Rare causes of acute non-variceal upper gastrointestinal bleeding: A comprehensive review

Martino A et al. Rare causes of acute NVUGIB
Abstract
Non-variceal upper gastrointestinal bleeding (NVUGIB) is a common gastroenterological emergency associated with significant morbidity and mortality. Gastroenterologists and other involved clinicians are generally assisted by international guidelines in its management. However, NVUGIB due to peptic ulcer disease only is mainly addressed by current guidelines, with upper GI endoscopy being recommended as the gold standard modality for both diagnosis and treatment. Conversely, the management of rare and extraordinary rare causes of NVUGIB is not covered by current guidelines. Given they are frequently life-threatening conditions, all the involved clinicians, that is emergency physicians, diagnostic and interventional radiologists, surgeons, in addition obviously to gastroenterologists, should be aware of and familiar with their management, but also all the involved clinicians, including the emergency physicians, the diagnostic and the interventional radiologists, and the surgeons. Indeed, they typically require a prompt diagnosis and treatment, engaging a dedicated, patient-tailored, multidisciplinary team approach. The aim of our review was to extensively summarize the current evidence with regard to the management of rare and extraordinary rare causes of NVUGIB.

Key Words: Gastrointestinal bleeding; Upper gastrointestinal bleeding; Non-variceal upper gastrointestinal bleeding; Rare causes; Vascular causes; Upper endoscopy


Core Tip: Rare and extraordinary rare causes of non-variceal upper gastrointestinal bleeding (NVUGIB) are commonly life-threatening conditions. Thus, a prompt diagnosis and a subsequent equally early treatment are required, typically involving a patient-tailored, multidisciplinary team approach. However, given the rare occurrence,
their management is not covered by NVUGIB current guidelines. Our study aimed to review the current evidence with regard to the management of rare and extraordinary rare causes of NVUGIB.

**INTRODUCTION**

Acute upper gastrointestinal bleeding (UGIB) is a common medical emergency with an annual incidence of approximately 50/100000-150/100000 adults\[1-3\]. It is defined as hemorrhage originating above the ligament of Treitz, in the esophagus, stomach, or duodenum. According to its etiology and reflecting differences in its management, UGIB tends to be subclassified to variceal and non-variceal UGIB (NVUGIB). Peptic ulcer disease (PUD) is the most common cause for UGIB and accounts for approximately 35%-50% of cases, followed by erosive disease, esophagitis and Mallory-Weiss tear. Varices are another common source of UGIB, representing approximately 10% of all UGIB hospitalizations. Less common causes of UGIB include neoplasm, angiodysplasia, gastric antral vascular ectasia and portal hypertensive gastropathy. Finally, up to 5% of all UGIB cases are caused by rare and extraordinary rare sources\[1-3\].

Despite marked advances in its diagnosis and treatment, UGIB is still associated with high morbidity and mortality. Indeed, the overall mortality rate is approximately 8%-10% in *de novo* UGIB hospitalizations\[5-6\], increasing up to 40% in high-risk patients\[7\]. In accordance to current international guidelines, esophagogastroduodenoscopy (EGD) is recommended as the procedure of choice for both diagnosis and treatment of NVUGIB, with transcatheter angiographic embolization (TAE) or surgery only in case of refractory bleeding\[8-12\]. However, merely NVUGIB due to PUD is largely addressed by current guidelines. Conversely, rare and extraordinary rare NVUGIB causes very often require a dedicated, multidisciplinary approach, in order to provide prompt diagnosis and effective treatment\[13-16\]. The aim of our review was to summarize and discuss the current evidence with regard to most relevant rare and extraordinary causes of NVUGIB, in order to enrich the gastroenterologists and all involved physicians’
knowledge of the etiology of NVUGB and to broaden their judgment in its management.

**RARE CAUSES OF NVUGIB**

*Aorto-enteric fistula*

First described by Cooper[17], aorto-enteric fistulas (AEF) are rare though life-threatening pathological communications between the aorta and the wall of an adjacent segment of the GI tract. Pathogenesis is still not fully understood, most likely encompassing a combination of infection, aortic and GI wall degeneration, and chronic mechanical pulsatile trauma, finally resulting in erosion and fistula creation[18]. AEF are traditionally classified as either primary (PAEF) or secondary (SAEF). PAEF arise from the native aorta, in the setting most commonly of aortic aneurysm or less frequently of infection, malignancy, foreign bodies, radiation, trauma or inflammation[19]. Conversely, SAEF generally develop as late complication of either surgical or endovascular aortic reconstruction[20]. SAEF are much more common than PAEF, with a reported incidence of 0.3%-1.6% in patients after aortic reconstruction[21] and 0.02%-0.07% among general population[22], respectively. Reported mortality is still extremely high, even with prompt diagnosis and treatment[20].

