral Vascular Ectasia: A Systematic Review**

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**Background & Aims:** Few studies have compared the efficacy and complications of endoscopic or medical therapies for bleeding angiodysplasias or gastric antral vascular ectasias (GAVE). We conducted a systematic review to evaluate therapies.

**Methods:** We performed a PubMed search for studies (written in English from January 1, 1980, through January 1, 2013) of medical or endoscopic treatment of bleeding angiodysplasias and GAVE. Measured outcomes included levels of hemoglobin, transfusion requirements, rebleeding rates, complications, treatment failures, and overall mortality.

**Results:** We analyzed data from 63 studies that met inclusion criteria; 50 evaluated endoscopic treatment (1790 patients), 13 evaluated medical treatment (392 patients), and 12 were comparative studies. In patients with angiodysplasias, the combination of estrogen and progesterone did not significantly reduce bleeding episodes, compared with placebo (0.7/y vs 0.9/y, respectively), and increased mortality, compared with conservative therapy (33% vs 21%). A higher percentage of patients receiving octreotide were free of rebleeding at 1 and 2 years vs placebo (77% vs 55% and 68% vs 36%, respectively; $P = .03$). Thalidomide reduced the number of bleeding episodes (–8.96/y), compared with iron therapy (–1.38/y, $P < .01$), but neither treatment reduced mortality. More patients with GAVE treated by endoscopic band ligation were free from rebleeding (92%) than those treated with argon plasma coagulation (32%, $P = .01$).

**Conclusions:** In a systematic review, we found a low quality of evidence to support treatment of angiodysplasias with thalidomide or the combination of estrogen and progesterone and insufficient evidence to support treatment with octreotide. There is also insufficient evidence for endoscopic therapy of angiodysplasia or GAVE. Well-designed randomized controlled trials are needed to study the efficacy and complications of medical and endoscopic treatments for patients with angiodysplasias or GAVE.

**Keywords:** Systematic Review; Angiodysplasia; Gastric Antral Vascular Ectasia; Comparison Analysis.

Angiodysplasias and gastric antral vascular ectasia (GAVE) are 2 common causes of iron deficiency anemia. Angiodysplasias are thin-walled tortuous vessels found throughout the gastrointestinal (GI) tract, whereas GAVE is a collection of dilated tortuous vessels that appear to streak out from the pylorus. Patients with hereditary hemorrhagic telangiectasias (HHTs) and von Willebrand disease (VWD) have a high rate of GI malformations, which in turn increases the frequency of clinically significant bleeding episodes.1 Idiopathic angiodysplasias are more common, typically occur in patients older than 60 years, and are found incidentally in 1%–2% of all asymptomatic patients undergoing colonoscopy.2,3 Most angiodysplasias will never bleed, but those that do make up 5% of overt upper GI bleeds,4 7% of overt lower GI bleeds,5 and between 65% and 80% of lesions found in obscure GI bleeds.6–9 Many patients with GAVE are also asymptomatic, so the prevalence in the general population is unknown, but a screening study in cirrhotic patients reported a prevalence of 12%.10,11 GAVE accounts for 4% of all non-variceal bleeds in the general population11 and 6% of upper GI bleeds in cirrhotic patients.10 These etiologies
of GI bleeding have significant morbidity and financial impact, because patients are often hospitalized with each episode of bleeding for investigation of anemia and undergo endoscopic procedures to find and treat the source of bleeding. Surgery is occasionally used for patients who have failed medical and endoscopic therapies but is associated with high morbidity and mortality. Only 35% of patients were free of complications after surgery for angiodyplasias,\textsuperscript{12} with an associated 33% mortality.\textsuperscript{13} Surgery for GAVE has a 50% thirty-day mortality\textsuperscript{14} and perioperative mortality of 7.4%.\textsuperscript{15} Transjugular intrahepatic portosystemic shunt has also been attempted for GAVE with limited success because 7 of 8 people rebled after transjugular intrahepatic portosystemic shunt in one study,\textsuperscript{14} and all 14 patients in another study continued to require transfusions.\textsuperscript{16} Even though GAVE is often seen in patients with portal hypertension, successful reduction in the portal hypertension does not result in reduced risk of bleeding.

