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Management of the patient with acute pancreatitis

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Learning objectives

By reading this article you should be able to:

- Classify acute pancreatitis and list its common causes.
- Explain the principles of investigation and supportive management of patients with acute pancreatitis.
- Describe the local complications of acute pancreatitis and understand the indications and options for intervention.
- Discuss the potential long-term sequelae after acute pancreatitis and strategies to prevent its recurrence.

Key points

- Most patients with acute pancreatitis have a self-limiting disease that resolves with simple supportive measures.
- Patients with organ dysfunction should be managed in conjunction with critical care. Those with severe acute pancreatitis should be discussed with regional specialist pancreatic units.
- Local complications are managed conservatively as far as possible; the risk of intervention is particularly high in the first few weeks. When intervention is required, a 'step-up' strategy is adopted and an endoscopic approach may be preferred.
- Antibiotics are reserved for proved or strongly suspected sepsis.
- Parenteral nutrition is indicated when enteral nutrition fails or is contraindicated.

Acute pancreatitis (AP) is an acute inflammatory disorder of the pancreas. It is a leading cause of hospital admission for gastrointestinal (GI) disorders and the incidence is rising.[1] Although the vast majority of patients have a self-limiting illness, those with severe AP account for 2.4% of ICU beds occupied in England and Wales, and have an in-hospital mortality of 40%.[2] A previous article on severe AP was published in *Continuing Education in Anaesthesia, Critical Care & Pain* a decade ago.[3] This article provides an update on the classification and evidence-based management of AP.

Definitions and diagnostic criteria

AP is diagnosed and classified according to the revised Atlanta criteria.[4] Diagnosis requires the presence of two or more of the following: (i) abdominal pain consistent with AP (severe, acute, persistent epigastric pain, often radiating to the back); (ii) an increase in serum amylase or lipase to greater than three times the upper limit of normal; and (iii) imaging evidence of AP (most commonly with contrast-enhanced CT).

If AP is suspected on clinical grounds without a significant increase in serum enzymes (as may occur with delayed presentation), imaging may be required to confirm the diagnosis. Conversely, even if the above two clinical/biochemical criteria are fulfilled, early CT imaging may be required to confirm the diagnosis. This will also help exclude other confounding pathology including perforated peptic ulcer or ischaemic bowel.

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Table 1 Causes of AP

Mechanism	Example
Obstructive	• Gallstones or 'biliary sludge' • After ERCP • Neoplasm (rare) • Pancreas divisum (controversial) • Sphincter of Oddi (controversial) • Cystic fibrosis
Toxic	• Chronic alcohol excess • Hypertriglyceridaemia • Drugs: immunosuppressants (steroids, azathioprine); diuretics (furosemide, thiazides); oestrogens; sulphonamides; metronidazole • Hypercalcaemia • Hyperparathyroidism • Scorpion or snake bites (rare)
Ischaemia/ reperfusion	• Cardiopulmonary bypass • Shock states • Vasculitides
Infection	• Viruses: Cytomegalovirus, mumps, coxsackie B, Epstein-Barr virus • Parasites: Ascaris, Clonorchis
Trauma	• Blunt or penetrating trauma • Surgical
Other	• Hypothermia • Genetic (α_1-antitrypsin deficiency) • Autoimmune (sclerosing cholangitis) • Idiopathic
Other associated risk factors	• Diabetes • Obesity • Smoking

AP may be subdivided into two types: (i) interstitial oedematous pancreatitis and (ii) necrotising pancreatitis. The former accounts for more than 80% of cases and typically manifests as mild disease in which pancreatic inflammation resolves without lasting local or systemic effects. Necrotising pancreatitis manifests as necrosis of the pancreas, peripancreatic tissue, or both, and is a more aggressive form of the disease with a far greater propensity for systemic complications.

Defining severity of AP

The revised Atlanta classification (2012) now defines three levels of severity[4]: (i) Mild AP: the absence of organ failure or local complications; (ii) Moderate AP: the presence of 'transient' organ failure or local/systemic complications *without* persistent organ failure; and (iii) Severe AP: defined by the presence of persistent (>48 h) organ failure.