The most frequent involved site is the duodenum (62%), followed by the jejunum and ileum (12%), and the colon (5%). Aorto-esophageal and aorto-gastric fistula are only rarely encountered[18,20]. The classic triad of NVUGIB, abdominal pain, and pulsatile abdominal mass was initially described by Cooper[17]. However, it is currently believed that the combination of all 3 facets of the triad tends to occur infrequently[19]. The most common clinical presentation of AEF is NVUGIB, with or without sepsis[18]. AEF patients often present with a “sentinel or herald bleed”, in which self-limited episodes of bleeding are followed by the recurrence of massive exsanguinous hemorrhage hours or even to days later[23].

Multidetector computed tomography angiography (MDCTA) is the diagnostic modality of choice for AEF[18,24,25]. It has a relatively high sensitivity and specificity for
the diagnosis of AEF, approximately of 94% and 85% respectively\textsuperscript{25}. Although pathognomonic of AEF, active contrast medium extravasation from the aorta into the GI lumen is an exceptional MDCTA feature usually seen with ongoing exsanguination. MDCTA findings of AEF include para-aortic or intra-aortic foci of gas, loss of the fat plane between the aorta and the GI wall, and disruption of aortic wall or pseudoaneurysm. Moreover, MDCTA signs of SAEF encounter perigraft gas persisting more than 4 wk following repair of ruptured abdominal aortic aneurysm (AAA) and perigraft fluid and edema persisting more than 3 mo after elective AAA repair\textsuperscript{24-26}. Although EGD is the first line diagnostic modality in acute NVUGIB, its usefulness in the setting of AEF is limited. AEF may occasionally be suspected by means of EGD, with endoscopic findings suggestive of AEF including visible graft, bleeding, adherent clot, GI wall defect, ulcer/erosion or pulsatile mass\textsuperscript{27-29}. However, the experience of the GI endoscopist, a high index of suspicion and the careful exploration of the distal duodenum, are key factors to properly endoscopically identify AEF. Furthermore, given EGD may disturb the clot which had been preventing exsanguinous bleeding from the AEF, it should be performed in the operating theater and its adoption limited to hemodynamically stable patients, with other imaging suggestive of an occult AEF\textsuperscript{30}. Among patients admitted with massive NVUGIB and with an history and a clinical presentation suggestive for AEF, emergent MDCTA should be performed as the first-line diagnostic modality.

Treatment of AEF includes either an open surgical or an endovascular approach\textsuperscript{30}. Surgery aims to maintain perfusion while extirpating the infection and restoring GI patency. Strategies to maintain perfusion are grouped into in situ aortic reconstruction and extra-anatomic bypass with aortic ligation\textsuperscript{18}. Conversely, the most commonly used endovascular technique is stent-graft repair\textsuperscript{18,25}. Being associated with lower perioperative mortality rate as compared with open surgery, it is frequently adopted as the first-line treatment modality for AEF\textsuperscript{20}. Moreover, endovascular balloon occlusion may be used to gain rapid control of the aortic bleeding source in hemodynamically unstable patients. Similarly, coil and plug embolization might be used as a temporizing
measure to stop bleeding\textsuperscript{[18,25]}. Of note, surgical and endovascular management of AEF could be integrated in a complementary approach, by the adoption of endovascular treatment as a bridge to open repair\textsuperscript{[31]}. Finally, endoscopic treatment mainly as a part of multidisciplinary approach or as a bridge to definitive therapy has been anecdotally reported. The adopted endoscopic techniques mostly included clips, fully covered self-expanding metal stents, plastic stents and injection therapy\textsuperscript{[32-35]}. However, evidence regarding the role of endoscopic treatment is scarce and it may not be currently recommended. Worth pointing out, especially in the absence of active bleeding (\textit{i.e.}, adherent blood clot), the authors discourage any attempt of endoscopic hemostasis for AEF. Given the recent advent of endoscopic devices capable to realize full-thickness GI defect closure, such as endoscopic suturing systems and over-the-scope clips (OTSC), in the next future endoscopy might probably play a crucial role for the mini-invasive closure of the GI defect after endovascular aortic repair\textsuperscript{[36]}. A case of AEF is shown in Figure 1.

