

Postoperative Treatment of Severe Acute Pancreatitis in the Intensive Care Unit

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ABSTRACT

Severe acute pancreatitis is a clinical disorder associated with significant morbidity and mortality. The main characteristic of the disease is severe systemic inflammation which can be complicated by multiple organ failure and infection of pancreatic necrosis. Repeated assessment of acute pancreatitis severity based on clinical signs, intensive care monitoring, blood tests and imaging tools should be performed to determine the optimal way of treatment for each patient. Infectious complications in severe acute pancreatitis are important problem and have an impact on outcome in patients who survived the first inflammatory hit of the disease. Diagnosis of infected pancreatic necrosis is often challenging, but should not delay adequate treatment, which consists of source control and antimicrobial agents. At this moment, the only rational indication for antibiotic treatment is documented infection. Surgical treatment of severe acute pancreatitis is nowadays delayed and includes minimally invasive techniques. Postoperative care of patients with severe acute pancreatitis is oriented towards supportive treatment and prevention of complications.

INTRODUCTION

Severe acute pancreatitis (SAP) is severe inflammatory disorder associated with significant morbidity and mortality. According to different studies, mortality from SAP ranges from less than 10% to more than 80% (1). Early phase of SAP is characterized by severe systemic inflammatory response and subsequent multiple organ failure. In later stages, SAP can be complicated by infection of pancreatic and peripancreatic necroses and sepsis which further deteriorate multiple organ dysfunction. Surgical management of SAP was the gold standard of therapy in previous decades. Lately, this approach has changed due to many reports of better survival in patients in whom surgical treatment was delayed or was minimally invasive. Nevertheless, surgery should be performed in some patients. The main goals of postoperative management are to provide adequate supportive treatment and to prevent or timely recognize complications. Approach to postoperative intensive care management of patients with SAP is reviewed in this article.

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IDENTIFICATION AND TREATMENT OF ORGAN DYSFUNCTION

Circulation

Extensive hemodynamic monitoring of patients with SAP is important not only in postoperative period but in general. Systemic inflammatory response syndrome (SIRS) is present from the beginning of SAP (1, 2). Postoperatively, hemodynamic instability results not only from severe inflammation but can be a consequence of severe postoperative bleeding or sepsis. PiCCO™ and Lidco™ technology and rarely Swan-Ganz catheter (in the case of heart failure and acute respiratory distress syndrome (ARDS)) are used for continuous hemodynamic monitoring. Echocardiography is also used for non-invasive evaluation of circulatory status of such unstable patient. In the early stage of SAP, it is important to stabilize the patient with adequate fluid resuscitation. Inadequate fluid resuscitation and consequent prolongation of shock aggravate organ failure, which is strongly related to early mortality (3, 4). Postoperatively, the main concern should be not to overload the patient with intravenous fluids. Vigorous fluid resuscitation that was used in the past is nowadays not acceptable anymore because of many negative side effects which can deteriorate patient's status (aggravation of intra-abdominal hypertension (IAH) with deterioration of abdominal organ blood flow and their function). Endpoints of randomized controlled trials (RCT) are that conservative fluid resuscitation in comparison to liberal is associated with lower incidence of organ dysfunction (odds ratio 0.69) and lower mortality (odds ratio 0.40) (5). Most of such patients are mechanically ventilated, and fluid resuscitation should be applied to maintain stroke volume variability (SVV) or pulse pressure variability (PPV) around 10% which indicate euvolemic status. SVV and PPV are both dynamic variables of preload and are superior in mechanically ventilated patients in comparison to static variables (for example central venous pressure, intra-thoracic blood volume index, global end-diastolic volume index) (6, 7). After optimization of patient's fluid status, mean blood pressure of 65 mmHg should be main-

tained by the use of vasoactive drugs. Urine output should be kept at least 0.5 mL/kg/hour while monitoring pulse, blood pressure, oxygen saturation, and blood tests. Balanced electrolyte infusions (Ringer lactate) are recommended by IAP/APA (International Association of Pancreatology/American Pancreatic Association), while some studies indicate increased mortality in SAP if colloid infusions are used (8, 9, 10). In some cases, specific electrolyte solutions are used to correct electrolyte disturbance.

