

# World Journal of *Gastroenterology*

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## Pancreatitis: Preventing catastrophic haemorrhage

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### Abstract

Pancreatitis represents nearly 3% of acute admissions to general surgery in United Kingdom hospitals and has a mortality of around 1%-7% which increases to around 10%-18% in patients with severe pancreatitis. Patients at greatest risk were those identified to have infected pancreatic necrosis and/or organ failure. This review seeks to highlight the potential vascular complications associated with pancreatitis that despite being relatively uncommon are associated with mortality in the region of 34%-52%. We examine the current evidence base to determine the most appropriate method by which to image and treat pseudo-aneurysms that arise as the result of acute and chronic inflammation of pancreas. We identify how early recognition of the presence of a pseudo-aneurysm can facilitate expedited care in an expert centre of a complex pathology that may require angiographic, percutaneous, endoscopic or surgical intervention to prevent catastrophic haemorrhage.

**Key words:** Complication of pancreatitis; Splenic artery; Pancreatitis; Haemorrhage; Pseudoaneurysm

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**Core tip:** Pancreatitis represents nearly 3% of acute admissions to general surgery in United Kingdom hospitals. The presence of a fluid collection, necrosis and infection can directly contribute to such vascular complications which are associated with a significant morbidity and mortality. Early recognition of the presence of a pseudo-aneurysm can facilitate expedited care in an expert centre of a complex pathology that



may require angiographic, percutaneous, endoscopic or surgical intervention to prevent catastrophic haemorrhage.

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## INTRODUCTION

Pancreatitis represents nearly 3% of acute admissions to general surgery in United Kingdom hospitals<sup>[1]</sup>. Although this may seem like a relatively small proportion of patients the impact of the pancreatic patient has a significant influence on hospital services due to the sizeable morbidity and mortality associated with pancreatitis. The annual incidence of acute pancreatitis ranges from 13 to 45 per 100000 persons worldwide and is around 13-45 per 100000 people in the United Kingdom which is increasing at a rate of 2.7% each year<sup>[2-6]</sup>. The number of admissions due to pancreatitis in the US has doubled since 1988. There are now nearly 275000 admissions each year due to pancreatitis<sup>[7,8]</sup>. It is estimated that between 20%-30% of patients will have a further episode of acute pancreatitis and 10% of patients will go on to develop chronic pancreatitis<sup>[9-12]</sup>. The current incidence rates of chronic pancreatitis are around 5-23 per 100000 people<sup>[5,13,14]</sup>. Pancreatitis has a mortality of around 1%-7% which increases to around 10%-18% in patients with severe pancreatitis<sup>[1-4,15]</sup>. Patients at greatest risk were those identified to have infected pancreatic necrosis and/or organ failure<sup>[16]</sup>.

In order to appropriately manage patients with pancreatitis multiple scoring systems have been created to try to determine the severity of pancreatitis and the risk of morbidity and mortality including the Glasgow score, Ransom score, Balthazar score, Apache 2 score, and the modified Marshall score<sup>[17-19]</sup>. Many continue to be used routinely in clinical practice to improve the treatment of patients with pancreatitis. Understanding that certain patients with more severe pancreatitis have a higher risk of morbidity and mortality allows clinicians to maintain a high index of suspicion in order to identify early the complications of pancreatitis. The revised Atlanta guidelines identify two key phases to acute pancreatitis. In early phase it is associated with systemic disturbances as the result of the host response to local pancreatic injury<sup>[17]</sup> (Table 1). The cytokine cascade as the result of pancreatic inflammation can be clinically manifested as a systemic inflammatory response syndrome which in turn may precipitate organ failure. The presence and duration of organ failure is a key determinant in defining severity

of acute pancreatitis (Table 2). Late phase pancreatic inflammation is defined by the presence of ongoing systemic symptoms of inflammation such as persistent organ failure or local complications.