The treatment goals for bleeding angiodyplasias or GAVE include resolution of anemia, reduced transfusion requirements, and reduction in the incidence of rebleeding. The current treatment of choice appears to be endoscopic intervention with argon plasma coagulation (APC), whereas systemic medical therapies are traditionally reserved for patients who have either failed endoscopic treatment or challenging lesions in terms of location and number to be managed endoscopically. Endoscopic techniques destroy lesions locally, whereas medical therapies work systemically. A substantial amount of literature exists on the use of endoscopic and medical therapies, but there are no recent comprehensive systematic reviews evaluating efficacy and harm of endoscopic or medical therapies. Our goal was to conduct a systematic review on the efficacy and harms of medical and endoscopic therapies for angiodyplasia and GAVE.

**Methods**

**Data Collection and Selection**

A PubMed search was performed on the Medline database for all studies in the English language published between January 1, 1980, and January 1, 2013, including the medical subject heading (MeSH) angiodyplasia/therapy (GAVE is categorized within the MeSH term angiodyplasia) and angiodyplasia or gastric antral vascular ectasia cross-referenced with thalidomide, octreotide, estrogen, progesterone, lenalidomide, atorvastatin, tranexamic acid, argon plasma coagulation, neodymium: yttrium aluminum garnet laser, cryotherapy, band ligation, bipolar, coagulation, heater probe, and radiofrequency ablation. We searched by hand the references of studies included from the original search and included additional studies that fit inclusion criteria. We also searched the Cochrane database.

**Inclusion Criteria**

For treatment efficacy, we included studies with a comparator, such as randomized controlled trials (RCTs), and cohort studies with comparators that reported at least one of our predefined primary outcomes: change in hemoglobin, transfusion requirements, and/or bleeding data for the therapeutic modality being studied. For complication outcomes we included case series with more than 5 patients. Complications included adverse events, perforations, failed therapy, and overall mortality.

**Exclusion Criteria**

We excluded reviews, editorials, animal studies, nonclinical studies or those with less than 5 patients, studies that were not GAVE or angiodyplasia of the GI system, and studies where patients were primarily with surgery or interventional radiology. In addition, we excluded studies where patients were asymptomatic (without evidence of active bleeding) and had incidental finding of GAVE and/or angiodyplasia. A flow chart of this search strategy is shown in Figure 1.

**Definitions**

We synthesized the results by using the exact definitions the authors used for assessing efficacy and complications.

- **Change in hemoglobin**: Studies reported hemoglobin as the groups’ average change in hemoglobin after therapy.
- **Transfusion requirements**: Studies reported transfusion requirements in 3 different ways: the number of patients requiring transfusions after therapy, the groups’ average number of units of blood transfused during a set period of time after therapy, or the change in the groups’ average blood transfusion requirements after therapy.
- **Bleeding**: Studies reported bleeding as the total number of bleeding episodes or change in frequency of bleeding episodes after therapy during a set time period; the ratio of patients who rebled in the treatment group; the number of patients with cessation of bleeding or the percent of patients free of rebleeding during a certain time period. When possible, we converted to a percent of patients free of rebleeding by dividing the number of patients who rebled by the total number of patients in the study group minus those lost to follow-up (if available).
- **Failure rates**: A failure of therapy was defined as any patient who stopped therapy or changed therapy to a different endoscopic, surgical, or medical therapy.
Types of Therapies

Therapies included in this review are estrogen with progesterone, octreotide, thalidomide, APC, neodymium-doped yttrium aluminum garnet (Nd:YAG), heater probe, monopolar coagulation, bipolar coagulation, sclerotherapy, endoscopic band ligation (EBL), and cryotherapy.

Types of Comparators

We used comparators as reported by the individual studies. These included placebo, conservative or supportive treatment, or another active agent such as heater probe or surgical resection.

Data Synthesis and Analysis

This was completed by using recently published guidelines.17 We rated study quality by the following criteria: adequate allocation concealment based on the approach by Schulz and Grimes,18 blinding methods (participant, investigator, or outcome assessor), analysis by intention to treat, and lost to follow-up. The quality of the overall evidence was rated by the investigators according to the Grading of Recommendations, Assessment, Development, and Evaluation group.19 A consensus on the evidence was reached by all investigators on the basis of the 4 domains (risk of bias, consistency, directness, and precision), and subsequently, the level of evidence on each modality of therapy for angiodysplasia and GAVE was ranked as high, moderate, low, or insufficient.