Ventilation

Acute respiratory failure (ARF) in SAP is usually a combination of hypoxemic and hypercapnic ARF. Hypoxemia is a result of capillary endothelial and alveolar epithelial damage, which promote development of ARDS. These changes are surrogate for ventilation-perfusion mismatch, for decrease of diffusion capacitance for oxygen and formation of right-left intrapulmonary shunt. On the other hand, ileus, ascites and meteorism of gut increase intra-abdominal pressure (IAP) which together with pleural effusions decreases compliance of respiratory system. This increases work of breathing which causes exhaustion of respiratory muscles, leading to hypercapnic respiratory failure. Patients with SAP suffer from severe pain, and concomitant use of strong opioid analgesics can depress respiratory drive and aggravate hypercapnic ARF. In mild forms of acute pancreatitis, non-invasive ventilation can be performed but only in hypoxemic type of ARF, while in SAP the ventilatory support is mostly invasive and is completely based on algorithms for protective lung ventilation. All approaches that are usually used in ARDS patients for setup ventilation parameters (see below) can also be used in patients with ARDS caused by SAP. Prone positioning is relatively contraindicated in case IAP is high or if intra-abdominal operation with negative pressure wound therapy insertion was performed. The primary targets for ARDS treatment are to ensure adequate gas exchange while minimizing the risk of ventilator-induced lung injury. Both pharmacologic (muscle relaxation by using neuromuscular blocking agents, inhaled vasodilators, corticosteroids) and non-pharmacologic strategies (lung

recruitment, positive end-expiratory pressure (PEEP) selection, tidal volume setting, O_2 and CO_2 target matching protective ventilatory strategies, prone positioning and extracorporeal assistance) are used to reach this objective (11, 12). The gravity is the main reason for collapsing dorsal part of lung parenchyma in ARDS patient. This phenomenon is even more pronounced in extra-pulmonary ARDS as is the case in SAP where elevated diaphragm, because of IAH, compresses lung tissue even more. IAH has serious impact on function of respiratory as well as peripheral organs. In the presence of alveolar capillary damage, which occurs in ARDS, IAH promotes lung injury as well as oedema, impedes the pulmonary lymphatic drainage, and increases intra-thoracic pressure, leading to atelectasis, airway closure and deterioration of respiratory mechanics and gas exchange. In these regions, during each breath cycle, the lung tissue opens during inhalation and collapses during exhalation, causing the formation of atelectrauma. Talmore et al. described a protocol of PEEP adjustment by using transpulmonary pressure (P_{TP}) (difference between airways (P_{AW}) and oesophageal (P_{ESO}) pressure) which must be positive at the end of expiration to prevent atelectrauma to occur (13). P_{ESO} is usually measured at the level of the heart. It very closely reflects the pressure in surrounding collapsed lung tissue. P_{ESO} is not the same as pleural pressure, but it is very closely related to changes in pleural pressure. In this study, PEEP setting guided by P_{ESO} improved oxygenation, respiratory system compliance and cumulative survival in comparison to conventional protocol guided by ARDSnet PaO_2/FiO_2 tables. At the moment, there is lack of data from RCT on how to manage ARDS patients with IAH although some suggestions have been made. According to these, optimal ventilator management of patients with ARDS and IAH would include the following: a) measurement of intra-abdominal and P_{ESO} and hemodynamic monitoring; b) ventilation setting with protective tidal volume, recruitment manoeuvre, and level of PEEP set according to the 'best' compliance of the respiratory system or the lung; c) deep sedation with or without neuromuscular paralysis in severe ARDS; and d) open abdomen in selected patients with severe abdominal compartment syndrome (14, 15).

Intra-abdominal hypertension

Incidence of IAH in SAP is between 60–85% (16). This high incidence is the reason that IAP should be measured in each SAP patient admitted to intensive care unit. Main reasons for IAH in SAP are inflammatory process in retroperitoneal space, formation of ascites and ileus. Four levels of IAH are described by World Society for Abdominal Compartment Syndrome (WSACS): grade I IAP 12–15 mmHg; grade II: IAP 16–20 mmHg; grade III: IAP 21–25 mmHg; grade IV: IAP > 25 mmHg. For normal function of abdominal organs the abdominal perfusion pressure (APP), defined by the difference between mean arterial pressure (MAP) and intra-abdominal pressure ($APP = MAP - IAP$), should be ≥ 60 mmHg. ACS is present when IAP above 20 mmHg and $APP \leq 60$ mmHg is accompanied by failure of at least one organ (most frequently associated with decrease in diuresis pointed out as acute renal failure) (17). The other important moment is the speed of IAH development. In acute development (in a few hours), ACS can occur at lower or higher levels of IAP and APP. When IAH develops within several weeks or months (like in pregnancy or obesity), ACS does not occur.