More than a dozen pancreatitis-specific scoring systems have been developed in an attempt to identify patients at risk of complications early. However, these are typically cumbersome and do not predict outcome robustly in a timeframe that is useful for clinical practice. Instead, it is recommended that patients with AP undergo thorough clinical assessment, frequent monitoring (e.g. with Early Warning Scores), and regular review in order that organ dysfunction is recognised and addressed early.[5] Predictive scoring systems may have a role in disease stratification in the context of clinical trials.

Aetiology

Gallstones and alcohol are the commonest causes of pancreatitis and account for more than two-thirds of all cases. Other causes are outlined in Table 1.

Table 2 Local complications of AP

Pancreatic or peripancreatic collections	• Acute peripancreatic fluid collection • Acute necrotic collection • Walled-off necrosis • Pancreatic pseudocyst
Local vascular complications	Thrombotic: • Splenic vein thrombosis • Superior mesenteric vein thrombosis • Portal vein thrombosis Haemorrhagic: • Acute haemorrhage • Pseudoaneurysm formation (e.g. splenic or gastroduodenal artery)
Regional	Pancreatic fistulae Abdominal compartment syndrome Paralytic ileus

The lifetime risk of AP in patients with incidentally detected gallstones is estimated to be less than 2%.[6] However, when gallstones migrate into the biliary tree, they may cause transient obstruction of the pancreatic duct. This provokes premature intracellular activation of digestive enzymes, 'autodigestion' of pancreatic cells, and an intense inflammatory response. This 'obstructive' mechanism may also occur at the time of contrast injection into the biliary tree during endoscopic retrograde cholangiopancreatography (ERCP), and so account for the high incidence of AP after this procedure.

Alcohol is thought to initiate AP via a direct toxic effect, although binge drinking does not appear to be a trigger. Instead the risk seems to be related to sustained high alcohol intake. The lifetime incidence of AP amongst chronic heavy drinkers in one German study was estimated to be less than 3%, indicating the importance of other factors such as genetics.[7] Additional risk factors for developing AP include: type II diabetes, social deprivation, smoking, and obesity. Morbid obesity is associated with adverse outcomes in AP, including increased organ failure and mortality.

Pathophysiology

Two overlapping phases of AP are described.[4] The early phase is characterised by systemic inflammation as a result of the host response to pancreatic injury. Although the term 'systemic inflammatory response syndrome (SIRS)' is no longer used in the most recent definitions of sepsis, it is a useful descriptor in the setting of AP. The spectrum of severity of systemic inflammation in AP may range from simple 'SIRS' with no organ dysfunction, to a precipitous decline with multi-organ failure and death. The clinical features may be indistinguishable from those of sepsis, and mortality relates to the severity of organ failure and the number of systems involved. Whilst local complications may be evident in the early phase of the disease, these do not tend to determine an early adverse outcome. For most patients, inflammation simply resolves, but a minority progress to develop a late phase, characterised by the evolution of local complications (with or without organ failure).

Local complications include: necrosis and acute peripancreatic fluid collections (both of which may be either sterile or infected), vascular complications and pancreatic fistula (see Table 2). The most feared local complication is that of infected necrosis, but it is the presence or absence of

accompanying organ failure that is the main determinant of mortality. This observation has prompted calls for a four-tier classification to include the term '*critical pancreatitis*' in cases where infected necrosis is accompanied by organ failure.[8]

Investigation: confirming the diagnosis, assessing aetiology, and complications

Patients typically present with acute abdominal pain and routinely undergo blood tests including: FBC, U&Es, liver function tests (LFTs), glucose, and serum amylase (or lipase). Women of childbearing age should also have a pregnancy test, as hyperamylasaemia may occur with ectopic pregnancy. Further laboratory investigations such as coagulation screen, lactate, C-reactive protein, calcium, and arterial blood gas analysis are used to assess the magnitude of inflammatory response and physiological compromise. A chest X-ray will exclude significant pneumoperitoneum (though cannot *exclude* a perforated viscus) and may also demonstrate pleural effusions or pulmonary complications. A 12-lead ECG should also be performed to look for evidence of myocardial ischaemia.

