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Prompt diagnosis and treatment will improve outcomes in acute pancreatitis

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Abstract

Acute pancreatitis (AP) has an overall incidence of 30.0 per 100,000 population in the UK with an annual increase of 2.7% per year. Alcohol and gallstones are the aetiology in more than 90% of cases. While alcoholic pancreatitis is more common in men, gallstone pancreatitis is seen more commonly in women over the age of 60. Any patient presenting with acute abdominal pain should be assessed for a possible diagnosis of AP. A thorough history of the presenting illness is needed to determine the onset, duration, progress and nature of the pain. AP pain typically presents as severe epigastric pain radiating to the back and is worsened by movement, and classically leaning forwards alleviates the pain. The pain is often associated with anorexia, nausea, vomiting and decreased oral intake. On examination patients with AP are often hypovolaemic and may also have tachypnoea, diaphoresis and tachycardia.

Any patient presenting with acute severe abdominal pain outside of A&E, such as in primary care, should be urged to attend A&E promptly to facilitate a rapid diagnosis and to commence treatment (most importantly intravenous fluids), which will improve outcomes in AP and in other causes of acute severe abdominal pain. Embarking on tests in primary care such as serum amylase if AP is being considered is unlikely to be worthwhile.

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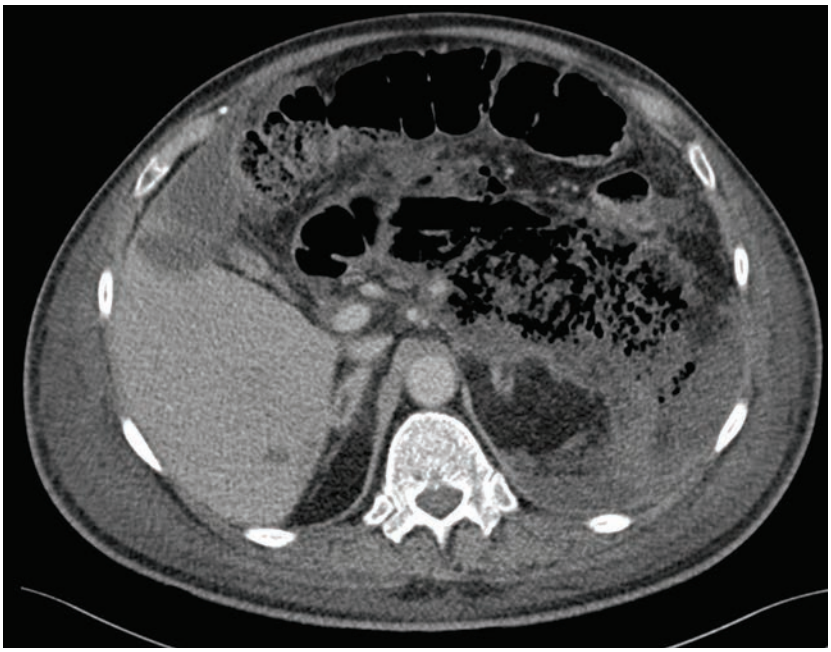

FIGURE 1
CT scan of severe pancreatitis with a large semi-solid and gas filled walled off necrotic (WON) collection in the retroperitoneum with no viable pancreas.
The gas suggests either fistulation of the collection into the bowel, or bacterial infection.
EUS-guided transmural drainage of the WON from the stomach with a lumen-apposing stent was undertaken

What are the main causes of acute pancreatitis?

How should patients be examined?

What are the management approaches?