Local complications of pancreatitis often cause patients to develop a late phase pancreatitis. Interstitial oedematous pancreatitis with or without necrosis may be complicated by the presence of pancreatic and peri-pancreatic collections. The presence of such collections can be broadly divided into five categories. Acute peri-pancreatic fluid collections usually arise in the acute phase of pancreatitis and are confined with normal anatomical planes. They commonly remain sterile however if they persist for greater than 4 wk they commonly form into a pseudocyst. A pancreatic pseudocyst is formed beyond 4 wk and demonstrates a walled off fluid collection in the absence of necrosis. The presence of necrosis can be categorised as either an acute necrotic collection (ANC) or a walled off necrosis (WON). Infected necrosis may occur in either ANC or WON and will present with the presence of gas within the collection on imaging or positive microbiological samples taken directly from the area of necrosis (Table 3). Acute and chronic inflammation as a result of pancreatitis can cause both thrombotic and haemorrhagic complications. The presence of a fluid collection, necrosis and infection can directly contribute to such vascular complications which are associated with a significant morbidity and mortality.

## ARTERIAL COMPLICATIONS IN ACUTE PANCREATITIS

### *Incidence, causes, and presentations*

Vascular complications are relatively uncommon and occur in between 1%-23% of patients with pancreatitis. Venous complications are significantly more common than arterial complications. Arterial complications occur in around 1.3%-10% of patients<sup>[20-28]</sup>. Thrombosis of the portal and splenic vein has been shown to occur up to 23% and 22% of patients with pancreatitis respectively<sup>[23,29]</sup>. Portal vein thrombosis increases to 30% in those with peri-pancreatic collection and as high as 57% in patients with necrotising pancreatitis (Table 4)<sup>[29]</sup>.

It is important to identify arterial complications early and treat aggressively as they are associated with a mortality of between 34%-52%<sup>[26,28,30-35]</sup>. Sixty percent of all acute haemorrhage in the presence of pancreatitis occurs as the result of ruptured pseudo-aneurysms in the presence of necrotising pancreatitis. Haemorrhagic pseudocysts without pseudoaneurysms and capillary, venous or small vessel haemorrhage only account for approximately 20% of cases<sup>[22]</sup>.

Arterial complications often arise as the result of arterial wall disruption in the presence of free lipolytic and proteolytic enzymes. Severe pancreatic inflammation and necrosis leads to the disruption

**Table 1 Early vs late pancreatitis**

| Early phase pancreatitis   | Late phase pancreatitis                        |
|--|--|
| Systemic disturbances result from the host response to local pancreatic injury.        | Persistence of systemic signs of inflammation. |
| Clinical manifestation with associated SIRS response.                                  | Presence of local complications.               |
| Usually lasts less than one week but may extend into the second week.                  | Compensatory inflammatory response syndrome.   |
| Severity determined by presence of organ failure. Transient < 48 h. Persistent > 48 h. |  |

**Table 2 Defining pancreatic severity**

|                                      |  |
|--------------------------------------|--|
| Mild acute pancreatitis              | No organ failure<br>No local complications   |
| Moderately severe acute pancreatitis | Organ failure that resolves within 48 h (transient organ failure) and/or<br>Local or systemic complications without persistent organ failure |
| Severe acute pancreatitis            | Persistent organ failure (single/multiple) > 48 h  |

**Table 3 Defining pancreatic and peri-pancreatic collections**

|  |   |
|--|---|
| Acute peri-pancreatic fluid collection | Do not have well defined walls<br>Homogenous, confined to normal fascial planes in retroperitoneum<br>May be multiple<br>Likely to develop into a pseudocyst if they persist > 4 wk |
| Pancreatic pseudocyst                  | Fluid collection in peri-pancreatic tissues<br>Occasionally partly/totally intra-pancreatic<br>Well defined wall with essentially no solid material<br>Occur typically after 4 wk   |
| Acute necrotic collection              | Fluid collection within the first 4 wk containing necrotic tissue and fluid.<br>Presence of necrosis differentiates it from APFC  |
| Walled off necrosis                    | Necrotic tissue contained within an enhancing wall of reactive tissue<br>Usually occurs > 4 wk after the onset of necrotising pancreatitis  |
| Infected necrosis                      | Presence of gas within collection<br>Positive cultures post FNA   |