Early CT imaging should be performed where there is 'diagnostic uncertainty' and in all patients requiring ICU admission, to robustly confirm the diagnosis and exclude other pathology. I.V. contrast medium should be used, even in the setting of significant renal failure, in an effort to increase diagnostic yield. The presence of an ongoing significant inflammatory response or organ dysfunction in the first week merits CT imaging to look for local complications. Patients with local complications, persistent organ failure, or both will require regular imaging to monitor evolution of local complications and determine management.

It is important to establish the aetiology, beginning with a thorough history including: alcohol consumption, medications, preceding symptoms of viral illness, and family history of pancreatitis. All patients presenting with AP should undergo an ultrasound scan to look for gallstones and to assess for evidence of biliary dilatation. If negative, this should be repeated before discharge, as false negative results are not uncommon early in the disease. Hypercalcaemia, as a potential causes of AP, should be assessed on admission. If negative this should also be repeated in the convalescent phase. Conversely, hypertriglyceridaemia in the acute setting may occur as a consequence of the illness and testing should be repeated after recovery from acute illness. Whilst some patients have 'idiopathic pancreatitis' every effort should be made to determine aetiology, as this offers the potential for prevention of further attacks. In particular, patients with minimal alcohol consumption, recurrent episodes, or both should undergo endoscopic ultrasound to evaluate the gallbladder and biliary tree for microlithiasis.

Supportive management of AP

The majority of patients presenting with AP are assessed and managed in general surgical wards. Patients with evidence of organ dysfunction or at high risk of deterioration (e.g. elderly patients with chronic organ dysfunction or obese patients with evidence of significant systemic inflammatory response) are best managed in a critical care environment.

Treatment of AP is entirely supportive. As is the case with sepsis, numerous pharmacological strategies have been trialled to mitigate the inflammatory response or alter the outcome in AP, but without any notable success. The mainstays of initial management are resuscitation and analgesia with supplemental oxygen if hypoxaemia is present.

Intravenous fluids

Patients frequently have significant depletion of intravascular volume caused by decreased oral intake, vomiting, capillary leak, and increased insensible losses (fever/tachypnoea). In addition to absolute hypovolaemia, there may also be '*relative hypovolaemia*' secondary to vasodilatation. Preclinical data suggest that pancreatic hypoperfusion occurs in AP and this may be attenuated by resuscitation and treatment with i.v. crystalloids in high volumes. Evidence from prospective clinical trials is limited and observational studies are difficult to interpret, given the likely confounding effect of disease severity on prescribing of i.v. fluids.[9]

Guidelines from the American College of Gastroenterology recommend initial i.v. fluids resuscitation rates of 250–500 ml h^{-1} and suggest the benefit of resuscitation with fluids is probably limited to the first 12–24 h.[5] It is likely that too much fluid is as harmful as too little, including increased risk of intra-abdominal hypertension or abdominal compartment syndrome.[10] However, it is difficult to determine the optimal strategy for resuscitation with i.v. fluids. A large international study in ICUs worldwide suggests that fluid-prescribing is highly variable and often irrational.[11] Whilst a 'one size fits all' fluid resuscitation protocol is illogical, it is also difficult to define end-points for individualised resuscitation. A systematic review of fluids administration in AP could not find any good quality evidence on which to base recommendations on type, volume, or rate of administration of fluid; nor could it make recommendations regarding specific end-points for resuscitation.[9]

In the absence of specific good quality evidence, it seems reasonable to extrapolate from practice in patients with sepsis. Balanced crystalloid solutions should be used to maintain organ perfusion targeting a urine output of >0.5 ml kg^{-1} h^{-1} and return to normal values of serum lactate. When systemic hypotension is present, vasopressors may also be required and early addition of vasopressor therapy may help to limit harmful effects of high volume fluid resuscitation.

