Severe acute pancreatitis: eight fundamental steps revised according to the ‘PANCREAS’ acronym

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ABSTRACT

Severe acute pancreatitis remains a life-threatening condition, responsible for many disorders of homeostasis and organ dysfunction. By means of a mnemonic ‘PANCREAS’, eight important steps in the management of severe acute pancreatitis are highlighted. These steps follow the principle of goal-directed therapy and should be borne in mind after diagnosis and during clinical treatment.

The first step is perfusion: the goal is to reach a central venous pressure of 12–15mmHg, urinary output 0.5–1ml/kg/hour and inferior vena cava collapse index greater than 48%. Next is analgesia: multimodal, systemic and combined pharmacological agent and epidural block are possibilities. Third is nutrition: precocity, enteral feeding in gastric or post-pyloric position. Parenteral nutrition works best in difficult cases to achieve the individual total caloric value. Fourth is clinical: mild, moderate or severe pancreatitis according to the Atlanta criteria. Radiology is fifth: abdominal computed tomography on the fourth day for prognosis or to modify management. Endoscopy is sixth: endoscopic retrograde cholangiopancreatography (cholangitis, unpredicted clinical course and ascending jaundice); management of pancreatic fluid collection and ‘walled-off necrosis’. Antibiotics come next: infectious complications are common causes of morbidity. The only rational indication for antibiotics is documented pancreatic infection. The last step is surgery: the dogma is represented by the ‘three Ds’ (delay, drain, debride). The preferred method is a minimally invasive step-up approach, which allows for gradually more invasive procedures when the previous treatment fails.

KEYWORDS

Necrotising acute pancreatitis – Classification – Imaging diagnosis – Complications – Surgery

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Introduction

We review most important aspects of the management of severe acute pancreatitis, based on current evidence. By means of a mnemonic method using the acronym ‘PANCREAS’ (perfusion, analgesia, nutrition, clinical and radiological assessment, endoscopy, antibiotics, and

surgery), eight fundamental steps in the management of severe acute pancreatitis are highlighted.¹ This acronym could be used as a flowchart to decision making in the emergency room. It has been written according to the principle of goal-direct therapy, to make it easy to apply in many scenarios.

The PANCREAS (eight steps) acronym

P = perfusion

The goals of fluid resuscitation in severe acute pancreatitis are to maintain perfusion of the pancreatic microcirculation and to prevent systemic hypovolaemia caused by capillary leakage syndrome, which results in increased third-space loss and decrease in intravascular volume.² There is still no agreement on infusion regimens, total volume, type of fluid and duration of treatment, but serum creatinine and elevated haematocrit can be an indicator of severe dehydration and more severe disease.^{3,4}

According to Monnet and Teboul,⁵ the haemodynamic status management cannot be ascertained using a simple clinical parameter. They argue that transpulmonary thermodilution is the technique of choice, because it provides a full haemodynamic assessment including cardiac output. It also provides continuous monitoring of many other parameters such as end-diastolic volume of the cardiac cavities, a marker of cardiac preload and the systolic function of the ventricles. Transpulmonary thermodilution has the advantage that extravascular fluid in the lungs, which indicate the volume of pulmonary oedema and its vascular permeability, can be estimated at the bedside. Both parameters are useful for guiding fluid therapy strategy, especially in the case of acute respiratory distress syndrome.⁵

Targeted therapy should be based on maintaining a central venous pressure of 12–15mmHg, urinary output of 0.5–1ml/kg/hour and the inferior vena cava collapse index greater than 48% (predicted fluid reposts, sensitivity 84%, specificity 90%).^{1,8} In cases of pancreatitis-associated shock, vasoactive agents and invasive haemodynamic monitoring are indicated.⁶

The speed of fluid resuscitation in severe acute pancreatitis has been debated. The timing of fluid rehydration intervention (12–24 hours of the onset of symptoms) seems to be important. Crystalloid solutions have been recommended. However, the volume to be administered is still uncertain. Studies in favour of early and aggressive fluids in severe acute pancreatitis employing diverse strategies (more or less than 33% of total fluids within 24 hours) and another administering 3.5 litres or 2.4 litres intravenously within the first 24 hours showed that those receiving more aggressive intravenous fluid volumes within the first 24 hours tend to have improved outcomes, including improved mortality rates.⁷ The infusion of 200–500ml/hour or 5–10ml/kg/hour in the first 24–48 hours (about 2500–4000ml/24 hours of fluid infusion) may be necessary until the outlined parameter is reached.⁸ It is further suggested that the use of Ringer lactate results in a significant reduction in systemic inflammation in relation to the use of saline solution.⁹

A = analgesia

Abdominal pain is often the predominant symptom in patients with acute pancreatitis. In addition, uncontrolled pain may contribute to haemodynamic instability. The pain

should be managed in an aggressive way. A multimodal approach to pain and early mobilisation is recommended.^{10,11} Systemic and combined pharmacological treatment is considered the first choice and opioids have proved to be effective and safe.