APFC: Acute peri-pancreatic fluid collection.

of pancreatic tissue and subsequent pancreatic fluid release which has a high enzymatic content. These disruptive processes are further proliferated by the cytokine cascade that develops due to pancreatitis. Such processes in combination with pressure necrosis can lead to pseudo-aneurysm formation or spontaneous arterial rupture. Bleeding may also develop from the disruption of the wall of a pseudocyst or WON.

The presence of radiologically inserted drains can also cause direct trauma to vessels. Drains can perpetuate local inflammation which in turn can further diminish arterial wall integrity. Surgical intervention in the form of necrosectomy can disrupt arterial integrity

**Table 4 Different types and incidence of vascular complications in pancreatitis**

| Vascular complications of pancreatitis           | Incidence                                    |
|--|--|
| Arterial complications                           | 1.3%-10% of patients with pancreatitis       |
| Ruptured pseudo-aneurysm                         | 60% of all acute haemorrhage in pancreatitis |
| Haemorrhagic pseudocysts without pseudoaneurysms | 20% of all acute haemorrhage in pancreatitis |
| Capillary, venous or small vessel haemorrhage    | 20% of all acute haemorrhage in pancreatitis |
| Venous complications                             | 1%-23% of patients with pancreatitis         |
| Portal vein thrombosis                           | 23% of patients with pancreatitis            |
| Splenic vein thrombosis                          | 22% of patients with pancreatitis            |
| Superior mesenteric vein thrombosis              | 19% of patients with pancreatitis            |

and lead to the development of arterial complications. Multi organ failure, necrosis, peri-pancreatic infection, long-term anticoagulation and underlying vasculitis all increase the risk of vascular complications<sup>[35]</sup>. Pancreatic necrosis is specifically associated with an increased risk of major haemorrhage<sup>[28]</sup>. There is no evidence to confirm that fungal infections confer an increased risk of pseudoaneurysm formation in pancreatitis as compared to bacterial infection, however anecdotally in immunosuppressed patients fungal infections are closely associated with pseudoaneurysm formation. Due to the significant structural integrity of arteries the time taken for a pseudo-aneurysm to form can vary greatly from weeks to even years<sup>[22,29,36]</sup>.

Although we are aware of certain risk factors for haemorrhage associated with pseudo-aneurysms it is challenging to quantify the impact that acute vs chronic inflammation has on vessel stability. Current evidence on acute haemorrhage is predominantly small volume case series of a mixed population of patients who have been treated for acute haemorrhage. However Zyromski *et al*<sup>[37]</sup> identified 24 patients with a pseudoaneurysm associated with pancreatitis of which 22 patients had acute on chronic pancreatitis and 2 patients presented during their first episode of acute pancreatitis. Twenty-one patients had a collection or pseudocyst and 2 had identifiable necrosis. Sethi *et al*<sup>[38]</sup> demonstrated that of those undergoing mesenteric angiography for bleeding associated with pancreatitis 8 had acute pancreatitis and 8 had chronic pancreatitis. Within the acute population three patients were diagnosed with necrotising pancreatitis and one required necrosectomy. Seven of the eight patients with chronic pancreatitis had confirmed pseudocyst formation and one developed acute necrosis on a background of chronic pancreatitis. Udd *et al*<sup>[21]</sup> looked at 33 patients with chronic pancreatitis and bleeding pancreatic pseudoaneurysms. They showed that 1.7% of admissions related to chronic pancreatitis

