7-1-2023

AGA Clinical Practice Update on interventional EUS for vascular investigation and therapy: Commentary

Marvin Ryou

John M DeWitt

Koushik K Das

Vanessa M Shami

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on Interventional EUS for Vascular Investigation and Therapy: Commentary

Marvin Ryou, MD,[1] John M. DeWitt, MD,[2] Koushik K. Das, MD,[3] and Vanessa M. Shami, MD[4]

[1]Division of Gastroenterology, Hepatology, and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts; [2]Department of Gastroenterology and Hepatology, Indiana University Health, Indianapolis, Indiana; [3]Division of Gastroenterology, Washington University School of Medicine in St Louis, St Louis, Missouri; and [4]Division of Gastroenterology and Hepatology, University of Virginia Medical Center, Charlottesville, Virginia

DESCRIPTION: **The purpose of this AGA Institute Clinical Practice Update is to review the available evidence supporting and examine opportunities for future research in endoscopic ultrasound–guided vascular investigation and therapies.**

METHODS: **This Clinical Practice Update was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. This expert commentary incorporates important as well as recently published studies in this field, and it reflects the experiences of the authors who are advanced endoscopists with expertise in endoscopic ultrasound–guided vascular investigation and therapy.**

Keywords: EUS-Guided; Injection Therapies; Gastric Variceal Coiling; Portal Pressure Gradient Measurement; Ectopic Varices; Rectal Varices; Splenic Artery Embolization; Arterial Bleeding; Pseudoaneurysms; Portal Vein Sampling; Intrahepatic Portosystemic Shunt.

The first endoscopic ultrasound (EUS)–guided vascular intervention was reported in 2000 and evaluated the utility of EUS for sclerotherapy of esophageal varices.[1] Currently, the most widely utilized EUS-guided vascular interventions include gastric variceal therapy and portosystemic pressure gradient (PPG) measurements. Emerging interventions include treatment of ectopic and rectal varices, splenic artery embolization, therapy of arterial bleeding including pseudoaneurysms, and portal venous sampling. Additional experimental EUS-guided vascular interventions include portosystemic shunt creation.

This review of EUS-guided vascular investigation and therapy aims to critically evaluate the evidence for these interventions, examine opportunities for future research, and identify clinical scenarios that may be considered for EUS-directed therapy. This article is not a formal systematic review, but rather is based on a literature review to provide practical advice. No formal rating of the quality of evidence or strength of recommendation was performed.

Clinically Available EUS-Guided Interventions

EUS-Guided Injection Therapies of Gastric Varices

Although less prevalent than esophageal varices, gastric variceal hemorrhage is often more severe and associated with higher mortality.[2] In particular, endoscopic treatment of bleeding cardiofundal varices (isolated gastric varices type 1 and gastroesophageal varices type 2) tends to be very challenging due to their larger size and location.[3] Direct endoscopic injection (DEI) of these varices with cyanoacrylate glue is the most widely utilized modality for immediate hemostasis, but treatment requires a clear field of view during endoscope retroflexion, and intravascular needle placement may be inaccurate.

Gastric variceal injection therapy under EUS guidance confers potential advantages over conventional endoscopic visualization. EUS enhances the precision of injection (ie, during acute bleeding when direct visualization is impaired) and expands available treatment options (ie, hemostatic coils). Additionally, EUS uses Doppler interrogation to provide real-time feedback of hemostasis. Based on initial experience with DEI, the original choice of injectate for EUS guidance was cyanoacrylate glue. At least 1 retrospective comparative study has shown EUS-guided cyanoacrylate injection to be superior to DEI.[4] To improve hemostasis and decrease

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2023.03.027

adverse events, hemostatic coils designed for use by interventional radiology (IR) were subsequently used in conjunction with EUS-guided cyanoacrylate injection. These coils (Supplementary Figure 1) are constructed from soft platinum wires with spaced synthetic fibers, and placement within the vessel is postulated to initiate thrombus formation. The most published current technique is injection of 1–3 coils (usually Nester or MReye embolization coils; Cook Medical, Bloomington, IN) within the gastric varices to provide a scaffold onto which an adjunct, such as cyanoacrylate, can be subsequently injected to potentially minimize postprocedure embolic events.

