Management of the Patient with Acute Pancreatitis

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MeSH Key Words:

Pancreatitis

Pancreatitis, acute necrotizing

Pancreatitis, alcoholic

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 as 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 proven or strongly suspected sepsis. TPN is indicated when enteral nutrition fails or is contraindicated.

- Aetiology should be addressed to prevent recurrence.

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
- Consider the potential long-term sequalae of patients following acute pancreatitis and strategies to prevent recurrence.

Acute pancreatitis (AP) is an acute inflammatory disorder of the pancreas. It is a leading cause of hospital admission for gastrointestinal disorders and the incidence is rising.[1] Although the vast majority of these patients have a self-limiting illness, severe acute pancreatitis has been shown to account for 2.4% of ICU bed occupancy in England & Wales with a corresponding hospital mortality of 40%.[2] A previous article on Severe Acute Pancreatitis was published in *Continuing Education in Anaesthesia, Critical Care & Pain* a decade ago[3]. This article provides an update on 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 two or more of the following three criteria:

1) Abdominal pain consistent with AP (severe, acute, persistent, epigastric pain, often radiating to the back)
2) Serum amylase or lipase rise to greater than three times upper limit of normal
3) Imaging evidence of AP (most commonly with contrast-enhanced CT)

If there is clinical suspicion of acute pancreatitis without a significant serum enzyme rise (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.

Acute pancreatitis may be subdivided into two types: *interstitial oedematous pancreatitis* and *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 and/or peripancreatic tissue and represents 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:

1) Mild AP: The absence of organ failure or local complications
2) Moderate AP: Presence of 'transient' organ failure or local/systemic complications *without* persistent organ failure.
3) Severe AP: Defined by the presence of persistent (>48 hours) organ failure

More than a dozen pancreatitis-specific scoring systems have been developed in an attempt to identify early those at risk of complications. However, these are typically cumbersome and do not robustly predict outcome in a timeframe that is clinically useful. 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.

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 ERCP, accounting for the high incidence of AP following this procedure.

Alcohol is thought to initiate AP via a direct toxic effect, though binge drinking does not appear to be a trigger. Instead the risk seems 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 characterized by systemic inflammation as a result of the host response to pancreatic injury. Although the term 'Systemic Inflammatory Response Syndrome (SIRS)' is no longer utilised in the most recent sepsis definitions, it is a useful descriptor in this setting. 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 picture may be indistinguishable from that 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 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*) as well as 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&E's, LFT's, 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, CRP, 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. Intravenous contrast medium should be used, even in the setting of significant renal failure, in an effort to increase diagnostic yield. On-going significant inflammatory response or organ dysfunction in the first week merits CT imaging to look for local complications. Patients with local complications and/or persistent organ failure 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 prior to 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 should be repeated in the elective setting. Whilst some patients have “idiopathic pancreatitis” every effort should be made to determine aetiology as this offers potential for prevention of further attacks. In particular, patients with minimal alcohol consumption and / or recurrent episodes 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 on 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 fluid resuscitation and analgesia with supplemental oxygen if hypoxaemia is present.

Fluid therapy:

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

Guidelines from the American College of Gastroenterology recommend initial fluid resuscitation rates of 250-500ml/hour and suggest the benefit of fluid resuscitation is probably limited to the first 12-24 hours.[5] It is likely that too much fluid is as harmful as too little, including increased risk of intra-abdominal hypertension or abdominal compartments syndrome.[10] However,

quantifying optimal fluid resuscitation remains an elusive goal. A large international study of fluid prescribing behaviour in ICU's worldwide suggests that fluid-prescribing behaviour is highly variable and often irrational [11] and whilst a 'one size fits all' fluid resuscitation protocol is illogical, it is also difficult to define end points for individualized fluid resuscitation. A systematic review of fluid administration in AP could not find any good quality evidence on which to base recommendations on fluid type, volume or rate of administration, nor could it make recommendations regarding specific resuscitation end points.[9]

In the absence of specific good quality evidence it seems reasonable to extrapolate from practice in septic patients. Balanced crystalloid solution should be used to maintain organ perfusion targeting a urine output of >0.5ml/Kg/hr and 'normalisation' of serum lactate. In the setting of systemic hypotension, the addition of vasopressors may be required and early addition of vasopressors may help to limit deleterious effects of high volume fluid resuscitation.