ACUTE PANCREATITIS (AP) HAS AN OVERALL INCIDENCE OF 30 PER 100,000 POPULATION IN the UK with an annual increase of 2.7% per year. Alcohol and gallstones are the aetiology in more than 90% of cases.[1]

Over Christmas and New Year, the incidence of alcohol related AP in the UK increases significantly by 48%.[1] AP has a mortality rate of 1-7% which can increase to about 20% in the presence of pancreatic necrosis.[2]

Development of other organ complications increases the mortality rate significantly which can be as high as 44% for patients requiring mechanical ventilation.[3]

While alcoholic pancreatitis is more common in men, gallstone pancreatitis is the other common cause of acute pancreatitis and is seen more commonly in women over the age of 60.[4]

AETIOLOGY AND PATHOGENESIS

There are a range of causes for AP which many will remember from student days with the mnemonic 'I GET SMASHED' (see table 1, p18). The aetiology in 30% of AP cases remains unidentified initially and the condition is classified as idiopathic, on subsequent investigation most are found to be caused by gallstones/microlithiasis.[5]

AP is often initiated by events leading to acinar cell injury. Impaired secretion of zymogen granules through various mechanisms at the cellular level leads to premature conversion of trypsinogen to trypsin which leads to acinar cell injury.

The pathogenesis of AP broadly involves three different mechanisms – ductal obstruction, acinar cell injury and defective intracellular transport. Increased intraductal pressure, such as in gallstone pancreatitis, leads to retrograde flow of pancreatic juice leading to intrapancreatic enzyme activation. Raised calcium, triglycerides, hereditary and autoimmune aetiologies cause defective intracellular transport precipitating AP.[6]

CLINICAL PRESENTATION

Any patient presenting with acute abdominal pain should be assessed for a possible diagnosis of AP. A wide range of differential diagnoses should be considered when these patients are assessed which include intestinal obstruction, perforated peptic ulcer, mesenteric ischaemia, biliary colic, cardiovascular causes such as inferior wall myocardial infarction, dissecting aortic aneurysm and possible gynaecological causes such as ruptured ectopic pregnancy.

HISTORY

A thorough history of the presenting illness is needed to determine the onset, duration, progression and nature of the pain. AP pain typically presents as severe epigastric pain radiating to the back and is worsened by movement, and classically leaning forwards alleviates the pain. The pain is often associated with anorexia, nausea, vomiting and decreased oral intake.[7]

Risk factors for pancreatitis should also be assessed when the history is taken. Alcohol and gallstones are the two most common aetiologies of AP.

Other aetiologies, mentioned in table 1, p18, should also be explored in the history, in particular family history can indicate possible hereditary pancreatitis or familial cancer syndromes.

EXAMINATION

On examination patients with AP are often hypovolaemic and may also have tachypnoea, diaphoresis and tachycardia.

The presence of a fever should alert the clinician that there may be acute »

Table 1

Causes of pancreatitis

I Idiopathic, ischaemia
G Gallstones
E Ethanol
T Trauma
S Steroids, sphincter of Oddi dysfunction
M Viruses such as mumps, malignancy, mucinous tumours
A Autoimmune
S Scorpion venom
H Hypercalcaemia, hypertriglyceridaemia, hypothermia, hereditary
E ERCP (iatrogenic)
D Drugs e.g. thiazides, azathioprine

cholangitis complicating an episode of gallstone pancreatitis, although the fever may be secondary to the inflammatory response. Pancreatic necrosis or acute pancreatic collections can also be the cause of a fever, but these usually take time to evolve and so are a less common feature during the acute presentation. Pleural effusions may be present at initial presentation or develop later as a complication.[8]

Examination of the abdomen would usually demonstrate a tender, often distended, abdomen with voluntary guarding. Patients may also have an associated ileus which is determined by noting diminished or absent bowel sounds, and often abdominal distension.

Other rarer complications of AP may also be evident during clinical examination such as signs of hypocalcaemia and haemorrhagic pancreatitis which can be detected as ecchymosis over different areas of the abdomen, e.g. Cullen's sign (over periumbilical skin), Grey-Turner's sign (over the flanks), Fox's sign (over the inguinal ligament). However, these signs are rare in AP and other differentials of retroperitoneal haemorrhage should be considered when eliciting these signs.

Patients with AP may have associated cholangitis which should also be considered during the clinical assessment. Significant complications include acute pancreatic fluid collections, which after 4 weeks are known as pseudocysts, by which time they have encapsulated into discrete collections. If there is localised tissue necrosis this is known as acute peripancreatic necrosis in the early stages, and after 4 weeks the term walled off necrosis (WON) is used (see figure 1, p17). Hence by definition a pseudocyst is purely fluid filled and WON has both fluid and solid components with possible loculations.[9]

The presence of gas in either lesion indicates either fistulation of the collection into the gut (usually the duodenum or small bowel), or that there is infection within the lesion which would be an indication for drainage.

