Algorithm for the multidisciplinary management of hemorrhage in EUS-guided drainage for pancreatic fluid collections

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Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest.

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Received: May 17, 2018
Peer-review started: May 21, 2018
First decision: June 20, 2018
Revised: July 5, 2018
Accepted: July 15, 2018
Article in press: July 16, 2018
Published online: September 26, 2018

Abstract
Pancreatic fluid collections (PFCs), common sequelae of acute or chronic pancreatitis, are broadly classified as pancreatic pseudocysts or walled-off necrosis according to the revised Atlanta classification. Endoscopic ultrasound (EUS)-guided drainage is often considered a standard first-line therapy preferable to surgical or interventional radiology approaches for patients with symptomatic PFC. EUS-guided drainage is effective and successful; it has a technical success rate of 90%-100% and a clinical success rate of 85%-98%. Recent studies have shown a 5%-30% adverse events (AEs) rate for the procedure. The most common AEs include infection, hemorrhage, perforation and stent migration. Hemorrhage, a severe and sometimes deadly outcome, requires a well-organized and appropriate treatment strategy. However, few studies have reported the integrated management of hemorrhage during EUS-guided drainage of PFC. Establishing a practical therapeutic strategy is an essential and significant step in standardized management. The aim of this review is to describe the current situation of EUS-guided drainage of PFCs, including the etiology and treatment of procedure-related bleeding as well as current problems and future perspectives. We propose a novel and meaningful algorithm for systematically managing hemorrhage events. To our limited knowledge, a multidisciplinary algorithm for managing EUS-guided drainage for PFC-related bleeding has not been previously reported.

Key words: Pancreatic fluid collections; Hemorrhage; Endoscopic ultrasound-guided; Treatment algorithm; Adverse events

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Core tip: Currently, endoscopic ultrasound (EUS)-guided drainage has been viewed as the optimal therapy for symptomatic pancreatic fluid collections (PFCs). Bleeding is one of the most dangerous adverse events.
However, few studies have addressed the treatment of hemorrhage in the EUS-guided drainage of PFCs. The aim of this review is to describe the etiology, therapy, and prevention of EUS-guided drainage procedure-related bleeding and to present current problems and future perspectives. Moreover, we propose a meaningful and multidisciplinary algorithm for the clinical management of hemorrhagic events in EUS-guided drainage for PFCs.

Jiang TA, Xie LT. Algorithm for the multidisciplinary management of hemorrhage in EUS-guided drainage for pancreatic fluid collections. World J Clin Cases 2018; 6(10): 308-321 Available from: URL: http://www.wjgnet.com/2307-8960/full/v6/i10/308.htm DOI: http://dx.doi.org/10.12998/wjcc.v6.i10.308

INTRODUCTION

Pancreatic fluid collections (PFCs) occur in approximately 50% of cases of acute pancreatitis (AP)\(^1\). PFCs are defined by the revised Atlanta classification as “a collection” that develops over time (usually at or after 4 wk), including pancreatic pseudocyst (PPC) and walled-off necrosis (WON)\(^2\). Recent studies have recognized endoscopic ultrasound (EUS)-guided drainage as the standard first-line therapy for symptomatic PFCs due to its minimal invasiveness, lower mortality and morbidity, shorter length of hospital stays, better physical recovery and lower cost compared to non-endoscopic treatments\(^3\)-\(^5\).

EUS-guided drainage with stents is recognized as the gold standard for symptomatic PFCs because of its high technical success rate of 90%-100% and clinical success rate of 85%-98%, and low mortality rate of 1%-5%\(^6\)-\(^7\). Furthermore, multiple previous studies have indicated that EUS-guided drainage is effective, successful, and increasingly used. Despite the advantages of EUS-guided drainage for PFC compared to surgical and percutaneous methods, previous research has also found that it is associated with a significant number of adverse events (AEs), namely, bleeding, infection, perforation and stent migration\(^8\)-\(^10\). Hemorrhage in particular is fatal and difficult to control once it begins. Several published studies have revealed a 3%-20% bleeding rate\(^11\)-\(^13\), and some cases have even ended in death\(^14\),\(^15\). However, to date, there are minimal data regarding the optimal management of procedure-related hemorrhage. The establishment of an adequate and effective treatment strategy is an essential step for standardized management.

The purpose of this review is to describe the development of EUS-guided drainage of PFCs and the present situation and future perspective of procedural-related bleeding. Moreover, we propose a novel and meaningful algorithm for the treatment of hemorrhage. To our limited knowledge, this is the first report of an integrated and multidisciplinary method for the management of EUS-guided drainage of PFCs with bleeding.

WHAT ARE PanCREATIC FLUID COLLECTIONS?

PFCs develop due to the sequelae of acute pancreatitis, exacerbations of chronic pancreatitis, trauma, malignancy and surgery\(^16\)-\(^18\). The majority of PFCs are asymptomatic and will resolve spontaneously; however, patients with obvious abdominal pain, gastric outlet obstruction, biliary obstruction, and organ failure warrant intervention\(^19\),\(^20\). PFCs are being recognized at a growing frequency largely because of the increased use of abdominal crosssectional imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI)\(^10\). Recently, the role of EUS has evolved, and its increasing reproducibility allows it to further identify these collections\(^21\)-\(^25\). Furthermore, EUS is not only a diagnostic approach but a therapeutic one. PFCs are being identified at an increasing frequency, mainly due to the enhanced use of abdominal imaging approaches\(^26\).