Figure 1 and Supplementary Video 1 demonstrate the technique for EUS-guided gastric variceal therapy. Prior to treatment, the patient is intubated and placed in the left lateral decubitus position. About 100–200 cm^3 of water is instilled through the echoendoscope and retained in the gastric fundus to enhance the delineation of intramural vessels (ie, gastric varices) from

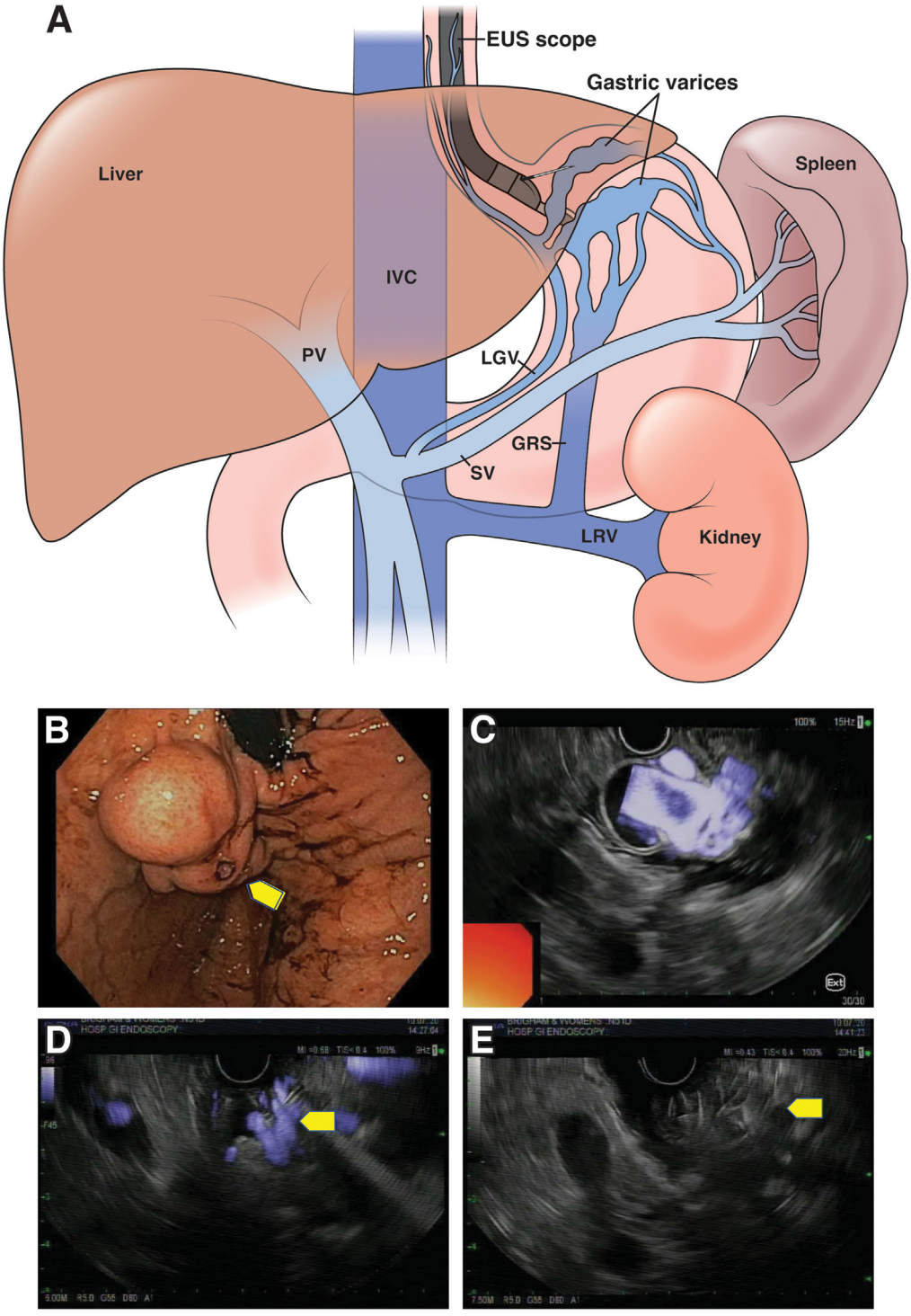

Figure 1. EUS-guided coil injection of gastric varices. (*A*) Cartoon of EUS-guided injection of gastric varices. (*B*) Endoscopic view of a large cardiofundal gastric varix with stigmata (arrow). (*C*) EUS view of a gastric varix with baseline Doppler flow assessment. (*D*) EUS appearance of intravariceal needle delivery of coil with diminution of Doppler flow (arrow). (*E*) Final EUS appearance of intravariceal coil (arrow). GRS, gastro-renal shunt; IVC, inferior vena cava; LGV, left gastric vein; LRV, left renal vein; PV, portal vein; SV, splenic vein.

extramural collaterals and perforator vein(s), the latter identified by tracing the extramural vessels across the muscularis propria into the intramural varix. A 22-gauge or 19-gauge fine needle aspiration needle is used to access the gastric varix using a transesophageal or transgastric approach. When utilized, 1 or more coils are sequentially placed into the targeted vessel. Of note, there are no definitive data regarding whether the varix itself or the perforator vein(s) should be targeted. Doppler interrogation during coil placement can be used to guide the number of coils required. Fluoroscopy with or without varicealography can be helpful, particularly early in the learning curve, but is not required. When there is a significant reduction or near-absent Doppler flow, an adjunctive agent such as cyanoacrylate can be injected. The multiple steps involved in this technique require adequate training of nurses and technicians. Repeat treatment of other varices can be performed as required.

There is growing evidence to support EUS-based gastric variceal therapies over DEI for improved control of acute bleeding, durability of hemostasis, and lower complication rates. For EUS-based therapies, 3 retrospective series[5–7] and 2 small randomized controlled trials[8,9] have shown very high (~99%) rates of technical success and control of bleeding and low rates of rebleeding (0%–16%) and adverse events (0%–7%). One recent meta-analysis suggested that any EUS-guided therapy was superior to DEI, with similar treatment efficacy of 94% vs 91%, respectively, but