Management of Moderately Severe Pancreatitis: Individualised Treatment for Each Patient

Yasir Bashir*, Donal O'Connor, Kevin C Conlon
Professorial Surgical Unit, Department of Surgery, The University of Dublin Trinity College, Tallaght Hospital, Dublin, Ireland
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ABSTRACT

Acute pancreatitis is an inflammatory condition of the pancreas that is painful and at times deadly. Severe acute pancreatitis constitutes 20% of the patients presenting to hospital with acute pancreatitis. In acute pancreatitis early recognition, vigorous fluid resuscitation, careful pulmonary care and close supervision is required. In severe cases patients will also require intensive care unit admission. Although the incidence of acute pancreatitis is on the rise, due to more systematic approach and specialist care outcomes have improved over the last decade. But this improvement comes at a cost and acute pancreatitis is considered as a significant burden on health systems across the world. Before 2012, acute pancreatitis was categorised as mild or severe. In 2012 with revised classification of acute pancreatitis two phases early and late, while three categories of severity mild, moderate and severe were identified. Moderately severe pancreatitis is defined by the presence of transient organ failure, local complications (peripancreatic fluid collections, pancreatic and peripancreatic necrosis) or exacerbation of co-morbidities. In this review article we have outlined symptoms, causes, diagnosis and management of moderately severe pancreatitis and complications arising because of the disease process. It also provides simple but clear guideline and suggestions to clinicians for management of this illness.

INTRODUCTION

Acute pancreatitis is one of the most common gastrointestinal diseases diagnosed worldwide. The severity of inflammation can vary from very mild self-limiting inflammation to severe disease causing severe inflammation and necrosis of pancreas, which can result in multiple organ failure and is associated with mortality. Pancreatitis can be a very challenging and complex disease for clinicians.

The incidence of pancreatitis varies worldwide ranging from 5 to 80 per 100000. Approximately 20% of patients admitted with acute pancreatitis have severe form of the disease and need admission to intensive care unit. As the number of patients suffering from pancreatitis are increasing as shown by epidemiological study conducted by our unit (1), so is the number of patients with severe acute pancreatitis. This results in significant burden on intensive care services accounting for 8.7% intensive therapy unit bed occupancy in tertiary referral centres in

*Assistant Professor Yasir Bashir, MD, PhD
Department of Surgery, Room 1.40, Trinity Centre of Learning and Development, Tallaght Hospital, Dublin 24, Ireland
E-mail: ybashir@tcd.ie

Scotland (2). The financial cost of treating acute pancreatitis in UK had been estimated at £200 million per year in 2012 (3). While acute pancreatitis-related estimated cost was $3.7 billion in US in 2004 (4).

The incidence is on the rise; the clinical outcome of pancreatitis has improved over the recent decades due to a systematic approach to diagnosis, better understanding of pathology, monitoring and management of the patients by specialists dedicated to managing pancreatitis and its complications. The focus of this review will be the management of complications of moderately severe acute pancreatitis.

SYMPTOMS

The most common presentation of pancreatitis is severe, sharp epigastric pain which often radiates through to back. Onset of pain is usually sudden and reaches maximum intensity in matter of minutes to hours. Pain is classically described as boring knife like constant pain which is not relieved by simple analgesics. Nausea, vomiting and dry retching are common associated symptoms. Depending on severity of disease patients could appear from well to extremely ill with shock.

AETIOLOGY

The two most common causes of pancreatitis are cholelithiasis and alcohol accounting for about 80% of the cases. There is regional and gender based variation as to the aetiology of the pancreatitis. Alcohol being more common cause among men while cholelithiasis remained most common cause of pancreatitis in females. There is also geographical variation found for example gallstones being the predominant cause in Greece while alcohol being most common cause in Hungary (5). There is a steady rise in alcohol related pancreatitis in many countries especially in young population (1). But it is not uncommon to diagnose pancreatitis in patients in absence of these two aetiologies. The other causes of pancreatitis are iatrogenic, hereditary, autoimmune (6), hyperlipidaemia, trauma, neoplasms, drugs, toxins and idiopathic. List of possible aetiologies are given in Table 1.