EUS-GUIDED MANAGEMENT OF PANCREATIC FLUID COLLECTIONS

The management of symptomatic PFCs (PPC or WON) has evolved over time. Traditionally, the drainage of PFCs was connected to surgical or percutaneous methods. Currently, endoscopic drainage is now generally preferred over non-endoscopic drainage procedures and has become an optimal approach, preferable to surgical or percutaneous methods\(^26\),\(^27\). EUS has developed as a backbone of PFC management, representing a rapid advance in clinical medicine that has markedly improved the treatment level of this complex disease. With the availability of EUS, the safety and efficacy of PFC drainage has improved further. Because the surgical approach has the disadvantages of invasiveness, high mortality, long hospital stays and high costs, endoscopic options have increasingly been used for initial management\(^28\). Recent studies have also favored the endoscopic approach for the management of PFCs when endoscopic and surgical techniques were compared\(^29\),\(^30\). Siddiqui et al\(^31\) revealed that the percutaneous approach is associated with infection, a high recurrence rate, and fistula formation. A 14-year experience study by Keane et al\(^32\) also confirmed that endoscopic drainage was superior to percutaneous drainage. Several studies in the literature have demonstrated that endoscopic drainage is superior to surgical and percutaneous drainage in terms of minimal invasiveness, lower morbidity, significantly better clinical success, lower re-intervention rates, shorter lengths of hospital stay, a better post-operative condition of the patient, and lower cost\(^33\),\(^34\). EUS-guided drainage has the following advantages compared with other non-EUS-guided drainage
options\textsuperscript{[35-37]}: (1) EUS can be used to determine lesion characteristics, such as whether the lesion is a simple cyst or whether significant necrotic debris is present. Thus, EUS can distinguish PPC from different true cysts, cystic tumors, WON, lymphoceles, and the gallbladder; (2) EUS-guided drainage is widespread to enhance the diagnosis of cystic pancreatic lesions and enable real-time image-guided control of cystic drainage; (3) EUS Doppler can identify the vessels and potentially reduce the risk of bleeding; and (4) EUS can adjust the angle of the transducer (up and down) in order to acquire better Doppler signal and ultrasound imaging (Figure 1).

OUTCOME MEASURES AND ADVERSE EVENTS OF EUS-GUIDED DRAINAGE

Over the past 30 years, diagnostic and therapeutic EUS has been applied to both benign and malignant diseases of the pancreas; its use to diagnose and treat patients with symptomatic PFC in particular has vastly expanded. Recently, Lang et al\textsuperscript{[38]}, in their retrospective single-center study of 103 PFC patients treated by EUS-guided drainage, used both double-pigtail plastic stents (DDPS) and lumen-apposing covered self-expanding metal stents (LAMS). They concluded that the overall technical success rate was 99%, the overall clinical success rate as determined by complete resolution was 95% after 6 mo of follow-up; furthermore, AEs occurred in 19 out of 103 patients (18%) and mainly included hemorrhage (5%), perforation (1%), and unplanned endoscopy (13%). In addition, a retrospective multicenter trial of a nationwide database involving all hospitals in Spain performed EUS-guided drainage for patients with PFC\textsuperscript{[35]}. This study included 211 patients (53% PPC and 47% WON) and reported 91% technical success, 93% clinical success, and 21% AEs. The AEs included infection (11%), bleeding (7%), and stent migration and/or perforation (3%). These findings are in accordance with a systematic review that demonstrated treatment success rates of 98% and 93% for technical success and clinical success, respectively\textsuperscript{[40]}. In another retrospective study, Bang et al\textsuperscript{[6]} reported 100% technical success and 93% treatment success for EUS-guided transmural drainage of symptomatic PPC with plastic stents. One of the largest prospective studies was reported by Shah et al\textsuperscript{[41]} and used LAMS to drain PFC. They reported a technical success rate of 91% and a PFC resolution rate of 93%. Similar results have been shown by Fabbri et al\textsuperscript{[42]} and Penn et al\textsuperscript{[43]}. These studies included 20 patients each and reported rates of 100%, 81%, and 15% for technical success, clinical success and AEs, respectively. A recently published retrospective study by Rinniella et al\textsuperscript{[44]} performed at 13 experienced institutions and including 93 PFCs drained with LAMS reported a 99% technical success rate, a 92% clinical success rate and a 5% AE rate. They indicated major procedure-related AEs, mainly including massive hemorrhage (1%), infection (1%), perforation (1%), stent migration (1%) and pneumoperitoneum (1%). In another prospective multicenter European

![Figure 1 Imaging findings of pancreatic pseudocyst. A: A contrast-enhanced computed tomography (CECT) scan of the upper abdomen. A relatively homogenous cystic mass is identified in the region of the pancreatic tail (arrow). B: Endoscopic ultrasound (EUS) image showing a pancreatic pseudocyst (PPC) (arrow). C: Endoscopic image showing plastic stent deployment. D: Digital subtraction angiography (DSA) image revealing double pigtail plastic stent deployment.](image-url)
study, Walter et al reported success rates of 93% for pseudocysts and 81% for WON and a 9% rate of major AEs, which included infection (7%) and perforation (2%). In a retrospective two-center study of 49 PFC patients who underwent EUS-guided drainage, Ang et al reported the following rates for AEs: 2% infection, 4% bleeding, 2% perforation and 2% pneumoperitoneum. Therefore, the high success rate is the best indicator of the great development of EUS-guided drainage for PFC. The detailed outcome measures for EUS-guided drainage of PFCs are described in Table 1.