gastric variceal obliteration of 84% vs 63%, respectively ($P = .02$). Additionally, in subgroup analyses, EUS-guided combination therapy with coils and glue had significantly fewer recurrences (5%) than treatment with glue or coils alone. Another recent meta-analysis also showed EUS-guided combination therapy (coil + glue) to be the preferred strategy, due to hemostasis of 96%–98% and adverse event rates of 10% compared with EUS-guided monotherapy with glue alone (96% and 21%, respectively) and coils alone (90% and 3%, respectively).[10,11] Other adjuncts like absorbable gelatin sponge (GELFOAM; Pfizer, New York, NY) in lieu of cyanoacrylate have also shown encouraging results with similar low rebleeding rates and reintervention rates when used in conjunction with coils.[12,13] EUS-guided thrombin injection for gastric varices has also been reported in a small series.[14] Supplementary Table 1 summarizes the literature for EUS-based gastric variceal therapy.

As use of EUS-guided injection therapy of gastric varices increases, certain issues merit investigation and clarification. First, the treatment technique is heterogeneous, including the choice of targeted vessel (intramural varix or perforator vein), the size and number of coils, and the type of injectate used. The development of a consensus technique would be helpful. Second, larger multicenter studies are required to confirm the technical success, safety, and durability of hemostasis and generalizability across centers that offer this modality. Third, additional randomized controlled trials comparing EUS vs other therapies (in particular, IR endovascular therapies such as balloon-assisted retrograde transvenous obliteration and transjugular intrahepatic portosystemic shunt) would help delineate the role of EUS-guided gastric variceal therapies relative to other treatment options. Importantly, these treatment decisions should continue to be made in a multidisciplinary setting with hepatology and IR, to identify optimal cases for IR or endoscopic therapy. Fourth, should EUS-based therapy be offered for primary prophylaxis or only for acute bleeding and secondary prophylaxis? Finally, there are questions about how endosonographers should be trained in EUS injection therapy of gastric varices, which of note is not currently Food and Drug Administration approved, and whether this might include formal didactic and hands-on training sessions or even a mentorship program, given the infrequency of bleeding gastric varices outside of large referral centers.