Severe AP can be associated with a severe inflammatory response and organ failure and may need ITU support. The exact mechanism leading to systemic inflammatory response syndrome (SIRS) is unclear, however several factors are implicated which include activated pancreatic enzymes, cytokines released by pancreatic inflammation, bacterial cell wall endotoxins (lipopolysaccharides), oxidative stress and defects in the autophagic pathway.[10,11] These lead to activation of complex immune cascades via mediators such as Toll-like receptors and nuclear factor kappa B.[10,12]

DIAGNOSIS AND INVESTIGATION

The diagnosis of acute pancreatitis requires two of the following criteria to be present as per the revised Atlanta classification:[9]

- Abdominal pain in keeping with pancreatitis
- Serum amylase and/or lipase more than 3 times the upper limit of normal
- CT or MRI findings consistent with acute pancreatitis

Blood tests

Laboratory blood tests are important in diagnosing acute pancreatitis and all patients should have routine blood tests including full blood count, urea and electrolytes, C-reactive protein (CRP) and a clotting screen. When acute pancreatitis is suspected liver function tests, amylase, lipase, calcium and serum triglyceride levels should also be obtained. AP patients are at risk of third space fluid loss resulting in intravascular hypovolaemia which can result in acute kidney injury indicated by elevated urea and creatinine levels in blood tests. Haemoconcentration can also be seen on blood tests which is associated with increased risk of developing pancreatic necrosis.

An elevation of ALT above 150 U/L (3 times the upper limit of normal) has a positive predictive value of 95% for the aetiology of AP being gallstones.[13]

Although raised serum amylase and lipase levels support the diagnosis of AP, these tests are not pathognomonic of the condition. Also, their performance in aiding diagnosis decreases in hours to days after the onset of AP. It should be noted that in some patients these enzymes may not be elevated above the diagnostic threshold. These tests should therefore be interpreted with caution in patients with high clinical suspicion of AP and additional imaging should be undertaken.

Serial CRP measurement is a good marker of severity and progression of AP. Arterial blood gas sampling should also be considered for assessing and monitoring oxygenation and acid-base balance and any hypoxia detected should be treated with supplemental oxygen.[6] Serum procalcitonin levels are considered sensitive to detect infected necrosis and low levels have a high negative predictive value in assessing the risk of infected necrosis.[14]

Imaging

A chest or abdominal radiograph may demonstrate pleural effusions with atelectasis and calcified gallstones. In chronic pancreatitis, calcification within the pancreas may also be seen. However, the usefulness of an abdominal radiograph is limited as calcified gallstones are detected in only 15-20% of all proven gallstone cases.[15] It may, however, be useful in other causes of acute abdominal pain such as perforated peptic ulcer; although in the UK an urgent abdominal CT would now be done before a radiograph in the context of 'acute abdomen'.

In suspected gallstone pancreatitis, the preferred initial imaging study is a transabdominal ultrasound as it allows for examination of the gallbladder and the biliary tree. Ultrasound has a sensitivity of 75% to detect AP, however, in 20-30% of patients, this is limited by the presence of overlying gas in the bowel.[16]

Further cross-sectional imaging such as multiphase contrast CT needs to be considered to rule out any complications of AP such as peripancreatic collections, necrosis, abscess or vascular complications e.g. portal vein thrombosis, haemorrhage or pseudoaneurysms. This is particularly important if the patient is not improving or worsens systemically.