Results

A total of 429 citations resulted from the original search, of which only 49 studies fit inclusion criteria, with the largest percentage (35%) being excluded because of a sample size less than 5 patients. Fourteen additional studies that fit inclusion criteria were found by manually reviewing citations of other included articles. Of the 63 reviewed studies on GAVE and angiodysplasia, 50 were endoscopic (n = 1790) and 13 were medical (n = 392), with only 12 studies that used comparators included in the systematic review (Figure 1).

Angiodysplasia

Medical therapies. These studies are summarized in Table 1.

Estrogen with progesterone. One double-blind RCT (n = 68) showed that compared with placebo, there was no difference in the number of units of blood transfused per year (0.9 vs 0.7), change in bleeding episodes per year (0.7 vs 0.9), or percent of patients free of rebleeding at 1 and 2 years, respectively (69% vs 55% and 50% vs 36%).20 A second, retrospective study (n = 64) found no difference in units of blood transfused per month compared with conservative management (1.5 vs 1.6).21

Octreotide. A prospective study (n = 65) found that octreotide failed to show a difference in units of blood transfused per year (1.1 vs 0.7) compared with placebo; however, it did show fewer chronic bleeding episodes per year (0.03 vs 0.2, P = .04) and a higher percent of
**Table 1. Studies With a Comparator**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of therapy</th>
<th>Comparator</th>
<th>Study type</th>
<th>No. of patients requiring transfusions</th>
<th>Duration of drug therapy or mean no. of sessions (range)</th>
<th>Duration of drug therapy or mean no. of sessions (range)</th>
<th>Change in hemoglobin (g/dL)</th>
<th>Transfusion requirements</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junquera et al (2001)</td>
<td>DB-RCT</td>
<td>Estrogen with progesterone (Ethinylestradiol 0.01 mg and northeisterone 2 mg daily)</td>
<td>Placebo</td>
<td>68 (33 vs 35)</td>
<td>13.5 mo (12–36)</td>
<td>13.5 mo (12–36)</td>
<td>NR</td>
<td>Units/y: 0.9 vs 0.7</td>
<td>Episodes/y: 1 y: 69 vs 55 0.7 vs 0.9 2 y: 50 vs 36</td>
</tr>
<tr>
<td>Lewis et al (1992)</td>
<td>Retro cohort</td>
<td>Estrogen with progesterone (Premarin 0.625 mg/day for 6 patients and Enovid 10 mg/day for 24 patients)</td>
<td>Conservative</td>
<td>64 (30 vs 34)</td>
<td>15.6 mo (2–31) vs 13.4 (1–23)</td>
<td>NR</td>
<td>Units/mo: 1.5 vs 1.6</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Junquera et al (2007)</td>
<td>Prosp cohort</td>
<td>Octreotide</td>
<td>Placebo</td>
<td>65 (30 vs 35)</td>
<td>13 mo (12–36)</td>
<td>13 mo (12–36)</td>
<td>NR</td>
<td>Units/y: 1.1 vs 0.7</td>
<td>Episodes: 1 y: 77 vs 55 0.3 vs 0.2 2 y: 68 vs 36</td>
</tr>
<tr>
<td>Ge et al (2011)</td>
<td>Open-label RCT</td>
<td>Thalidomide</td>
<td>Iron therapy</td>
<td>52 (26 vs 26)</td>
<td>4 mo (8–52)</td>
<td>4 mo (8–52)</td>
<td>NR</td>
<td>Units/mo: 1.1 vs 0.7</td>
<td>Episodes: 1 y: 77 vs 55 0.2 vs 0.3 2 y: 68 vs 36</td>
</tr>
<tr>
<td>Saperas et al (2009)</td>
<td>Retro cohort</td>
<td>APC</td>
<td>Conservative</td>
<td>57 (34 vs 23)</td>
<td>NR (33)</td>
<td>NR (33)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Askin et al (1996)</td>
<td>Retro cohort</td>
<td>Heater probe</td>
<td>Conservative</td>
<td>83 (55 vs 28)</td>
<td>1.94 (1–7)</td>
<td>30 vs 26</td>
<td>NR</td>
<td>Δ units/mo: 2.1 vs 0.96</td>
<td>NR</td>
</tr>
<tr>
<td>Gupta et al (1995)</td>
<td>Retro cohort</td>
<td>Heater probe, surgery</td>
<td>Transfusion, observation</td>
<td>32 (16, 9 vs 4, 3)</td>
<td>1.25 (1–2)</td>
<td>13.5 (3–42)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Richter et al (1999)</td>
<td>Retro cohort</td>
<td>Monopolar coagulation, surgery</td>
<td>Conservative, asymptomatic</td>
<td>101 (19, 31 vs 36, 15)</td>
<td>NR (22)</td>
<td>22 (1–120)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