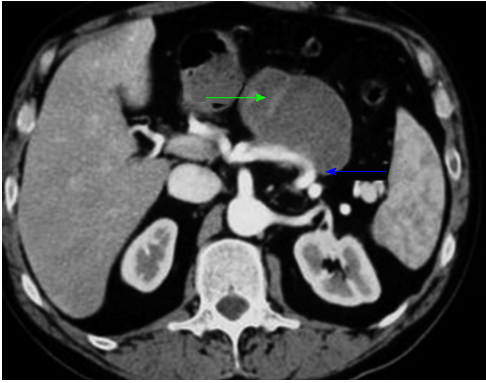


Figure 1 Computed tomography arterial and venous phase showing a pseudocyst (green arrows) eroding the splenic artery (blue arrows)<sup>[90]</sup>.

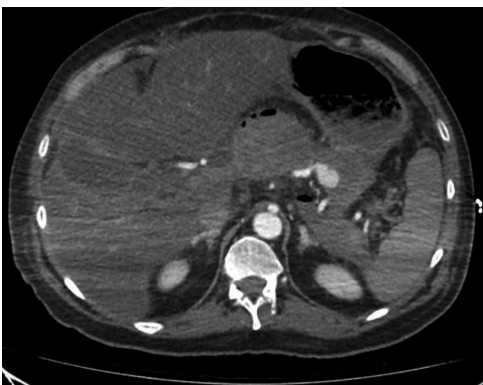


Figure 2 Computed tomography arterial and venous phases showing a pseudoaneurysm in a patient with necrotizing pancreatitis.



Figure 3 Three-D coronal maximum-intensity-projection computed tomography image in a 45-year-old man who had remote history of pancreatitis presented with back pain showing 2.0-cm pseudoaneurysm (arrow) arising from splenic artery<sup>[91]</sup>.

were due to haemorrhage. They found that within the study population seven had pseudocysts two of which required percutaneous drainage and six patients had undergone a previous operation. There is no definitive evidence to show that patients with chronic pancreatitis and pseudocyst formation are at greater risk of developing arterial complications as compared to patients with severe acute pancreatitis with necrosis

yet both are at high risk.

Symptomatic pseudo-aneurysms can present in varying ways however the most common symptom described is abdominal pain. Around 29.5% of patients will have abdominal pain which may reflect bleeding in the retroperitoneum. However there is a degree of ambiguity in the cause of such symptoms as pancreatitis in itself is painful. Bleeding into the gastrointestinal tract can occur in around 26.5% with haemosuccus pancreaticus (haemorrhage into pancreatic duct) being present in 20% of patients and also bleeding in pancreatic pseudocyst (Figure 1)<sup>[39]</sup>. Symptomatology is also dependent on the anatomical location of the pseudo-aneurysm.

