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Position Paper

Consensus guidelines on severe acute pancreatitis

The Italian Association for the Study of the Pancreas (AISP)

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ABSTRACT

This Position Paper contains clinically oriented guidelines by the Italian Association for the Study of the Pancreas (AISP) for the diagnosis and treatment of severe acute pancreatitis. The statements were formulated by three working groups of experts who searched and analysed the most recent literature; a consensus process was then performed using a modified Delphi procedure. The statements provide recommendations on the most appropriate definition of the complications of severe acute pancreatitis, the diagnostic approach and the timing of conservative as well as interventional endoscopic, radiological and surgical treatments.

1. Introduction

In 2010, the Italian Association for the Study of the Pancreas (AISP) released practical guidelines for acute pancreatitis (AP) [1] and decided that periodical revisions would be implemented as appropriate. At that time, the guidelines were formulated using the ADAPTE process [2]. Four years later, AISP revised the guidelines, and the Governing Board decided the process should be limited to evaluation of the recent literature on the severe forms of AP, which account for the greatest morbidity and mortality [3].

2. Methodology

AISP produced the present consensus guidelines considering the characteristics of the Italian National Health System. They are divided into three sections: (1) definitions of the complications of severe AP, together with the related diagnostic procedures, (2) conservative treatment and (3) interventional treatments. The definitions of the complications are substantially derived from those of the recently revised Atlanta classification system [4,5]. The Governing Board considered this an essential background for the subsequent sections, in which treatment of these complications is described. Each section contains 18 questions. The Governing Board of the Guidelines and the multidisciplinary panels comprised 6 surgeons, 5 internists/gastroenterologists, 5 endoscopists, 4 radiologists, and 1 anaesthesiologist (Supplementary Table S1).

The literature search was carried out on the PubMed database by an expert librarian in June 2014, taking into account the MESH terms and the search period (the last 10 years). After the first draft, consensus was reached for each statement according to the Delphi procedure [6], and both the evidence level and the recommendation grade were reported according to the Oxford criteria [7].

The Consensus Conference was held in Bologna on September 18, 2014; the members of the Governing Board as well as the members of the three panels participated as voters, except the methodologist who acted as a non-voting participant and chaired the discussion. As reported in Supplementary Table S2, in addition to the members of the panels, there were also 32 voters (representatives of general practitioners, 19 gastroenterologists, 6 surgeons, 3 endoscopists, 1 radiologist, 1 oncologist, 1 laboratory medicine physician) and one non-voting participant representing the patients. Thus, the total number of voters was 51.

For the purpose of these guidelines, severe AP was defined as the presence of persistent or progressive organ failure and/or local pancreatic complications [8]. This is an "*a posteriori* definition" in which criteria are applied after the patient has recovered or has died from AP; the purpose was to ensure the studies on AP were comparable.

New severity categories for AP have recently been suggested [4,5], one introduces the class of moderate AP (characterised by transient organ failure, local complications or exacerbation of co-morbidities) [4]; the other introduces two additional classes,

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namely moderate AP (characterised by sterile necrosis and/or transient organ failure), and a critical form (characterised by infected pancreatic necrosis and persistent organ failure) [5]. These classes are also *a posteriori* classes. However, from a clinical point of view, reliable criteria are needed as soon as possible to predict the course of the disease. Thus, for predicting the severity of AP, careful clinical assessment, and the use of a multiple factor scoring system and imaging studies are suggested. Presently, an acute physiology and chronic health evaluation (APACHE)-II score equal to or greater than 8 [1] has been confirmed as an optimal score for predicting the severity of AP [9,10].

3. Consensus statements

3.1. Definitions and diagnostic procedures for work-up

3.1.1. What are the minimum hospital prerequisites to care for patients with severe AP?

Statement: The minimal requisites for treating patients with severe AP are the availability of an intensive care unit, interventional radiology and interventional endoscopy.
Evidence level 5, Recommendation grade D
Comment: Specific technical facilities are needed for the adequate management of patients with severe AP, and the presence of a multidisciplinary team is strongly recommended. In addition, similarly as reported in pancreatic surgery, a volume-outcome relationship is also true in the setting of AP. Better outcomes were variably described at a volume size of at least 24 AP patients per year (having either mild or severe illness) [11,12], 118 admissions per year [12] and more than 14 severe AP cases per year [13].

3.1.2. What is the definition of "abdominal fluid collection"?

Statement: An abdominal fluid collection is a homogeneous collection without a wall, confined by normal anatomical planes.
Evidence level 5, Recommendation grade D
Comment: An abdominal fluid collection usually resolves spontaneously; if it persists more than 4–6 weeks, it may evolve into a pseudocyst having a well-defined wall [4].

3.1.3. What is the best imaging study for diagnosing the presence and extent of an abdominal fluid collection?

Statement: Contrast-enhanced computed tomography (CT) scan and contrast-enhanced magnetic resonance imaging (MRI) are the best imaging studies for diagnosing the distribution and extent of abdominal fluid collections.
Evidence level 5, Recommendation grade D
Comment: No comparative studies between CT and MRI exist on this topic, but they are both considered reliable in describing the collection characteristics and the absence of a well-defined wall [14–16].