\*NR = Not reported
Thalidomide. An open-label RCT (n = 52) compared low-dose thalidomide with a positive control of iron supplements for 4 months.\textsuperscript{23} Compared with iron, thalidomide had a significant rise in hemoglobin (2.88 vs -0.05 g/dL, \(P < .01\)), fewer patients needing transfusions (3 vs 13, \(P < .01\)), and a larger change in the number of bleeding episodes per year (-8.96 vs -1.38, \(P < .01\)).\textsuperscript{23}

The quality of the studies was low, with only 2 RCTs found. Studies were small in size, and reporting of outcomes was variable. We found low evidence for efficacy of thalidomide and estrogen with progesterone, with insufficient evidence of efficacy of octreotide for angiodysplasia (Supplementary Table 1).

Complications. The RCT found estrogen with progesterone had more side effects than placebo (45% vs 14%, \(P < .01\)) and similar mortality (0% vs 3%) (Table 1).\textsuperscript{20}

The prospective study found side effects in 57% of treated patients, with similar rates to placebo requiring surgery (17% vs 24%) and a higher overall mortality rate (33% vs 21%).\textsuperscript{21} Octreotide had more side effects than placebo (53% vs 14%, \(P = .01\)), diarrhea being most frequent, with similar percentages stopping therapy (3% vs 0%) and similar mortality (0% vs 3%).\textsuperscript{22} Thalidomide had more side effects than iron therapy (73% vs 35%, \(P < .01\)); fatigue, constipation, and dizziness being most common, with similar stopping rates (8% vs 0%) and the same mortality rate (0% vs 0%).\textsuperscript{23}

Case series. Three case series (n = 66) evaluated estrogen with progesterone and found side effects in 32% (0%–44%) of patients, a 20% (0%–44%) stopping rate, and a 23% (0%–28%) overall mortality (Table 2).\textsuperscript{8,24,25} Octreotide had 3 case series (n = 45) that found a complication rate of 2.2% (0%–8%), failure rate of 13% (0%–46%), and no mortality (0%).\textsuperscript{26–28} A single case series on thalidomide (n = 12) found 17% of patients had side effects, 25% stopped therapy, and no mortality (0%).\textsuperscript{29}

Endoscopic therapies. These studies are summarized in Table 1.

Argon plasma coagulation. A retrospective study (n = 57) found no difference in the percent of patients free of rebleeding compared with conservative therapy at 1 or 2 years, respectively (87% vs 73% and 74% vs 52%, \(P = .06\)).\textsuperscript{30}

Heater probe. Two retrospective studies fit inclusion criteria.\textsuperscript{13,31} The larger study (n = 83) evaluated the change in transfusion requirements before and after therapy in patients treated with heater probe (n = 55) versus those managed conservatively (n = 28) and found no difference (2.1 vs 0.96, \(P = .19\)).\textsuperscript{31} The second study (n = 32) had 4 arms of therapy: heater probe (n = 16), surgery (n = 9), transfusions only (n = 4), and observation (n = 3). There was no difference in percent free of rebleeding between heater probe and the 3 comparators, respectively (66%, 100%, 66%, 100%).\textsuperscript{13}
Table 2. Complications, Perforations, Failures, and Mortality in Case Series