Analgesia:

AP is a painful condition and immediate and effective analgesia is the priority. Whilst this is given primarily on compassionate grounds it also impacts positively on patient 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 strategy in AP and clinical practice generally follows the standard analgesic ladder.[12] An international multicenter RCT, which aims to

investigate the role of epidural anaesthesia in patients with AP admitted to ICU is currently ongoing.[13]

Non-steroidal analgesics should be avoided and parenteral opiates and paracetamol used instead until reliable gut absorption is demonstrated. Multimodal anti-emetics are given as required. A minority of patients may require patient controlled analgesia in order to effectively manage their pain.

Antibiotics:

Pancreatitis is a sterile inflammatory process. Although bacterial infection may co-exist 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 large volume fluid resuscitation and pulmonary complications and AP is a potent stimulus for development of ARDS. After the initial resuscitation period (in which the aim is to restore circulating volume) fluid administration should be minimised. Supplemental oxygen aims to maintain oxygen saturations greater than 94% and increasingly, high flow nasal oxygen has been used to avoid 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 crystalloid resuscitation may avoid adverse renal outcomes associated with starch solutions and chloride-rich resuscitation fluids.

Glycaemic control:

Hyperglycaemia commonly accompanies AP. This is likely due to 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 (<10mMol/l) in AP and the former may be harmful.[15] This is compatible with the findings of a large, multinational, randomized controlled study in a mixed ICU population.[16]

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.[17]

Nutritional support is recommended if normal diet cannot be established within 5-7 days.[18] In these circumstances, enteral nutrition appears to lead to fewer complications than parenteral nutrition. Enteral feed should be delivered via the NG route. The NJ route is only required when NG feeding is not tolerated (e.g. gastric outlet obstruction due to 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.[19] 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 definitively managed 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 prior to 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. MRCP) 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 acute pancreatitis, unless there is co-existing cholangitis (when it is required urgently to allow decompression of the biliary system for 'source control'). This may be a difficult judgement call as deranged LFT, an elevated serum amylase and an inflammatory response may occur in both acute pancreatitis 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 serial LFT for the first 24-48 hours helps differentiate these conditions: a transient rise in bilirubin suggests a passed stone in a patient with AP, whilst a persistent or rising bilirubin is more likely consistent with biliary obstruction and cholangitis.

Indications for Tertiary Referral:

It is recommended that patients with severe pancreatitis or those with a hospital stay of more than two weeks after the onset of symptoms should be

managed by, or in consultation with, a specialist pancreatic team.[20] 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 conservatively manage local complications unless forced to act by: 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 two weeks of severe acute pancreatitis 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.[20]

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, liquefaction of the contents, and formation of a defined wall around the collection.[21] Indications for intervention include: confirmed or suspected infection of necrotic tissue and persistent organ failure with a walled-off collection.[20] 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.[22] There is randomized controlled trial evidence 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% when compared to open necrosectomy, and more than one third of patients in the ‘step up’ group required only percutaneous drainage.[23] 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. Consideration should therefore be given to the siting of the initial drain and a left flank approach is often preferred. Endoscopic necrosectomy is gaining traction and involves accessing the collection from the foregut (usually stomach) under EUS guidance. A recent Dutch randomised trial comparing endoscopic versus 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.[23] 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 sepsis resolution 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] They are therefore very rare after acute pancreatitis as necrosis to some extent is invariably present. These usually evolve more than four weeks after onset of pancreatitis 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 open or laparoscopic approach). A recent systematic review comparing these strategies found inadequate evidence to strongly support practice but concluded that endoscopic ultrasound guided drainage appeared to be advantageous in drainage of pancreatic pseudocysts located adjacent to the stomach or duodenum.[24] A tailored therapeutic approach involving a specialist multidisciplinary team including: 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 has been reported in