\textbf{Ruptured visceral artery aneurysms}

First reported in 1809 by Wilson\textsuperscript{[37]}, ruptured visceral artery aneurysms (VAA) are a rare but potentially lethal cause of acute NVUGIB. Histopathologically, VAA are broadly divided into true aneurysms (TVAA) and pseudoaneurysms (VAPA). TVAA are defined as focal arterial dilatations greater than 1.5 times the diameter of the original vessel involving all 3 layers of the arterial wall, whereas VAPA, also termed false aneurysms, result from a tear in the vessel wall with extravasated blood contained by only 1 or 2 arterial wall layers\textsuperscript{[38,39]}. The main cause of TVAA is atherosclerosis, followed by fibromuscular dysplasia, connective tissue diseases, inflammatory conditions, and other rare inherited illnesses. Conversely, VAPA may be secondary to trauma, inflammatory conditions such as pancreatitis, cholecystitis, and ulcer, infection, or iatrogenic injury, including surgical, endoscopic and interventional radiological procedures. To be noted, the leading cause of VAPA is chronic pancreatitis (CP).
Indeed, more than half of VAPA are secondary to pancreatitis and pseudocyst formation, with up to 17% of CP patients developing VAPA\textsuperscript{[38,39]}. Their reported incidence is approximately 0.1%-2\%\textsuperscript{[38-40]}. However, because of the widespread use of advanced imaging techniques and increased aging population, VAA are being incidentally diagnosed with increased frequency\textsuperscript{[41]}. Depending on size, location, and associated clinical conditions (i.e., pregnancy), VAA rupture may be associated with a 20%-80% mortality rate\textsuperscript{[42]}. The splenic artery (SA) is the most common site of VAA, followed by the hepatic artery (HA), accounting for nearly 60% and 20%, of cases, respectively. Less common sites include in decreasing order of frequency superior mesenteric (SMA) and coeliac arteries (CA). The gastric or gastroepiploic, jejunal-ileal-colic, pancreaticoduodenal (PDA), gastroduodenal (GDA), and inferior mesenteric arteries are rarely involved\textsuperscript{[39,42]}. The natural history of VAA and their potential for rupture or other complications are relatively poorly defined because of their overall scarcity. However, depending on location, size, etiology, subtype, and associated clinical conditions (i.e., pregnancy), the reported risk of rupture ranges widely from 2% to up to 80\%\textsuperscript{[42]}. Furthermore, pseudoaneurysms, CA, SMA, gastric and gastroepiploic, GDA, PDA and colic aneurysms are associated with a significantly higher risk of rupture regardless of size, requiring prompt treatment upon diagnosis\textsuperscript{[41,44]}. Rupture of VAA occurs more frequently within the GI tract, manifesting with life-threatening NVUGIB, or into the peritoneal cavity. Rupture may less commonly occur into the retroperitoneal space. Finally, rupture within the hepatobiliary tract or the pancreatic duct may be rarely observed, causing hemobilia or hemosuccus pancreaticus (HP), respectively\textsuperscript{[39,43]}. MDCTA is currently regarded as the diagnostic tool of choice, providing accurate vascular anatomy characterization and interventional planning. Indeed, it is frequently regarded as the “new” gold-standard, alongside with angiography\textsuperscript{[39]}. Rupture is seen as an extravasation of contrast medium which is not contained within a round structure and often flows away from the point of injury. On delayed images, there will be
washout of the aneurysm, whereas extravasation will persist\textsuperscript{[30]}. Given the common presentation with NVUGIB, patients with ruptured VAA may undergo EGD if hemodynamically stable. However, the role of EGD in this setting is limited, mainly directed to exclude more common sources of NVUGIB. GI rupture of VAA may occasionally be suspected by means of EGD, with unspecific reported endoscopic findings mainly encountering gastric or duodenal ulcer/erosion with or without adherent clot, submucosal bulging mass and visible vessel\textsuperscript{[45,46]}. However, a highly experienced GI endoscopist along with a high index of suspicion are necessary to suspect GI rupture of VAA. Furthermore, a detailed medical history focusing on well known risk factors for VAA development and rupture, including pancreatitis and its local complications, atherosclerosis, and recent traumatic or iatrogenic injury, such as percutaneous or endoscopic ultrasound (EUS)-guided procedures, is crucial in the diagnostic process of ruptured VAA within the GI tract.