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Type of therapy</th>
<th>No. of studies</th>
<th>Sum of patients</th>
<th>Weighted mean of average follow-up, mo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% With complications&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% With perforations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Failure rate&lt;sup&gt;a&lt;/sup&gt; (%)</th>
<th>% Overall mortality&lt;sup&gt;a&lt;/sup&gt; from bleeding or therapy complication&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiodysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estrogen with progesterone</td>
<td>3</td>
<td>66</td>
<td>16 (12–18)</td>
<td>32 (0–44)</td>
<td>NR</td>
<td>20 (0–44)</td>
<td>23 (0–28)</td>
</tr>
<tr>
<td></td>
<td>Octreotide</td>
<td>3</td>
<td>45</td>
<td>29 (14–39)</td>
<td>2.2 (0–8)</td>
<td>NR</td>
<td>13 (0–46)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>1</td>
<td>12</td>
<td>24–36</td>
<td>17</td>
<td>NR</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>EBL</td>
<td>2</td>
<td>29</td>
<td>16 (12–18)</td>
<td>14 (11–18)</td>
<td>0.0</td>
<td>0.0</td>
<td>14 (11–18)</td>
</tr>
<tr>
<td></td>
<td>APC</td>
<td>7</td>
<td>493</td>
<td>19 (6–55)</td>
<td>2.4 (0–6)</td>
<td>0.6 (0–2)</td>
<td>1.6 (0–14)</td>
<td>9 (5–34)</td>
</tr>
<tr>
<td></td>
<td>Nd:YAG laser</td>
<td>6</td>
<td>359</td>
<td>15 (12–24)</td>
<td>13 (4–32)</td>
<td>2.6 (0–5)</td>
<td>8 (1–17)</td>
<td>8 (3–27)</td>
</tr>
<tr>
<td></td>
<td>Heater probe</td>
<td>2</td>
<td>34</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Monopolar coagulation</td>
<td>2</td>
<td>50</td>
<td>17</td>
<td>4 (0–9)</td>
<td>2</td>
<td>6</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Bipolar coagulation</td>
<td>1</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sclerotherapy</td>
<td>1</td>
<td>8</td>
<td>29</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>GAVE</td>
<td>Estrogen with progesterone</td>
<td>1</td>
<td>6</td>
<td>8</td>
<td>50.0</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>APC</td>
<td>10</td>
<td>192</td>
<td>17 (9–30)</td>
<td>21 (0–80)</td>
<td>0.0</td>
<td>1.8 (1–14)</td>
<td>25 (0–57)</td>
</tr>
<tr>
<td></td>
<td>Nd:YAG laser</td>
<td>8</td>
<td>185</td>
<td>30 (9–55)</td>
<td>20 (0–51)</td>
<td>1.6 (0–14)</td>
<td>6 (0–13)</td>
<td>28 (9–63)</td>
</tr>
<tr>
<td></td>
<td>Heater probe</td>
<td>1</td>
<td>12</td>
<td>21</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Monopolar coagulation</td>
<td>1</td>
<td>6</td>
<td>NR</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Cryotherapy</td>
<td>2</td>
<td>26</td>
<td>3</td>
<td>20 (7–33)</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup>When reported.
Monopolar coagulation. Two retrospective studies fit inclusion criteria.32,33 One study (n = 101) had 4 arms of therapy: monopolar coagulation (n = 19), right hemicolectomy with ileal resection (n = 31), conservative therapy (n = 36), and observation of asymptomatic patients (n = 15).32 The percent of patients free of rebleeding was no different between monopolar coagulation, surgery, and medical management at 1 year (66%, 84%, 74%) or 3 years (47%, 76%, 54%), whereas 100% of patients with asymptomatic lesions were free of bleeding.32 The second study (n = 56) had 3 arms of therapy: monopolar coagulation (n = 20), surgical resection (n = 17), and transfusions only (n = 11).34 This study found no difference in the percent free of rebleeding between monopolar coagulation and transfusions (50% vs 55%, P = .79) or coagulation or trans- fusion versus surgery (76%; P = .08 and P = .21 respectively).33

The quality of the studies was low with no RCTs. Studies were all retrospective and small in size, and reporting of outcomes was variable. We found insufficient evidence of efficacy for any single endoscopic therapy for angiodysplasias (Supplementary Table 1).