3.1.4. What is the definition of a "pseudocyst"?

Statement: A pancreatic pseudocyst is a fluid collection surrounded by a well-defined wall, containing no solid material; it usually occurs more than 4 weeks after the onset of the pancreatitis.
Evidence level 5, Recommendation grade D
Comment: When solid necrotic material is present within a largely fluid-filled cavity, the term pseudocyst should not be used and the term walled-off necrosis (WoN) is indicated. According to this new definition, the development of a pseudocyst is a rare event [7,14–17].

3.1.5. What is the best imaging study for diagnosing the presence and extent of a post-AP pseudocyst?

Statement: Contrast-enhanced CT and contrast-enhanced MRI are the best imaging studies for diagnosing the presence and the extent of a post-AP pseudocyst.
Evidence level 5, Recommendation grade D
Comment: On contrast-enhanced CT, pseudocysts are usually seen as thin-walled (1–2 mm), round- or oval-shaped cystic lesions with a density <20 Hounsfield units (HU). Their walls may be thick and irregular and develop calcification over time [18]. Pancreatic pseudocysts have been reported to communicate with the pancreatic duct in 25–58% of cases [18], and the demonstration of this communication determines pseudocyst management. [19]. According to the new pseudocyst definition, communication of a pseudocyst with the main duct probably occurs rarely. However, when searching for such communication, MRI is the preferred imaging study.

3.1.6. What is the definition of "pancreatic necrosis"?

Statement: Pancreatic necrosis is non-viable tissue located in the pancreas alone, in both the pancreas and the peripancreatic tissue or, more rarely, in the peripancreatic tissue alone, without a defined wall.
Evidence level 5, Recommendation grade D
Comment: In the first two or three weeks after the onset of the disease, pancreatic necrosis is characterised by the absence of a defined wall. On imaging studies it can be solid or semisolid (partially liquefied) [4,5].

3.1.7. What is the best imaging study for diagnosing the presence and extent of pancreatic necrosis?

Statement: Contrast-enhanced CT and contrast-enhanced MRI are equally useful in diagnosing the presence and the extent of pancreatic necrosis. For the highest sensitivity, they must be carried out no less than 72 hours after the onset of AP.
Evidence level 5, Recommendation grade D
Comment: The current approach is to use contrast-enhanced CT which is widely available and shows the presence of non-viable tissue [4,20–22]. The iodinated contrast media used for contrast-enhanced CT can aggravate the systemic injuries of AP; overhydratation must be used to prevent these side effects [23].

3.1.8. What is the definition of "walled-off necrosis" (WoN)?

Statement: Walled-off necrosis is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis which has developed a well-defined inflammatory wall; it occurs more than four weeks after the onset of necrotising pancreatitis.
Evidence level 5, Recommendation grade D
Comment: Walled-off necrosis contains heterogeneous and partially non-liquefied variably loculated material; there may be multiple areas of WoN [4,21,22,24,25].

3.1.9. What is the best imaging study for diagnosing the presence and extent of WoN?

Statement: Contrast-enhanced CT and contrast-enhanced MRI are equally useful in diagnosing the presence and extent of WoN.
Evidence level 5, Recommendation grade D
Comment: Even if CT is considered equal to MRI, CT may have a limited role in differentiating the different types of peri- and intrapancreatic collections, such as necrosis with pus, necrosis without pus and fluid collection without necrosis [4]; these findings may be better defined by MRI [20].

3.1.10. How can infection of a fluid collection, pancreatic necrosis, or of WoN be diagnosed? When should the investigations be performed?

Statement: The presence of gas bubbles at CT scan and/or a positive fine needle aspiration (FNA) culture can diagnose an infected collection, necrosis or WoN. Clinical deterioration should determine the timing of the investigations.

Evidence level 5, Recommendation grade D

Comment: Gas bubbles at CT scan can be considered pathognomonic of infection; FNA should be used selectively when there is no clinical response to adequate therapy, or when the clinical and/or imaging features of infection are uncertain [26–29].

3.1.11. What is the definition of pancreatic "fistula" in the context of AP?

Statement: Pancreatic fistula is defined as an abnormal communication between the ductal pancreatic systems, and other spaces or organs due to the leakage of pancreatic secretions from damaged pancreatic ducts.

Evidence level 5, Recommendation grade D

Comment: The occurrence of fistulae during AP can be spontaneous or may occur after interventional approaches. An external pancreatic fistula occurs when the pancreatic ducts communicate with the abdominal wall (pancreatico-cutaneous fistula) whereas an internal pancreatic fistula communicates with the peritoneal cavity, the mediastinum or other spaces. The pancreatic juice can lead to pancreatic ascites, pleural effusion and enzymatic mediastinitis [30]. The disruption of the main duct gives rise to a persistent pancreatic fistula in the so-called "disconnected pancreatic duct syndrome" [17].

3.1.12. What is the best imaging study for diagnosing a pancreatic fistula complicating AP?

Statement: Magnetic resonance cholangio-pancreatography (MRCP) is the best imaging study for diagnosing the presence of a pancreatic fistula [17,30–34].

Evidence level 5, Recommendation grade D

3.1.13. Which vascular complications can occur during the course of severe AP?

Statement: Vascular complications include thrombosis of the splenic vein (with possible left-sided portal hypertension) or, more rarely, the porto-mesenteric vein; damage of the peri-pancreatic arteries may lead to pseudoaneurysm or vascular erosion.