**MANAGEMENT OF HEMORRHAGE: WHERE DO WE STAND?**

Although the EUS-guided drainage procedure is effective, and has a high success rate, which diminishes the risk of death, AE rates of 5%-30% have been previously reported. As with any endoscopic procedure, EUS and its guided interventions may be accompanied by AEs, which mainly include bleeding, infection, perforation and stent migration. The adverse events associated with EUS-guided drainage of PFC are presented in detail in Table 2. In particular, bleeding is a dangerous, even deadly, adverse event. Further details regarding hemorrhage are shown in Table 3. An Italian study by Cavallini et al revealed that 11% of patients with massive hemorrhage died from a pseudoaneurysm of the gastroduodenal artery. Similarly, Mukai et al and Rinninella et al reported bleeding-related mortality rates of 3% and 1%, respectively. However, there are minimal data regarding the causes of and optimal treatments for hemorrhage. Recently, a researcher studied EUS-guided drainage of PFC with LAMS and DPPS. The hemorrhages that occurred in the DPPS group were due to plastic stent erosion into the opposite gastric wall. Esophagogastroduodenoscopy was conducted, and a visible vessel was cauterized for durable hemo-
stasis. In the LAMS group, 4 bleeding episodes were observed. One was a collateral vessel bleed and was managed by conservative therapy, such as blood transfusion. The second was an intracavitary vessel bleed and was treated with balloon tamponade under endoscopic guidance. No further hemorrhage was noted. Another two patients developed bleeding caused by splenic artery pseudoaneurysm. One patient underwent successful hemostasis with left gastric and splenic artery embolization. Unfortunately, the other patient died before his embolization procedure. In a randomized controlled trial by Bang et al using LAMS for PFC drainage, three patients presented with serious gastrointestinal tract bleeding that required intensive care unit admission and blood transfusions. Furthermore, on EUS, interlacing vessels were visualized within the distal flange of the LAMS and CT angiograms, confirming pseudoaneurysms. All three patients were successfully managed by interventional radiology-guided coil embolization.

Furthermore, Bapaye et al reported a 10-year respective study of 133 patients who underwent EUS-guided drainage for WON with multiple plastic stents (MPS) and fully covered bi-flanged metal stents (BFMS). Five patients in the MPS group developed hemorrhage due to tract dilatation and required blood transfusion. Bleeding was controlled by endoscopic clip application in all except one patient, who required surgery. Another two patients in the BFMS group developed hemorrhage due to the erosion of the splenic artery by the indwelling inner end of the stent; their bleeding was controlled with embolization. In another multicenter study, nine patients (4%) experienced hemorrhagic events. Two patients developed severe hemorrhage due to the inadvertent puncture of an artery and were successfully treated with interventional radiology (IR)-guided coil embolization. A prospective randomized trial reported by Varadarajulu et al showed that one patient suffered post-procedural bleeding. On endoscopy and arteriography, hemorrhage was distinct from the site of stent placement or a branch of the gastric artery, but it could not be controlled with epinephrine injection or coil placement. The patient had to undergo surgery. However, the patient then developed hemorrhage at the site of venous access, indicating the presence of acquired factor VIII inhibitors; it was corrected by administering anti-inhibitor coagulant complex. Finally, the patient was discharged on the sixth post-operative day. Interestingly, a respective study by Vazquez-Sequeiros et al revealed that in 64% of patients who developed delayed hemorrhage and portal hypopertension, imaging studies showed that splenic vein thrombosis was the cause, and antithrombotic therapy with stent-induced ulceration may have contributed to this. This was a first clinically significant observation, and it will need to be supported with larger prospective randomized studies in the near future.