Complications. The study on APC only reported APC-induced hemorrhage and found a higher rate with therapy (9% vs 0%) (Table 1).30 One study found fewer patients change therapy with heater probe than with conservative management (11% vs 25%).31 The second study reported no side effects with heater probe (0%), a need for surgery in 6% of patients, and a lower mortality with heater probe than surgery but higher than trans- fusion and observation (6%, 33% vs 0%, 0%).13 Monopolar coagulation had higher adverse events than all 3 comparators in one study (5%, 0% vs 0%, 0%),32 whereas it had equal percentages to surgery and conserva- tive management (0%, 0% vs 0%) in the second study.33 Surgery to abolish rebleeding was required at a higher rate in monopolar coagulation than in the 3 comparators (10%, 0% vs 0%, 0%).32 Monopolar coagulation had more patients change therapy (25%, 18% vs 6%),33 and both studies reported overall mortality of all patients in the study at 22% and 23%.32,33

Case series. There were 2 case series on EBL (n = 29), which found complications in 14% (11%–18%) of pa- tients, no perforations or failed therapy (0%), and an overall mortality of 14% (11%–18%) (Table 2).34,35 There were 7 case series on APC (n = 493) that found complications in 2.4% (0%–6%) of patients, perforations in 0.6% (0%–2%), 1.6% (0%–14%) failed therapy, and 9% (5%–34%) overall mortality, whereas 19% (0%–100%) of the mortality was bleeding related.36–42 There were 6 case series on Nd:YAG (n = 359) that found 13% of patients (0%–32%) had complications, 2.6% (0%–5%) had perforations, 8% (1%–17%) failed therapy, and 8% (3%–27%) overall mortality, with 6% (0%–9%) of mortality therapy or bleeding related.43–48 There were 2 case series on heater probe (n = 34), with a 4% complication rate, no perforations or therapy failures (0%), and 9% overall mortality.49,50 There were 2 case series on monopolar coagulation (n = 50); 4% of patients (0%–9%) had complications, 2% had perfora- tions, 6% failed therapy, and neither study reported mortality data.51,52 Bipolar coagulation had a single case series (n = 11), with no complications or perforations (0%), whereas 18% of patients required surgery, and there was no mortality (0%).53 A single case series on sclerotherapy with ethanolamine (n = 8) found 25% of patients had complications, and there were no perfora- tions or therapy failures (0%) and 13% overall mortality (1 death), with 100% of mortality being a therapy- related complication.24

Gastric Antral Vascular Ectasia

Medical therapies. No studies with comparators evaluated medical therapy for GAVE.

Case series. A single case series (n = 6) on estrogen with progesterone found 50% of patients had side ef- fects, none failed therapy, and no mortality data were reported (Table 2).55

Endoscopic therapies. These studies are summarized in Table 1.

Endoscopic band ligation. Two retrospective studies compared EBL with APC.56,57 Of the patients in the EBL treatment arms, 50% and 44% had previously failed APC therapy before enrolling in the study.56,57 The first study included 34 cirrhotic patients with class A (n = 6), class B (n = 21), and class C (n = 7) and found a higher percent of patients free of rebleeding with EBL than with APC (92% vs 32%, P = .01).56 The second study (n = 22) included 9 patients treated with EBL and 13 treated with endoscopic thermal therapy: APC only (n = 10), bipolar coagulation only (n = 1), or both APC and bipolar coagulation (n = 2). Ten of 22 patients (45%) had cirrhosis. This study found EBL required fewer treatment sessions (1.9 vs 4.7, P = .05), had a greater increase in hemoglobin (2.8 vs 0.9 g/dL, P = .05), a greater decrease in the number of transfused units of blood (−12.7 vs −5.2, P = .02), and a higher percent of patients who had cessation of bleeding (56% vs 23%, P = .04).57 Outcomes by underlying portal hypertension were not reported.

The quality of the studies was low with no RCTs. Studies were both retrospective and small in size, and reporting of outcomes was variable. We found insufficient evidence of efficacy for either endoscopic therapy for GAVE (Supplementary Table 1).