23% of patients with acute pancreatitis undergoing imaging. Approximately half of these patients go on to develop splenomegaly and gastro-oesophageal varices due to 'segmental portal hypertension' and an associated GI bleeding rate of 12% is reported.[25] Spontaneous recanalisation occurs in approximately one third of cases. Risks and benefits of anticoagulation in should be assessed on a case-by-case basis. In general, thrombus involving the superior mesenteric vein or portal vein is managed with anticoagulation for 3-6 months in the absence of a contra indication. Splenic vein thrombosis is usually managed without anticoagulation.

Arterial Pseudoaneurysm:

Major vascular complications occur with a frequency of up to 6% in acute pancreatitis and the mortality associated with this is reported to be greater than 30%.[26] 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 bleeding patient. This is determined by patient physiology and the unstable patient should bypass CT and be transferred directly to the interventional radiology (IR) theatre for resuscitation concurrent with haemorrhage control.

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 transgastrically.

Sequalae of Acute Pancreatitis 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. Transition from acute pancreatitis to chronic pancreatitis predominantly occurs in alcohol-induced AP and smoking is a risk factor for this.

Patients with significant necrosis should be assumed to have exocrine insufficiency and empirically treated 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 acute pancreatitis may have long-term impairment of organ function. Patients admitted to ICU with AP have a length of stay twice that of the average critical care patient.[2] Consequently they are particularly prone to the sequalae 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, auto-immune 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. Those with moderate/severe disease, however, may require extensive critical care resources and specialist radiological, endoscopic and surgical input. This is best provided in conjunction with regional specialist units.

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. *Continuing Education in Anaesthesia Critical 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**(1):102-11

5) Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American college of gastroenterology guideline: Management of acute pancreatitis. *Am J Gastroenterol* 2013;**108**(9):1400-15

6) Lowenfels AB, Lankisch PJ, Maissonneuve P. What is the risk of biliary pancreatitis in patients with gallstones? *Gastroenterology* 2000 **119**(3)879-80

7) Lankisch PJ, Lowenfels AB, Maissonneuve P. What is the risk of alcoholic pancreatitis in heavy drinkers? *Pancreas* 2002;**25**(4):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**(6):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**(2):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**(1):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**(9):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**(3):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**(5):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**(5):CD002941

15) Qin Y, Shi Z, Tang S et al. Two different glycemic control ways applied to treat severe acute pancreatitis. *Biomed Research* 2017; **28**(9):4009-12

16) Finfer S, Chittock DR, Su SY et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; **360**(13):1283-97

17) 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**(21):1983-93

18) Gianotti L, Meier R, Lobo DN et al. ESPEN guidelines on parenteral nutrition: Pancreas. *Clin Nutr* 2009; **28**(4):428-35

19) 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**(11):1243-52

20) Johnson D, Besselink G, Carter R. Acute pancreatitis. *BMJ* 2014;**349**: g4859.

21) Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. *N Engl J Med* 2016; **375**(20):1972-81

22) Runzi M, Niebel W, Goebell H,Gerken G, Layer P: Severe acute pancreatitis: nonsurgical treatment of infected necroses. *Pancreas*, 2005; **30**(3):195-9

23) 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**(16): 1491-1502

24) VanBrunschot 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**(391):51-8

25) 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**(12): 839-45

26) 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**(1): 8-14

Legends to Tables and Figures:

Table 1: Causes of acute pancreatitis.