Evidence level 2c, Recommendation grade B

Comment: The splenic vein is the most commonly affected vessel because of its extensive contact with the pancreatic gland. Left-sided portal hypertension and oesophago-gastric varices may subsequently develop with the risk of bleeding [35]. The most commonly involved arteries are the gastroduodenal artery and the splenic artery, and their branches. Arterial bleeding can occur in WoN, a pseudocyst, the gastrointestinal tract or the peritoneal cavity, usually leading to acute haemorrhagic shock [36–40].

3.1.14. Which is the best imaging study for diagnosing vascular complications?

Statement: Contrast-enhanced CT (CECT) is the best imaging study for evaluating vascular complications.

Evidence level 2c, Recommendation grade B

Comment: CECT offers good evaluation of vascular complications affecting both veins (i.e. thrombosis) and arteries (i.e. pseudoaneurysm) [41–43]. When arterial abnormalities are seen at CECT, angiography is necessary for treatment [40,44,45].

3.1.15. What is the definition of "abdominal compartment syndrome" associated with severe AP?

Statement: Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure (IAP) > 20 mmHg (>27 cm H2O) associated with new organ dysfunction/failure.

Evidence level 1b, Recommendation grade A

Comment: Severe AP is frequently associated with intra-abdominal hypertension, defined as a sustained or repeated elevation of IAP >12 mmHg (>16 cm H2O) [46–49]. In severe AP, intra-abdominal hypertension is partially related to the effects of the inflammatory process causing retroperitoneal oedema, collections, ascites and ileus, and it partially results from medical intervention, especially aggressive fluid resuscitation [48,49]. Sustained IAP >20 mmHg (>27 cm H2O) can affect several intra-abdominal and extra-abdominal organs with frequent involvement of the cardiovascular system, splanchnic vessels, lungs, kidneys and central nervous system [46–50]. The association of sustained IAP >20 mmHg (>27 cm H2O) with dysfunction/failure of one or more organs (up to multi-organ dysfunction syndrome) defines the clinical scenario of ACS [46]. ACS is associated with increased mortality in patients with severe AP [51,52].

3.1.16. How is ACS associated with AP diagnosed?

Statement: Measurement of the IAP using a bladder catheter is required for diagnosing ACS.

Evidence level 1b, Recommendation grade A

Comment: The diagnosis of ACS requires a high index of suspicion in high-risk patients. It is suggested by increased abdominal girth, associated with difficulty in breathing or decreased urine output as well as with symptoms and signs of hypovolaemia [46–49]. Intra-abdominal pressure can be measured directly using a peritoneal catheter or indirectly measuring intra-vesicular pressure using a bladder catheter [46]. The latter is the most common technique since IAP can easily be monitored by measuring bladder pressure. Clinical and/or laboratory evidence of dysfunction/failure of one or more organs (i.e. kidney, lung, cardiovascular system) is required in association with IAP > 20 mmHg (>27 cm H2O) in order to reach a diagnosis of ACS [48–51].

3.1.17. What is the definition of "cholangitis" during the course of severe AP?

Statement: Acute cholangitis is a morbid condition with acute inflammation and bacterial or non-bacterial infection of the bile duct, usually in the setting of biliary obstruction.

Evidence level 5, Recommendation grade D

Comment: This definition is valid in the setting of AP. Acute cholangitis is a clinical syndrome characterised by fever, jaundice and abdominal pain (Charcot's triad) which develops as the result of a partial or complete obstruction and infection in the biliary tract. It is estimated that 15–72% of patients present with this triad [53]. Fever and abdominal pain are seen together in up to 80% of patients, and jaundice in 60–70% [54,55].

3.1.18. How is cholangitis diagnosed during the course of severe AP?

Statement: In diagnosing cholangitis in the case of severe acute pancreatitis, clinical and laboratory signs of cholestasis associated with systemic inflammation and imaging findings of biliary obstruction must be present.

Evidence level 5, Recommendation grade D

Comment: In patients with severe AP, a definite diagnosis of cholangitis is difficult since systemic inflammation is always present and cholestasis is a frequent finding when the head of the pancreas is enlarged by pancreatitis [56,57].

3.2. Conservative treatment

3.2.1. What is the role of fluid resuscitation in patients with severe AP?

Statement: Early fluid resuscitation plays a critical role as it aims to improve tissue oxygenation and microcirculation perfusion in order to preserve not only pancreatic, but also renal and cardiac perfusion.

Evidence level 2b, Recommendation grade B

Comment: Haemodynamic instability plays a major role in the pathogenesis of systemic inflammation, tissue hypoxia and multiple organ dysfunction syndrome associated with severe AP. Fluid replacement is the key intervention for haemodynamic support in these patients, and has to be administered early upon admission to the emergency room. Early fluid administration is associated with a lower rate of pancreatic necrosis, multiple organ dysfunction and mortality as compared with the late administration of fluids [58,59].

3.2.2. What is the optimal amount of fluid to be administered in patients with severe AP, and which solution is preferred?

Statement: In the first 24 hours after admission, the fluid resuscitation dose should be 2 ml/kg/h, with an initial bolus of 20 ml/kg within 30–45 minutes. The best combination is represented by crystalloids, with lactated ringer solution preferred to normal saline, and colloids, with a 3:1 ratio.