EUS-Guided PPG Measurement

Portal hypertension develops with liver disease and can result most commonly in variceal bleeding, ascites, and encephalopathy. The hepatic venous pressure gradient (HVPG), performed by interventional radiologists, indirectly measures the portal pressure gradient and is defined as the difference between the free hepatic vein pressure and wedged hepatic vein pressure. An HVPG >10 mm Hg is correlated with the development of esophageal varices, whereas an HVPG >12 mm Hg is associated with an increased risk of bleeding esophageal varices. Measurement of wedged hepatic vein pressure has several drawbacks, which include (1) the required use of radiation and contrast and (2) its indirect nature, which can lead to a misdiagnosis of noncirrhotic/presinusoidal portal hypertension.[15–17] EUS-guided PPG (EUS-PPG) is a novel technique that allows measurement of the direct hepatic vein portal pressure gradient and is performed with the Food and Drug Administration–approved EchoTip Insight system (Cook Medical, Winston-Salem, NC).

EUS-PPG is performed with the patient supine, preferably under general anesthesia, to minimize movement. One dose of prophylactic antibiotics (eg, ciprofloxacin or cefazolin) is usually administered. The compact manometer is first leveled at the midaxillary line/level of the right heart and kept at this level for the remainder of the procedure. Using a linear echoendoscope, the hepatic veins are identified anatomically and confirmed by Doppler (Supplementary Video 2). The middle or left hepatic vein is targeted with a 25-gauge needle via a transgastric approach (Figure 2*A*). A minimum of 3 consecutive pressure measurements (using a one-needle-stick approach) are taken, and the average measurement is calculated. The intrahepatic portal vein is then identified and confirmed by Doppler (Figure 2*B*), after which pressure measurements are repeated as described previously. The EUS-PPG is then calculated by

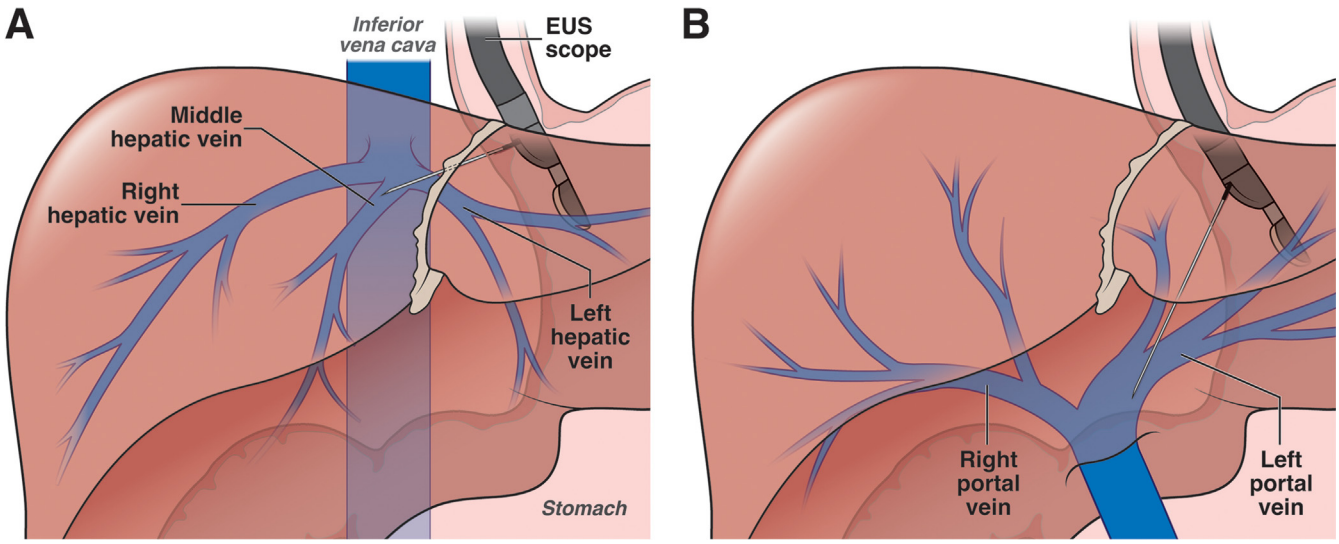

Figure 2. EUS-PPG measurement. (*A*) Transgastric pressure measurement of middle hepatic vein. (*B*) Transgastric pressure measurement of left portal vein.

subtracting the mean hepatic pressure from the mean portal pressure.