In patients with SAP, IAP should be measured each 4–6 hours. In daily practice, IAP is measured by using additional pressure setup placed on urinary catheter which is inserted into urinary bladder. Alternative approach is to insert additional balloon catheter into the stomach or to insert commercially available NutriVent™ probe which allows to measure P_{ESO} , needed for P_{TP} calculation, and gastric pressure (P_{GA}) which represents intra-abdominal one (18).

With non-surgical approaches, the IAP should be kept ≤ 15 mmHg and $APP \geq 60$ mmHg with no signs of intra-abdominal organ failure. Non-surgical procedures for lowering IAP are:

1. Improving compliance of abdominal wall:
 - adequate analgesia and sedation,
 - inclination of upper body $< 20^\circ$,
 - use Trendelenburg position if possible, and
 - the use of neuromuscular blocking agents.

2. Removal of content from intra-abdominal cavity:
 - gastric and gut decompression by insertion of nasogastric or rectal tube,
 - the use of prokinetic drugs (neostigmine),
 - the use of enema,
 - reduction or abolishment of enteral feeding,
 - colonoscopic decompression, and
 - insertion of urinary catheter.
3. Optimization of fluid resuscitation:
 - avoid excessive fluid infusion,
 - the use of hypertonic or colloid solutions,
 - the use of diuretics in hemodynamically stable patients, and
 - in the case of oliguric or anuric acute renal failure replacement renal therapy should be used.
4. Optimization of systemic and regional organ blood flow:
 - continuous hemodynamic monitoring for optimization of preload and the use of inotropic/vasoactive drugs for optimal oxygen delivery, and
 - optimal ventilation (see above).

In case of secondary ACS where IAP, despite non-surgical interventions, is above 20 mmHg and organ failure occurs, surgical methods for abdominal decompression have to be employed. Surgical laparostomy should be performed either by median laparotomy or even more frequently by bilateral transversal laparotomy (19, 20). Three different methods for temporary laparostomy formation are currently used: a) technique for skin closure; b) technique for fascia closure; c) closure technique by continuous negative pressure in use (VAC technique).

Infection control

More than 80% of patients with SAP die due to secondary infections of pancreatic and peripancreatic necrosis (21). Main source of infection is intestinal microbiota, which is translocated to pancreatic tissue from hyperpermeable gut during systemic inflammation. The most common pathogens are *Escherichia coli* (26%), *Pseudomonas* spp. (16%), *Staphylococcus*

spp. (15%), *Klebsiella* spp. (10%), *Proteus* spp. (10%), *Streptococcus* spp. (4%), *Enterobacter* spp. (3%), *Enterococcus* spp. And anaerobic bacteria (16%). By rule, fungal superinfection occurs late in the disease course, usually several weeks to months after the beginning of inflammation (8).

At the moment there is lack of data on effectiveness of prophylactic antibiotic treatment (22). In the review article by Villatoro et al. which included seven RCTs with 404 patients, there was no significant difference in mortality between patients who received prophylactic antibiotic treatment versus patients who received placebo (8.4% versus 14.4%, non-significant). At the same time, there were no differences in the amount of infected necrosis between the groups (19.7% versus 24.4%, non-significant). There was only significant reduction in overall infection rate in the group that received treatment (37.5% vs. 51.9%). When fluoroquinolones in combination with metronidazole were used, there were no differences in mortality rate, incidence of secondary pancreatic necrosis infections and incidence of overall infections rate, respectively. On the other hand, when imipenem was used instead, there was significant reduction in incidence of secondary pancreatic necrosis infections, but again without any impact on survival. Conclusion of the study was that there were not enough data to support prophylactic use of antibiotics in SAP (23). In 2012 another meta-analysis in SAP was published and failed to confirm positive effect of prophylactic antibiotic treatment on survival rate. They calculated that 1429 patients have to be treated by antibiotics to prevent one death (24). Similar data were published by Wittau et al. in another meta-analysis of 14 RCTs and no differences were observed in mortality rate, the incidence of infected pancreatic necrosis and non-pancreatic infection, as well as the rate of surgical interventions between treatment and control group (25). In a prospective randomized study by Maravi-Poma et al., incidence of local and systemic mycoses was tripled in SAP patients who received prolonged antibiotic treatment (26). Improper use of antibiotics increases the incidence of antibiotic-associated diarrhea and diarrhea caused by *Clostridium difficile*. As side effects of prophylactic antibiotic treat-

ment seem to outweigh its benefits, routine use of antibiotics in SAP cannot be recommended (27).