Evidence level 2b, Recommendation grade B

Comment: Fluid resuscitation should be patient-tailored with a goal-directed approach in order to avoid overly aggressive resuscitation which could exacerbate tissue oedema and its effects on organ dysfunction [60–62]. Initial fluid replacement must ensure the achievement of the following values: urinary output > 0.5–1 ml/kg/h; mean arterial pressure (MAP) > 65 mmHg; heart rate (HR) < 120 beats per minute; blood urea nitrogen (BUN) < 20 mg/dL or, if greater, a reduction of at least 5 mg/dL in the first 24 hours; haematocrit levels (Hct) between 35% and 44%; and, if necessary, monitoring of central venous pressure with values ranging from 8 to 12 mmHg. Fluid requirements should be evaluated every 8–12 hours during the first 24–48 hours after admission [63–67].

3.2.3. Is nasogastric suction recommended in patients with severe AP?

Statement: Routine nasogastric suction is not recommended in patients with severe AP.

Evidence level 2b, Recommendation grade B

Comment: There is no indication for performing standard routine nasogastric suction unless gastric retention, resulting in dilatation of the stomach, obstruction or a paralytic ileus, is diagnosed [68,69].

3.2.4. Are proton pump inhibitors recommended in patients with severe AP?

Statement: The routine use of proton pump inhibitors is not recommended in patients with severe AP.

Evidence level 2b, Recommendation grade B

Comment: With the exception of an RCT conducted in Korea [70] which showed no influence on the clinical course of AP, there are no studies investigating the effect of proton pump inhibitors or of other acid suppressant drugs in the setting of AP. The need for these drugs might be considered on a case-to-case basis if specific indications, such as peptic disease or bleeding.

3.2.5. Are protease inhibitors recommended for reducing complications or mortality in patients with severe AP?

Statement: Anti-proteases are not recommended for reducing the mortality and early complications of AP.

Evidence level 1a, Recommendation grade A

Comment: Although the efficacy of protease inhibitors in AP is still a matter of controversy, a recent meta-analysis reported no significant reduction in the mortality risk. The results were more heterogeneous for the risk of complications, but no clear benefit was reported [71]. However, as the majority of studies investigated 90-day mortality, and anti-proteases work mainly in the very early phases of severe AP, their efficacy might have been undervalued as other factors, mainly infection, play a major role in determining 90-day mortality. It has also been reported that continuous regional intra-arterial, but not intravenous infusion of infusion of anti-proteases determines a lower incidence of complications as compared to patients treated with surgery [72,73].

3.2.6. Are somatostatin or its analogues recommended for reducing complications or mortality in patients with severe AP?

Statement: Somatostatin or its analogues are not recommended for reducing complications or mortality in patients with AP.

Evidence level 1b, Recommendation grade A

Comment: Conflicting and inconclusive results appear from the clinical trials available, characterised by non-homogeneous study designs and wide variations in dosage [74,75]. However, a recent meta-analysis demonstrated no effect of somatostatin and/or its analogues on the major outcomes of AP [76].

3.2.7. Is routine antibiotic prophylaxis recommended in severe AP?

Statement: Routine intravenous antibiotic prophylaxis is not recommended in severe AP.

Evidence level 1a, Recommendation grade A

Comment: There have been contrasting results in the clinical trials conducted in the past 30 years regarding the role of antibiotic prophylaxis in severe AP. Findings of the most recent meta-analyses of RCTs do not support a role for the routine use of antibiotic prophylaxis in patients with severe AP for avoiding pancreatic necrosis infection [77,78]. The use of antibiotic prophylaxis is also not associated with reduction in mortality and in the incidence of non-pancreatic infections, although, for this latter outcome, the pooled results are closer to significance. In the case of pancreatic necrosis involving more than 50% of the gland, antibiotic prophylaxis might be considered on a case-to-case basis due to the high risk of infection. Among the different antibiotics employed, a carbapenem-based prophylaxis has a trend towards efficacy, yet without significance. This class of antibiotics should be considered as a first line empiric treatment for patients with suspected infected pancreatic necrosis. Extra-pancreatic infections (cholangitis, sepsis, urinary tract infections, pneumonia) should receive appropriate antibiotic treatment.

3.2.8. Is routine antifungal prophylaxis recommended in patients with severe AP?

Statement: Routine antifungal prophylaxis is not recommended for preventing fungal infections in patients with severe AP.

Evidence level 5, Recommendation grade D

Comment: There are no high quality studies supporting the routine use of antifungal agents in patients with severe AP [79].

3.2.9. Are probiotics recommended to prevent necrosis infection in patients with severe AP?

Statement: The use of probiotics is not recommended in the setting of severe AP.

Evidence level 1a, Recommendation grade A

Comment: The use of probiotics has been associated with positive outcomes in preclinical studies [80]. However, a very recent meta-analysis [81] has summarised the findings of six RCTs and concluded that there is no evidence for either a beneficial or an

adverse effect of probiotics on the clinical outcomes of patients with predicted severe AP. In only one of those studies [82] was the use of probiotics associated with increased mortality due to non-occlusive mesenteric ischaemia [83]. Whether this negative effect was due to the dose or the specific mixture of strains, or to the enteral route of administration in a scenario of severely impaired gut barrier function, has not yet been completely clarified [84].

3.2.10. Which nutritional support is recommended in patients with severe AP?

Statement: Enteral nutrition (EN) is the recommended nutritional support in patients with severe AP.