Cohen et al reported a case that used the tamponade of fully covered self-expandable metal stent (FCSEMS) to control bleeding and addressed dangerous hemorrhage. Similar events were also reported by Akbar et al. Talreja et al reported a prospective case series in which patients who experienced bleeding from the pseudocyst wall were treated with balloon tamponade and arterial embolization. Furthermore, Lakhtakia et al, Siddiqui et al and Itoi et al described several cases of minor bleeding that were self-limiting and did not require treatment. However, some studies did not explain why the hemorrhage occurred; furthermore, several researchers did not describe how to address the hemorrhage, and some studies did not demonstrate the methods used to diagnose the bleeding. Although these studies were limited to describing the etiology and treatment of these hemorrhagic episodes, future prospective studies
| Study                  | Year | Country       | Design                  | Single/multi-center | Success | Failure | Cause of death                                                                 |
|-----------------------|------|---------------|-------------------------|--------------------|---------|---------|--------------------------------------------------------------------------------|
| Jiang TA et al. [9]    | 2018 | United States | RS                      | Single             | 94%     | 5%      | Due to bleeding from splenic artery pseudoaneurysm                              |
| Al-Habib et al. [3]    | 2018 | United States | DPPS                    | Single             | 96%     | 4%      | Died from septic shock                                                           |
| Sklodowska et al. [4]  | 2017 | India         | RS                      | Single             | 94%     | 6%      | Died from progressive sepsis                                                   |
| Bępotka et al. [5]     | 2017 | India         | RS                      | Single             | 94%     | 6%      | Died from multi-organ failure                                                  |
| Raposo et al. [6]      | 2016 | Spain         | RCT                     | Single             | 100%    | 0%      | Died of progressive sepsis                                                     |
| Lukińska et al. [7]    | 2016 | Poland        | RS                      | Single             | 96%     | 4%      | Died because of multi-organ failure and massive bleeding                       |
| Goral et al. [8]       | 2016 | Poland        | FCSEMS                  | Single             | 96%     | 4%      | Died due to portal hypertension                                                |
| Dadhichi et al. [9]    | 2016 | Japan         | NF                      | Single             | 96%     | 4%      | Died due to delayed bleeding                                                    |
| Ang et al. [10]        | 2016 | Singapore     | PFC                     | Single             | 98%     | 2%      | Died from multiple-organ failure                                                |
| Varathana et al. [11]  | 2016 | Thailand      | PS                      | Single             | 95%     | 5%      | Died because of progressive sepsis                                              |
| Sharifi et al. [12]    | 2015 | Netherlands   | NC                      | Single             | 99%     | 1%      | Died due to delayed bleeding                                                    |
| Rimma et al. [13]      | 2015 | India         | FCSEMS                  | Single             | 99%     | 1%      | Died due to delayed bleeding                                                    |
| Milti et al. [14]      | 2015 | Japan         | PPC                     | Single             | 100%    | 0%      | Died due to delayed bleeding                                                    |
| Lee et al. [15]        | 2014 | South Korea   | FCSEMS                  | Single             | 100%    | 0%      | Died due to delayed bleeding                                                    |
| Yamamoto et al. [16]   | 2013 | Japan         | FCSEMS                  | Single             | 98%     | 2%      | Died due to delayed bleeding                                                    |
| Bar MAN et al. [17]    | 2013 | India         | FCSEMS                  | Single             | 96%     | 4%      | Died due to delayed bleeding                                                    |
| Lekhajae et al. [18]   | 2012 | India         | FCSEMS                  | Single             | 99%     | 1%      | Died due to delayed bleeding                                                    |
| Vargas et al. [19]     | 2011 | United States | MR                      | Single             | 98%     | 2%      | Died due to delayed bleeding                                                    |
| PFC: Pancreatic pseudocyst; WON: Walled-off necrosis; PFC: Pancreatic fluid collections; RS: Retrospective study; RCT: Randomized controlled trial; Single: Single-center; Multi: Multi-center; FCSEMS: Fully covered self-expanding metal stent; LAMS: Lumen-apposing metal stent; DPPS: Double-pigtail plastic stent; MTS: Multiple transpapillary gastrostomy technique; NR: Not reported.
| Study                  | Year | Country     | Design | Single/multi-center | Stent style     | No.   | PFC style | Infection | Bleeding | Perforation | Migration | Occlusion | Other adverse events                           |
|-----------------------|------|-------------|--------|---------------------|----------------|-------|-----------|-----------|----------|-------------|-----------|-----------|-----------------------------------------------|
| Lang et al[38]        | 2018 | United States | RS     | Single              | LAMS/DPPS      | 103   | 80 PP     | 0%        | 5%       | 1%          | 0%        | 0%        | 13% Unplanned endoscopy                      |
| Aburajab et al[39]    | 2018 | United States | RS     | Single              | LAMS with DPPS/with no DPPS | 46    | PP        | 9%        | 0%       | 2%          | 15%       | 0%        | 9% Re-intervention                           |
| Siddiqui et al[40]    | 2017 | United States | RS     | Multi               | LAMS/ DPPS/FCSEMS | 313   | WON       | 3%        | 3%       | 2%          | 1%        | 8%        | 12% (No details)                            |
| Bapaye et al[41]      | 2017 | India       | RS     | Single              | BFMS / MPS     | 133   | WON       | 2%        | 5%       | 0%          | 2%        | 0%        | 14% Persistent stenosis                      |
| Bang et al[42]        | 2017 | United States | RCT    | Single              | LAMS/ DPPS     | 21    | WON       | 0%        | 14%      | 0%          | 0%        | 0%        | 2% Buried stent                              |
| Bang et al[43]        | 2017 | United States | RS     | Single              | LAMS/ DPPS     | 60    | 21 PP     | 12%       | 0%       | 0%          | 5%        | 0%        | 28% Re-intervention                          |
| Lakhtakia et al[44]   | 2016 | India       | RS     | Single              | FCSEMS         | 205   | WON       | 0%        | 3%       | 1%          | 1%        | 10%       | 1% Buried stent                              |
| Shah et al[45]        | 2016 | United States | RS     | Multi               | LAMS           | 124   | WON       | 6%        | 3%       | 0%          | 6%        | 0%        | 19% Re-intervention                          |
| Gorulkar et al[46]    | 2016 | Spain       | RS     | Single              | LAMS           | 12    | WON       | 17%       | 17%      | 0%          | 0%        | 0%        | None                                          |
| Siddiqui et al[47]    | 2016 | United States | RS     | Multi               | LAMS           | 82    | 14 PPC    | 6%        | 7%       | 0%          | 0%        | 5%        | None                                          |
| Ang et al[48]         | 2016 | Singapore   | RS     | Multi               | FCSEMS / DPPS  | 49    | 68 WON    | 2%        | 4%       | 2%          | 0%        | 0%        | 5% Pneumoperitoneum                          |
| Vazquez-Sequeiros et al[49] | 2016 | Spain       | RS     | Multi               | FCSEMS         | 211   | 112 PP    | 23%       | 7%       | -           | 5%        | 0%        | 3% Pneumoperitoneum                          |
| Shah et al[50]        | 2015 | United States | PS     | Multi               | LAMS           | 33    | PFC/ WON  | 6%        | 0%       | 0%          | 3%        | 0%        | None                                          |
| Walter et al[51]      | 2015 | The Netherlands | PS   | Multi               | LAMS           | 61    | PFC/ WON  | 7%        | 0%       | 2%          | 0%        | 0%        | None                                          |
| Shaibani et al[52]    | 2015 | United States | RS     | Multi               | FCSEMS         | 112   | PFC       | 14%       | 4%       | 3%          | 1%        | 7%        | None                                          |
| Rinninella et al[53]  | 2015 | Italy       | RS     | Multi               | FCSEMS         | 93    | WON 52    | 1%        | 1%       | 1%          | 1%        | 0%        | None                                          |
| Mukai et al[54]       | 2015 | Japan       | RS     | Single              | FC BFMS / DPPS | 70    | WON       | 0%        | 4%       | 1%          | 4%        | 0%        | 1% Mediastinal emphysema                     |
| Lee et al[55]         | 2014 | South Korea | PS     | Single              | FCSEMS/ DPPS   | 50    | PFC       | 0%        | 2%       | 0%          | 4%        | 0%        | None                                          |
| Yamamoto et al[56]    | 2013 | Japan       | RS     | Multi               | FCSEMS         | 9     | 5 PFC     | 0%        | 11%      | 0%          | 11%       | 0%        | None                                          |
| Bang et al[57]        | 2013 | United States | RS     | Multi               | MTGT           | 76    | WON       | 8%        | 1%       | 1%          | 4%        | 0%        | None                                          |
| Puri et al[58]        | 2012 | India       | PS     | Single              | DPPS           | 40    | 40 PFC    | 3%        | 3%       | 0%          | 0%        | 0%        | 3% Pneumoperitoneum                          |
| Itoi et al[59]        | 2012 | Japan       | RS     | Multi               | LAMS           | 15    | 9 PFC     | 0%        | 20%      | 0%          | 7%        | 0%        | None                                          |
| Varadaraju et al[60]  | 2011 | United States | RS     | Single              | DPPS           | 211   | 154 PFC   | 3%        | 1%       | 1%          | 1%        | 0%        | None                                          |