Table 1. List of causes of pancreatitis

Aetiologies of acute pancreatitis
Common causes:
• Gallstones (including microlithiasis)
• Alcohol
• Idiopathic
• Hyperlipidaemia
• Hypercalcemia
• Sphincter of Oddi dysfunction
• Drugs and toxins
• Post-endoscopic retrograde cholangiopancreatography
• Traumatic
• Postoperative
Uncommon causes:
• Pancreas divisum
• Periampullary cancer
• Cancer of the pancreas
• Periampullary diverticulum
• Vasculitis
Rare causes:
1. Infective:
• Coxsackie virus
• Mumps
• HIV
• Parasitic
• Ascariasis
2. Autoimmune:
• Systemic lupus erythematosus
• Sjogren's syndrome a-1
• Antitrypsin defificiency

DIAGNOSIS

History and examination consistent with pancreatitis along with raised amylase or lipase (more than three times the normal limit) is considered diagnostic for acute pancreatitis. Serum amylase concentration increases almost immediately after the onset of an acute episode, but the magnitude of increase in serum amylase has no correlation with severity of the disease. Milder form of pancreatitis is often associated with higher level of amylase as compared to the critical disease. In addition author and co-workers demonstra-

ted that a rise of 90 mg/dL in C-reactive protein from admission to 48 hours can predict the severity of pancreatitis (7). Glasgow-Imrie Criteria (8) and APACHE-II are used to determine severity of the disease. It takes into account number of variables which are explained in detail in Table 2. Imrie score of three or more is considered as high risk for severe pancreatitis. The laboratory values are usually evaluated at 48 hours after admission, not upon admission. This scoring system was developed in the 1980s, prior to significant advances in the treatment and evaluation of pancreatitis, including advanced imaging.

Table 2. Glasgow criteria – a scoring index for severity of acute pancreatitis. PaO_2 – arterial partial pressure of oxygen, WBC – white blood count, LDH – lactate dehydrogenase

	Yes	No
PaO_2 < 59.3 mmHg (7.9 kPa)	+1	+0
Age > 55 years	+1	+0
WBC >15 x 10ł/µL (10^9/L)	+1	+0
Calcium < 8 mg/dL (2 mmol/L)	+1	+0
Urea > 44.8 mg/dL (16 mmol/L)	+1	+0
LDH > 600 IU/L	+1	+0
Albumin <3.2 g/dL (32 g/L)	+1	+0
Glucose >180 mg/dL (10 mmol/L)	+1	+0

Diagnosis of pancreatitis is confirmed by radiological investigation usually contrast-enhanced CT scan due to other conditions associated with hyperamylasaemia. Once diagnosis of pancreatitis is made, accurately predicting the severity of the disease helps in following appropriate management strategy for the patient. Many scoring systems have been devised to report severity of the disease, but none of them has proven perfect. Clinical judgment based upon clinical and laboratory data at admission might underestimate the severity of acute pancreatitis. These scoring systems are superior to clinical judgment for triaging patients to more intensive care and aggressive therapy.

CLASSIFICATION

In 1992, the Atlanta classification for acute pancreatitis was introduced as a universally applicable classification system for the various manifestations of acute pancreatitis. This system was designed to facilitate understanding and correlation of findings seen by gastroenterologists, pathologists, radiologists, and surgeons. This approach was to be particularly useful for assessment and treatment of the various fluid collections identified during acute pancreatitis. This initial Atlanta classification system represented major progress, but advancing knowledge of the disease process, improved imaging, and ever-changing treatment options such as minimally invasive radiologic, endos-

Table 3. Original Atlanta classification and Revised Atlanta classification

<table>
<tr><th colspan="2">Classification of Acute Pancreatitis</th></tr>
<tr><th>Atlanta Classification 1992</th><th>Revised Atlanta Classification 2012</th></tr>
<tr><td>Mild acute pancreatitis
(Acute interstitial/oedematous pancreatitis)
• Absence of organ failure
• Absence of local complications</td><td>Mild acute pancreatitis
• No organ failure
• No local or systemic complications</td></tr>
<tr><td rowspan="2">Severe acute pancreatitis
(acute haemorrhagic necrotising pancreatitis)
• Local complications
• Organ failure</td><td>Moderately severe acute pancreatitis
• Organ failure that resolves within 48 hours
• Local or systemic complications without persistent organ failure</td></tr>
<tr><td>Severe acute pancreatitis
• Persistent organ failure (> 48 hours)
Single organ failure
Multiple organ failure</td></tr>
</table>