Being associated with lower perioperative morbidity and mortality than open surgery, emergent endovascular treatment, most commonly by means of coil embolization, is currently recommended as the first-line interventional modality for ruptured VAA. Conversely, open surgery is nowadays generally reserved in case of anatomically unfeasible or failed EVT\textsuperscript{[43,44]}. To date, endoscopy plays no role in the treatment of ruptured VAA. Endoscopic cyanoacrylate or epinephrine injection has been anecdotally reported\textsuperscript{[45,46]}. However, we do not recommend endoscopic hemostasis attempt when GI VAA rupture is suspected or diagnosed, especially in the absence of active bleeding during endoscopic examination. Finally, EUS-guided embolization by the use of thrombin or glue injection, alone or in combination with coil deployment, has been successfully reported for the treatment of VAPA\textsuperscript{[47-49]}. Although evidence is currently lacking, with growing experience, EUS-guided obliteration could represent a minimally-invasive and fashionable alternative to an endovascular approach for the treatment of selected ruptured VAPA among referral centers\textsuperscript{[50]}. A case of rupture of VAA into the GI tract is shown in Figure 2.
**Gastric submucosal arterial collaterals**

First reported by Spriggs\textsuperscript{[51]} in 1984, bleeding gastric submucosal arterial collaterals (GSAC) are an extraordinary rare cause of severe NVUGIB, with only few cases reported up to date, including a fatal one\textsuperscript{[52]}. They result from either occlusion or congenital absence of the SA, being not related to portal hypertension. SA occlusion may be congenital, idiopathic, or secondary to various conditions, including surgery, endovascular intervention, trauma and extrinsic compression. In the case of SA occlusion, in order to provide splenic blood supply, extensive collaterals may arise from adjacent proximal patent arteries, such as the pancreatic, left gastric, gastroepiploic, and short gastric arteries, and pass through the gastric wall\textsuperscript{[53]}. GSAC may be clinically asymptomatic or may less frequently present with severe NVUGIB from erosion of GSAC.

Since GSAC appear endoscopically as varicose shaped and tortuous submucosal vessels located at the gastric fundus\textsuperscript{[52]}, the differential diagnosis mainly includes type 1 isolated gastric varices (IGV)\textsuperscript{[54]}. Indeed, GSAC have a very similar endoscopic appearance to IGV, being frequently misinterpreted on EGD\textsuperscript{[52]}. However, they are, as opposed to GSAC, secondary to cirrhotic portal hypertension or left-sided portal hypertension\textsuperscript{[5-4]}. Therefore, given their different management, an accurate differential diagnosis between these two entities is crucial. Indeed, endoscopic cyanoacrylate glue injection (ECGI), currently recommended as the first-line therapeutic option for bleeding IGV\textsuperscript{[55]}, may be complicated by systemic embolization and life-threatening adverse events when applied to an arterial source\textsuperscript{[56,57]}. Conversely, being potentially associated with severe adverse events, endoscopic mechanical hemostasis is currently not recommended for the treatment of IGV\textsuperscript{[55]}.

Proper diagnosis is only made by MDCTA and/or digital subtraction angiography (DSA)\textsuperscript{[52]}. Thus, in case of endoscopic evidence of fundal varicose shaped submucosal vessels among UGIB patients without portal hypertension history or clinico-laboratory signs, emergent MDCTA should be performed prior to any endoscopic treatment attempt, if feasible (i.e., absence of active bleeding at the time of EGD).
Definitive treatment is mainly represented by surgical splenectomy and arterial ligation with or without gastrectomy. However, effective treatment by means of endovascular embolization has also been reported. As mentioned before, endoscopic mechanical hemostasis rather than ECGI may be used for the bleeding control among experienced centers, if needed, mainly in a step-up approach[52]. A case of bleeding GSAC is shown in Figure 3.

Dieulafoy’s lesions

Dieulafoy’s lesion (DL) is a rare cause of acute NVUGIB, accounting for approximately 1.5% of cases, with a tendency to cause severe, life-threatening, recurrent GI bleeding[58,59]. It was originally reported by Gallard[60] in 1884 and subsequently referred to as “exulceratio simplex” in 1898 by the French surgeon Dieulafoy[61], who believed it was the first stage of a gastric ulcer. DL is a vascular abnormality, consisting of a pathologically dilated submucosal caliber-persistent artery, that typically protrudes through a small 2-5 mm mucosal defect and erodes into the GI lumen, in the absence of any abnormality such as ulcers, erosions or aneurysms[58,59]. Similarly to primary AEF, DL bleeding is thought to occur as a result of the mucosal surface disruption due to the persistent mechanical pressure perpetrated by the underlying submucosal ectatic artery[58,59].