Evidence level 1a, Recommendation grade A

Comment: A number of RCTs conducted in patients with moderate to severe AP and subsequent meta-analyses have demonstrated that EN, when compared to parenteral nutrition, is able to reduce pancreatic and extra-pancreatic infective complications, multi-organ failure, surgical intervention, and mortality [85,86]. Parenteral nutrition should therefore be avoided unless the enteral route is not available or not tolerated, and intravenous hydration should be decreased gradually after admission as the enteral feeding infusion rate is progressively brought to the target.

3.2.11. When should EN be started in patients with severe AP?

Statement: EN should be started within 24–48 hours from admission, after obtaining haemodynamic control.

Evidence level 1a, Recommendation grade A

Comment: Retrospective cohort studies, RCTs and a meta-analysis have suggested that EN started within 24–48 hours after admission is superior not only to parenteral nutrition but also to EN started after 48 hours as it is associated with reduced complications [87–90]. In a retrospective study, early EN is also associated with lower mortality [91]. This "cut-off" time point is also recommended by the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines [92].

3.2.12. What is the optimal route for administering EN in patients with severe AP?

Statement: Nasogastric (NG) and nasojejunal (NJ) delivery of enteral feeding appear comparable in terms of efficacy and safety.

Evidence level 1a, Recommendation grade A

Comment: Randomised trials and non-controlled studies [93–97], and a meta-analysis [98] comparing EN by NG versus a NJ route in severe AP have demonstrated similar outcomes, with no statistical difference in terms of mortality, tracheal aspiration, diarrhoea, exacerbation of pain and meeting energy balance. The NG route has the advantage of being simpler and potentially cheaper. Continuous EN infusion is preferred over cyclic or bolus administration.

3.2.13. What is the optimal EN formula to be administered?

Statement: Either elemental or polymeric EN formulations can be used in AP.

Evidence level 2b, Recommendation grade B

Comment: Both elemental and polymeric diets are well tolerated in patients with pancreatitis, and they are equally recommended [99–104]. Enteral feeding with immune-enhancing ingredients (arginine, glutamine, nucleotides, and omega-3 fatty acids) which modulate the host inflammatory and immune response have recently attracted great interest but, at the moment, there are very few published trials and the results are too discordant to make any treatment recommendation; to date the role of arginine, glutamine and omega-3 fatty acids in AP is still uncertain.

3.2.14. What are the indications for parenteral nutrition in patients with severe AP?

Statement: Parenteral nutrition should be considered in patients with AP only when EN fails or if the requested nutritional goal is not reached.

Evidence level 5, Recommendation grade D

Comment: Parenteral nutrition is indicated only when EN is not tolerated [85,92,105,106] due to increased pain, ascites or elevated fistula output, or when EN cannot be administered due to occlusion or ileus.

3.2.15. If parenteral nutrition is administered, which formula is recommended?

Statement: The nitrogen supply during parenteral nutrition should be 0.2–0.24 g/kg per day (amino acid delivery of 1.2–1.5 g/kg per day), glucose should be the preferred carbohydrate energy source (5–6 g/kg per day) and fat emulsions are recommended (from 0.8 to 1.5 g/kg per day); a daily dose of multivitamins and trace elements is recommended.

Evidence level 5, Recommendation grade D

Parenteral glutamine supplementation (>0.30 g/kg Ala–Gln dipeptide) should be considered; antioxidant supplementation does not improve outcome.

Evidence level 2b, Recommendation grade B

Comment: The parenteral administration of amino acids, carbohydrates and lipid emulsions does not affect pancreatic secretions. The nitrogen supply should be reduced to 0.14–0.2 g nitrogen/kg per day in the case of hepatic or renal failure. Monitoring urea excretion may be helpful in tailoring the actual nitrogen need [105,106].

Glucose should be the preferred carbohydrate energy source. Parenteral carbohydrates should not exceed 4–7 mg/kg per min (5–6 g/kg per day). Meticulous attention is required to avoid hyperglycemia (exogenous insulin is recommended to maintain euglycaemia). Lipids provide an efficient source of calories, but hypertriglyceridemia must be avoided (serum triglyceride should be monitored and kept below 12 mmol/L) [107–109]. There is no evidence regarding the administration of antioxidants, such as vitamin C, selenium or acetylcysteine [110].

3.2.16. What is the optimal timing for restarting oral feeding in patients with AP?

Statement: Early oral refeeding in severe AP is usually not tolerated, and its timing depends on clinical improvement.

Evidence level 5, Recommendation grade D

Comment: While early refeeding is advisable in mild-moderate AP [111,112], in severe AP, refeeding is often not tolerated due to pain, nausea and vomiting related to ileus or extrinsic compression from fluid collections impairing gastric emptying. EN is indicated for at least 7–10 days in such cases [113]. At the time of literature search and guidelines discussion, a single randomised study has shown that early, low volume, oral feeding might be a safe alternative to EN, even in the setting of severe AP [114]. However, after the present recommendations were discussed, a RCT was published, comparing nasoenteric tube feeding within 24 hours after randomisation (early group) or to an oral diet initiated 72 hours after presentation (on-demand group), with tube feeding provided if the oral diet was not tolerated in 208 patients with predicted severe acute pancreatitis. Notably, in the on-demand group, 72 patients (69%) tolerated an oral diet and did not require tube feeding. This study showed a similar rate of infections and death, and their composite, in patients receiving early nasoenteric tube feeding, as compared with an oral diet after 72 hours. This recent study suggests that an oral diet might be proposed early to patients with severe AP, as two thirds of them would tolerate it, without a worse outcome [115].