#### Site of pseudoaneurysm

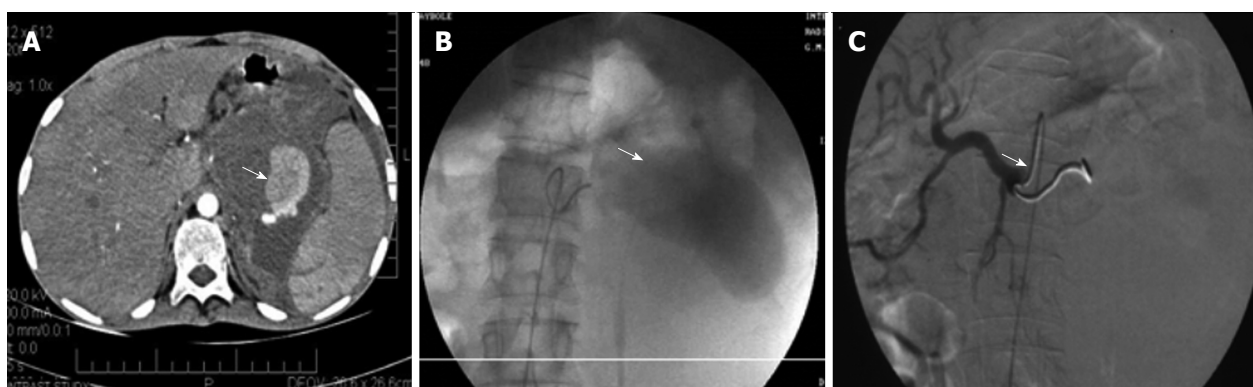
The most common site for pseudo-aneurysms is the splenic artery which occurs 35%-50% of occasions (Figures 2 and 3). The gastroduodenal and pancreaticoduodenal vessels each account for 20%-25% of pseudo-aneurysms. Mesenteric, colic and hepatic vessels commonly make up the remaining sites<sup>[20,31,40-50]</sup>. Aortic involvement can occur in up to 0.5% of cases<sup>[51,52]</sup>. Case reports have also identified individual cases of the left sub-capsular renal artery and the left phrenic artery<sup>[53,54]</sup>. Vessels in close proximity to the gastrointestinal tract have a greater risk of manifesting as luminal bleeding.

#### Imaging diagnosis

Identification of a pseudo-aneurysm is typically by CT imaging however the indication for imaging can vary<sup>[22,30,55]</sup>. Ultrasound has been shown to be less sensitive than CT in identifying such complications however, still has an important role in identifying venous complications such as portal vein thrombosis<sup>[29,56]</sup>. It may also have a limited role in those allergic to iodine and certain cases of renal insufficiency<sup>[57]</sup>. Current guidance for patients with complicated pancreatitis with evidence of significant inflammation, infection and/or organ dysfunction is to undergo planned cross-sectional imaging in order to determine whether there is a complication of pancreatitis. Cross-sectional imaging for pancreatitis should occur a minimum of 72 h after the onset of symptoms unless there is diagnostic ambiguity<sup>[58]</sup>. At present there is no strong evidence to differentiate between the use of CT and MRI however MRI may show greater detail in differentiating the different types of peri- and intra-pancreatic collections, such as necrosis with pus, necrosis without pus and fluid collection without necrosis; these findings may be better defined by MRI<sup>[17,59]</sup>.

Present evidence supports contrast enhanced triple phase CT as the best imaging modality for vascular complications<sup>[34,60,61]</sup>. When a pseudo-aneurysm is identified subsequent management can be planned accordingly with the aid of both CT and angiographic guidance<sup>[62,63]</sup>. Due to the greater accessibility and





**Figure 4** Splenic artery pseudoaneurysm before and after embolization. A: Post contrast computed tomography scan showing the pseudoaneurysm rising from the splenic artery; B: Pre embolization selective splenic arterial DSA angiography image showing pseudoaneurysm; C: Post embolization DSA image showing the coils inside the splenic artery with its resultant embolization<sup>[92]</sup>.

improved vascular imaging triple phase contrast CT has become the imaging modality of choice in severe pancreatitis. Cross-sectional imaging may identify local pancreatic complications that may benefit from antibiotics, radiological intervention or very rarely surgery which in turn will aim to potentially speed the recovery of the patient. Less frequently pseudoaneurysms will rupture causing acute haemodynamic compromise and emergency imaging is performed to determine the underlying cause. There is currently little evidence to specify the timing of follow up imaging and this should be guided by clinical assessment.