Analgesia

AP is a painful condition and immediate, effective analgesia is the priority. Whilst this is given primarily on compassionate grounds, it also has a positive impact on the patient's physiology by reducing the stress response and minimising pulmonary complications such as atelectasis, lobar collapse, and lower respiratory tract infection. There is no good quality evidence to guide analgesic therapy in AP and clinical practice generally follows the standard analgesic ladder.[12] An international multicentre RCT investigating the role of epidural anaesthesia in patients with AP admitted to ICU is currently ongoing.[13]

Non-steroidal analgesics should be avoided; parenteral opioids and paracetamol should be used instead until reliable gut absorption is demonstrated. Multimodal antiemetic drugs are given as required. A minority of patients may require PCA in order to manage their pain effectively.

Antibiotics

Pancreatitis is a sterile inflammatory process. Although bacterial infection may coexist with AP (e.g. concomitant cholangitis or pneumonia) or develop in previously sterile sites (e.g. infected pancreatic necrosis), the routine use of antibiotics is not recommended.[5,14] Instead, antibiotics should be reserved for those with proven or suspected bacterial infection, ideally based on cultured organisms. In particular, positive drain cultures should not be treated with antibiotics unless there is concern regarding adequacy of source control. Fine needle aspiration of collections for culture was previously advocated, but concerns regarding inoculation of sterile collections have led to this technique falling out of favour.

Prevention of pulmonary complications

Early effective analgesia aims to prevent complications associated with 'diaphragmatic splinting' and hypoventilation.

There is an association between resuscitation with large volumes of i.v. fluids and pulmonary complications, and AP is a potent stimulus for the development of acute respiratory distress syndrome. After the initial resuscitation period (in which the aim is to restore circulating volume) fluids administration should be minimised. Supplementary oxygen should be used to maintain Spo_2 >94% and increasingly, high flow nasal oxygen has been used in order to avoid the need for mechanical ventilation.

Prevention of renal complications

Nephrotoxic drugs should be stopped on admission to hospital. Intravascular volume and an adequate perfusing pressure should be restored as part of the initial resuscitation as outlined above. Balanced resuscitation with crystalloids may avoid the adverse renal outcomes associated with starch solutions and chloride-rich resuscitation fluids.

Glycaemic control

Hyperglycaemia commonly accompanies AP. This is likely to result from a combination of stress-mediated 'counter regulatory' hormones and loss of functioning pancreatic islet cells. There is no evidence to support 'intensive' glucose control over 'conventional' glucose control (<10 mmol L^{-1}) in AP and the former may be harmful.[15] This is compatible with current practice in the general ICU population.

Nutrition

Patients with mild AP can eat and drink as soon as they desire. There is no evidence to support 'resting' the pancreas, nor is there evidence to support early enteral nutritional support.[16]

Nutritional support is recommended if normal diet cannot be established within 5–7 days.[17] In these circumstances, enteral nutrition appears to lead to fewer complications than parenteral nutrition. Enteral feed should be delivered via the nasogastric route. The nasojejunal route is only required when nasogastric feeding is not tolerated (e.g. gastric outlet obstruction resulting from local complications), or occasionally when feeding distal to a foregut fistula is required.

Traditionally, elemental and semi-elemental feeds have been used based on the assumption that these cause less pancreatic stimulation than standard polymeric feeds, but there is inadequate evidence to support this practice.[18] Similarly, probiotics and specific immunonutrition supplementation cannot currently be recommended.

Total parenteral nutrition is used rarely and is largely reserved for those patients with either a non-functioning gut or those with complex enteric fistulae.