3.2.17. Is evaluation of exocrine pancreatic function recommended after recovery from severe AP?

Statement: The evaluation of the exocrine pancreatic function is recommended every 6 months after recovery from severe AP for a period of at least 18 months.

Evidence level 2b, Recommendation grade B

Comment: The rate of exocrine insufficiency from a severe AP episode ranges from 60.5% to 85% during the following year [116–118]. In 20–60% of cases, the exocrine pancreatic function is restored after 3 years [119,120].

Some specific subgroups of patients should be monitored more stringently and for a longer period of time, such as those who underwent necrosectomy and patients with an alcoholic aetiology.

3.2.18. Is evaluation of endocrine pancreatic function recommended after recovery from severe AP?

Statement: Monitoring endocrine pancreatic function is recommended every 6 months after recovery from severe AP for a period of at least 18 months.

Evidence level 2b, Recommendation grade C

Comment: Endocrine pancreatic function is impaired in approximately one-third of patients after severe AP [121,122]; these patients should be carefully followed. The patients at a higher risk of developing pancreatic insufficiency are those patients who underwent necrosectomy and those with an alcoholic aetiology of pancreatitis. The rate of diabetes after AP has recently been estimated to be of 23% in a meta-analysis [123].

3.3. Interventional treatment

3.3.1. What are the indications for invasive treatment of a fluid collection?

Statement: The indications for the invasive treatment of a fluid collection are the presence of obstructive symptoms and infection.

Evidence level 2b, Recommendation grade B

Comment: A recent prospective multicentre study [124] regarding the natural history of pancreatic fluid collections in AP showed that conservative management usually leads to a decrease in size or spontaneous resolution; these results justify invasive treatment only when complications occur [124–127].

3.3.2. If treatment of a fluid collection is needed, which is the best timing and the interventional strategy?

Statement: The timing of fluid collection treatment is determined by the onset or persistence of complications.

Evidence level 5, Recommendation grade D

The best interventional strategy for a fluid collection is percutaneous drainage.

Evidence level 4, Recommendation grade C

Comment: A percutaneous approach is the preferred treatment in acute fluid collections due to absence of a well-defined wall [25,126,128–130]. The high rate of spontaneous resolution of fluid collections makes the need for invasive treatment rare [124].

3.3.3. What are the indications for invasive treatment of pancreatic necrosis?

Statement: Invasive treatment of pancreatic necrosis (infected or not infected) is indicated after the failure of adequate medical management, in cases of persistent organ failure or new onset organ failure.

Evidence level 5, Recommendation grade D

Comment: The great majority of patients with sterile necrotising pancreatitis can be managed conservatively, and even patients with infected necrosis (gas bubbles on CT scan or a positive FNA culture) who remain clinically stable can be managed without the need for intervention [4,113,131–140]. The common indications for intervention (radiological, endoscopic or surgical) in necrotising pancreatitis are clinical deterioration and ongoing organ failure while waiting for evolution towards WoN (usually 4–8 weeks after the onset of pancreatitis). The less common indications for intervention are gastric outlet obstruction, duodenal obstruction or persistent obstructive jaundice.

3.3.4. If treatment of pancreatic necrosis is needed, which is the best timing and the interventional strategy?

Statement: The interventional strategy for necrotising pancreatitis should be delayed as long as possible, preferably until 4 weeks after the onset of disease.

Evidence level 1B, Recommendation grade A

According to local expertise, the optimal interventional strategy for patients with pancreatic necrosis is the minimally invasive step-up approach, including percutaneous drainage or, if this is not possible, endoscopic drainage followed, if necessary, by video-assisted retroperitoneal debridement.

Evidence level 1B, Recommendation grade A

Comment: Delayed intervention is associated with lower mortality, as has been demonstrated in a multicentre prospective observational cohort study [132]. The intervention should be delayed until the necrosis evolves into WoN, and this process generally requires 4 weeks [4,21,137,139–149,27,150,151]. At present, the step-up approach [144], consisting of percutaneous or transgastric drainage followed, if necessary, by a drain-guided minimally invasive necrosectomy can be considered the treatment of choice when invasive treatment is required.

3.3.5. Which are the indications for invasive treatment of WoN?

Statement: Indications for intervention in WoN are infection or clinical deterioration after the failure of conservative management, or persistent symptoms such as gastric, intestinal or biliary obstruction, or pain due to the mass effect of WoN.

Evidence level 5, Recommendation grade D

Comment: In all studies, treatment of WoN was carried out in the presence of infection, sepsis or other symptoms, such as abdominal pain, increased size, obstructive symptoms of the stomach, duodenum or biliary tract, portal thrombosis or clinical deterioration [4,131,132,137,138,140,141,144,147,148,152,153].

The management of asymptomatic patients is still unclear [136]. To date, there are no studies regarding the outcome of treated asymptomatic WoN.

3.3.6. If treatment of WoN is needed, which is the best interventional strategy?

Statement: Endoscopic transmural drainage or percutaneous drainage are indicated when WoN requires treatment. Surgery is indicated after the failure of a less invasive approach.