There have been several prior studies demonstrating the safety and efficacy of EUS-PPG. In 2014, EUS-PPG was performed successfully on the first human patient.[18] A subsequent case series by Huang et al[19] demonstrated an excellent correlation between HVPG measurements obtained by EUS-PPG and the endoscopic findings of portal hypertension in 28 patients with suspected cirrhosis. Additionally, in a single-center retrospective study of 64 patients with chronic liver disease who underwent EUS-PPG and liver biopsy, there was an excellent correlation between EUS-PPG measurements and histologic hepatic fibrosis stage, clinical portal hypertension, thrombocytopenia, splenomegaly, aspartate aminotransferase-to-platelet ratio index score >2, and Fibrosis-4 score >3.25.[20] There were no reported adverse events. The same group published a series of 83 patients and noted that EUS-PPG correlated well with clinical markers of portal hypertension, such as thrombocytopenia and varices.[21] Again, no adverse events were reported.

Performing EUS-PPG also improves clinical efficiency, given the concurrent ability to perform esophagogastroduodenoscopy and EUS as a one-stop shop during which PPG, liver biopsy, and endoscopic features of portal hypertension (esophageal varices, portal hypertensive gastropathy) can all be evaluated, obtained, and potentially treated during a single procedure.[22] EUS-PPG may be indicated or clinically helpful when evaluating patients with discordant data regarding the presence or absence of portal hypertension (eg, isolated thrombocytopenia, isolated splenomegaly, normal HVPG but possible presinusoidal portal hypertension); supplementing preoperative clearance (including pretransplant workup) to a patient with known or suspected cirrhosis; or monitoring response to medications or other intervention.

While the procedure is feasible and safe, further investigation is warranted to determine if the values of portal hypertension (HVPG >5 mm Hg) and clinically significant portal hypertension (HVPG ≥10 mm Hg) might differ when acquired using an EUS or standard percutaneous endovascular approach. The type of sedation used during the procedure (general anesthesia as opposed to conscious sedation traditionally used for transjugular HVPG measurements) might also affect the absolute measurements of the hepatic vein pressure and portal vein pressure. Last, head-to-head trials comparing the safety and utility of EUS-PPG vs HPVG is warranted.

Emerging EUS-Guided Interventions

EUS-Guided Injection of Ectopic or Rectal Varices

Rectal varices may occur secondary to portal hypertension, mesenteric venous thrombosis, vascular anomalies, or other conditions. Reports of successful use of EUS to target rectal submucosal or penetrating vessels with sclerosants, coils, or cyanoacrylate are limited to single case reports.[23,24] EUS-guided treatment of ectopic varices has also been described (Supplemental Video 3). Fujii-Lau[7] described glue injection with or without coils for treating duodenal (n = 3) or choledochal (n = 5) varices. Larger series describing EUS-guided interventions for these sites are needed.

EUS-Guided Splenic Artery Embolization

In cirrhotic patients with hypersplenism and variceal bleeding, partial splenic embolization by interventional radiologists reduces splenic volume and hepatopetal splenic vein blood flow and therefore lowers portal pressure. Zhang et al[25] recently reported using various combinations of endoscopic variceal ligation and EUS-guided injection of cyanoacrylate and/or coils to treat

portal hypertension, hypersplenism, and recent variceal bleeding in 5 patients. All patients had fever and abdominal pain after treatment, but no splenic abscesses were encountered. Postprocedure computed tomography portal venography and imaging showed a reduction in vein diameter, improvement in cytopenias, and a mean splenic embolization rate of 65%. Future multidisciplinary research is required to determine what vascular anatomy, indications, and choice of an endoscopic or radiologic approach should be utilized for partial splenic embolization in these patients.