copic, and laparoscopic procedures soon rendered some of the definitions inadequate or ambiguous, presenting a need to revise and update the Atlanta classification. In 2008, a global consensus statement was developed that included broad and international participation of many experts in the field of pancreatitis and was led by the Acute Pancreatitis Classification Working Group. This working group gathered input and revised the Atlanta classification system to improve clinical assessment and management of acute pancreatitis and to clarify appropriate terms for peripancreatic fluid collections, pancreatic and/or peripancreatic necrosis, and their changes over time. The Revised Atlanta Classification in 2012 (9) specifically introduced a new category of moderately severe pancreatitis Table 3.

Mild acute pancreatitis is characterised by the absence of organ failure and absence of local or systemic complications. Patients with mild acute pancreatitis respond well to conservative management and mortality is very rare (10).

Moderately severe acute pancreatitis is characterised by the presence of transient organ failure and local or systemic complications. Moderately severe acute pancreatitis may resolve without intervention but may require prolonged specialist care. Moderately severe pancreatitis is associated with less mortality than severe pancreatitis (11), but frequently requires interventional management of local complications and surveillance for long term complications and progression to chronic pancreatitis.

Severe acute pancreatitis is characterised by persistent organ failure (12, 13). Organ failure that develops during the early phase is set in motion by the activation of cytokine cascades resulting in systemic inflammatory response syndrome (SIRS) (12, 14, 15). When SIRS (Table 4) is present and persistent (12, 13, 16), there is an increased risk of progression to persistent organ failure. Persistent organ failure may be single or multiple organ failure. Patients who develop persistent organ failure within the rst few days of the disease are at increased risk of death, with a mortality as high as 50% (12–14). The development of infected necrosis among patients with persistent organ failure is associated with high mortality.

MANAGEMENT

Management of acute pancreatitis is initially conservative and supportive involving analgesia, fluid resuscitation, oxygen therapy and monitoring of intake and output. Early and adequate fluid resuscitation (first 24–48 hours of admission) is associated with decreased rates of persistent SIRS and organ failure (17). After a brief period of fasting, oral diet should be introduced and there is no evidence to support prolong fasting in mild cases (18). The most important considerations in mild cases involve defining aetiology to reduce the risk of further attacks and performing early cholecystectomy in the setting of mild biliary pancreatitis (19, 20). In acute severe pancreatitis with persistent organ failure, management should be in an intensive care setting for multiple organ support and goal directed monitoring and therapy. Otherwise the management principles will be as outlined below for moderately severe pancreatitis.

MANAGEMENT PRINCIPLES IN MODERATELY SEVERE ACUTE PANCREATITIS

In moderate cases, frequent non-invasive monitoring, observations and investigations are required to monitor progress of disease. Patients should receive high dose proton pump inhibitors due to the risk of stress ulceration and gastrointestinal bleeding. There should be early consideration for consultations with and transfer to specialist units with access to radiological, endoscopic and surgical expertise. Early systemic complications such as pleural effusions should be drained if causing respiratory compromise.

We advocate early initiation of enteral feeding which is associated with reduced infective complications and reduced hospital stay of patients (21). Nasojejunal feeding can be safely and effectively established at the bedside (22) (Figure 1). The benefit over parenteral nutrition may be partly due to preservation of the gut

membrane, reduced bacterial translocation and therefore less infective transformation of pancreatic necrosis and fluid collections (23). Nasogastric feeding has been demonstrated to be as effective as nasojejunal in small trials (17). A randomised trial has also shown that in severe cases, oral feeding can be initiated early if tolerated by the patient (24). However, nasojejunal feeding has the advantage of maintaining the enteral route even in patients with persistent nausea, vomiting and delayed gastric emptying. Parenteral feeding should be second-line only, where enteral feeding is not tolerated or difficult to establish, or occasionally in the management of persistent pancreatic fistula.