AP can be diagnosed without the need for imaging in 80% of patients based on clinical presentation and laboratory tests.[17]

Unless there is diagnostic uncertainty, a CT within 48 hours of admission is generally not advised as it may lead to underestimation of the extent of pancreatic necrosis which takes time to develop and is not found to improve patient outcomes.[18] A contrast enhanced CT scan at 72-96 hours after

onset of symptoms is the optimal timing recommended for the first CT scan.[14]

Magnetic resonance cholangiopancreatography (MRCP) is the preferred modality for serial imaging as it facilitates diagnosis and confirmation of possible aetiology e.g. biliary or pancreatic stones, better characterisation of pancreatic parenchyma and also helps differentiate solid and liquid components in the pancreatic collection which is useful information to help formulate the optimal drainage strategy.[19]

An urgent endoscopic retrograde cholangiopancreatography (ERCP) is only recommended in the specific context of the suspicion of gallstone pancreatitis when there is associated cholangitis. In most cases of gallstone pancreatitis, the stone will have passed spontaneously by the time imaging is done, and if a bile duct stone is confirmed on imaging yet there is no suggestion of cholangitis, then an ERCP can be done electively when the patient has been optimised.

Cross-sectional imaging also helps identify the presence of a pancreatic neoplasm as the potential cause of pancreatitis, particularly in patients aged over 50 at the time of presentation.

Endoscopic ultrasound (EUS) is able to use higher frequencies and hence achieves better image definition than transabdominal ultrasound and so is the most sensitive modality for detecting grit or microlithiasis in the gallbladder.

EUS can also reveal the presence of a neoplasm and allow for tissue or cyst sampling. EUS is therefore an important diagnostic test in the context of idiopathic pancreatitis, particularly when the AP is recurrent.[6]

MANAGEMENT

Any patient presenting with acute severe abdominal pain outside of A&E, such as in primary care, should be urged to attend A&E promptly to facilitate a rapid diagnosis and to commence treatment (most importantly intravenous fluids), which will improve outcomes in AP and in other causes of acute severe abdominal pain. Embarking on laboratory tests in primary care such as serum amylase if AP is being considered is therefore unlikely to be worthwhile.

Severe pancreatitis is associated with a high mortality rate and there are several scoring systems available such as SIRS, APACHE II, Ranson, BISAP and the Modified Glasgow score which can be used to score the severity of pancreatitis. A guideline published by the World Society of Emergency Surgery in 2019 suggests that the BISAP score is accurate and simple to apply in everyday practice to predict acute severe pancreatitis.[14]

Escalation to ITU should be considered based on the clinical state of the patient especially if there is evidence of SIRS and/or organ failure.

Analgesia

Severe abdominal pain is the primary presenting complaint in pancreatitis. There are no specific analgesic agents recommended for AP and pain should be optimised using the analgesic ladder and local acute pain management guidelines.

NSAIDs are avoided in the presence of acute kidney injury and patient controlled analgesia should be considered for severe ongoing pain.[14] Morphine and fentanyl are commonly used, and it is important to optimise pain control to prevent diaphragmatic splinting which can cause further respiratory compromise.[6] Other supportive measures such as antiemetics for vomiting should be prescribed.

Antibiotics

Antibiotics are not indicated and are not recommended in non-infected pancreatic necrosis as prophylactic antibiotics are not known to improve outcomes in AP.[20] Although the decision to start antibiotics is mainly determined on clinical grounds, it has been suggested that a combination of high procalcitonin level, haematocrit, urea and CRP may predict development of infected pancreatic necrosis.[21] Presence of gas on imaging is also indicative of infection. Local antibiotic guidelines should be followed when prescribing antibiotics in suspected infected pancreatitis.

Fluid balance

Patients with AP are generally fluid deplete due to a combination of reduced oral intake and fluid loss from vomiting and third-spacing of fluid from peripancreatic inflammation. Hence initial fluid resuscitation forms an important part of early management and should be initiated at 5-10 ml/kg/hr.[22]

Ringer lactate solution is recommended by several international guidelines[22,23,24] as it is associated with an anti-inflammatory effect and, in comparison with normal saline, it decreases the risk of developing SIRS at 24 hours.[25,26]

General principles of fluid balance should be followed and fluid resuscitation should be tailored to the individual patient giving due consideration to other comorbidities such as heart failure and chronic kidney disease. Although early effective fluid resuscitation is important to reduce organ failure and in-hospital mortality, overaggressive resuscitation should be avoided as it is associated with higher rates of sepsis and mortality and increased need for mechanical ventilation.[6]

Nutrition

Dietitians with experience of AP should be involved in the care of all but the very mildest cases of AP during their hospital admission and convalescence.

