Management of Acute Pancreatitis in the Early Stage

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ABSTRACT

Acute pancreatitis (AP) is a potential fatal disease with an overall mortality around 5%. The current treatment for AP relies on supportive medical therapy, sometimes associated with endoscopic procedures and/or surgical interventions. In this review we discuss the recent concepts regarding the fluid therapy, pain management, antibiotic prophylaxis, apheresis for hypertriglyceridemia-induced AP, timing and indications for ERCP and cholecystectomy in biliary AP. For each component, the importance and the impact of early phase treatment is presented in terms of benefits and risks.

Keywords: acute pancreatitis, early phase, early treatment, fluid therapy, nutrition, ERCP

INTRODUCTION

Despite tremendous advances in pathophysiology, imaging, and intensive care treatment during the last decades, acute pancreatitis remains a potentially lethal disease with an unpredictable evolution. The new revision of Atlanta classification stratifies the acute pancreatitis in three grades of severity: mild, moderate and severe (1). Despite a high mortality for the severe cases around 50%, due to higher prevalence of mild and moderate cases one can explain the global rate of mortality in acute pancreatitis around 5%. The early phase of acute pancreatitis is defined by the same classification as the first 7 days from onset (can be extended to 10-14 days). Almost 50% of deaths from acute pancreatitis occur during this phase due to SIRS and multiple organ failure (1,2). Therefore, a correct and energetic treatment during this period is crucial to reduce early deaths and to optimize evolution of predicted severe forms. The purpose of the present article is to review the significance and impact of the current early treatment of acute pancreatitis.

FLUID RESUSCITATION

One important step in the pathogenesis of acute pancreatitis is represented by alteration of the pancreatic microcirculation including ischemia-reperfusion injury and microthrombi that can lead to ischemia and later to necrosis. These changes are most marked in...
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the first 24 to 72 hours of the illness. Therefore the theoretical goal of the early intravenous fluid resuscitation is to prevent or even to reverse these alterations, leading to improve morbidity and mortality (3). Hemococoncentration as hematocrit of >44-47% on admission along with failure to decrease it after 24 hours was reported as a good risk factor for development of necrosis (4). Clinical practice guidelines recommend vigorous fluid resuscitation, but the optimal type of fluid, rate of administration and end-points of adequate resuscitation are still without consensus (5).

The recommended rate of fluid resuscitation is 250-500 mL/h for the first 24-48 hours (6,7). However, several reports showed that overly aggressive fluid therapy fluid therapy is associated with increased morbidity and mortality (8,9). One prospective trial analyzed 247 patients showed that administration of more than 4100 mL fluids during the first 24 hours was associated with higher incidence of persistent organ failure and acute collections, compared with volumes between 3100 and 4100 mL (10). For this reason the total amount for the first 24 hours is not recommended to exceed 4000 mL (11). Instead of firm rate for fluid resuscitation was suggested to start as a bolus followed by maintenance (7). The Pittsburgh group is using a bolus of 1000-2000 mL of Lactated Ringer’s (or 20 mL/Kg) in the emergency room, followed by 3 mL/kg/hour for the first 24 hours (12). The effectiveness of fluid therapy can be also improved by using a “controlled” resuscitation in order to maintain effective mean arterial pressure and urine output >0.5 mL/Kg (13).

The optimum type of fluid is considered the lactated Ringer’s solution (6, 11). One double-blinded randomized controlled study including 40 patients with 4 arms (early-directed fluid therapy vs standard therapy and further normal saline vs lactated Ringer’s solution) showed that lactated Ringer’s group was associated with lower SIRS frequency (84% vs 0%, p = 0.035) and lower CRP level (51.5 vs 104 mg/dL, p = 0.02) (14).

In conclusion, fluid therapy in acute pancreatitis can be seen as double edge sword with risk of necrosis through tissue hypoperfusion by using low fluid quantities and liquid sequestration and increased morbidity with too high volumes (15). Therefore a safe and effective approach for fluid therapy for patients with acute pancreatitis should be most probably an individualized protocol.