EUS-Guided Therapy of Arterial Bleeding, Including Pseudoaneurysms

Arterial aneurysms are collections of blood within a true, dilated, or bulging vascular lumen. Pseudoaneurysms, however, result from inflammation, infection, or other cause and may present incidentally on cross-sectional imaging or with minimal symptoms or life-threatening bleeding. Treatment of upper abdominal aneurysms or pseudoaneurysms is usually radiologic, yet visceral arteries may be inaccessible due to difficult localization or vessel tortuosity. Rai et al[26] described EUS-guided injection of coils and glue in 6 patients with splenic artery pseudoaneurysms (maximal diameter size range 2.5–6.5 cm) after failed radiologic embolization. Technical success (coil and glue injected) was achieved in all patients without adverse events, and occlusion of all 6 collections was present at 3-month follow-up.[26] Similarly, Maharshi et al[27] reported EUS-guided injection of thrombin in 8 patients with symptomatic aneurysms (maximal diameter size range 1.9–5.0 cm) of the splenic artery (n = 5), left hepatic artery (n = 2), and gastroduodenal artery (n = 1) who were unable to undergo embolization. Technical success was 100%, and 2 (25%) patients experienced postprocedure abdominal pain requiring intravenous analgesia. At repeat EUS at 12 weeks following injection, lumen obliteration was seen in 7 (88%) of 8 and recurrence was noted in 1 (12%) of 8.[27] These case series highlight the utility of salvage EUS-guided treatment of visceral artery aneurysms or pseudoaneurysms. Further multicenter center studies investigating rescue therapy or use as primary or initial treatment for aneurysms are indicated.

EUS-Guided Portal Vein Sampling

The portal circulation includes the venous drainage from the entire gastrointestinal system and represents approximately 70% of vascular input to the liver. In theory, portal blood may be "enriched" with metabolites, gastrointestinal tumor cells, and xenobiotic substances not readily detectable in peripheral venous blood due to hepatic processing and filtration. In small clinical series, EUS-guided portal venous sampling has been shown to be safe and feasible.[28] In a single-center cohort study of 18 patients with suspected pancreaticobiliary cancers, 100% of portal samples contained circulating tumor cells compared with <25% of peripheral blood samples, highlighting the potential for portal liquid biopsy to study the pathogenesis of metastases.[29]

Experimental EUS-Guided Interventions

EUS-Guided Intrahepatic Portosystemic Shunt

IR typically performs decompression of a hypertensive portal system as a transjugular intrahepatic portosystemic shunt. During this procedure, an endovascular stent is placed to bridge the hepatic and portal vein. However, preclinical (porcine) studies have successfully demonstrated that a similar self-expanding metal stent can be deployed via EUS to function as a portosystemic shunt.[30,31] Future development of this concept for patient care would require creating a dedicated endovascular stent compatible with EUS delivery and identifying clinical scenarios in which an EUS approach proves advantageous over an IR approach.

Conclusions

There are 2 prerequisites to demonstrate the clinical utility of EUS-guided vascular interventions. The first is a vascular target in or near the gastrointestinal wall, which may confer an advantage to an endoscopic rather than percutaneous access. The second is demonstrating a clinical efficacy and safety profile comparable, if not superior, to current alternatives.

While satisfying the first prerequisite, the EUS-guided vascular interventions described herein are in varying states of addressing the second prerequisite. At this time, EUS-guided coil injection therapy of gastric varices arguably makes the strongest case for inclusion at centers of expertise. The overall supporting data are restricted to uncontrolled series and small comparative studies. However, available data show that EUS-guided gastric variceal therapy is safe, with excellent acute hemostasis and low rebleeding rates, and likely superiority over traditional direct endoscopic glue injection. Larger comparative studies are required to delineate its place in the treatment algorithm, particularly relative to IR endovascular therapies. Concerning EUS-PPG measurements, the strongest argument for inclusion is likely when there is another indication for endoscopy, such as variceal screening or liver biopsy. Other EUS-guided interventions, such as treatment of rectal and ectopic varices, splenic artery embolization, and treatment of arterial bleeding, have been reported in small case series and require further supporting studies. EUS-guided portal sampling appears safe but should be

performed as part of a research protocol. As these procedures mature, endosonographers should be trained in interventional EUS and operate as part of a multidisciplinary team.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.03.027.