Keeping patients fasted in mild pancreatitis is not recommended and oral intake can be commenced as soon as the abdominal pain improves and the patient feels like eating.[27] Patients will benefit from a nutrition plan devised by a dietitian who should be involved in the initial days of admission to hospital. In cases of severe pancreatitis, enteral feeding should be initiated after 48 hours post initial resuscitation, although usually a patient will not be able to take anything orally.[22]

A nasogastric or nasojejunal tube may be used depending on the tolerance to oral feeds, although optimal enteral feeding may be impossible if there is associated ileus. Hence, parenteral nutrition (PN) needs to be considered when nutrition goals are not being met, however an enteral diet is recommended to prevent infection of pancreatic collections and necrosis and an enteral feed can be given alongside PN.[14] Electrolytes, including calcium and magnesium should be checked and corrected as required.

Patients suspected of having pancreatic enzyme insufficiency should be started on pancreatic enzyme supplements when oral or enteral feeding is commenced.[28] Strict glucose control should be maintained with insulin as it is shown to reduce mortality and morbidity in critically ill patients.[29] AP is also associated with thrombosis of the portal venous system which if present should be treated with anticoagulation for 3 to 6 months.[30]

Complications

Other rare but important complications of acute pancreatitis include pseudoaneurysm and bleeding that can cause acute deterioration. In these cases, patients should receive appropriate initial resuscitation with fluids and blood products followed by urgent CT angiogram to determine the »

key points

SELECTED BY

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Acute pancreatitis (AP) has an overall incidence of 30.0 per 100,000 population in the UK with an annual increase of 2.7% per year. Alcohol and gallstones are the aetiology in more than 90% of cases. AP has a mortality rate of 1-7% which can increase to about 20% in the presence of pancreatic necrosis. Development of other organ complications increases the mortality significantly which can be as high as 44% for patients requiring mechanical ventilation. While alcoholic pancreatitis is more common in men, gallstone pancreatitis is the other common cause of acute pancreatitis seen more commonly in women over the age of 60.

The pathogenesis of AP broadly involves three different mechanisms – ductal obstruction, acinar cell injury and defective intracellular transport. Increased intraductal pressure, such as in gallstone pancreatitis, leads to retrograde flow of pancreatic juice leading to intrapancreatic enzyme activation. Raised calcium, triglycerides, hereditary and autoimmune aetiologies cause defective intracellular transport precipitating AP.

Any patient presenting with acute abdominal pain should be assessed for a possible diagnosis of AP. A wide range of differential diagnoses should be considered which include intestinal obstruction, perforated peptic ulcer, mesenteric ischaemia, biliary colic, cardiovascular causes such as inferior wall myocardial infarction, dissecting aortic aneurysm and possible gynaecological causes such as ruptured ectopic pregnancy.

A thorough history of the presenting illness is needed to determine the onset, duration, progress and nature of the pain. AP pain typically presents as severe epigastric pain radiating to the back and is worsened by movement, and classically leaning forwards alleviates the pain. The pain is often associated with anorexia, nausea, vomiting and decreased oral intake. Risk factors for pancreatitis should also be assessed at the time of history taking. Although alcohol and gallstones are the two most common causes other aetiologies should also be explored, in particular family history can indicate possible hereditary pancreatitis or familial cancer syndromes. On examination patients with AP are often hypovolaemic and may also have tachypnoea, diaphoresis and tachycardia.

Any patient presenting with acute severe abdominal pain outside of A&E, such as in primary care, should be urged to attend A&E promptly to facilitate a rapid diagnosis and to commence treatment (most importantly intravenous fluids), which will improve outcomes in AP and in other causes of acute severe abdominal pain. Embarking on tests in primary care such as serum amylase if AP is being considered is unlikely to be worthwhile. The diagnosis of acute pancreatitis requires two of the following criteria to be present as per the revised Atlanta classification: abdominal pain in keeping with pancreatitis; serum amylase and/or lipase more than 3 times the upper limit of normal; CT or MRI findings consistent with acute pancreatitis.

source of bleeding, which would usually be treated by an interventional radiologist in the first instance.