PFC: Pancreatic pseudocyst; WON: Walled-off necrosis; PFC: Pancreatic fluid collections; PS: Prospective study; RS: Retrospective study; RCT: Randomized controlled trial; Single: Single-center; Multi: Multi-center; FCSEMS: Fully covered self-expandable metal stent; LAMS: Lumen-apposing metal stents; DDPS: Double-pigtail plastic stents; BFMS: Fully covered bi-flanged metal stents; MPS: Multiple plastic stents; MTGT: Multiple transluminal gateway technique; NR: Not reported.
| Study            | Year | Country | Design | Center | Stent style | No. | PFC style | Location of drainage | Age | Male | Bleeding rate | Cause and treatment of bleeding                                                                 |
|------------------|------|---------|--------|--------|-------------|-----|-----------|---------------------|-----|------|---------------|-----------------------------------------------------------------------------------------------|
| Lang et al[38]   | 2018 | United States | RS     | Single | LAMS       | 19  | PPC/WON   | TG                  | 51.6| NR   | 19%           | 1. Splenic artery pseudoaneurysms-left gastric and splenic artery embolization after cystgastrostomy; |
|                  |      |          |        |        |            |     |           |                     |     |      |               | 2. Collateral vessel bleed-conservative transfused blood; 3. Intracavitary variceal bleed-endoscopically using balloon tamponade Stent erosion into the gastric wall-EGD was performed, and a visible vessel was treated with cautery for durable hemostasis |
| Siddiqui et al[46]| 2017 | United States | RS     | Multi  | LAMS       | 86  | WON       | TG/TD/Multiport      | 51.5| 89%  | 7%            | Related to stent erosion into a vessel as the WON cavity wall collapses or related to pseudoaneurysm in the cavity wall-significant hemorrhage treated by coil embolization by interventional radiology |
|                  |      |          |        |        |            |     |           |                     |     |      |               | Due to inadvertent puncture of an artery; another was not reported- Successfully treated with coil embolization by interventional radiology |
| Bapaye et al[13] | 2017 | India    | RS     | Single | BFMS       | 72  | WON       | Mostly TG            | 43.8| 86%  | 3%            | Because of erosion of the splenic artery by the indwelling inner end of the stent-treated by blood transfusion; splenic artery angiography embolization |
|                  |      |          |        |        |            |     |           |                     |     |      |               | Because of tract dilatation-Blood transfusion; endoscopic clip application; surgery Angiograms |
| Bang et al[50]   | 2017 | United States | RCT    | Single | LAMS       | 12  | WON       | NR                  | 40.6| 88%  | 8%            | With the resultant friction against regional vasculature surrounding the necrotic cavity precipitating bleeding-Blood transfusions interventional radiology-guided coil embolization |
|                  |      |          |        |        |            |     |           |                     |     |      |               | EUS and CT angiograms |
| Lakhtakia et al[9] | 2016 | India   | RS     | Single | FCSEMS     | 205 | WON       | NR                  | 34.8| 88%  | 3%            | No details of the cause of bleeding-Minor bleeding was self-limiting; major bleeding treated by selective coil embolization; another major bleeding treated by surgery. |
|                  |      |          |        |        |            |     |           |                     |     |      |               | None Abdominal angiography |
| Siddiqui et al[31] | 2016 | United States | RS     | Multi  | LAMS       | 82  | PPC/WON   | TG/TD               | 53.1| 67%  | 7%            | No details of the cause of bleeding-Self-limited bleeding |
| Ang et al[28]    | 2016 | Singapore | RS     | Multi  | FCSEMS     | 12  | PPC/WON   | NR                  | 50  | 58%  | 0%            | No details of the cause of bleeding-Treated by blood transfusion |
| Vazquez-Sequeiros et al[39] | 2016 | Spanish | RS     | Multi  | FCSEMS     | 211 | PPC/WON   | TG/TD               | 58.1| 69%  | 7%            | Portal hypertension due to splenic vein thrombosis and antithrombotic drug therapy in the presence of stent-induced ulceration may have been responsible-Interventional radiology embolization; surgical intervention; repeated endoscopic treatments (sclerotherapy); percutaneous radiology-guided drainage |
| Shariana et al[7] | 2016 | United States | RS     | Multi  | LAMS       | 124 | WON       | NR                  | 54.2| 61%  | 2%            | No details of the cause of bleeding-Embolization by interventional radiology |
| Shariana et al[10] | 2015 | United States | RS     | Multi  | ECSEMS     | 112 | PPC       | TG/TD               | 53.2| 55%  | 4%            | Significant bleeding due to inadvertent puncture of an artery-Successfully treated with coil embolization by interventional radiology |
| Gomals et al[51] | 2015 | Spain    | RS     | Single | DIPS       | 118 | PPC       | TG/TD               | 52.2| 69%  | NR            | All fluid is evacuated and the cavity lumen is collapsed, or due to a vessel injury from the inner stent end-Arteriography plus endoscopic treatment |
| Rinninella et al[44] | 2015 | Italy    | RS     | Multi  | FCSEMS     | 93  | PFC       | TG/TD               | 60  | 76%  | 1%            | Massive bleeding related to the concomitant use of a NCDC-Surgery |