The mortality has markedly declined from up to 80% during the pre-endoscopy era to 9%-13% currently with advances in endoscopic hemostasis[58,59]. The most common DL site is by far the stomach, typically the proximal lesser curvature within 6 cm from the gastroesophageal junction[58]. This predilection may be related to the local blood supply. Indeed, the gastric lesser curve is not irrigated by a submucosal plexus, receiving its arterial blood supply directly from the branches of the left and right gastric arteries[62]. Other less common locations include in decreasing order of frequency the duodenum, the colon, surgical anastomoses, the small bowel, and the esophagus[58].

Given the arterial nature of the bleeding, typical clinical presentation of DL include severe painless NVUGIB, most commonly manifesting with both hematemesis and
melena and frequently associated with signs of hemodynamic instability\textsuperscript{[59]}. In the absence of prompt treatment, recurrent bleeding within 72 h after the initial bleed is frequently observed, being commonly more severe. If unidentified and left untreated, DL mortality is extremely high\textsuperscript{[63]}.

Endoscopy is the first-line diagnostic modality and is regarded as the gold standard method for the diagnosis of DL\textsuperscript{[38,59]}. The reported endoscopic criteria for the diagnosis of DL include: (1) Active arterial spurting bleeding from a small (< 3 mm) mucosal defect or through normal mucosa; (2) Protruding vessel, with or without active bleeding, within a small mucosal defect or normal mucosa; or (3) Fresh adherent clot to a minute mucosal defect or to normal-appearing mucosa\textsuperscript{[64]}. However, the reported diagnostic yield of initial EGD is only 70%, and repeat endoscopic examinations may thus be required. Main reasons for diagnostic failure of EGD encounter small lesion size, intermittently active bleeding, DL site between folds or underneath an adherent clot, or presence of a large amount of fresh blood within the gastric cavity\textsuperscript{[65]}. Thus, especially in the setting of non-actively bleeding DL, endoscopic diagnosis may be challenging and a high index of clinical suspicion is required. A meticulous examination especially of the gastric cardia should be performed during EGD. In addition to adequate insufflation, in case of negative EGD, the execution of a provocative endoscopy by the use of water-jet irrigation to target wash as much of the gastric cardia as possible, particularly along the lesser curvature, has been suggested in order to disrupt a fibrin plug and provoke active bleeding from an underlying DL\textsuperscript{[13]}. Of interest, in the setting of non-active bleeding, EUS may be useful to confirm the diagnosis of DL, being capable to clearly depict the pathological submucosal vessel penetrating the muscularis propria\textsuperscript{[66]}.

Further diagnostic modalities include MDCTA and DSA. MDCTA findings encounter abnormally enlarged submucosal vessel, which may appear tortuous, linear or as a non-specific “blush” of contrast medium at the mucosal/submucosal level\textsuperscript{[14]}. However, diagnosis of DL by the use of MDCTA is usually challenging, and requires highly experienced radiologists. Conversely, angiographically, DL appears as a non-tapering,
tortuous vessels in the arterial phase with no early venous return, with or without contrast medium extravasation within the GI tract\cite{87}.

Treatment is recommended for virtually all identified DL, even in the absence of recent bleeding stigmata. Dual combination endoscopic therapy with epinephrine injection followed by mechanical or thermal contact hemostasis is recommended as the first-line treatment modality for DL, being effective in more than 90% of cases. Although requiring higher endoscopic skill and experience, especially if performed in a gastric retroflexion position as frequently needed, mechanical therapy by means of band ligation or endoclips placement is currently favored over thermal hemostasis\cite{59}. Moreover, given the risk of perforation, especially in GI tracts with thin walls such as the gastric fundus, and the risk of bands drop off with rebleeding, endoscopic band ligation may be less desirable than endoscopic clipping, especially in inexperienced hands\cite{59,68}. Finally, mechanical hemostasis by means of OTSC has been successfully reported with good outcomes, not only for refractory cases\cite{69,70}.

