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# Management of chronic pancreatitis complicated with a bleeding pseudoaneurysm

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and to evaluate the associated complications such as pseudocyst formation, followed by arterial embolization to stop the bleeding and to achieve early stabilization of the patient's condition. With advances and improvements in endoscopic devices and techniques, therapeutic endoscopy for pancreatic pseudocysts is technically feasible, safe and effective. Surgical intervention is recommended for a bleeding pseudoaneurysm in patients with chronic pancreatitis who are in an unstable condition, for those in whom arterial embolization of the bleeding pseudoaneurysm fails, and when endoscopic management of the pseudocyst is unsuccessful. If a bleeding pseudoaneurysm is located over the tail of the pancreas, resection is a preferential procedure, whereas if the lesion is situated over the head or body of the pancreas, relatively conservative surgical procedures are recommended.

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**Key words:** Chronic pancreatitis; Pseudocyst; Pseudoaneurysm bleeding; Arterial embolization; Endoscopy; Surgery

## Abstract

Chronic pancreatitis is an ongoing disease characterized by persistent inflammation of pancreatic tissues. With disease progression, patients with chronic pancreatitis may develop troublesome complications in addition to exocrine and endocrine pancreatic functional loss. Among them, a pseudoaneurysm, mainly induced by digestive enzyme erosion of vessels in proximity to the pancreas, is a rare and life-threatening complication if bleeding of the pseudoaneurysm occurs. At present, no prospective randomized trials have investigated the therapeutic strategy for this rare but critical situation. The role of arterial embolization, the timing of surgical intervention and even surgical procedures are still controversial. In this review, we suggest that dynamic abdominal computed tomography and angiography should be performed first to localize the bleeders

**Core tip:** Chronic pancreatitis complicated with a bleeding pseudoaneurysm is a life-threatening condition. Therapeutic strategies for this rare disease remain controversial. In this review, surgical treatment as a first-line therapy is associated with a high mortality rate in emergency situations. Dynamic abdominal computed tomography and angiography should be performed as the initial management strategy to localize the bleeder, followed by embolization to control the bleeding to achieve early stabilization of the patient's condition. Surgical intervention should be performed for patients who are unable to undergo or who fail arterial embolization for pseudoaneurysm bleeding, or when endoscopic management of the pseudocyst is unsuccessful.

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## INTRODUCTION

Chronic pancreatitis (CP) is a long-standing disease characterized by chronic persistent inflammation, leading to permanent duct deformity and insufficiency of both endocrine and exocrine functions. The real incidence and prevalence of CP is hard to estimate due to the lack of exact diagnostic criteria. In general, CP patients present with the classic triad of pancreatic calcifications, steatorrhea, and diabetes mellitus, which are usually seen in very advanced disease. The diagnosis of CP mainly depends on the presentation of typical clinical presentations, imaging findings, pathological features, or exocrine functional insufficiency alone or in combination<sup>[1]</sup>.

The approximate annual incidence of CP is around 7-10 per 100000 people<sup>[2]</sup>. The causes of CP are complex and involve both environmental and genetic factors. Alcohol consumption, nicotine usage, pancreatic duct obstruction, hyperlipidemia, hypercalcemia, and autoimmune diseases are thought to be the most common causes<sup>[1,3,4]</sup>. Among them, alcohol has been deemed as the leading cause of CP, accounting for 60% and 35% of CP patients in Western countries and China, respectively<sup>[3]</sup>. The cumulative incidence of CP was 13% in 10 years and 16 % in 20 years<sup>[5]</sup>. Whether acute pancreatitis (AP) may progress to CP is still controversial. Post-mortem examinations in 405 patients who died of AP showed that the majority of patients had no histological signs of CP<sup>[6]</sup>. Different experimental models of AP did not provide evidence of AP progressing to CP<sup>[7,8]</sup>. A study recruiting 532 patients with initial attack of AP with an average follow-up time of 7.8 years showed that the progression from AP to CP occurred only in alcoholics. In addition, smoking significantly enhanced the risk of progression from alcoholic AP to CP<sup>[5]</sup>. Besides the insufficiency of endocrine and exocrine functions, abdominal pain is the major symptom of CP. Moreover, during CP development and progression, complications such as pseudocyst formation, mechanical obstruction of the gastrointestinal tract and common bile duct, pancreatic ascites, pleural effusion, splenic vein thrombosis with portal hypertension and subsequent varices bleeding, and pseudoaneurysm formation may occur<sup>[4]</sup>. Due to the recent improvements in endoscopy techniques and instrumentation, most of the abovementioned complications can be treated by endoscopy and medical treatment<sup>[9]</sup>. The exception is a pseudoaneurysm, which can be a lethal complication of CP if bleeding occurs. For patients without appropriate treatment, the mortality rate may be as high as 90%. Even with a rapid diagnosis and immediate therapy, the reported mortality rate still ranges from 15% to 50%<sup>[10,11]</sup>. With advances in