Layer *et al*, in a placebo-controlled clinical trial, studied the effect of systemic administration of local anaesthesia in the management of acute pancreatitis.¹² They used continuous intravenous procaine infusion for 72 hours (2g/day). The study concluded that systemic administration of local anaesthetics can improve pain control and accelerate clinical recovery severe acute pancreatitis. The mechanism involves complex pharmacological pathways including anti-inflammatory, anti-infectious, neuroprotective and motility-modulating effects.¹²

The Epidural Analgesia for Pancreatitis (EPIPAN) trial is a prospective randomised multicentric study, which included 148 patients in two arms. EPIPAN compared the application of epidural analgesia containing a mixed solution of ropivacaine (2mg/ml) and sufentanil (0.5µg/ml) in a continuous infusion rate of 5–15ml/hour (six to nine thoracic vertebra) for at least 72 hours, plus standard analgesia (opioids plus non-opioid drugs with or without other adjuvant drugs) compared with standard analgesia only. The study highlights the possibility that epidural analgesia may be superior to standard analgesia alone in patients with severe acute pancreatitis in the acute care unit. Its use may become the standard of care in selected centres.¹⁵

N = nutrition

The current evidence points to the primary pathophysiologic aspects in severe acute pancreatitis being the systemic inflammatory response and consequent vascular leakage syndrome, which promotes significant loss of circulating volume to the third space. These mechanisms result in impairment of organ perfusion and subsequent dysfunction. Moreover, breakdown of the intestinal mucosal barrier highlights the need for precocity of enteral/parenteral nutrition to prevent bacterial translocation and changes in intestinal microbiota, towards a sustained proinflammatory status. So, the idea of 'pancreatic rest' in severe acute pancreatitis is an old paradigm that should be abandoned.^{14–16}

Severe acute pancreatitis is characterised by sustained protein catabolism and increased energy requirements. All patients are at risk of malnourishment and should be evaluated with attention from the start to nutritional support. Enteral nutrition is considered the gold standard of care; it should be given in different situations, including in the presence of complications. Parenteral nutrition is well established and should be employed only in those patients who are unable to tolerate targeted demand. It is indicated when the gut has failed or the administration of enteral nutrition is impossible for other reasons (eg prolonged ileus, complex pancreatic fistulae or abdominal compartment syndrome).¹⁷

The nasogastric tube has been demonstrated to be safe and useful, as has the nasojejunal tube. Studies have

shown that there are no differences in terms of mortality, tracheal aspiration, diarrhoea, exacerbation of pain and meeting energy balance between the two.¹⁸ The start of enteral nutrition in severe acute pancreatitis is crucial and should not be postponed. Studies have demonstrated the benefits of enteral compared with parenteral nutrition when the enteral nutrition was introduced within the first 48 hours of the onset of the symptoms.¹⁹

Regarding non-protein caloric value, 25kcal/kg/day up to a maximum of 30kcal/kg/day with 1.2–1.5g/kg of protein/day has been recommended. The burden of carbohydrate should be decreased to 15–20kcal/kg/day in cases of systemic inflammatory response syndrome or organ dysfunction. Carbohydrates and lipid intake should be 3–6g/kg/day and up to 2g/kg/day, respectively, and the glycaemic rate should not exceed 10mmol/l (180mg/dl) and, if persistent (over 72 hours) hypertriglyceridaemia occurs (greater than 12mmol/l), lipid infusion should be temporarily discontinued.^{17,18}

A small peptide or peptide-based formula and medium-chain triglyceride oil are the macro elements of choice, but the standard formula could be an option if it is well tolerated.¹⁸ The use of glutamine supplementation, except in parenteral nutrition (greater than 0.50g/kg alanine–glutamine dipeptide) is not supported as a routine approach.¹⁷ In addition, immune nutrition, prebiotics or probiotics are not advised.²⁰ Thus, a prompt and adequate nutritional therapy may reduce the morbidity, hospital stay, costs and mortality in patients suffering from severe acute pancreatitis.