Evidence level 4, Recommendation grade C

Comment: A promising technique gaining worldwide popularity is endoscopic transluminal drainage followed, if necessary, by necrosectomy. However, at present, there are no studies comparing the percutaneous with the endoscopic treatment of WoN [132,140,142,144,145,148,153–161].

3.3.7. What are the indications for the invasive treatment of post-AP pseudocysts?

Statement: The indications for post-acute pseudocyst treatment are persistent pain and complications, such as infection, mass effect (gastric, intestinal, or vascular and biliary obstruction) and rupture.

Evidence level 2b, Recommendation grade B

Comment: All published papers are antecedent to the revised Atlanta classification; therefore, they do not contain the

differentiation of fluid alone collections (pseudocysts) from those resulting from necrosis and containing solid components (acute peripancreatic fluid collections, acute necrotic collections, infected necrosis and WoN). Currently, the indications for invasive treatment of post-AP pseudocysts are based on cohort studies [124,162–164], but studies comparing the outcome of treated/non-treated pseudocysts are still lacking. The natural history of post-AP pseudocysts showed a decrease in size or spontaneous resolution with conservative management in an elevated percentage of patients. A small size (<4 cm) is a predictor of spontaneous resolution [165–168].

3.3.8. If treatment of a post-AP pseudocyst is needed, which is the best interventional strategy?

Statement: The effective treatments for pseudocysts are either endoscopic or percutaneous transmural drainage. Surgery is required in case of failure of these approaches.

Evidence level 2b, Recommendation grade B

Comment: According to the new definition of post-AP pseudocyst, it is not possible to obtain useful information from previous published papers regarding its treatment. In the case of surgery, both laparoscopic and open approaches can be used [4,162,166–175].

3.3.9. If endoscopic transluminal drainage is indicated, which is the technique of choice?

Statement: Endoscopic ultrasound-guided endoscopic transgastric or transduodenal drainage with stent positioning is the first choice.

Evidence level 3c, Recommendation grade C

Comment: Transmural, minimally invasive endoscopic debridement of WoN is an effective and repeatable technique with an acceptable safety profile [137,162]. The most common approach is transgastric with a median tract dilation diameter of 18 mm; the median number of procedures needed for successful treatment is 3; complications occur in approximately 14% of cases [147]. Endoscopic ultrasound decreases the risks associated with endoscopic drainage and is essential in cases without a bulge within the gastrointestinal lumen [176–180].

3.3.10. If radiological percutaneous drainage is indicated, which is the technique of choice?

Statement: A percutaneous technique is dictated by the site and size of the collection; access should be chosen via the most direct route, considering that retroperitoneal access is preferable. CT guidance is preferred to avoid vital structures. Seldinger or Trocar techniques are appropriate and large size, single or multiple catheters are necessary.

Evidence level 5, Recommendation grade D

Comment: The major consideration in choosing access routes is to avoid crossing the small or large bowel, or major vessels. Large (12–24 F) catheters are required, and two or more catheters are frequently used in an attempt to achieve a "sump" effect. Retroperitoneal CT-guided approach (more commonly left) is preferred thereby facilitating minimally invasive video-assisted retroperitoneal debridement (VARD) if a step-up approach is planned. Vigorous irrigation with normal saline should be performed at least once every 8 hr. Catheters should be removed when drainage is less than 10 ml in a 24-hour period. CT should be performed before drainage removal to ensure that the cavity is obliterated and that no fistula is present [132,137,140,144–149].

3.3.11. If surgical treatment is indicated, which is the technique of choice?

Statement: The surgical treatment of choice, whenever possible, is the VARD technique guided by previously placed percutaneous drainage.

Evidence level 2b, Recommendation grade B

Comment: Until the results of a step-up approach versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER) trial [144], open necrosectomy was considered the procedure of choice. It is currently still a feasible option, but a minimally invasive necrosectomy is preferred. Necrosectomy should ideally be delayed until the collection has become walled off, even if initial percutaneous catheter drainage had been undertaken earlier [142,144,145,149].

3.3.12. What are the indications for invasive treatment of a post-AP pancreatic fistula?

Statement: Indications for invasive treatment of a pancreatic fistula are persistence of the fistula despite medical treatment, pancreatic ascites, pancreatico-pleural fistula or a high output external fistula.

Evidence level 2b, Recommendation grade B

Comment: Invasive treatment should only be considered after failure of the medical approach [181,182] since the overall success rate of the conservative treatment is high (68–100% of cases) [34,183].

3.3.13. If treatment of post-AP pancreatic fistula is needed, which is the best interventional strategy?

Statement: The endoscopic approach is suggested. A surgical approach is indicated only for patients in whom the endoscopic approach has failed or in those not eligible for endoscopic approach [34,183].