Table 2: Local complications of acute pancreatitis

Table 1

'Obstructive' mechanism	Gallstones
	ERCP
	Neoplasm (rare)
	Pancreas Divisum (controversial)
	Sphincter of Oddi (controversial)
	Cystic Fibrosis
'Toxic' mechanism	Chronic Alcohol Excess
	Hypertriglyceridaemia
	Drugs: Steroids, Azathioprine, Oestrogens, Furosemide, Thiazides, Sulphonamides, Metronidazole
	Hypercalcaemia
	Hyperparathyroidism
	Scorpion / Snake bites (rare)
Genetic causes (rare)	Alpha-1-Antitrypsin deficiency
Autoimmune (rare)	Sclerosing cholangitis
Trauma	Blunt or Penetrating
Infection	Viruses: CMV, mumps, coxsackie B, EBV
	Parasites: Ascaris & clonorchis
Ischaemia/ reperfusion	Cardio-pulmonary bypass
	Shock states
	Vasculitides
Hypothermia	
Idiopathic	
Other associated risk factors	Diabetes, Obesity, Smoking

Table 2

Local inflammation	Pancreatic / peripancreatic collections • Acute Peripancreatic Fluid Collection • Acute Necrotic Collection • Walled of Necrosis • Pancreatic Pseudocyst
	Pancreatic abscess
	Pancreatic Fistulae
Vascular complications	Splanchnic Venous Thromboses • Splenic vein • Superior mesenteric vein • Portal vein thrombosis
	Arterial • Pseudoaneurysm (splenic, gastroduodenal, aorta) • Bleeding
Other regional	Abdominal Compartment Syndrome
	Paralytic ileus
Systemic	Systemic venous thrombosis
	Acute respiratory distress syndrome
	Acute Kidney Injury

MCQ's:

A 35-year-old man with a history of type II diabetes and morbid obesity (Body Mass Index 37 Kg/m^2) presented to hospital with severe upper abdominal pain and vomiting and was found to have a serum amylase that was seven times the upper limit of normal. He had just returned from a 'stag weekend' during which he had consumed more than 20 units/day of alcohol, though he does not habitually drink alcohol. Chest X-ray showed no abnormalities.

a) A CT scan of the abdomen is mandatory to confirm the diagnosis of acute pancreatitis
b) The most likely aetiology of acute pancreatitis in this case is alcohol
c) Diabetes is a risk factor for acute pancreatitis
d) Obesity is a risk factor for developing severe acute pancreatitis
e) Serum calcium should be checked on admission to exclude hypercalcaemia as the cause of acute pancreatitis

Answers:

a) False. CT imaging is only required when there is diagnostic uncertainty. It is not mandatory and acute pancreatitis is most commonly diagnosed on the basis of typical clinical features and serum enzyme (amylase or lipase) rise.

b) False. Gallstones are the commonest cause of acute pancreatitis and 'binge drinking' (cf. chronic heavy alcohol use) does not appear to confer risk.

c) True

d) True. Morbid obesity is associated with adverse outcomes in acute pancreatitis, including increased organ failure and increased mortality.

e) False. A serum calcium level may be informative if high, however, calcium may be 'sequestered' in necrotic tissue during an episode of acute pancreatitis and may, therefore, give a false negative result in the acute phase. Hypercalcaemia as an aetiology cannot be excluded acutely and the serum calcium level should be re-checked in the convalescent stage.

Abdominal ultrasound scan has demonstrated multiple gallstones in the gallbladder and dilation of the common bile duct (8mm). He was initially jaundiced but this has now resolved. Blood test confirm that his bilirubin has fallen to 28 micromoles/litre. He is exhibiting an ongoing 'Systemic Inflammatory Response Syndrome' six days after the onset of pain though there is no evidence of organ dysfunction. Contrast CT revealed decreased enhancement of the body of the pancreas consistent with pancreatic necrosis. He is not on antibiotics.

a) This patient has severe acute pancreatitis
b) An urgent ERCP is indicated to decompress the biliary tree
c) Antibiotics are not currently indicated
d) Enteral Nutrition is preferred over Parenteral Nutrition.
e) He should undergo a Cholecystectomy within 7 days to prevent further episodes of acute pancreatitis

Answers:

a) False: He has local complications (necrosis) but does not currently have organ failure. By the revised Atlanta classification this would be considered 'moderate' rather than severe disease currently.