Management of gallstones

It is imperative that gallstones, when present, are identified and managed definitively in a bid to prevent recurrent pancreatitis. Timing of cholecystectomy is dependent on the severity of pancreatitis. In mild disease, it is recommended that cholecystectomy be performed before discharge, though this often poses logistical challenges. In severe pancreatitis, months of convalescence may be required before surgery is considered. Choledocholithiasis (stones in the bile duct) may be identified on pre-operative imaging (e.g. magnetic resonance cholangiopancreatography) or via cholangiography at the time of surgery. Strategies for managing bile duct stones include ERCP and operative bile duct exploration at the time of cholecystectomy. ERCP and endoscopic biliary sphincterotomy may also be utilised as 'definitive management' in a bid to prevent recurrent attacks in those deemed unfit to undergo cholecystectomy. ERCP has no role in the early management of AP, unless there is coexisting cholangitis (when it is required urgently to allow decompression of the biliary system for 'source control').[5] This may be difficult to judge as deranged LFTs, an increased serum amylase, and an inflammatory response may occur in both AP and cholangitis. Every effort should be made to avoid unnecessary ERCP in the context of AP, as the risks are high, including inoculation of previously sterile necrosis or collections. A pragmatic strategy of measuring LFTs serially for the first 24–48 h helps differentiate these conditions: a transient increase in bilirubin concentrations suggests a gallstone that has passed in a patient with AP, whilst a persistent or rising bilirubin is more likely consistent with biliary obstruction and cholangitis.

Indications for referral to a tertiary centre

It is recommended that patients with severe AP or those with a hospital stay of more than 2 weeks after the onset of symptoms should be managed by, or in consultation with, a specialist pancreatic team.[19] Local referral pathways should be agreed. Early discussion with the specialist unit is advised and many patients are now co-managed 'remotely' with the assistance of electronic radiology systems.

Endoscopic, radiological, and surgical management of local complications

'First, do nothing'

The majority of local complications do not require any intervention and the prevailing ethos should be to manage local complications conservatively, unless forced to act because of uncontrolled sepsis, bleeding, or failure to progress.

Necrosis

There is no role for prophylactic antibiotics and sterile necrosis rarely requires intervention (except in rare circumstances when it causes obstruction of the GI tract or biliary tree). The main indication for intervention is the development of infected necrosis. It is widely accepted that intervention in

the first 2 weeks of severe AP should be avoided if at all possible because of the high associated mortality. In rare cases, such as major intra-abdominal haemorrhage or secondary bowel ischaemia requiring laparotomy in the first weeks, it is best to avoid disturbing the pancreatic inflammatory mass if possible.[19]

If required, pancreatic intervention should be delayed until 'walled-off necrosis' has developed, typically 3–5 weeks after the onset of symptoms. This allows demarcation of the boundary between healthy and necrotic tissue with liquefaction of the contents and formation of a more defined wall. Indications for intervention include: confirmed or suspected infection of necrotic tissue and persistent organ failure with a walled-off collection.[19] If infected necrosis is suspected, then antibiotics should be initiated. Antibiotics may permit drainage or debridement to be safely delayed until maturation of walled-off necrosis, and antibiotics alone may suffice in some patients.[20] There is evidence from RCTs to support a 'step-up' approach of antibiotics with percutaneous drainage, followed by minimally invasive surgical necrosectomy if required. This approach reduced major morbidity by 43% compared with open necrosectomy, and more than one-third of patients in the 'step up' group required only percutaneous drainage.[21] Minimally invasive necrosectomy is performed by 'upsizing' the percutaneous drain under general anaesthesia. This tract is then used to access and debride the necrotic collection with a rigid endoscope. Therefore, the position of the initial drain site should be considered carefully and an approach via the left flank is often preferred. Endoscopic necrosectomy is increasingly popular and involves accessing the collection from the foregut (usually stomach) under endoscopic ultrasound guidance. A recent randomised trial comparing endoscopic with surgical step-up approach suggested equivalence in terms of a composite end-point of mortality or major complications, but shorter hospital stay and reduced pancreatic fistulae with endoscopic therapy.[22] Regardless of the approach, the key principle is the same: control of sepsis by relieving 'pus under pressure'. Debridement of necrotic tissue *per se* is not required for the resolution of sepsis but rather to facilitate drainage of pus.