If feasible (i.e., absence of active bleeding), the so called acoustic Doppler mapping technique, by the use of a through-the-scope endoscopic Doppler ultrasound (DopUS) probe to delineate the subsurface route and path of the pathologically large-caliber artery, may be performed prior to endoscopic treatment, in order to treat the entire length of the superficially located artery, thus maximizing its efficacy. Furthermore, following endoscopic hemostasis achievement, the DopUS may be used to show the blood flow cessation, thus proving the successful eradication of the lesion\cite{71}.

Worth mentioning, endoscopic tattooing of the DL site should also be performed, in order to facilitate endoscopic or surgical localization in case of rebleeding occurrence\cite{58,59}. Intriguingly, various EUS-guided treatments have been reported with good outcomes among case reports and small case series, mainly in the setting of DL refractory to standard endoscopic hemostasis. As previously mentioned, despite standard endoscopic treatment, complete ablation of a DL may be accurately evaluated at the end of treatment by Doppler EUS showing the absence of blood flow in the targeted vessel. However, up to date, evidence is still anecdotal and their adoption
should be limited to referral centers in a research context. TAE represents a useful second-line treatment modality, whereas surgical wedge resection has currently become the last resort for uncontrolled or unidentified DL bleeding. A case of DL is shown in Figure 4.

Cameron lesions
Initially reported by Truesdale in 1924 and subsequently extensively illustrated by Cameron in 1976, Cameron lesions (CL) refer to linear gastric erosions or ulcerations located on the mucosal folds at the distal neck of a hiatal hernia (HH), in close proximity to the diaphragmatic impression. CL are thought to occur as a result of mechanical trauma and local ischemia, secondary to repetitive movement of the hernia sac against the diaphragm during respiratory excursions, and acid injury. Their estimated prevalence is between 3% and 5% in the presence of a HH, reaching up to 10%-20% among patients with large HH (> 5 cm). Moreover, they have been reported to be the source of overt UGIB in 0.2% of cases.

Although commonly incidentally diagnosed during EGD, CL may clinically present with either acute or chronic NVUGIB. EGD is considered the gold standard for the diagnosis of CL. However, they may often be missed at the index EGD. Meticulous endoscopic evaluation of the HH neck and sac, especially in a retroflexed view, is thus required.

Although technically demanding, due to CL anatomical location requiring a retroflexed position and the movement of the HH sac with respiration, endoscopic hemostasis is indicated in case of active bleeding, visible vessel or adherent clot, similarly to peptic ulcers. Injection of epinephrine, thermal contact therapy, clipping and band ligation may be adopted. However, because of the thin wall and the lack of fibrous support tissue in the gastroesophageal junction, caution is needed when attempting endoscopic therapy, given the potential risk of deep ulcer or perforation. Finally, a surgical approach with laparoscopic or open fundoplication
should be considered in patients with refractory or recurrent CL bleeding\textsuperscript{75,80}. A case of CL is shown in Figure 5.

**HP**

First described in 1931 by Lower and Farrell\textsuperscript{84}, HP is an exceptionally rare cause of potentially fatal NVUGIB, with a reported incidence of about one in 1500 cases\textsuperscript{85}. Also referred to as pseudohemobilia or wirsungorrhagia, the term HP was coined in 1970 by Sandblom\textsuperscript{84}. It is defined as bleeding within the pancreatic duct exteriorizing through the major duodenal papilla. Of note, hemorrhage can also occur via the minor duodenal papilla, also known as santorinirrhage, in case of pancreas divisum. The reported mortality rate of HP is high, reaching up to approximately 10\%\textsuperscript{85}. If untreated, the mortality rate may increase up to 90\%\textsuperscript{87}.

HP is commonly observed among patients with an history of pancreatic diseases, mainly including acute or CP and less frequently pancreatic neoplasms\textsuperscript{87}. The most common cause of HP is ruptured VAPA\textsuperscript{87}. Indeed, VAPA formation and rupture in the setting of pancreatitis, are thought to be secondary to local leakage of proteolytic enzymes with destruction of the arterial wall. Alternatively, they may also result from erosion of nearby pseudocysts or walled-off necrosis into adjacent arteries\textsuperscript{88}. Given its close anatomical relationship with the pancreas, SA is the most common involved site of pseudoaneurysm, followed by the GDA, the PDA, and the HA\textsuperscript{87}. Less common causes of HP include pancreatic neoplasms, pseudocysts, pancreas divisum, vascular malformations, TVAA, and traumatic or iatrogenic injuries, including endoscopic retrograde cholangiopancreatography (ERCP) and EUS interventional procedures\textsuperscript{87,88}.