Evidence level 2a, Recommendation grade B

Comment: The choice of treatment depends on the characteristics of the patient and the fistula. Endoscopic procedures include various drainage techniques, comprehensive of cannulation of the injured pancreatic duct and stent positioning. Some patients are not eligible for the above-mentioned treatments, mainly due to the technical limitations of endoscopic retrograde cholangiopancreatography (ERCP), related to duodenal and pancreatic duct stricture or post-surgical anatomy [34,183]. Endoscopic transmural drainage has become the procedure of choice for complete duct disruptions which result in a pseudocyst formation and fistulae. Treatment of a disrupted duct without peripancreatic collections necessitates bridging of the pancreatic leak with transpapillary stents or diverting the pancreatic duct flow [34,183]. However, complete disruption of the pancreatic gland could be refractory to transpapillary stenting [184,185]. Surgical treatment has an elevated success rate of approximately 90% but also has a significant mortality rate of 6–9% [186,187]. Percutaneous procedures have also been suggested, consisting in the placement of percutaneous transgastric drainage in the associated fluid collection followed, after a mean period of 7–10 days, by the positioning of prosthesis between the collection and the gastric lumen. The prosthesis should be removed after a few weeks (6–8).

3.3.14. What are the indications for the invasive treatment of vascular complications?

Statement: The indications for the invasive treatment of vascular complications are pseudoaneurysm and/or active bleeding from vascular erosion due to the pancreatic inflammatory process [188–196].

Evidence level 2b, Recommendation grade B

Comment: Acute bleeding is one of the life-threatening complications of acute necrotising pancreatitis. All visceral pseudoaneurysms should be treated, regardless of size, even in absence of active bleeding.

3.3.15. If treatment of active bleeding due to vascular complications is needed, which is the best interventional strategy?

Statement: Angiography with transcatheter arterial embolisation is considered the first choice for active bleeding and pseudoaneurysms.

Evidence level 2b, Recommendation grade B

Comment: The endovascular procedure consists of superselective catheterisation of the artery involved with distal and proximal embolisation of the lesion and the endoluminal sac of the pseudoaneurysm, mainly with the use of coils, N-butyl-2-cyanoacrylate or onyx. Surgery is indicated in patients with haemodynamic instability, after failure of endovascular procedures or with venous bleeding [188–196].

3.3.16. What are the indications for the invasive treatment of ACS associated with AP?

Statement: Invasive decompression is indicated in patients with a sustained intra-abdominal pressure >20 mmHg having new onset organ failure refractory to medical therapy and nasogastric/rectal decompression.

Evidence level 2C, Recommendation grade B

Comment: ACS is defined by an intra-abdominal pressure higher than 20 mm Hg with signs of new organ failure. Although the necessity of decompression of ACS is a rare event in severe AP, it may be lifesaving [46,51,197–201].

3.3.17. If treatment of ACS associated with AP is needed, which is the best interventional strategy?

Statement: Percutaneous catheter drainage should be considered as the first-line treatment in patients with ACS. If external drainage is ineffective, surgical treatment is indicated (midline laparostomy, bilateral subcostal laparostomy, or subcutaneous linea alba fasciotomy) [46,51,197–201].

Evidence level 2c, Recommendation grade B

Comment: If intra-abdominal drainable fluid is present, percutaneous drainage could lead to immediate and sustained improvement [46,199]. If not, surgical decompression should be performed immediately. The standard surgical treatment is a decompressive midline laparotomy. To avoid an open abdomen and its negative effects of evisceration of the intestines, fluid losses and contamination, primary closure with Mesh-grafts can be considered after an open laparotomy.

3.3.18. What are the indications and optimal timing for ERCP in severe AP?

Statement: Urgent ERCP should be performed within 24 hours in patients with acute cholangitis [202,203].

Evidence level 1a, Recommendation grade A

ERCP should be performed within 72 hours from admission when an impacted biliary stone has been demonstrated [203,204].

Evidence level 2a, Recommendation grade B

Comment: ERCP plays a major role in acute biliary pancreatitis (ABP). Patients presenting with ABP with suspected impacted bile duct stones benefit from early ERCP and sphincterotomy which should be carried out within the first 72 hours from the onset of pain; in the presence of signs of acute cholangitis, the optimal time is within 24 hours. Without evidence of stones, other imaging modalities, such as MRCP and EUS, are recommended before performing ERCP in mild AP. In patients with ABP, MRCP or EUS should be performed before ERCP [205–207], but no specific data are present in the setting of severe AP. There are also no data regarding the role of pancreatic sphincterotomy and/or pancreatic stent placement as a possible method of improving the outcome of patients with severe AP.

4. Conclusions

New guidelines [1,208–218] and updates of previous guidelines [100,106,113,219] regarding AP have been published in recent years. Renewed interest in this disease relies mainly on a notable amount of new data from the recent literature with several high quality papers which have contributed to changing some old concepts regarding the natural history of AP, indications for treatment and modalities of treatment. Acute pancreatitis is now regarded as a dynamic process in which systemic involvement is the main determinant of outcome whereas local complications often no longer need "*per se*" treatment. The therapeutic approach is becoming much more conservative than in the past, and the role of surgery has lost much of its previous relevance, in favour of interventional radiology and endoscopy. All these changes have given rise to the need for re-evaluating the current guidelines of treatment of AP, in particular the severe forms which are those mainly involved by the afore-mentioned changes. The present guidelines represent the answer to this need; they are tailored to the new terminology and definitions proposed by the revised Atlanta classifications [4,5] and provide several statements for specific clinical questions, evaluating indications, timing and modalities of treatment. Our aim is that these guidelines will contribute to standardising and improving the treatment of AP in accordance with the current knowledge of the disease; they too are to be considered a dynamic process, and we expect to update them in the near future on the basis of additional ongoing prospective studies.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.03.022.

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