Pancreatic pseudocyst

This is an encapsulated collection of fluid with a well-defined inflammatory wall, usually outside the pancreas, with minimal or no necrosis.[4] Pseudocysts are therefore very rare after AP, as necrosis is invariably present to some extent. When they occur, pseudocysts usually evolve more than 4 weeks after the onset of AP and contain sterile, enzyme-rich fluid. Secondary infection can occur. Most resolve spontaneously without any intervention. The main indications for intervention are: persistent pain, infection of the pseudocyst, bleeding, and obstructive symptoms (e.g. gastric outlet obstruction). Pseudocysts may be drained percutaneously, endoscopically, or surgically (e.g. drainage into the stomach via an open or laparoscopic approach). A recent systematic review comparing these strategies found inadequate evidence to strongly support a particular practice, but concluded that endoscopic ultrasound-guided drainage appeared to be advantageous in the drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum.[23] A tailored therapeutic approach involving a specialist multidisciplinary team including a radiologist, therapeutic endoscopist, and pancreatic surgeon is recommended.

Splenic/mesenteric/portal venous thrombosis

Intense inflammation adjacent to major venous structures may lead to splanchnic venous thrombosis, most commonly affecting the splenic, portal, or superior mesenteric veins. Splenic vein thrombosis has been reported in 23% of patients with AP undergoing imaging. Approximately half of these patients subsequently develop splenomegaly and gastro-oesophageal varices because of 'segmental portal hypertension', and an associated 12% rate of GI bleeding is reported.[24] Spontaneous recanalisation occurs in approximately one-third of patients. The risks and benefits of anticoagulation should be assessed on a patient-by-patient basis. In general, thrombus involving the superior mesenteric vein or portal vein is managed with anticoagulant drugs for 3–6 months in the absence of a contraindication. Splenic vein thrombosis is usually managed without anticoagulants.

Arterial pseudoaneurysm

Major vascular complications occur in up to 6% of patients with AP, with an associated mortality reported to be >30%.[25] Asymptomatic arterial pseudoaneurysm of splenic or hepatic arterial branches may be identified on CT imaging. These are associated with a high risk of bleeding and prophylactic transcatheter arterial embolisation is recommended. Embolisation is also the first-line treatment in the event of acute haemorrhage. CT angiography may provide a 'roadmap' in the patient who is bleeding. This is determined by the patient's physiology; if unstable, the patient should not undergo CT imaging and be transferred directly to the interventional radiology (IR) operating theatre for resuscitation concurrent with control of haemorrhage.

In the event that IR fails, a surgical approach is often necessary. This is one of the most technically challenging operative procedures in pancreatic surgery. Access to the culprit vessel is compromised by the inflammatory process and the most rapid approach to the retroperitoneum is often best achieved via the transgastric route.

Sequelae of AP and preventing recurrence

The majority of patients have mild disease and pancreatic inflammation resolves without long-term effects. Furthermore, the majority of those with local complications (e.g. acute fluid collections) resolve spontaneously without intervention. The transition from AP to chronic pancreatitis occurs predominantly in cases of alcohol-induced AP and smoking is an additional risk factor for this.

Patients with significant pancreatic necrosis should be assumed to have exocrine insufficiency and treated empirically with enzyme supplements. There may be some functional recovery over the ensuing months and exocrine function can be reassessed by means of faecal elastase testing or on clinical grounds. Endocrine insufficiency should also be considered and monitored in these patients. Survivors of severe AP may have long-term impairment of organ function. The duration of stay of patients with AP needing admission to the ICU is twice that of other patients admitted to critical care.[2] Consequently, they are particularly prone to the sequelae of 'post-ICU syndrome', including cognitive, psychiatric, and physical disabilities.

Prevention of recurrence requires a thorough search for causative factors, most notably a thorough search to exclude

and manage gallstones. Those with alcohol-induced AP should receive structured support to promote abstinence. Other modifiable causes (hypertriglyceridaemia, hypercalcaemia, medications, autoimmune disease) should also be addressed.

Summary

The incidence of AP is increasing. For the vast majority of patients, it is a self-limiting disease requiring ward-based supportive care and a thorough assessment of aetiology in a bid to prevent recurrence. However, those with moderate or severe disease may require extensive critical care resources and specialist radiological, endoscopic, and surgical input. This is best provided in conjunction with regional specialist units.