**Table 3: Details of hemorrhage associated with endoscopic ultrasound-guided drainage of pancreatic fluid collections**
PFC: Pancreatic pseudocyst; WON: Walled-off necrosis; PFC: Pancreatic fluid collections; PS: Prospective study; RS: Retrospective study; RCT: Randomized controlled trial; Single: Single-center; Multi: Multi-center; FCSEMS: Fully covered self-expandable metal stent; LAMS: Lumen-apposing metal stents; DDPS: Double-pigtail plastic stents; BFMS: Fully covered bi-flanged metal stents; MPS: Multiple plastic stents; MTGT: Multiple transluminal gateway technique; TG: Trans-gastric route; TD: Trans-duodenal route; TE: Trans-esophageal route; TJ: Trans-jejunal route; CT: Computed tomography; EUS: Endoscopic ultrasound; NCDC: Nasocystic drainage catheter; NR: Not reported.

In light of previous experiences with hemostasis in the literature, we propose a simple and meaningful hemostasis algorithm for the management of bleeding during EUS-guided drainage of PFCs. According to the above analysis, the main causes of hemorrhage in cases of EUS-guided drainage of PFC are intra-procedural bleeding and post-procedural bleeding. Intra-procedural bleeding events are usually caused by pseudoaneurysms, inadvertent puncture of vessels, and the bursting of collateral vessels. Post-procedural bleeding events are associated with stent erosion into vessels, and coagulation disorders. In addition, the main methods for checking hemorrhage are EUS angiograms and CT angiograms. There are four major hemostatic approaches: conventional treatment, endoscopic treatment, interventional radiology-guided embolization, and surgery. Among these treatment approaches, the endoscopic methods used to control bleeding during or after EUS drainage include medicine injection, electrocautery, balloon tamponade, and the placement of large-diameter FCSEMS. Most importantly, once conventional treatment, endoscopic intervention, and radiological embolization have failed, surgery is performed immediately. Details are shown below.

Regarding intra-procedural hemorrhage
Pseudoaneurysm events are a common general AE, and IR-guided embolization is the most commonly used method for controlling hemorrhage. If an intracavitary vessel or cystic wall bleed occurs, it can be treated endoscopically using a balloon or FCSEMS tamponade. If required, a balloon dilator or FCSEMS may provide more sustained tamponade. Hemorrhage can also be caused by the inadvertent puncture of vessels or the bursting of a collateral vessel. The main principles of treatment are as follows: (1) For mild bleeding, first observe for self-limited bleeding; if the hemoglobin levels continue to decrease, then conservative treatment such as intensive care unit admission and blood transfusion may be needed; and (2) For moderate to severe hemorrhage, endoscopic therapy such as clip application, cautery, and balloon tamponade should
be performed. Embolization by IR or surgery should be performed if endoscopic intervention fails.

**Regarding post-procedural hemorrhage**

Bleeding caused by stent erosion is common during post-procedural events, and the typical therapy is endoscopic or radiologic treatment. The principle of management is the same as in 1c above. Coagulation disorders are a dangerous cause of hemorrhage that requires conservative treatment.

As presented above, this study proposes an integrated, multidisciplinary and helpful hemostasis algorithm that offers appropriate therapeutic strategies to address the emergence of serious bleeding. The detailed multidisciplinary treatment algorithm is shown in Figure 2.

**WHAT PROBLEMS SHOULD WE FOCUS ON?**

There is evidence that EUS-guided drainage has become the first-line and most successful therapeutic method for PFC. However, there are still some problems to be addressed. Some common factors that may or may not affect the bleeding rate require further exploration. Herein, first of all, we present an in-depth exploration of whether the type of stent affects AEs (including hemorrhage), which remains controversial. Several studies have compared the use of plastic vs metal stents in the EUS-guided drainage of PFCs. A recent retrospective study of EUS-guided drainage for PFCs using both LAMS and DDPS revealed hemorrhagic episodes in 21% of the LAMS group compared with 1% of the DPPS group, a difference that was statistically significant (P = 0.0003). Furthermore, the study confirmed that LAMS was associated with higher rates of AEs, specifically hemorrhage. A retrospective single-center analysis of EUS-guided drainage in 103 PFC patients reported by Bang *et al.* demonstrated that there were significantly more bleeding episodes in the LAMS group (19%) than in the DPPS group (1%). Interestingly, both Lang *et al.* and Bang *et al.* speculated that perhaps the quick decompression of the cyst lumen by LAMS leads to irritating friction of the surrounding vessels and causes hemorrhage. In particular, Lang *et al.* suggested that the wide cavity of the LAMS may allow more gastric acid to enter the cyst lumen, which leads to a low pH that may irritate the intracavitary vessels and stimulate hemorrhage. A multicenter retrospective study by Siddiqui *et al.* compared the clinical outcomes and AEs of EUS-guided drainage in WON patients with three different stents: DPPS, FCSEMS and LAMS. There was no statistically significant difference in the technical success among the three groups (99.05% vs 100% vs 97.7% respectively, P = 0.37). At a 6-mo follow-up, the clinical success rates of WON drainage using FCSEMS and LAMS were higher than in drainage performed with DPPS. More importantly, the hemorrhage rates were 1%, 0% and 7% with DPPS, FCSEMS and LAMS, respectively. The hemorrhage rate associated with WON drainage in the LAMS group was lower than that in the DPPS group (1%...
vs 7%).