radiological techniques and instrumentation in the past decade, angiography followed by embolization has been widely used and plays an important role in the diagnosis and management of this situation. To date, therapeutic strategies for CP complicated with pseudoaneurysm bleeding remain controversial. The urgent condition of CP-associated pseudoaneurysm bleeding complicates the management, and thus makes prospective randomized trials difficult. Reports on CP complicated with pseudoaneurysm bleeding are mainly retrospective, and most are from a single institute or limited case reports. Arterial embolization or surgical intervention is currently widely utilized in managing this rare life-threatening condition. In this review, we focus on CP complicated with pseudoaneurysm bleeding with the aim of providing better and reasonable therapeutic strategies to treat this rare but critical situation.

## ASSOCIATION OF CP AND PSEUDOANEURYSMS

Pseudoaneurysm formation associated with CP is a rare complication resulting from the erosion of pancreatic or nearby vessels by leaked pancreatic juice. This persistent vessel erosion leads to permanent communication of invaded vessels to the CP-induced pseudocyst, giving rise to the formation of a pancreatic pseudoaneurysm. The majority of related studies have included cases of CP-related vessel injury, which is not associated with pseudocyst formation, as pancreatic pseudoaneurysms for analysis. Three possible mechanisms have been reported to account for the formation of pancreatic pseudoaneurysms: (1) vessel disruption with pseudoaneurysm formation due to severe inflammation and/or pancreatic enzyme autodigestion of a pancreatic or peripancreatic artery; (2) communication of an established pseudocyst and a peripancreatic vessel converting the pseudocyst into a large pseudoaneurysm; and (3) a pseudocyst eroding the bowel wall with bleeding<sup>[12,13]</sup>. Although the occurrence of a pseudoaneurysm in CP is uncommon, once ruptured it may bleed into the gastrointestinal tract or pancreatic duct, both mimicking gastrointestinal tract bleeding and delaying the correct diagnosis, or directly bleed into the peritoneal or retroperitoneal cavity leading to unstable hemodynamic status and a high mortality rate. The reported incidence of CP complicated with pseudoaneurysm bleeding ranges from 4% to 10%<sup>[14-17]</sup>. The splenic artery is most frequently involved, followed by the gastroduodenal, pancreaticoduodenal, and hepatic arteries<sup>[18]</sup>.

## DIAGNOSIS OF CP COMPLICATED WITH PSEUDOANEURYSM BLEEDING

Since gastrointestinal tract bleeding in patients with CP is usually attributable to stress-related peptic ulcers, erosive gastritis, or varices over the gastric fundus, and as a

pseudoaneurysm may also bleed into the digestive tract, it is difficult to differentiate pseudoaneurysm bleeding from other causes of gastrointestinal tract bleeding in patients with CP. However, the early detection and localization of a bleeding pseudoaneurysm is very important for further management, and key to improving patient survival. Ultrasonography is of little value in this respect, although several studies have demonstrated a successful diagnosis of a pseudoaneurysm using this method<sup>[19]</sup>. Marshall *et al.*<sup>[20]</sup> reported that dynamic-contrast abdominal computed tomography (CT) should be the first choice of diagnostic tool for CP complicated with a pseudoaneurysm, as it can delineate the anatomy and location of the bleeding pseudoaneurysm in detail. In addition, Balthazar *et al.*<sup>[21]</sup> also suggested that dynamic CT can not only identify the bleeding pseudoaneurysm but also other CP-associated complications. Several studies have shown that angiography is extremely valuable, with sensitivity rates of more than 90% in localizing bleeding pseudoaneurysms<sup>[10,18,22,23]</sup>. In agreement with their findings, our previous study demonstrated that sonography and dynamic abdominal CT identified pseudoaneurysms in 2 of 5 patients (40.0%) and 4 of 7 patients (57.1%), respectively<sup>[24]</sup>. Furthermore, angiography led to a correct diagnosis in 7 patients with a sensitivity rate of 100%<sup>[24]</sup>. Collectively, angiography seems to be a preferential diagnostic tool for CP complicated with pseudoaneurysm bleeding, and we suggest that it should be performed as soon as possible if there is a high index of suspicion of this diagnosis.