C = clinical

The most practical and reproducible aspect in acute pancreatic diagnosis is to recognise its severity based on clinical features, according to the international consensus was reached in Atlanta in 2013. The disease should therefore be classified as mild, moderate and severe pancreatitis, taking into account the presence of organ dysfunction and whether it lasts for more than 48 hours despite resuscitative procedures in severe pancreatitis. There are also severe forms with locoregional complications: acute inflammatory fluid collections and/or acute necrotic collection. After four weeks this is termed 'walled-off necrosis' (sterile or infected).²⁸ The mortality rate can reach 30%, especially in patients who evolve with persistent organ dysfunction and infected pancreatic necrosis 'critical' pancreatitis.²¹

Simple laboratory confirmation at the admission of elevated blood urea nitrogen level or its subsequent rise in the next 24 hours of hospitalisation is an independent risk for mortality.²² Interleukin-6 level also seems to be an acceptable predictor of severe acute pancreatitis with sensitivities ranging from 81.0% to 83.6% and specificities from 75.6% to 85.3% and should be employed in the first 72 hours.²³

R = radiology

At least two of the following criteria are necessary for diagnosis of acute pancreatitis: typical pain and/or lipase amylase levels three times greater than plasma concentration

and characteristic imaging findings on computed tomography (CT) or magnetic resonance imaging (MRI).²⁵ According to Japanese guidelines, ultrasonography and MRI should be requested for acute pancreatitis because it is more useful than CT in diagnosing bile duct stones causing pancreatitis and haemorrhagic necrotising pancreatitis. Contrast-enhanced CT is useful for the diagnosis of active haemorrhage and thrombosis associated with severe acute pancreatitis.²⁴

Transabdominal ultrasound is the image of choice for the initial evaluation of acute pancreatitis, especially in gallstone aetiology. In addition, contrast-enhanced CT is better done at first week (third or fourth day) from the onset of symptoms, because it is very difficult the complete evaluation of the extension and the pancreas and peripancreatic fluid collection and/or necrosis in the early days. An early CT may be needed for differential diagnosis, in cases with an unpredicted course or when treatment revision strategy is needed. MRI is necessary for planning of the clearance of the common bile duct in the case of common bile duct stones or other causes of bile ducts obstruction.¹

Severe acute pancreatitis, according to the Japanese severity score, is present when the prognostic contrast-enhanced CT score is greater than 2. It is based on accumulated points acquired with progressive extrapancreatic inflammation (pararenal space = 0, root of mesocolon = 1, beyond lower pole of kidney = 2). In addition, take into account the compromised hypoenhanced segments of the pancreas (head, body and tail). One segment or peripancreatic = 0 point, two segments = 1 point, more than two segments = 2. The total score is graded accordingly (grade 1 = score 0 or 1; grade 2 = score 2; grade 3 = score 3 or more).²⁵

E = endoscopy

Endoscopic retrograde cholangiopancreatography (ERCP) should be performed early (within 24–48 hours) in patients with severe acute pancreatitis with gallstone aetiology, associated with bile duct obstruction or cholangitis. Another option in unstable patients with the same condition is the placement of a percutaneous transhepatic gallbladder drainage tube, if ERCP is not safe. In addition, endoscopic ultrasonography is an alternative to drainage of pancreatic collection or pancreatic walled-off necrosis. Drainage should be postponed until its liquefaction unless the infected necrosis is responsible for organ dysfunction.^{26,27}

Endoscopic ultrasound-guided diagnosis of infection necrosis and intervention has become an important tool for the management of pancreatic fluid collection and is considered the option of first choice for most patients in centres of excellence. Two endoscopic procedures were described to manage infected walled-off necrosis: direct endoscopic necrosectomy and lumen-apposing metal stenting. The first procedure, despite temporising patient recovery and treating the infected necrosis, is associated with very high morbidity and mortality. On the other hand, the second represents a significant promise of improved and simplified management of these collections.²⁸

A = antibiotics

Infectious complications are common causes of morbidity and mortality in patients with severe acute pancreatitis. The controversy over using antibiotics should be focused on pancreatic necrosis. In fact, patients with infected necrosis have a higher mortality rate than those with sterile necrosis.⁴⁰ Although early non-randomised trials suggested that administration of antibiotics may prevent infectious complications in patients with sterile necrosis,^{29,50} other better-designed trials have failed to confirm the advantage of antibiotic prophylaxis in acute pancreatitis.^{51–55} Guidelines do not therefore recommend antibiotic prophylaxis in patients with acute pancreatitis. The only rational indication for antibiotics is documented pancreatic infection and antibiotics should be always given to treat patients with infected necrosis.^{26,51,52}

Although the diagnosis of infection in severe acute pancreatitis may be difficult based on clinical parameters, infected necrosis should be considered in patients who deteriorate or fail to improve after 7–10 days of hospitalisation. An empirical antibiotic regimen should be given in these patients. After empirical antibiotic therapy, a targeted antibiotic treatment can be based on the results of the cultures from the necrosis. A CT-guided fine-needle aspiration for Gram stain and culture can guide clinicians in choosing a further individualised antibiotic regimen.²⁶