Complications. Higher rates of complications were reported with EBL than with APC in both studies (8% vs 0% and 11% vs 8%), with no failures in EBL or APC and a lower mortality with EBL than with APC (16% vs 32% and 33% vs 38%) (Table 1).56,57

Case series. There were 10 case series on APC (n = 192) that found 21% of patients (0%–80%) had adverse events, no perforations (0%), 2% (1%–14%) failed therapy with 25% (0%–57%) overall mortality, and 12% (0%–50%) of mortality was therapy or
bleeding related (Table 2).\textsuperscript{58–67} There were 10 case series on Nd:YAG therapy (n = 185) that found 20% of patients (0%–51%) had complications, 1.6% (0%–14%) had perforations, 6% (0%–13%) failed therapy, and there was 28% (9%–63%) overall mortality, and 10% (0%–25%) of mortality was therapy or bleeding related.\textsuperscript{68–75} A single case series on heater probe (n = 12) found 33% of patients had complications, but there were no perforations, therapy failures, or mortality (0%).\textsuperscript{76} A single case series on monopolar coagulation (n = 6) found 33% of patients had complications, no perforations or therapy failures (0%), and mortality data were not reported.\textsuperscript{11} Two case series on cryotherapy (n = 26) found 20% of patients (7%–33%) had complications, no perforations or therapy failures (0%), and mortality data were not reported.\textsuperscript{77,78}

We also pooled all studies on APC and Nd:YAG (angiodysplasia and GAVE) that reported perforation outcomes. There were fewer perforations with APC compared with Nd:YAG (3 of 662 vs 11 of 484).

**Hereditary Hemorrhagic Telangiectasia and Von Willebrand Disease**

There were 2 randomized controlled crossover trials that included patients with HHT; however, the first study was not included because it was replicated in the second study plus 3 additional patients (Table 1).\textsuperscript{79,80} The crossover trial (n = 14) had 8 patients with HHT, 1 with HHT and VWD, and 5 with angiodysplasia. Therapy consisted of 6 months of estrogen with progesterone, followed by 6 months of placebo to a group of 8 patients, and vice versa to a group of 6. This study found fewer patients needed transfusions when actively being treated with estrogen and progesterone compared with placebo (3 of 13 vs 12 of 13, \textit{P} < .01), but all patients in follow-up (8 of 8) required transfusions after therapy was completed, even though the study reported 25% of patients were free of rebleeding.\textsuperscript{79}

**Complications.** The single study reported more complications in patients who received estrogen with progesterone than placebo (38% vs 23%), a higher rate of patients requiring surgery (7% vs 0%), and similar mortality (7% vs 14%) (Table 1).

**Case series.** There were 6 larger case series that had subsets of patients with HHT. Because most patients in those studies had either angiodysplasia or GAVE and the complications were reported for all patients in the study, these results were discussed in the GAVE or angiodysplasia sections.\textsuperscript{46,43–46,48}

**Discussion**

Overall, we found insufficient or low evidence regarding the efficacy for currently used modalities and agents. Most studies were small, retrospective, heterogeneous in population and setting, did not report the number or location where lesions were found, and had considerable variation in reporting outcomes across and within treatment modalities. Pooling results was not permissible, and determining generalized estimates of clinically relevant treatment effects was not feasible. Our findings are summarized in Table 3.

The current standard of care, APC therapy, failed to show a difference in rebleeding versus conservative management in angiodysplasia.\textsuperscript{40} The other 2 endoscopic therapies studied (monopolar coagulation and heater probe) failed to show benefit versus conservative therapy in angiodysplasia. For studies on GAVE, APC was inferior to EBL at reducing rebleeding in GAVE,\textsuperscript{56,57} and no study has compared the efficacy of EBL with conservative therapy. Of note, these studies included a large percentage (100% and 45%) of patients with cirrhosis and therefore may not be applicable to all patients with GAVE.

We found low evidence for efficacy of estrogen with progesterone for angiodyplasia because 2 studies demonstrated no improvement in clinical outcomes and showed high complication rates and higher mortality than conservative therapy.\textsuperscript{20,21} Octreotide showed decreased risk of bleeding with equal rates of mortality versus conservative therapy but was of insufficient evidence because of the study design, small number of patients, and uncontrolled allocation of patients.\textsuperscript{22} Although thalidomide showed a decrease in the risk of rebleeding and equal rates of mortality versus conservative therapy, we rated it as low evidence because the RCT was open labeled, with a small number of patients and large confidence intervals.\textsuperscript{23}

Because of the small number of patients, retrospective nature, and uncontrolled patient populations, we found insufficient evidence to determine the efficacy of APC, heater probe, and monopolar coagulation.\textsuperscript{13,30–33} Although EBL appears superior to APC with regard to bleeding and mortality for the treatment of GAVE, the data are from 2 very small, nonrandomized patient populations and therefore of insufficient evidence.