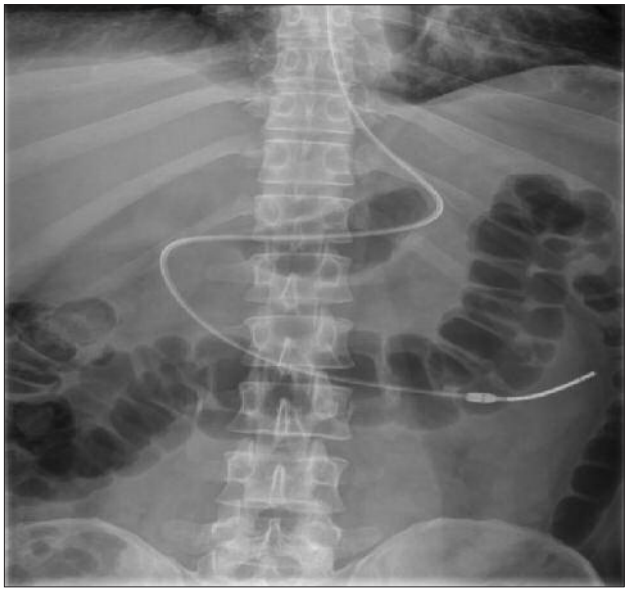

Figure 1. Plain film demonstrating good position of a nasojejunal feeding tube

A major focus of the management in moderately severe pancreatitis involves the timing and methods of intervention for the most common local complications; pancreatic necrosis and peripancreatic fluid collections. These can be classified practically as acute pancreatic necrosis and acute pancreatic fluid collections (PFCs). Invasive intervention should be delayed if possible for four weeks to allow maturation to walled-off necrosis (WON) and chronic fluid collections or pseudocysts. If patient is asymptomatic, stable and no signs of infection are present, collections can be managed conservatively. Reasons for intervention include suspected infected necrosis or mechanical complications of PFCs or pseudocysts such as gastric outlet or biliary obstruction (Figure 2). It is now well established that initial radiologically guided, percutaneous catheter drainage should be undertaken rather than open primary surgical necrosectomy. This can be followed by minimally invasive, video-assisted, retroperitoneal debridement if necessary (25).

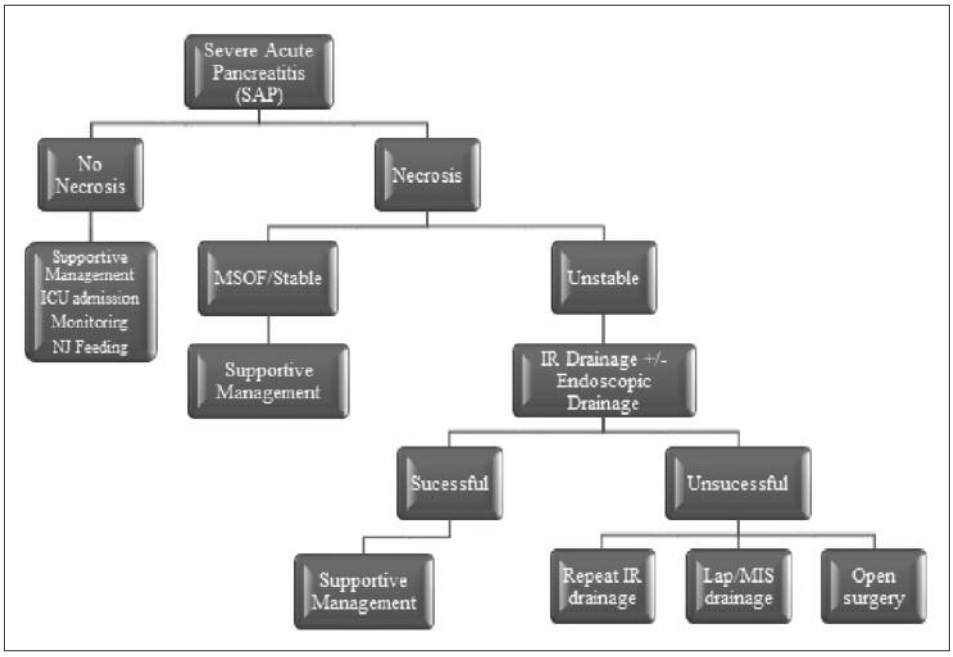

Figure 2. Algorithm explaining the pathway for the management of collections in pancreatitis

In many cases, percutaneous drainage alone will be sufficient for WON (Figure 3). More recently, a completely endoscopic approach has become an attractive alternative for both WON and acute PFCs. This consists of endoscopic ultrasound-guided transluminal drainage followed, if necessary, by endoscopic necrosectomy (26). In some cases, lapa-

roscopic (24) or open surgery is still required for persistent phlegmon or persistent fistula. The over-riding principle of all forms of interventional management should favour an organ-preserving approach, which involves debridement or necrosectomy combined with a drainage strategy that maximizes post procedural evacuation of retroperitoneal debris and exudate (27).