## MANAGEMENT OF ACUTE HAEMORRHAGE

Historically the management of pseudo-aneurysm was primarily surgical however over the past two decades the first line intervention is now interventional radiology. Since there have been marked improvements in the field of interventional radiology the spectrum of pathologies that can be treated successfully has expanded greatly. In the United Kingdom the provision of interventional radiology services varies significantly and is concentrated in tertiary centres. This is particularly evident out of hours where few hospitals have a 24-h on call interventional radiology service. A study of the provision of services for acute upper GI haemorrhage has shown that of hospitals in the United Kingdom 46% were able to offer out of hours interventional radiology services whether that be at the hospital in question or *via* a network<sup>[64]</sup>. Acute haemorrhage in district general hospitals is therefore unlikely to be treated with interventional radiology and certainly the mortality of acute haemorrhage from pseudo-aneurysm secondary to pancreatitis may reflect this. Some patients in the acute setting may be suitable for transfer depending on haemodynamic stability. In a semi-elective setting appropriate patients can be transferred to regional centres with greater expertise in managing pseudo-aneurysms where they would have

greater facilities to manage such complicated patients.

Trans-arterial embolisation of pseudo-aneurysms is commonly achieved by the placement of stainless steel or complex helical coils in the proximal and distal feeding vessel in order to isolate inflow and prevent back filling *via* collaterals (Figure 4). Haemostasis can be augmented by *N*-butylcyanoacrylate glue, ethiodised oil, gelfoam, thrombin, polyvinyl alcohol and other particles<sup>[21,37,38,41,43,65-69]</sup>. Increasingly in visceral aneurysm treatment covered stents have been used to exclude inflow to the aneurysm however they are less commonly used in the treatment of pseudo-aneurysms. Complications can arise both in failed and successful procedures. Access related complications might occur in the form of haematoma, dissection, pseudo-aneurysm and emboli. Complications may arise local to the pseudo-aneurysm including rupture, end vessel infarction, dissection and coil migration.

Mortality of pseudo-aneurysms secondary to pancreatitis has been shown to be between 34%-52%<sup>[26,28,30-35]</sup>, however the literature shows significant improvement in case series of those who have undergone radiological intervention. It is important to note that a proportion of patients will have been too unstable for intervention and therefore this mortality may not be reported as widely in the studies of radiological or surgical intervention. Kim *et al*<sup>[65]</sup> in 2015 demonstrated that of 37 patients undergoing angiographic embolisation it was unsuccessful in only three patients. Two of whom re-bleed from the primary pseudo-aneurysm and one developed a new pseudo-aneurysm. Of the 34 patients who underwent successful angiographic embolisation there were no episodes of re-bleeding with a mean follow up of 38 wk. Two patients died as a result of splenic abscesses and subsequent sepsis due to procedure related splenic infarction giving a mortality of 5%.

Udd *et al*<sup>[21]</sup> in 2007 identified 33 patients who were identified to have pancreatitis related pseudo-aneurysms at angiography however only 23 were suitable for embolization. Four of the 23 re-bleed and

only three of those patients received successful repeat radiological intervention. Radiological intervention was successful in 22/33 patients (67%). The remaining 10 patients went on to require surgical cessation of bleeding. One patient who underwent interventional radiology and one patient who underwent surgery died giving a mortality of 6%. Bergert *et al*<sup>[20]</sup> 2005 identified 35 patients with bleeding secondary to pancreatitis related pseudo-aneurysms. Twenty six patients were identified to have pseudo-aneurysms at angiography however angiographic embolisation was the primary treatment in only 16. Two patients re-bled post-angiographic embolization. Nineteen patients required surgery to potentially stop bleeding. Three patients undergoing radiological intervention and four patients undergoing surgery died giving a mortality of 20%. The discrepancies in the number of patients undergoing radiological intervention and the mortality between Bergert *et al*<sup>[20]</sup> and Kim *et al*<sup>[65]</sup> may be reflected in the improvement of clinical practices from the related study dates of 1993-2004 and 2000-2012 respectively. Over the past two decades radiological provision, equipment and technical skills have improved significantly.