## ARTERIAL EMBOLIZATION IN CP COMPLICATED WITH PSEUDOANEURYSM BLEEDING

With the enormous improvements in radiological techniques and instrumentation, angiography has been widely used to detect visceral arterial bleeding sites with subsequent arterial embolization to stop the bleeding in the past decade. A radiological vascular approach has been shown to be effective for CP patients with pseudoaneurysm bleeding. In the study of Udd *et al.*<sup>[17]</sup>, 33 patients with CP complicated with pseudoaneurysm bleeding were identified from 745 CP patients, and angioembolization successfully stopped the bleeding in 22 of these patients. Only 3 patients experienced rebleeding requiring re-embolization. The success rate varied according to the bleeding site, with an 80% success rate for bleeders around the pancreatic head and 50% for those of the splenic artery<sup>[17]</sup>. Tulsyan *et al.*<sup>[25]</sup> reported that endovascular treatment of visceral artery aneurysms and pseudoaneurysms was technically successful in 98% of 48 procedures, with a 30-d mortality rate of 8.3% ( $n = 4$ ). However, 3 patients required secondary interventions for persistent flow ( $n = 1$ ) and rebleeding from the previously embolized aneurysms ( $n = 2$ )<sup>[25]</sup>. In addition, Bergert *et al.*<sup>[22]</sup> enrolled 35 patients (8 with necrotizing

pancreatitis and 27 with CP) with bleeding pseudoaneurysms treated over a period of 10.5 years with a median follow-up of 4.6 years. Angiographic embolization was performed as the initial treatment in 16 patients (61% embolization rate) with 2 rebleeding, and a mortality rate of 19% for the patients undergoing embolization. In our previous study, 2 of 9 patients with CP complicated with pseudoaneurysm bleeding received emergency angioembolization as first-line therapy<sup>[24]</sup>. The bleeding was stopped after the procedure, however, both patients developed rebleeding later<sup>[24]</sup>. To date, the rebleeding rate of pseudoaneurysm bleeding in patients with CP after angioembolization is unclear due to the high heterogeneity of patients recruited in each study. Nevertheless, the application of angiography and angioembolization as first-line therapy to locate the bleeding site and stop the bleeding to stabilize vital signs in patients with bleeding pseudoaneurysms seems to be a reasonable therapy strategy, and is widely used in current clinical practice<sup>[17,22,23,26,27]</sup>.

## SURGERY FOR PSEUDOANEURYSM BLEEDING IN PATIENTS WITH CP

Since CP is a disease characterized by ongoing inflammatory processes, some studies recommend that embolization should be considered a temporary procedure to control bleeding, and that subsequent surgical intervention should be conducted as soon as possible to prevent rebleeding<sup>[26]</sup>. In general, surgical procedures including direct arterial ligation with drainage of a pseudocyst or partial pancreatectomy are used to treat pseudoaneurysm bleeding in patients with CP. Bresler *et al.*<sup>[12]</sup> reported the results of surgical therapy for 10 patients with CP complicated with pseudoaneurysm bleeding. The surgical procedures included trans cystic arterial ligation and external pancreatic pseudocyst drainage in 5 patients, distal pancreatectomy in 3 patients, and pancreaticoduodenectomy in 2 patients. One patient (10%) died of sepsis after pancreaticoduodenectomy. However, there was no rebleeding after surgery in their study leading them to conclude that surgical therapy is an acceptable procedure to treat pseudoaneurysm bleeding in patients with CP. Distal pancreatectomy was also recommended for patients with bleeders situated in the tail of the pancreas, while trans cystic arterial ligation was suitable for the patients with the bleeder located at the head and body of the pancreas<sup>[10]</sup>. In another study enrolling 6 patients with CP complicated with pseudoaneurysm bleeding, the authors suggested that primary resection of the pseudoaneurysm should be the treatment of choice<sup>[26]</sup>. The authors considered that although angiography followed by transcatheter embolization is effective in this regard, it should be considered as a bridging therapy and definite surgical intervention should be conducted as soon as possible, since CP is an ongoing process<sup>[26]</sup>. Udd *et al.*<sup>[17]</sup> also suggested that patients with unsuccessful arterial embolization should undergo emergency hemostatic