A current systematic review and meta-analysis suggested that LAMS have superior efficacy and safety in the management of PFCs\(^{40}\). They may be preferred over plastic stents as they are associated with better clinical success and a lower AE rate. Similarly, a recent meta-analysis concluded that metal stents are superior to plastic stents for endoscopic drainage of PFCs because metal stents have a higher success rate and a lower AE rate\(^{58}\). However, a Spanish multicenter study by Vazquez-Sequeiros\(^{39}\) and a Japanese retrospective trial by Yamamoto et al\(^{56}\) suggest that the type of stent used may not influence whether bleeding occurs. A systematic review by Bang et al\(^{59}\) did not find any difference in terms of AE rates and treatment success between metal and plastic stents for endoscopic drainage of PFCs. To date, whether the type of stent affects the hemorrhage rate is controversial. There is no consensus on these issues. We speculate that perhaps the different characteristics of different types of stents are related to the controversial problems. The use of metal stents for PFC has the advantages of quick and easy deployment, large calibers and a high technical success rate but also have the disadvantages of difficult extubation and possible gastrointestinal tract injury; in contrast, plastic stents have the advantages of low cost, easy extubation, small calibers and easy deployment but have the disadvantages of poor visibility under fluoroscopy and a long treatment period\(^{60}\).

Additionally, a large retrospective study by Sharaiha et al\(^{47}\) included 230 patients with PPC treated with EUS-guided drainage. There was no statistically significant difference in the technical success rate between the DPPS and FCSEMS groups (92% vs 98%, \(P = 0.06\)), and the use of PS was associated with lower clinical success rates (89% vs 98%, \(P = 0.01\)) and higher rates of procedural AEs (31% vs 16%, \(P = 0.006\)). Multivariate analysis revealed that patients treated with PS were almost three times more likely to experience AE than those treated with FCSEMS. Regarding WON, there were no differences in the success and AE rates between the plastic and metal stent groups. Therefore, the study found that clinical outcomes are directly correlated with the type of fluid collections, and thus, accurate distinction is critical before any interventional therapy is conducted. Furthermore, in a study of 211 patients with symptomatic PFC, the treatment success rate for infective PPC was 93.5%, compared with only 63.2% for WON\(^{27}\). The researchers concluded that clinical results are directly associated with the type of fluid collections, and thus, rigid classification is helpful for choosing the appropriate treatment for different types of collections. We presume that the type of pancreatic collections is related to the occurrence of bleeding, which is due to the different intracavitary components. Many randomized controlled trials are needed to prove this assumption.

In addition to the abovementioned factors that can impact the occurrence of hemorrhage, it is possible that the size and location of PFC, the diameter and length of stents, the time and steps of the procedure, the timing of stent removal, the operator’s experience, and the general health condition of the patient may be related to the hemorrhage rate. Moreover, it is necessary to explore whether cautery dilator affects the clinical outcomes and bleeding events or not. Further details are shown in Table 4. Despite recent advances in interventional endoscopy, many questions remain. Future prospective, randomized, comparative studies on the current topic are thus recommended.

**HOW TO PREVENT THE OCCURRENCE OF HEMORRHAGE?**

What can we draw from the literature to further improve the endoscopic management of patients with bleeding? There are five factors that are critical to improve the treatment of hemorrhage. First, the implementation of a standard procedure is the most significant step for safe and successful EUS-guided drainage of PFC. It is important to strictly comply with the indications and contraindications prior to the process. Before the initial EUS, patients must undergo cross-sectional imaging via CT or MRI\(^{10}\). In addition, to prevent bleeding, coagulation function should be checked in high-risk patients or those with relevant history\(^{46}\). Furthermore, correct categorization of the PFCs is a vital and appropriate step in therapeutic management. Patients with PPC can be drained by straightforward stent placement, while WON requires a multidisciplinary treatment approach\(^{19}\). In addition, EUS, although a safe procedure in experienced hands, is not without AEs (including bleeding and perforation), and not all endoscopists have the technical expertise to perform such complicated procedures. In addition to the ability to master the EUS technique, mastery in the management of AE is compulsory\(^{61}\). Thus, it is crucial for the operator to obtain sufficient knowledge of the techniques and potential risks and to undergo additional specific training before performing any procedure\(^{67}\). Moreover, establishing a standard follow-up system management is essential; for example, what items need to be reviewed after an operation? When should the imaging check be reviewed? When should the stent be removed? A multi-center respective study by Vazquez-Sequeiros\(^{39}\) revealed a higher rate of delayed bleeding 3-6 mo after drainage, which suggests that it may be rational to remove the stent no later than 3 mo after placement. Therefore, follow-up CT and US are suggested for early assessment of the therapeutic effect to maximally reduce the risk of AE and improve the treatment effects, especially for patients with pseudoaneurysms\(^{62}\). Finally, we recommend that EUS-guided procedures be performed under Doppler guidance, which can reduce the risk of hemorrhage and the incidence of stent erosion into vessels when the cavity wall collapses.
Table 4  Details of clinical outcomes between cautery and non-cautery dilator in endoscopic ultrasound-guided drainage for pancreatic fluid collections