### Table 3. Evidence for Therapies

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Angiodysplasia</th>
<th>GAVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen with progesterone</td>
<td>−</td>
<td>I</td>
</tr>
<tr>
<td>Octreotide</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>EBL</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td>APC</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>Nd:YAG laser</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>Heater probe</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>Monopolar coagulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar coagulation</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>X</td>
<td>I</td>
</tr>
</tbody>
</table>

+, Evidence for use; −, evidence against use; I, insufficient data; X, no data.
For patients with GI bleeding from HHT, we found insufficient evidence to determine the efficacy of any one therapy.

Endoscopic techniques appear effective for initial hemostasis by destruction of the lesion, but none have been shown to prevent long-term bleeding better than conservative therapy. Although octreotide and thalidomide work by different mechanisms than endoscopic therapies, they similarly have been shown to resolve lesions. A possible mechanism for the long-term rebleeding superiority of octreotide and thalidomide over endoscopic therapies is that endoscopic therapies treat locally, and 17% of patients who rebleed after endoscopic therapy bleed from new lesions that were not seen during the original endoscopy; thus, systemic treatment theoretically offers better control of new or missed lesions on the initial endoscopy. Another possible mechanism is the prevention of new lesion formation because both octreotide and thalidomide inhibit vascular permeability.

**Complications**

There was great variability between studies on what was reported as a failure of therapy. Medical therapies tended to report all side effects of therapy even if very minor (eg, bitter taste and dry eyes); therefore, it was not surprising to see more side effects than for those receiving placebo. Studies on endoscopic therapy seemed to only report major complications. It is worth noting that the complications from thalidomide and octreotide seem to be less serious because no patients required antibiotics for bacteremia, surgery for perforations, or antral stenosis. In fact, the most severe complication reported in thalidomide was a reversible polyneuropathy, whereas 1 patient on octreotide suffered a stroke, which was the same frequency as for placebo.

**Perforations**

Similar to other reports, we found that APC has fewer perforations than Nd:YAG, and notably no perforations were observed in EBL studies.

**Failure Rates**

There was substantial variability in what was reported as a failure of therapy. Medical therapies tended to report the number of patients stopping because of intolerance to medications. Estrogen with progesterone had the highest rate of patients stopping because of intolerance, followed by thalidomide and octreotide. Endoscopic therapies reported the percentage of patients who went to surgery or changed therapy. Because of the variability of how a failure was defined, it is difficult to compare among studies.

**Mortality**

Estrogen with progesterone was associated with a higher rate of mortality, whereas octreotide and thalidomide had similar rates to conservative therapy. Only 1 endoscopic study on angiodysplasia compared mortality with transfusion only therapy, whereas the rest did not report mortality data. Two small studies on GAVE (n = 56) that compared EBL with APC found lower mortality with EBL. Additional well-designed prospective studies are needed to determine whether there is a therapy-related mortality benefit.

Limitations of our review include only searching studies in the English language, not contacting authors, and limitations of the data because of the lack of uniform reporting among articles, most importantly including location and number of angiodysplasias and use of confounding drugs such as steroids, nonsteroidal anti-inflammatory drugs, antiplatelet, and anticoagulants that can affect initial bleeding, rebleeding, and transfusion requirements.

Future rigorous double-blind RCTs are needed to evaluate treatment efficacy and should clearly delineate the location of angiodysplasias and the number of lesions treated and use standardized measures for reporting outcomes. These studies should compare medical and endoscopic agents against one another, placebo, and conservative management. Last, there needs to be rigorous long-term safety data for these interventions with standardized complications reporting, which presently is lacking in most studies.

**Supplementary Material**

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at [http://dx.doi.org/10.1016/j.cgh.2013.08.038](http://dx.doi.org/10.1016/j.cgh.2013.08.038).

**References**


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