The classical Sandblom’s triad of clinical presentation associated with HP consists of abdominal pain radiating to the back, intermittent UGIB manifesting as melena, hematemesis, and rarely, hematochezia, and hyperamylasemia\textsuperscript{84}. Pain is secondary to transient increase in intraductal pancreatic pressure due pancreatic duct obstruction from blood clot. It is alleviated following bleeding episodes, due to clots clearance. Icterus from retrograde biliary obstruction may also occur\textsuperscript{88}.
Diagnosis of HP is challenging, requiring a multidisciplinary and integrative approach. Given the hidden and intermittent nature of the bleeding and its anatomical location, EGD was reported to be able to direct visualize active bleeding via the major duodenal papilla in only about 30%-75% of cases. **Suspicion for HP should be increased by indirect signs of bleeding, including clots within the duodenum in the absence of an alternative explanation.** Furthermore, when HP is suspected, repeated endoscopy and the adjunct of a duodenoscope to properly visualize the major papilla are often necessary to establish the diagnosis.

ERCP may highlight filling defects within the pancreatic ducts, favoring the diagnosis. However, being associated with potential bleeding worsening and pancreatic duct disruption, and having a limited therapeutic role especially in the setting of ruptured VAPA, ERCP is generally not recommended for the diagnosis and treatment of HP.

Intriguingly, EUS has been shown to be a promising tool in the diagnosis of HP, being capable to clearly depict bleeding within the pancreatic duct and its underlying cause. Among experienced centers, EUS could be performed immediately after EGD in suspected cases, in order to provide prompt diagnosis and treatment.

MDCTA represents a very useful diagnostic tool for HP, providing characterization of the local anatomy, detection of bleeding within the pancreatic duct and its underlying etiology, thus effectively guiding further management in most of cases. On pre-contrast MDCTA, the characteristic feature of clotted blood within the pancreatic duct, known as the sentinel clot sign, may also be observed. However, the diagnostic gold standard for HP is currently represented by DSA.

Percutaneous endovascular treatment, mainly by means of TAE, is currently recommended as the first choice of treatment for HP, with surgery being reserved for patients with persistent hemodynamic instability and unsuccessful embolization. Although therapeutic ECRP with pancreatic multistenting has been successfully reported for the tamponade of a iatrogenic post-ERCP case of HP, its adoption may not be recommended, especially in the setting of ruptured VAPA. Finally, the promising
role of EUS-guided embolization in the treatment of VAPA has been previously discussed. A case of HP is shown in Figure 6.

**Hemobilia**

First described in 1654 by Glisson on autopsy, hemobilia is defined as bleeding into the intra- or extra-hepatic biliary system exteriorizing via the major duodenal papilla. It occurs as a result of a fistula formation between a splanchnic blood vessel and the biliary system. Arterial vessels are more commonly involved, due to their higher intravascular pressure. However, biliary venous fistulas have also been reported, especially in the setting of portal hypertension.

Due to their increased adoption, the most common reported etiology of hemobilia is currently represented by iatrogenic causes involving hepatopancreatobiliary (HPB) manipulation, including percutaneous radiological interventions, ERCP, interventional EUS, and HPB surgery. In these situations, hemobilia may be secondary to traumatic arteriobiliary fistula formation or less frequently to rupture of a HA, or rarely cistyc artery, pseudoaneurysm. Less common etiologies include traumatogenic causes, HPB malignancies, portal biliopathy, chronic ductal obstruction, inflammatory conditions, such as cholecystitis, gallstone disease, ruptured HA true aneurysms, and intraductal infection.

The classic clinical presentation of hemobilia is Quincke’s triad, consisting of right upper quadrant pain, jaundice and UGIB, but all three findings are simultaneously observed in only 22%-35% of cases. The diagnosis of hemobilia may be challenging and a high index of suspicion, mainly based on a patient’s clinical presentation and suggestive medical history, is crucial. Furthermore, as with HP, bleeding can be intermittent and difficult to visualize endoscopically, even with the use of a side-viewing endoscope or a forward-viewing endoscope with distal attachment cap. ERCP can improve diagnosis by detecting findings suggestive of hemobilia, such as amorphous, tubular, or cast-like filling defects with unexplained dilation of the common or perihilar bile duct. However, it is rarely performed with a solely
diagnostic intent. Of note, the use of per oral cholangioscopy has been suggested in the management of unexplained hemobilia. Finally, a promising role of EUS in the diagnosis of hemobilia has been reported. Indeed, EUS was shown to be able to detect aneurysm or pseudoaneurysm in the hepatic vasculature, presence of blood within the gallbladder and common bile duct, presenting as mobile hyperechoic material, and bleeding from intra- and para-choledochal varices in portal biliopathy.