Declaration of interest

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

References

1. Goldacre MJ, Roberts SE. Hospital admission for acute pancreatitis in an English population, 1963-98: database study of incidence and mortality. *BMJ* 2004; **328**: 1466–9
2. Harrison DA, D'Amico G, Singer M. Case mix, outcome, and activity for admissions to UK critical care units with severe acute pancreatitis: a secondary analysis of the ICNARC case mix programme database. *Crit Care* 2007; **11**(Suppl. 1): S1
3. Young SP, Thompson JP. Severe acute pancreatitis. *Contin Educ Anaesth Crit Care Pain* 2008; **4**: 125–8
4. Banks PA, Bollen TL, Dervenis C *et al*. Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–11
5. Tenner S, Baillie J, DeWitt J, Vege SS. American college of gastroenterology guideline: management of acute pancreatitis. American College of Gastroenterology *Am J Gastroenterol* 2013; **108**: 1400–15
6. Lowenfels AB, Lankisch PJ, Maissonneuve P. What is the risk of biliary pancreatitis in patients with gallstones? *Gastroenterology* 2000; **119**: 879–80
7. Lankisch PJ, Lowenfels AB, Maissonneuve P. What is the risk of alcoholic pancreatitis in heavy drinkers? *Pancreas* 2002; **25**: 411–2
8. Dellinger EP, Forsmark CE, Layer P *et al*. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg* 2012; **256**: 875–80
9. Haydock MD, Mittal A, Wilms HR, Phillips A, Petrov MS, Windsor JA. Fluid therapy in acute pancreatitis: anybody's guess. *Ann Surg* 2013; **257**: 182–8
10. Ke L, Ni HB, Sun JK *et al*. Risk factors and outcome of intra-abdominal hypertension in patients with severe acute pancreatitis. *World J Surg* 2012; **36**: 171–8
11. Cecconi M, Hofer C, Teboul JL *et al*. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med* 2015; **41**: 1529–37
12. Meng W, Yuan J, Zhang C *et al*. Parenteral analgesics for pain relief in acute pancreatitis: a systematic review. *Pancreatology* 2013; **13**: 201–6
13. Bulyez S, Pereira B, Caumon E *et al*. Epidural analgesia in critically ill patients with acute pancreatitis: the multicentre randomised controlled EPIPAN study protocol. *BMJ Open* 2017; **7**, e015280
14. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010; **12**: CD002941
15. Qin Y, Shi Z, Tang S *et al*. Two different glycemic control ways applied to treat severe acute pancreatitis. *Biomed Res* 2017; **28**: 4009–12
16. Bakker OJ, van Brunschot S, van Santvoort HC *et al*. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014; **371**: 1983–93
17. Gianotti L, Meier R, Lobo DN *et al*. ESPEN guidelines on parenteral nutrition: Pancreas. *Clin Nutr* 2009; **28**: 428–35
18. Petrov MS, Loveday BP, Pylypchuk RD, McIlroy K, Phillips AR, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. *Br J Surg* 2009; **96**: 1243–52
19. Johnson D, Besselink G, Carter R. Acute pancreatitis. *BMJ* 2014; **349**: g4859
20. Runzi M, Niebel W, Goebell H, Gerken G, Layer P. Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas* 2005; **30**: 195–9
21. Van Santvoort HC, Besselink G, Bakker OJ *et al*. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; **362**: 1491–502
22. Van Brunschot S, Van Grinsven, Van Santvoort HC *et al*. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. *Lancet* 2018; **6**: 51–8
23. Teoh AYB, Dhir V, Jin ZD *et al*. Systematic review comparing endoscopic, percutaneous and surgical pancreatic pseudocyst drainage. *World J Gastroinest Endosc* 2016; **8**: 310–8
24. Butler JR, Eckert GJ, Zyromski NJ, Leonardi MJ, Lillemoe KD, Howard TJ. Natural history of pancreatitis-induced splenic vein thrombosis: a systematic review and meta-analysis of its incidence and rate of gastrointestinal bleeding. *HPB (Oxford)* 2011; **13**: 839–45
25. Flati G, Andren-Sandberg A, La Pinta M, Porowski B, Carboni M. Potentially fatal bleeding in acute pancreatitis: pathophysiology, prevention and treatment. *Pancreas* 2003; **26**: 8–14