PAIN MANAGEMENT

The most common and significant complain leading to the diagnosis of acute pancreatitis is pain and therefore adequate analgesia represents an important part of the treatment. In relation to severity of the pain one can use parenteral (nonsteroidal anti-inflammatory drugs, opioid analgesics and local anesthetic) and epidural analgesia (16). One experimental prospective study assessed the effect of sympathetic block by thoracic epidural anesthesia founded enhanced microcirculatory perfusion, end-organ perfusion and improved survival compared to control (17). However these positive experimental results are not automatically transposed in humans and several concerns were addressed (18). Despite historical reports of spasm in the sphincter of Oddi associated with opioids treatment of AP, a recent Cochrane review on five RCTs with a total of 227 patients founded no difference between opioids and other analgesia options regarding the risk of complications or clinically serious adverse events (19).

PROPHYLACTIC ANTIBIOTICS

The most common cause of late death in acute necrotizing pancreatitis is represented by organ failure through infected pancreatic necrosis (IPN) (20,21). Therefore there might be a theoretical benefit from antibiotic prophylaxis. For successful antibiotic treatment there should be considered the microbial pathogens causing IPN (most commonly Escherichia coli, Pseudomonas, Klebsiella, Enterococcus and more rarely fungi), pathogenesis of IPN (bacterial translocation through gastrointestinal mucosal barrier, altered gastrointestinal motility) and the pancreatic penetration of the antibiotics (most effective carbapenems and quinolones). However one must also consider risks associated with antibiotics use: selection of resistant bacteria, development of fungal infection, Clostridium difficile infection (22,23).

There are many RCTs and meta-analyses assessing the benefits of antibiotic prophylaxis in patients with acute pancreatitis, with contradictory results mostly due to differences in methodological design (24). As a matter of fact, the numbers of RCTs and meta-analyses on this
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NUTRITION

Prolonged bowel rest by nothing per os (NPO) to minimize pancreatic secretion was an important part of the therapy for any patient with acute pancreatitis. The concept of nutritional support in AP has gradually moved towards enteral feeding, due to large evidence proving safety and efficiency (31). Timing and mode of nutritional support in acute pancreatitis should be based on risk prediction of severity.

Several RCTs on mild acute pancreatitis suggested that oral feeding can be started immediately (32), directly with solids (33) and without waiting to normalize the lipase level (34). However, a more recent retrospective study on 323 patients with mild acute pancreatitis showed a rate of 12.4% intolerance to early refeeding (35). The multivariate logistic regression analysis of this study identified three factors that independently predicted refeeding intolerance: hypertriglyceridemia induced AP, elevated serum lipase (>2-fold of the upper limit of normal) the day before refeeding and the immediate feeding. The IAP/APA guidelines recommend that for mild AP the oral feeding can be started when symptoms are decreasing and the inflammatory markers are improving (11).

Enteral nutrition (EN) besides providing nutritional support, can preserve the gut function and potentially modulates the systemic inflammatory response syndrome (SIRS) that is associated with higher morbidity and mortality (36, 37). For this reason, patients with predicted severe acute pancreatitis should have a potential benefit from using enteral nutrition. A systematic meta-analysis involving 11 randomized controlled trials demonstrated a significantly reduced risk of multiple organ failure (RR 0.44; 95% CI 0.23, 0.84), pancreatic infectious complications (RR 0.46; 95% CI 0.27, 0.77) and mortality (RR 0.46; 95% CI 0.20, 0.99) in patients with acute pancreatitis who were enterally fed within the first 48 h of admission compared to parenteral feeding (38).

Enteral feeding can be started at a slow rate of 25mL/hour with elemental nutrient or polymeric formula for the first 24 hours, followed by gradual advanced by 25 mL/hour over the next 2-3 days. Both variants are safe according to one meta-analysis (39). There are currently several discussions about the moment and the method of enteral feeding. Enteral nutrition can be provided via nasogastric (NG) or nasojejunal (NJ). Despite of theoretical risk of pancreatic stimulation with NG, there are two RCT that showed that both routes are well tolerated with no difference in terms of infectious complications, length of hospital stay or mortality (40,41). A meta-analysis of four studies showed that NG feeding is efficient in 90% of patients with severe acute pancreatitis (42).