The indications for drainage of a pancreatic pseudocyst or WON are either infection or biliary or gastric outlet obstruction. In the convalescent period drainage of a pancreatic collection should be considered if it is likely to be the cause of ongoing pain.

The decision, and strategy, for drainage involves a multidisciplinary process and should be undertaken in high volume units that can provide interventional endoscopy, radiology and hepatobiliary surgical support.

Internal EUS guided drainage of a pancreatic pseudocyst or WON across the stomach or duodenal wall is preferred to percutaneous drainage where possible; it is more comfortable for the patient and a wide bore stent across the gut wall drains better than percutaneous drains. There is also no risk of a persistent cutaneous fistula. In practice though in very large, complicated collections arising from AP both modalities may be required.[31]

EUS guided drainage of WON should be with lumen-apposing metal stents as they provide a drainage channel between the stomach or duodenum of up to 20 mm which facilitates drainage of solid material and permits a subsequent direct endoscopic necrosectomy (debridement of the solid material of the WON through the stent endoscopically).

Open surgical procedures are no longer recommended after the landmark PANTER trial showed that such minimally invasive step-up approaches reduced the rate of major complications and death.[32]

ERCP would be indicated for patients with gallstone pancreatitis with biliary obstruction or cholangitis secondary to ductal stones to clear the stones from biliary ducts.

PREVENTION OF RECURRENCE

Patients presenting with alcohol related pancreatitis may need initial alcohol detoxification if they are found to be in alcohol withdrawal and should be treated with chordiazepoxide (oxazepam in case of liver dysfunction) and vitamin and nutritional supplementation. They should be counselled for alcohol cessation and referred to appropriate alcohol cessation services in the community.

Patients with gallstone pancreatitis should undergo an urgent cholecystectomy as soon as they are well enough after the index episode of pancreatitis to prevent recurrent pancreatitis. A recent study suggests that in necrotising pancreatitis, cholecystectomy should be performed before 8 weeks due to the high risk of recurrent biliary events after 8 weeks.[33]

In patients who are surgically unfit for cholecystectomy, a prophylactic sphincterotomy may be performed, however it may not reduce the rate of further biliary colic or cholecystitis. Whether the benefits of sphincterotomy outweigh the risks of ERCP in comorbid patients is controversial.[26] Smoking cessation should be advised as smoking is a risk factor for recurrent acute pancreatitis which in turn is a risk factor for progression to chronic pancreatitis.[34]

Pancreatic enzyme insufficiency (PEI) may develop after severe acute pancreatitis and requires pancreatic enzyme supplementation. After a significant episode of AP patients should be screened with a faecal elastase as PEI may be sub-clinical and patients may not describe classic steatorrhoea or diarrhoea. The patient should be investigated for fat soluble vitamin deficiency and this should be treated if found.

A recent meta-analysis suggested that the incidence of diabetes mellitus was 23% post acute pancreatitis and 15% had diabetes treated with insulin. Severe, alcohol related and necrotising acute pancreatitis had a higher incidence of diabetes in comparison with biliary causes and mild acute pancreatitis.[35]

Pharmacotherapy with fibrates, statins, niacin and omega 3 fatty acids is useful in patients with pancreatitis secondary to hypertriglyceridaemia and patients should be counselled with respect to dietary modifications, weight reduction and abstaining from alcohol.[26]

CONCLUSION

AP should be suspected in all patients presenting with severe acute abdominal pain. It is a common condition and can lead to potentially catastrophic outcomes. Once suspected diagnosis is straightforward using laboratory investigations and imaging. Prompt treatment with fluids is important, and a multidisciplinary approach is essential.

The management of AP in most cases is supportive, but AP can lead to severe associated complications that may require endoscopic or radiological interventions, with the need for surgery now being very unusual. With prompt specialist multidisciplinary involvement excellent outcomes can be achieved even in very severe necrotising pancreatitis.

Competing interests
Dr Gavin Johnson has undertaken educational consultancy work for Boston Scientific and Pentax. Dr Nichil Pednekar has no competing interests

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