b) False: The normalising bilirubin suggests he does not have cholangitis and therefore urgent ERCP is not required. He currently has no organ dysfunction. ERCP in this setting would confer a risk of introducing infection into what is most likely sterile pancreatic necrosis.

c) True. This is most likely a sterile process currently. Guidelines advocate avoiding prophylactic antibiotics, even in the setting of necrosis, and instead reserving antibiotics for proven or highly suspected infection.

d) True. Parenteral nutrition is really only indicated when the enteral route is unavailable.

e) False. In the setting of pancreatic necrosis or persistent organ dysfunction, definitive management of gallstones should be delayed. In patients with mild acute gallstone pancreatitis cholecystectomy would ideally be performed without delay to reduce the risk of recurrence.

10 days later he is receiving ventilatory support for severe respiratory failure (PaO_2: F_iO_2 = 12 KPa). Repeat CT imaging reveals widespread pancreatic necrosis containing gas locules. In addition, radiological features consistent with Acute Respiratory Distress Syndrome (ARDS) are evident.

a) Aggressive fluid resuscitation is required to improve pancreatic perfusion
b) CT imaging in this clinical setting should be performed with intravenous contrast.
c) Enteral feeding should preferentially be administered via a naso-jejunal tube
d) Prone ventilation should be considered
e) Urgent transfer to a regional pancreatic surgery unit is required for definitive management

Answers:

a) False. It is thought that fluid resuscitation in the first 12-24 hours may mitigate pancreatic hypoperfusion but this would not be likely to help at this stage of the illness. Furthermore, in the setting of ARDS, aggressive fluid resuscitation may be detrimental.

b) True. Contrast is required to adequately assess local complications, including vascular complications. The risk of contrast nephropathy is accepted in this setting.

c) False. Most patients can be fed via the naso-gastric route. Naso-jejunal feeding may be required if this fails.

d) True. Whilst there may be valid concerns regarding the effects of prone positioning on intra-abdominal hypertension in this setting, severe acute pancreatitis is not an absolute contra-indication to prone ventilation and it should be considered given his severely impaired oxygenation.

e) False. Whilst there is radiological evidence of infected necrosis it is too early to intervene. In the early phase, infected necrosis is best managed with antimicrobials and supportive care. Liaison with the regional pancreatic unit is recommended but currently the risks of transfer would not be justified.

2 months later his organ failure has resolved and he is recovering in the High Dependency Unit. He has undergone several *minimally invasive necrosectomy* procedures over the last 5 weeks. Splenic vein thrombosis was noted on recent imaging. He has a residual large drain in the left flank. He suddenly deteriorates with a large volume haematemesis and clinical evidence of shock. There is no evidence of blood in the drain.

a) An emergency upper GI endoscopy is required to achieve haemorrhage control
b) Gastric varices (secondary to segmental portal hypertension) as a result of splenic vein thrombosis is the most likely site of bleeding
c) He was likely to have been systemically anticoagulated given that splenic vein thrombosis had been diagnosed.
d) Vascular complication are rare in patients with severe acute pancreatitis (<1%)
e) The mortality associated with major bleeding complications exceeds 10%.

Answers:

a) False. Upper GI endoscopy is the usual first-line step for haemorrhage control in patients with haematemesis. However, in this setting, the most likely source of bleeding is rupture of a pseudo-aneurysm of one of the coeliac artery branches (e.g gastroduodenal or splenic artery branches). Mesenteric angiography will be required to control bleeding and should be considered first-line.

b) False. Gastric varices are a long-term complication of splenic vein thrombosis and do not typically cause early bleeding. Arterial complications are more likely.

c) False. Splenic vein thrombosis alone is not usually considered to be an indication for anticoagulation. Thrombosis affecting the superior mesenteric or portal vein may be considered to require anticoagulation.

d) False. Major arterial complications are reported to occur in 6% of patients and splanchnic vein thromboses may be detected in up to a quarter of all patients undergoing CT imaging.

e) True. The associated mortality is reported to be greater than 30%.