A retrospective study in a single institution have evaluated the optimal time of refeeding in severe acute pancreatitis comparing 526 patients in the early group versus 566 patients in the late group (43). The incidence of organ failure and mortality were statistically significant better for the early feeding group. The PYTHON trial performed by the Dutch Pancreatitis Study Group was a multicenter RCT that compared nasoenteric tube feeding initiated within 24 hours after randomization (the early group, 101 patients) or to an oral diet starting at 72 hours (the on-demand group, 104 patients) (44). This trial failed to show the superiority of early nasoenteric tube feeding due to similar rate of major infection (25% and 26%, respectively; \( p = 0.87 \)), multiple organ failure (10% and 8%, respectively; \( p = 0.77 \)), persistent multiple organ failure (6% and 5%, respectively; \( p = 1.00 \)), or death (11% and 7%, respectively; \( p = 0.33 \)). Another controlled RCT assessed the effectiveness and feasibility of early oral refeeding (EORF) based on hunger in 146 patients with moderate or severe acute pancreatitis (45). There was no difference in the number of adverse events or complications between the EORF and the conventional oral refeeding group. The results of this study showed that EORF is safe and effective, decreasing the length of hospital stay by 2 days.

Acute pancreatitis can be associated with intestinal ileus and delayed gastric emptying.
that can lead to abdominal pain, nausea and vomiting which can make intolerance oral feeding, prompting for parenteral support. Also patients that have intolerance for enteral feeding and nutritional support is required should start parenteral feeding as second-line therapy (11). Despite theoretical benefits of probiotic prophylaxis for patients with predicted severe acute pancreatitis, mortality was increased (16% vs 6%) in one RCT and therefore not indicated (46).

APHERESIS

Hypertriglyceridemia with serum triglyceride (TG) level of >1000 mg/dl is a well-recognized cause of acute pancreatitis (AP), representing the third identifiable etiology after gallstones and alcohol. Classical treatment of hypertriglyceridemia induced AP includes heparin, insulin or both. A more effective modality to reduce the TG level is represented by apheresis techniques. A recent systematic review including 301 patients founded a 85.4% reduction of the TG level using apheresis (47). The same study founded that 94.4% of patients were reported to have some form of improvement, with 93.1% improvement in severe acute pancreatitis and 88% with organ failure (47). The use of apheresis in patients with hypertriglyceridemia induced AP can be individualized according to level of TG at admission (>1000 mg/dl or >2000 mg/dl), timing of initiation (up to 96 hours after the onset of symptoms), number of sessions (unique or multiple), use of adjunct therapy (insulin, heparin, fibrate).

ENDOSCOPIC RETROGRADE COLANGIOPANCREATOGRAPHY (ERCP)

Around one third of the etiology of acute pancreatitis is represented by gallstones and the ERCP can be used as both diagnostic and therapeutic tool as well. However the procedure of ERCP associated with endoscopic sphincterotomy (ES) can lead to adverse events and therefore the indication should not be liberal. Several randomized controlled trials (RCT) have been published (Table 1) to define the role and indications of ERCP and ES for patients with acute pancreatitis. One must note that there is some degree of heterogeneity among these studies due to different inclusion and exclusion criteria, definition of severity of pancreatitis and timing to ERCP.

One meta-analysis including 644 patients with acute gallstone pancreatitis showed no evidence that early routine ERCP significantly improve local/systemic complications or mortality, regardless of predicted severity (48). The current indications for the ERCP in patients with predicted severe acute pancreatitis are

<table>
<thead>
<tr>
<th>First author, reference</th>
<th>Neoptolemos(50)</th>
<th>Fan(51)</th>
<th>Folsch(52)</th>
<th>Oria(53)</th>
<th>van Santvoort(54)</th>
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<td>Number of centers</td>
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<td>Unicentric</td>
<td>Multicenter</td>
<td>Unicentric</td>
<td>Multicenter</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Biliary acute pancreatitis</td>
<td>Acute pancreatitis of any etiology</td>
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<td>Biliary acute pancreatitis</td>
<td>Severe biliary acute pancreatitis</td>
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<td>Exclusion criteria</td>
<td>Bilirubin &gt;5 mg/dL</td>
<td>Acute cholangitis</td>
<td>Bilirubin &gt;5 mg/dL</td>
<td>Acute cholangitis</td>
<td>Acute cholangitis</td>
</tr>
<tr>
<td>Number of patients ERCP</td>
<td>59</td>
<td>97</td>
<td>126</td>
<td>51</td>
<td>81</td>
</tr>
<tr>
<td>Number of patients control</td>
<td>62</td>
<td>98</td>
<td>112</td>
<td>52</td>
<td>72</td>
</tr>
<tr>
<td>Timing of ERCP</td>
<td>Less than 72 hours from admission</td>
<td>Less than 24 hours from admission</td>
<td>Less than 72 hours from onset</td>
<td>Less than 48 hours from onset</td>
<td>Less than 72 hours from onset</td>
</tr>
<tr>
<td>Definition of severity for AP</td>
<td>Modified Glasgow criteria</td>
<td>BUN &gt;45 mg/dL, Glu &gt;198 mg/dL, Ranson score</td>
<td>Modified Glasgow criteria</td>
<td>APACHE II score</td>
<td>APACHE II score, Imrie score</td>
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<tr>
<td>Predicted severe PA</td>
<td>44%</td>
<td>41.5%</td>
<td>19.3%</td>
<td>36.9%</td>
<td>100%</td>
</tr>
<tr>
<td>Morbidity (ERCP vs Conservative)</td>
<td>17% vs 34% (p=0.03)</td>
<td>18% vs 29% (p=0.07)</td>
<td>46% vs 51%</td>
<td>21% vs 18% (p=0.8)</td>
<td>25% vs 54%* (p=0.02)</td>
</tr>
<tr>
<td>Mortality (ERCP vs Conservative)</td>
<td>2% vs 8% (p=0.23)</td>
<td>5% vs 9% (p=0.4)</td>
<td>11% vs 6% (p=0.1)</td>
<td>6% vs 2% (p=1)</td>
<td>6% vs 15% (p=0.213)</td>
</tr>
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*patients with cholestasis; ** patients without cholestasis