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Correspondence
Address correspondence to: Marvin Ryou, MD, Director of Endoscopic Innovations, 75 Francis St, Boston, MA 02115. e-mail: mryou@bwh.harvard.edu.

Author Contributions
All authors were involved in conceptualization, writing of the original draft, critical review, and revisions leading to the final manuscript

Conflicts of Interest
These authors disclose the following: Marvin Ryou has served as a consultant for Cook Medical, Boston Scientific, Olympus, Fuji, GI Windows, and EnteraSense; and has received research support from Olympus, Cook Medical, and Boston Scientific. John DeWitt has served as a consultant for Ariel Diagnostics and Boston Scientific; and has received grant support from Vyaire Medical; Vanessa Shami has served as a consultant for Cook Medical, Boston Scientific, and Olympus; and received research support from Cook Medical. Koushik Das discloses no conflicts.

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Supplementary Figure 1. Hemostatic coils.

Supplementary Table 1. Published Studies Reporting the Efficacy of EUS-Guided Injection Therapies for the Treatment of Acute Gastric Variceal Bleeding

	Study Type	N	Injectate	Mean Number of Sessions	Technical Success	Clinical Success	Rate of Adverse Events	Rate of Rebleeding	All-Cause Mortality
EUS CYA alone									
Lee (2000)[e1]	Prospective	54	CYA, repeated injection	2.2 ± 1.7	52/54 (96.3)	43/54 (79.6)	22/54 (40.7)	19/54 (35.2)	28/54 (51.9)
Lee (2000)[e1]	Prospective	47	CYA, on-demand injection	1.3 ± 0.5	45/47 (95.7)	—	9/47 (19.1)	33/47 (70.2)	35/47 (74.5)
Romero-Castro (2013)[e2]	Retrospective	19	CYA	1.5	17/19 (89.5)	19/19 (100)	11/19 (57.9)	—	—
Gubler (2014)[e3]	Retrospective	40	CYA	—	40/40 (100)	36/36 (100)	2/40 (5)	6/40 (15)	6/40 (15)
Bick (2019)[4]	Retrospective	64	CYA	1.2	—	62/64 (96.9)	13/64 (20.3)	5/56 (5.9)	—
EUS CYA + coil									
Binmoeller (2011)[6]	Retrospective	30	Coil + CYA	1	30/30 (100)	29/30 (100)	0/30 (0)	4/24 (16.6)	1/30 (3.3)
Robles-Medranda (2020)[8]	RCT	30	Coil + CYA	1	30/30 (100)	30/30 (100)	2/30 (6.6)	2/30 (6.6)	—
Fujii-Lau (2016)[7]	Retrospective	3	Coil + CYA	1	3/3 (100)	3/3 (100)	0/3 (0)	0/3 (0)	—
Lobo (2017)[9]	RCT	29	Coil + CYA	—	16/16 (100)	—	4/16 (25)[a]	—	—
Bhat (2016)[5]	Retrospective	152	Coil + CYA	—	151/152 (99.3)	—	9/125 (7.2)	20/125 (16)	—
EUS coil alone or non-CYA									
Romero-Castro (2013)[e2]	Retrospective	11	Coil	1.3	10/11 (90.9)	10/11 (90.9)	1/11 (9.1)	—	—
Robles-Medranda (2020)[8]	RCT	29	Coil	—	29/29 (100)	26/29 (89.7)	1/29 (3.4)	5/29 (17.2)	—
Fujii-Lau (2016)[7]	Retrospective	3	Coil	1	3/3 (100)	3/3 (100)	0/3 (0)	1/3 (33)	—
Bazarbashi (2020)[12,13]	Retrospective	10	Coil + GELFOAM	1	10/10 (100)	10/10 (!00)	0/10 (0)	0/10 (0)	1/10 (10)
Frost (2018)[14]	Retrospective	8	Thrombin	1	8/8 (100)	6/8 (75)	0/8 (0)	1/3 (33)	—

Values are mean ± SD or n/n (%), unless otherwise indicated.
CYA = cyanoacrylate; EUS, endoscopic ultrasound; RCT, randomized controlled trial;
[a]All had asymptomatic pulmonary embolism on per-protocol computed tomography.