| Study              | Year | Country     | Design | Center | Stent style | No. | PFC style | Overall Technical success | Overall Clinical success | Overall bleeding rate | Dilated approaches | Cautery dilator |
|--------------------|------|-------------|--------|--------|-------------|-----|-----------|---------------------------|-------------------------|---------------------|-------------------|------------------|------------------|
| Lang et al.        | 2018 | United States | RS     | Single | LAMS/DDPS   | 103 | PPC/WON   | 99%                       | 95%                     | 3%                  | A + B             | YES              |
| Siddiqui et al.    | 2017 | United States | RS     | Multi  | LAMS/DDPS   | 313 | WON       | 99%                       | 90%                     | 5%                  | A + B             | YES              |
| Bapaye et al.      | 2017 | India         | RS     | Single | BMS/MPS     | 133 | WON       | 100%                      | 82%                     | 5%                  | A + C             | YES              |
| Lakhtakia et al.   | 2016 | India         | RS     | Single | FCSEMS      | 205 | WON       | 99%                       | 75%                     | 3%                  | A + C             | YES              |
| Siddiqui et al.    | 2016 | United States | RS     | Multi  | LAMS        | 82  | PPC/WON   | 86% PPC                   | 100% PPC                | 7%                  | A + B             | YES              |
| Ang et al.         | 2016 | Singapore     | RS     | Multi  | FCSEMS/SDPS | 49  | PPC/WON   | 100%                      | 96%                     | 4%                  | A + B + C         | YES              |
| Vasquez-Sequeiros et al. | 2016 | Spanish       | RS     | Multi  | FCSEMS      | 211 | PPC/WON   | 97%                       | 94%                     | 7%                  | A + B + C         | YES              |
| Sharaiha et al.    | 2015 | United States | RS     | Multi  | LAMS/DDPS   | 124 | WON       | 100%                      | 86%                     | 3%                  | A + B + C         | YES              |
| Sharaiha et al.    | 2015 | United States | RS     | Multi  | ECSEMS/DDPS | 230 | PPC       | 96%                       | 90%                     | 4%                  | A + B             | YES              |
| Gormals et al.     | 2015 | Spain         | RS     | Single | LAMS        | 12  | WON       | 100%                      | 100%                    | 17%                 | A + C             | YES              |
| Mukai et al.       | 2015 | Japan         | RS     | Single | FC BFMS/DDPS| 70  | WON       | 100%                      | 96%                     | 4%                  | A + C             | YES              |
| Lee et al.         | 2014 | South Korea   | PS     | Single | Plastic FCSEMS/DDPS | 50 | PPC       | 100%                      | 10%                     | 2%                  | A + B             | YES              |
| Puri et al.        | 2012 | India         | PS     | Single | DDPS        | 40  | PPC       | 100%                      | 98%                     | 3%                  | A + B             | YES              |
| Itoi et al.        | 2012 | Japan         | RS     | Single | LAMS        | 15  | PPC       | 100%                      | 100%                    | 20%                 | A + C             | YES              |
| Bang et al.        | 2017 | United States | RCT    | Single | LAMS/DDPS   | 21  | WON       | NR                        | NR                      | 14%                 | A                | NO               |
| Rinninella et al.  | 2015 | Italy         | RS     | Multi  | FCSEMS      | 9   | PPC/WON   | 99%                       | 93%                     | 1%                  | A                | NO               |
| Yamaomo et al.     | 2013 | Japan         | RS     | Single | FCSEMS      | 9   | PPC/DPS   | 100%                      | 78%                     | 11%                 | A                | NO               |
| Bang et al.        | 2013 | United States | RS     | Multi  | MTGT        | 53  | WON       | NR                        | 70%                     | 1%                  | A                | NO               |
| Varadaraju et al.  | 2011 | United States | RS     | Single | DDPS        | 211 | PPC/WON   | NR                        | 85%                     | 1%                  | A + D             | NO               |
| Varadaraju et al.  | 2011 | United States | PS     | Single | DDPS        | 110 | PPC/WON   | 100%                      | 92%                     | 1%                  | A + D             | NO               |
| Talreja et al.     | 2008 | United States | PS     | Single | FCSEMS      | 18  | PPC       | 95%                       | 78%                     | 13%                 | A                | NO               |

PPC: Pancreatic pseudocyst; WON: Walled-off necrosis; PFC: Pancreatic fluid collections; PS: Prospective study; RS: Retrospective study; RCT: Randomized controlled trial; Single: Single-center; Multi: Multi-center; FCSEMS: Fully covered self-expandable metal stent; LAMS: Lumen-apposing metal stents; DDPS: Double-pigtail plastic stents; BFMS: Fully covered bi-flanged metal stents; MPS: Multiple plastic stents; MTGT: Multiple transluminal gateway technique; ERCP: Endoscopic retrograde cholangiopancreatography; NR: Not reported.

In conclusion, this study demonstrates for the first time that an integrated and novel algorithm can be used to manage hemorrhage in EUS-guided drainage of PFCs and provides an initial and clinically meaningful treatment strategy for AEs. Hemorrhage presents a challenging problem for physicians, and the multidisciplinary and multicenter collaboration of accomplished endoscopists, radiologists, biomedical engineers, and surgeons is necessary to manage cases of severe bleeding and other AEs. Prospective, multi-center studies with larger sample sizes may be necessary to overcome the limitations and generalize these results. In the future, we aim to formulate optimal treatments and present additional works on bleeding treatment. The development of new implementation and equipment is the basis for alternative minimally invasive approaches to various pancreatic diseases and will make this technique safer and more effective.
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P- Reviewer: Friedel D, Kitamura K, Velayos B S- Editor: Ma YJ L- Editor: Filipodia E- Editor: Wu YXJ