TABLE 1. Summary of RCT assessing the results of ERCP in acute pancreatitis.
co-existing biliary obstruction or cholangitis (11,48). There is a high likelihood of choledocholithiasis if bilirubin level is higher than 4mg/dL or bilirubin level between 1.8 and 4 mg/dL and dilated common bile duct on ultrasound (>6 mm, with gallbladder in situ) (49).

The optimal timing for ERCP is considered to be urgent (<24 hours) for patients with cholangitis; for biliary obstruction can be awaited 24-72 hours because of the possibility of spontaneous improvement. ERCP with ES can be also considered later during the same hospital admission for medical unfit patients for laparoscopic cholecystectomy (11).

**CHOLECYSTECTOMY FOR BILIARY ACUTE PANCREATITIS**

Patients with predicted mild acute gallstone pancreatitis (AGP) can be operated (laparoscopic cholecystectomy, LC) within the same hospital admission (55). One approach uses the trend in pancreatic enzyme level to guide the timing of an operation (56). A decreasing level makes the patient suitable for surgery, while a stable or an increasing level requires delay. Two studies from the same center evaluated operated patients with mild AGP within 48 hours from admission regardless of resolution of abdominal pain or abnormal laboratory values (57,58). A retrospective analysis compared 117 patients with early LC and 186 with delayed LC. The complication rates were similar between groups, but hospital stay was longer in the second group (3 vs 6 days, p<0.001) (57). The prospective study randomized 50 patients and founded the same results (58). However caution was suggested concerning this approach (59,60).

On the other hand, for cases with predicted severe AGP, cholecystectomy should be performed after an interval of 6 weeks along with resolution of abdominal pain and abnormal laboratory values; cholecystectomy can be also combined with drainage of pancreatic fluid collection or debridement of pancreatic necrosis (11). One retrospective study of 151 patients revealed a higher incidence of infected peripancreatic fluid collections in patients who underwent early cholecystectomy after severe pancreatitis (61). The overall management of AGP is described in Figure 1.

**EARLY NECROSECTOMY**

One prospective trial compared early necrosectomy (48-72 hours from the onset) with late necrosectomy (after 12 days) and founded a higher mortality for the early group (58% vs 27%) and therefore the first one is not indicated (62). Current guidelines proposed a delayed (four weeks after onset of pancreatitis) interventional management for pancreatic necrosis (11). Another potential indication for early surgery is represented by abdominal compartment-syndrome that is sustained intra-abdominal pressure (measured via bladder) > 25 mmHg that is associated with new onset organ failure that is refractory to medical treatment (63).

**CONCLUSION**

Acute pancreatitis is a potential life-threatening disease with a high mortality around 5% and the early phase represents the best window of opportunity for successful treatment. The current treatment for AP includes supportive medical therapy, endoscopic and surgical interventions. Despite different definitions for timing for each treatment component most of them revolve around 24-48 hours. This period allows an accurate diagnosis and severity stratification along with appropriate therapy. Due to multidisciplinary diagnostic and therapeutic requirements these patients should be treated by dedicated teams. Further studies are requested to better define the indications and limits of each type of therapy and to develop new classes of treatment.

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