In hemodynamically stable patients with suspected major hemobilia, MDCTA should be performed in order to rule out vascular complications, such as HA aneurysms, pseudoaneurysms and cholangiovenous or arterio-ductal fistulas, and thus guiding further management.

The aim of treatment consists of both hemorrhage control and maintenance of biliary patency. In the absence of vascular complications detected by MDCTA, ERCP is commonly the initial therapeutic procedure of choice, being able to provide simultaneous management of both bleeding and biliary obstruction. Several endoscopic hemostatic techniques have been reported, varying according to etiology, location, and source of hemobilia. In case of post-sphincterotomy hemobilia, which typically is a result of injury to the posterior branch of the superior PDA, or distal hemobilia, hemostasis may be achieved by epinephrine spraying or injection, monopolar or bipolar coagulation, fibrin sealant injection, clipping, balloon tamponade, and stenting. Conversely, biliary stenting is the preferred option for proximal hemobilia. In selected cases, biliary stents are capable to achieve immediate hemostasis, by creating a tamponade effect on the biliary wall, while maintaining luminal patency and thus bile flow. Of note, as compared with plastic stents, fully covered self-expanding metallic stents appear to have superior tamponade effect and greater patency, and should be favored in this setting. Finally, ERCP may provide bile flow restoration, by directly extracting intraductal blood clots and/or by biliary stenting, thus preventing complications related to biliary obstruction.

In case of vascular complications, refractory hemodynamic instability, or endoscopic treatment failure, interventional radiology is recommended. TAE is the most
widely adopted technique. However, it is contraindicated in liver transplant recipients, portal vein thrombosis, and cirrhosis with concomitant shock, due to compromised collateral blood flow from the portal vein and the consequent risk of severe hepatic ischemia. In this setting, arterial stenting should be preferred\textsuperscript{106}.

Intriguingly, EUS-guided obliteration has been recently successfully reported also in the setting of hemobilia due to cystic artery pseudoaneurysm\textsuperscript{107}. Surgery is typically reserved as a last resort, due to its high morbidity and mortality rate\textsuperscript{94,96}. A case of hemobilia is shown in Figure 7.

CONCLUSION
Upper GI endoscopy is currently recommended as the gold standard modality for both diagnosis and treatment of NVUGIB. However, NVUGIB due to PUD only is mainly addressed by current international guidelines, whereas rare causes of NVUGIB are not covered due to their scarcity. In these instances, EGD may often not represent the gold standard for the diagnosis and may not have any role in their treatment. Conversely, a multidisciplinary approach involving not only the GI endoscopists, but also the diagnostic and the interventional radiologists, and the general and the vascular surgeons, is in most cases needed for both diagnosis and treatment. Nevertheless, EGD is inevitably the most frequently first diagnostic modality performed or requested even in NVUGIB due to rare causes. Thus, the GI endoscopists are commonly the main actors in driving further diagnostic and therapeutic process, rising the suspect of rare NVUGIB causes when appropriated. In this setting, the diagnostic role of EGD is commonly limited, mainly directed to exclude common causes of NVUGIB, whereas the diagnostic gold standard is frequently represented by MDCTA and/or DSA.

Worth mentioning, NVUGIB due to rare causes are generally associated with morbidity and mortality significantly higher as compared with those secondary to common sources. Moreover, given any delay in proper diagnosis and/or treatment is inevitably associated with increased mortality, a prompt and effective management is crucial. Thus, not only the gastroenterologists, frequently the first actors involved in the
management of NVUGIB due to both common and uncommon causes, should be aware and very confident with rare NVUGIB causes, but also the diagnostic and the interventional radiologists, and the general and the vascular surgeons.

Finally, a multidisciplinary, patient-tailored, and minimally-invasive, when feasible, approach should be pursued for the management of most of the rare NVUGIB causes. Given their complexity, often requiring a strict cooperation between different specialists, rare and extraordinary rare causes of NVUGIB should be desirably managed among highly-experienced referral centers.
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