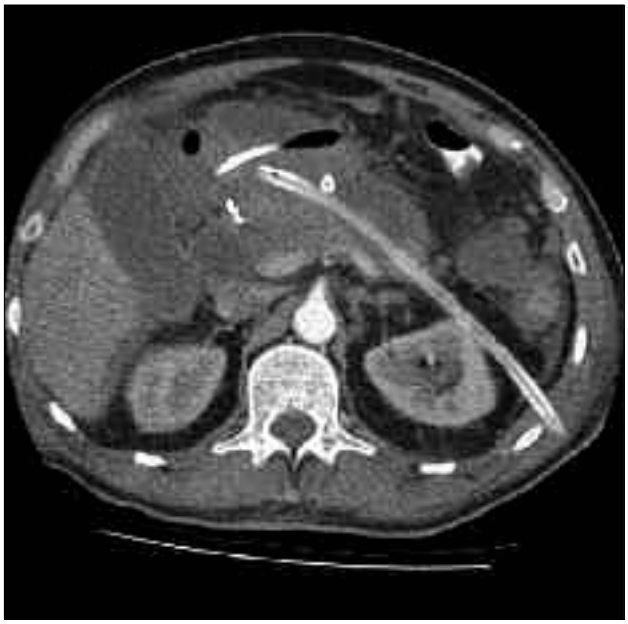

Figure 3. Computed tomography showing a large bore retroperitoneal percutaneous drainage catheter

Antibiotic prophylaxis remains controversial in moderately severe pancreatitis and should be carefully considered. Obtaining needle aspirations of WON or PFCs for culture is not practical and no longer recommended (17). In the absence of persistent organ failure, justification for antibiotic usage would include suspicion of infected necrosis due to persistent fever, raised inflammatory markers or radiological findings such as gas within necrotic collections.

Endoscopic drainage is very effective for mature pseudocysts and preferable to surgical pseudocyst-enterostomy (21, 22) (Figure 4). Endoscopic stenting of the main pancreatic duct is also a useful adjunct to percutaneous drainage in cases of main duct disruption with persistent pancreatic fistula which can occur in the setting of significant necrosis.

In the setting of moderately severe pancreatitis due to gallstones, urgent endoscopic retrograde choangiopancreatography (ERCP) for choledocholithiasis is only recommended if the patient develops cholangitis, otherwise it should be delayed until the acute episode is resolving. Definitive cholecystectomy should be delayed until resolution of WON and PFCs (17). In cases where there is a predicted long delay, consideration should be given to performing ERCP and sphincterotomy to avoid recurrent acute pancreatitis. Biliary obstruction can complicate acute pancreatitis of other aetiology due to compression initially or inflammatory strictures in later stages. ERCP and biliary stenting is usually effective but percutaneous transhepatic external biliary drainage may be required if there is concomitant duodenal compression or necrosis.