Tulsyan *et al*<sup>[68]</sup> in 2007 identified a mixed demographic of elective and non-elective patients (48 patients) with both visceral artery aneurysms and pseudo-aneurysms (28 patients) which showed marked success of radiological intervention. Forty seven of the 48 patients were embolised radiologically however three patients re-bled. Four patients died in the perioperative period all of whom were among the 22 patients who required urgent or emergent intervention because of hemodynamic instability giving a mortality of 18% in the non-elective group. Zyromski *et al*<sup>[37]</sup> in 2007 identified 37 patients with visceral pseudo-aneurysms 24 as the result of pancreatitis and 13 as the result of pancreatic surgery. Within the pancreatitis group 23 of the 24 patients underwent embolization and in each case it was successful at arresting haemorrhage. Initially in one patient a pseudo-aneurysm could not be identified at angiography but was confirmed after a repeat procedure. Twelve patients underwent surgery in an attempt to resolve the on-going pancreatic inflammatory process but not for treatment of a pseudo-aneurysm. One patient died as a result of a stroke unrelated to pseudo-aneurysm treatment.

Smaller studies assessing the management of pseudo-aneurysms secondary to pancreatitis have shown similar outcomes. Hsu *et al*<sup>[41]</sup> in 2006 (9 patients), Beattie *et al*<sup>[66]</sup> in 2003 (19 patients), Gambiez *et al*<sup>[67]</sup> in 1997 (14 patients) and Sethi *et al*<sup>[38]</sup> in 2010 (16 patients) identified that of a total of 58 patients radiological intervention was successful in only 35 patients (60%). Twenty patients subsequently underwent surgery (34%) and seven patients died (12%).

Angiographic embolisation of pancreatitis related

pseudo-aneurysm has been shown to be very successful however there are occasions where the pseudo-aneurysm is inaccessible and therefore embolisation is not feasible. Increasingly in these circumstance image guided thrombin injection has been shown to have a role. The current literature identifies a number of case reports detailing successful embolization of a pseudo-aneurysm with percutaneous thrombin<sup>[62,70-84]</sup>. Of the 23 patients identified who underwent percutaneous thrombin injections four patients re-bled and required further intervention. Two patients had repeated thrombin injections, one underwent angiographic coiling and one is unknown. Other than re-bleeding no significant complications were documented. Evidence is increasing to show that percutaneous therapy is a viable alternative to angiographic therapy. The delivery of thrombin has been successfully used angiographically and percutaneously however in certain scenarios neither can provide appropriate access to allow for successful embolisation. Endoscopic ultrasound has been shown in case reports to provide appropriate access for thrombin injection of pancreatitis related pseudo-aneurysms. Both aneurysms of the gastro-duodenal and splenic artery have been embolised endoscopically without the need for re-intervention<sup>[85-89]</sup>.

Surgery in patients with pancreatitis is known to be associated with significant morbidity and mortality which only increases in the presence of acute haemorrhage. With the improvement of minimally invasive techniques the role of surgery has diminished as angiographic, percutaneous and endoscopic techniques can appropriately exclude pseudo-aneurysms. However in spite of the technological advances in radiology and endoscopy, surgery will continue to play an important role in haemorrhage control where other techniques are not technically possible or available. There is currently no consensus on the surveillance of pseudo-aneurysms and the need for follow up. Patients with pancreatitis of a severity that leads to the formation of a pseudo-aneurysm will often undergo follow up imaging to ensure the resolution of local pancreatitis complications and in turn individually designed imaging follow up can be determined in coordination with the clinician and radiologist to ensure that the future re-bleed risks are mediated.

## CONCLUSION

Pancreatitis has a number of aetiologies and many more potential complications which leads to it being a common pathology seen in every surgical department. Arterial complications of pancreatitis although rare are associated with a high morbidity and mortality. It is important to maintain a high level of suspicion for pseudo-aneurysm as they can be easily missed despite cross-sectional imaging. Early recognition of the presence of a pseudo-aneurysm can facilitate expedited care of this complex pathology that may require

angiographic, percutaneous, endoscopic or surgical intervention to prevent catastrophic haemorrhage.

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