Appropriate spectrum and adequate tissue levels at the site of infection are the main aspects that should be considered when selecting an appropriate antimicrobial. Two factors should drive clinicians in choosing the antibiotics: the microbiologic flora and the penetration of the antibiotic agent in the necrotic pancreatic tissue. The spectrum of empirical antibiotic regimen should include both aerobic and anaerobic Gram-negative and Gram-positive microorganisms. The bacteria most frequently found were *Escherichia coli*, *Enterococcus*, *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, *Pseudomonas sp.* and *Streptococcus sp.*^{53,54}

Pancreatic penetration is good for fluoroquinolones, carbapenems, ceftazidime, cefepime, metronidazole and piperacillin-tazobactam.⁵⁵ When there is no or minimal residual infection following a source control procedure, a 7–10-day period of antibiotic therapy may be sufficient, based on the improvement of the patient's condition. *Candida* infections are often present in these patients and antifungal therapy should be based on previous exposure to antifungal agents, colonisation status of the patient and severity of the illness. Fluconazole remains the most widely used agent for antifungal treatment. When the patient has already been exposed to fluconazole or is colonised with non-albicans *Candida* or when the patient is haemodynamically unstable, therapy with echinocandins is suggested.⁵⁵

Routine fine-needle aspiration is not recommended due to high rates of false negativity, although it has been suggested to help direct antibiotics; prospective studies confirming the benefit of such a strategy are lacking.⁵⁶

S = surgery

Generally, the treatment for severe acute pancreatitis is a medical supportive therapy. However, serious complications may affect some patients, and the rate ranges from 10% to 30%.⁵⁷ During the early phase of severe acute pancreatitis, surgery is rarely indicated. The main reasons for an urgent laparotomy are abdominal compartment syndrome not responsive to clinical measures and intestinal perforation. In cases of intra-abdominal bleeding, angiography with embolisation is the first choice; surgery should be expedited in case of failure.⁵⁸

Interventional strategy, such as endoscopic drainage, minimally invasive or open necrosectomy, should be delayed when possible, at least for four weeks after the onset of symptoms, to liquefy the necrotic tissue and to allow the collection to evolve in walled-off necrosis. Thus, interventional strategy is indicated in cases of suspected or confirmed infected necrosis, continuing clinical deterioration with organ failure, despite maximum medical support; in case of persistent symptoms of gastric, intestinal or biliary obstruction deriving from mass effect. When an interventional approach is indicated, the dogma is represented by the 'three Ds' (delay, drain, debride), which summarise the contemporary strategy for the management of patients with necrotising acute pancreatitis.⁵⁹

The preferred method is a minimally invasive step-up approach, which consists of gradually more invasive procedures, when the previous procedure fails.⁴⁰ Many minimally invasive techniques are available to drain and debride infected necrotic pancreatic tissue. Percutaneous catheter or endoscopic drainage should be the treatment of first choice, indicated in case of infected acute necrotic collections or walled-off necrosis.⁴¹ The next step involves minimally invasive surgical debridement, such as minimal access retroperitoneal pancreatic necrosectomy (MARPN) or video-assisted retroperitoneal debridement (VARD), which are the two minimally invasive techniques for surgical necrosectomy. However, there is no strong evidence to support either as the better choice between VARD and MARPN; the differences are small, so they are interchangeable.⁴¹

Transperitoneal laparoscopic necrosectomy and drainage should be considered as the alternative procedure to MARPN or VARD, especially if the necrotic area is limited to the lesser sac,⁴² or when intra-abdominal distant collections require minimally invasive drainage. If they are multiple, located between intestinal loops and cannot be reached percutaneously. These minimally invasive strategies aim to reduce mortality and morbidity, which classically affect patients with severe acute pancreatitis undergoing more aggressive approaches, such as laparotomic necrosectomy. Therefore, open necrosectomy remains as the last step and it is indicated after failure of the minimally invasive approaches. However, laparotomy is associated with high morbidity and mortality and it should be considered only as a last resort.

Cholecystectomy should be performed during the index admission in patients who have mild acute pancreatitis and should be delayed until clinical resolution in patients who have severe acute pancreatitis.⁴² Thus, the best surgical strategy is multimodal and tailored on the clinical conditions of the patients and on the surgical expertise; a step-up approach should be considered, starting with a less invasive procedure and considering more aggressive techniques where the condition worsens. Open necrosectomy has rarely been performed in recent years. As mentioned by Trikudanathan *et al*,⁵⁶ the traditional management of infected necrosis with open surgical debridement and peritoneal lavage has been almost completely replaced by minimally invasive surgical and endoscopic approaches.⁵⁶

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