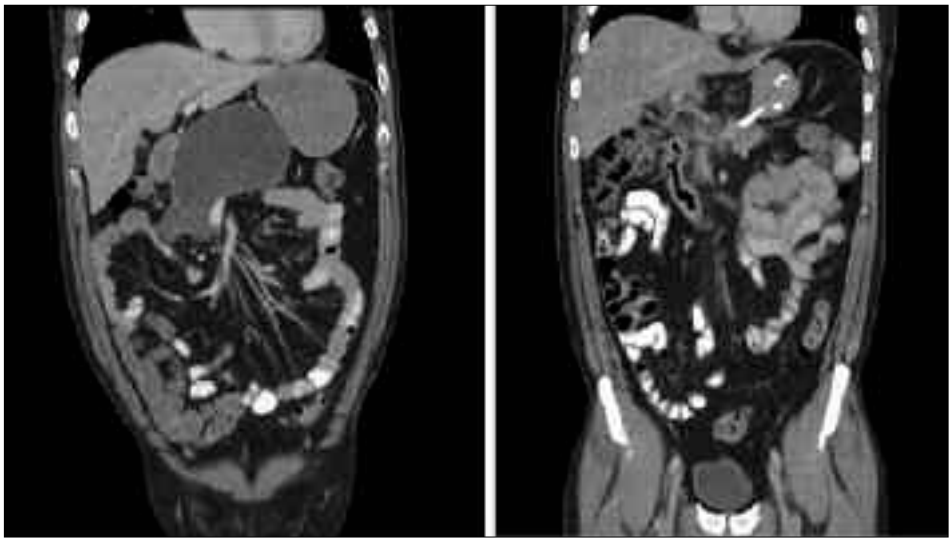

Figure 4. Computed tomography showing a pseudocyst (left) and endoscopically placed pseudocyst-gastrostomy stent with almost complete resolution (right)

Pseudoaneurysm formation is a relatively uncommon complication if both necrotising pancreatitis and persistent pseudocysts. Affected vessels include the gastroduodenal and splenic artery. They may be detected incidentally during contrast CT

scanning but may cause life-threatening haemorrhage. They can present with intra-abdominal or gastrointestinal tract bleeding. Image-guided thrombin injections or angiography and embolization are the preferred treatment methods (28) (Figure 5). Venous thrombosis of the splenic or portal vein is commonly observed in necrotising pancreatitis due to inflammation and direct venous compression. We do not advocate routine anti-coagulation although this should be considered if there is significant extension of thrombosis into either the intra-hepatic portal vein or the superior mesenteric vein.

Due to advances in management and modern interventional techniques, mortality in moderately severe pancreatitis is low but it comes with high morbidity (11). It is therefore crucial that specialist centres and referring hospitals develop follow-up protocols to deal with the long-term complications. It is estimated that one third of patients will develop diabetes. This pancreaticogenic or type 3c diabetes can be poorly managed if not recognised early and may require specialist endocrine input (29). We estimate that at least 10% will progress to chronic pancreatitis. Exocrine deficiency is often underdiagnosed and can become established at a much shorter interval previously thought (30). The associated malabsorption and systemic inflammation means that patients are at higher risk of osteoporosis (19).

In conclusion, moderately severe pancreatitis is a complex process that requires specialist input from surgeons, gastroenterologists, radiologists, nurse-specialists and dieticians and a multi-disciplinary team approach long-term management.

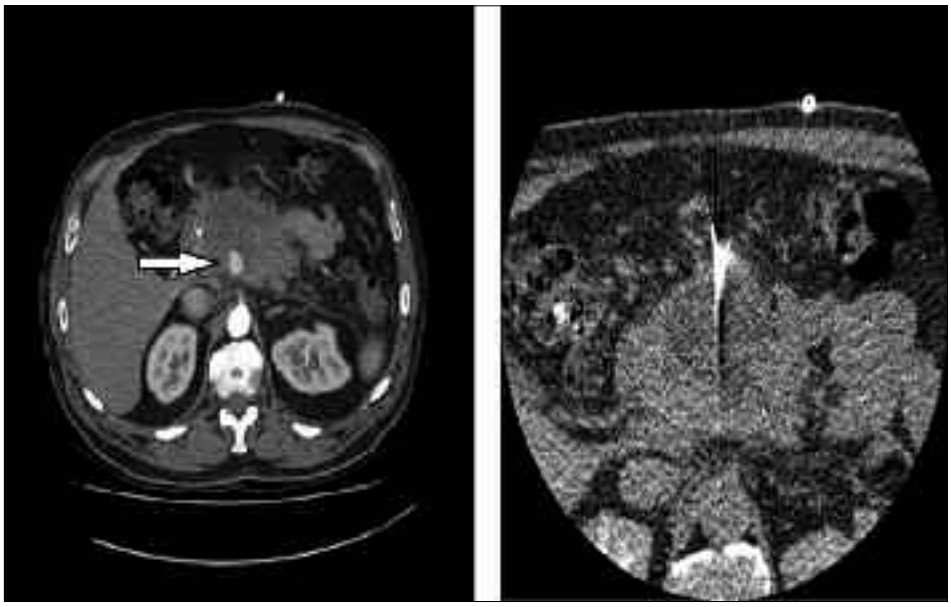

Figure 5. Computed tomography showing a gastroduodenal artery pseudoaneurysm in a patient with necrotising pancreatitis (white arrow: left) treated with image-guided thrombin injection (right)

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