**Table 1** Summary of studies concerning chronic pancreatitis-related bleeding

Ref.	Study design	n	Intervention	Comments
Gambiez <i>et al</i> <sup>[10]</sup>	Retrospective	14	Angioembolization or surgery	The immediate effectiveness of arterial embolization was remarkable. Subsequent surgery should be reserved for patients in a good general condition with other chronic pancreatitis (CP)-related complications that are not amenable to minimally invasive techniques
El Hamel <i>et al</i> <sup>[11]</sup>	Retrospective	15	Surgery	Favorable results were achieved in two-thirds of patients undergoing primary pancreatic resection which is recommended whenever possible for the treatment of bleeding pancreatic pseudocysts and pseudoaneurysms associated with CP
Udd <i>et al</i> <sup>[17]</sup>	Retrospective	33	Angioembolization or surgery	All hemodynamically stable patients with CP and bleeding pseudoaneurysms should undergo prompt initial angiographic evaluation and embolization if possible. Emergency hemostatic surgery is indicated for unsuccessful embolization
Bergert <i>et al</i> <sup>[22]</sup>	Retrospective	27	Angioembolization or surgery	Angioembolization is effective to stop CP-related bleeding. Partial pancreatectomy is superior to vessel ligation
Hsu <i>et al</i> <sup>[24]</sup>	Retrospective	9	Angioembolization and/or surgery	Angiography is valuable in localizing bleeding pseudoaneurysms. Patients with bleeding pseudoaneurysms associated with CP treated surgically seemingly obtained good outcomes
de Perrot <i>et al</i> <sup>[26]</sup>	Retrospective	6	Angioembolization and/or surgery	Angiography followed by transcatheter embolization is effective to stop bleeding. Pancreatic resection should be performed for the treatment of pseudoaneurysms
Savastano <i>et al</i> <sup>[27]</sup>	Retrospective	8	Angioembolization and/or surgery	Angioembolization is effective to stop acute bleeding in CP to achieve a stable condition quickly. Subsequent surgery is needed to obtain definite treatment
Bhasin <i>et al</i> <sup>[31]</sup>	Retrospective	8	Percutaneous thrombin injection/embolization and endoscopic retrograde transpapillary drainage of pseudocyst	Embolization followed by transpapillary drainage is effective to manage CP patients complicated with a bleeding pseudocyst

surgery with ligation of the bleeding vessel in the head of the pancreas, and distal pancreatectomy for bleeding from the splenic artery or its branch. Furthermore, Bergert *et al*<sup>[22]</sup> found that ligation or repair of the bleeding vessel was associated with higher rebleeding and reintervention rates, and that partial pancreatectomy was the preferred choice of treatment. In our previous investigation, 7 patients received emergency ( $n = 4$ ) and elective ( $n = 3$ ) surgery as the initial therapy, and all of them survived without rebleeding<sup>[24]</sup>. In addition, 5 patients underwent surgical treatment for associated pseudocysts, and no cases of rebleeding occurred<sup>[24]</sup>. With advances and improvements in endoscopic devices and techniques in the last decade, successful endoscopic management of CP-associated pseudocysts has been reported<sup>[28-30]</sup>. Weckman *et al*<sup>[29]</sup> reported 170 CP patients with pancreatic pseudocysts who were treated endoscopically, with a success rate of 86% and no procedure-related mortality. Nonetheless, 23 (14%) patients required surgical interventions because therapeutic endoscopy was unsuccessful or technically impossible<sup>[29]</sup>. In addition, Bhasin *et al*<sup>[31]</sup> reported 8 CP patients with pseudoaneurysms associated with pseudocysts who underwent radiological arterioembolization or thrombin injections followed by successful endoscopic transpapillary drainage through the major ( $n = 5$ ) or minor papilla ( $n = 3$ ), and resolution of the pseudocysts was noted within 6 wk with no significant complications related to the procedures. Taken together, the role of emergency surgery for bleeding pseudoaneurysms in patients with CP is still controversial. However, considering the substantial surgery-related morbidity

and mortality rates when used as the initial therapy for pseudoaneurysm bleeding in patients with CP under emergency conditions, most recent studies suggest that surgical intervention should be performed in patients who are unable to undergo or who fail arterial embolization for pseudoaneurysm bleeding, or when endoscopic management of the pseudocyst is unsuccessful<sup>[17,22,31,32]</sup>.

## CONCLUSION

A pseudoaneurysm is a rare complication in patients with CP, and is caused mainly by erosion of nearby vessels due to digestive enzyme leakage. Life-threatening conditions with subsequent high mortality rates may develop once pseudoaneurysm bleeding occurs without appropriate management. Table 1 summarizes the studies on interventions for CP patients complicated with pseudoaneurysm bleeding and comments on the treatment. To date, therapeutic strategies for pseudoaneurysm bleeding in patients with CP remains challenging and are still under debate due to the lack of prospective randomized trials and the available data having very high heterogeneity with different conclusions. Nonetheless, it is widely accepted that surgical treatment as a first-line therapy is associated with a high mortality rate in emergency situations. Most authors in recent publications suggest that dynamic abdominal CT and angiography should be performed as the initial management strategy to localize the bleeder, followed by embolization to control the bleeding to achieve early stabilization of the patient's condition. Surgical intervention should be per-



formed for patients who are unable to undergo or who fail arterial embolization for pseudoaneurysm bleeding, or when endoscopic management of the pseudocyst is unsuccessful. If a bleeding pseudoaneurysm is located over the tail of the pancreas, resection is the preferred procedure, whereas for lesions situated over the head or body of the pancreas, relatively conservative surgical procedures are recommended.

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