The only rationale for antibiotic use in SAP is proven infection of pancreatic necrosis (8). Clinically, it is very difficult to distinguish between sterile and infected necrosis. Infected pancreatic necrosis should be suspected when prominent SIRS persists for more than 7–10 days and if clinical condition worsens. In this case, CT-guided fine needle aspiration of suspected infected pancreatic or peripancreatic tissue should be performed. Pancreatic necrosis is present when bacteria are isolated from this material or when air inclusions are seen on CT scan. If percutaneous drainage of such areas is planned, CT-guided fine needle aspiration is not necessary.

At the moment, there is lack of data for empirical antibiotic treatment recommendation. Some studies favor imipenem and ertapenem, which penetrate pancreatic tissue very well and reach the tissue concentration above minimal inhibitory concentration for bacteria, most frequently found in pancreatic necrosis (28, 29). Similar data are available for moxifloxacin (30). In vitro efficacy of all three antibiotics against bacteria most often isolated from pancreatic necrosis (*E. coli*, *Enterobacter cloacae*, *Enterococcus faecalis* and *Bacteroides fragilis*) were very similar to each other, with only moxifloxacin being more efficient against *E. cloacae*, *E. faecalis* and anaerobic bacteria in mixed cultures (31). Precise data about length of the treatment are not available. Most authors suggest that treatment should be continued at least fourteen days after removal of infection source (8, 27, 32).

Mortality of SAP patient with infected pancreatic necrosis is up to 30% and is in 80% related to septic complications. In patients with infected pancreatic necrosis and multiple organ failure without surgical treatment, mortality is close to 100% (33). Mortality decreases if surgical procedures are employed. Dutch researchers published data about decreased mortality in patients where step surgical approach was used (percutaneous drainage or endoscopic transluminal drainage followed by minimally invasive retroperi-

toneal necrosectomy). If possible, surgical procedures should be delayed by the fourth week. In that time, pancreatic necrosis is expected to be surrounded by granulation tissue (34). Pancreatic abscess can occur late in the course SAP. Antibiotic treatment in combination with percutaneous drainage is usually sufficient treatment option. In case abscess persists, surgical drainage should be performed. For SAP in association with cholangitis, urgent endoscopic retrograde cholangiopancreatography (ERCP) is indicated in the first 24 hours while for the rest of the biliary pancreatitis there is lack of data for identification of proper period when ERCP should be performed (8).

Most common infection complications after pancreatic necrosectomy are infection of the remaining pancreatic tissue and common hospital infections such as ventilation-associated pneumonia, catheter-related infections, etc. Behrman et al. reported 17.8% occurrence of postoperative pancreatic infections in patients after elective pancreatic necrosis resection. Polymicrobial infections were seen in 55% of patients. Prolonged use of vancomycin was associated with occurrence of vancomycin-resistant enterococci (35).

Nutrition

Optimal nutritional support in SAP has been under debate for decades. Bowl at rest (nothing by mouth) strategy has been implemented conventionally to treat SAP (36, 37, 38). However, dietary restrictions exacerbate patient's malnutrition due to imbalance between reduced food intake and higher nutritional requirements, leading to further catabolism, bacterial translocation (39), and ultimate mortality (40). Evidence of clinical trials has demonstrated parenteral nutrition (PN) in preventing pancreatic stimulation and many benefits of enteral nutrition (EN). However, in daily practice, it remains challenging to predict whether EN will be tolerated in patients with acute pancreatitis (41). Strategic approaches to include nutritional supplements have also been attempted to provide additional immune regulatory and antioxidative effects. Probiotics and prebiotics have been shown to stabilize disturbed intestinal barrier.

However, currently, there is no firm evidence that probiotic use improves mortality in critically ill patients (42, 43). Due to immunosuppressive and inflammatory nature of the disease, immunonutrients like glutamine and omega-3 fatty acids have been added to parenteral or enteral formulas to modulate immune functions, suppress the hyperinflammatory responses, and re-establish tissue and organ homeostasis in clinical practice (44, 45). Supplements with antioxidative properties like glutamine and vitamin C have also been suggested to provide additional beneficial effects (46). In a meta-analysis by Yao H et al. where PN was compared with EN in SAP, EN was associated with a significant reduction in overall mortality (risk ratio 0.36, 95% CI 0.20–0.65, $p=0.001$) and the rate of multiple organ failure (risk ratio 0.39, 95% CI 0.21–0.73, $p=0.003$). Author concluded that EN should be recommended as the preferred route of nutrition for critically ill patients with SAP (47). In case oral feeding is not tolerated, enteral feeding through a nasogastric or nasojejunal feeding tube should be attempted within the first 72 hours of administration. PN should be minimized for its risks of infection and other complications. Only if enteral route is not available or tolerated, PN may be considered. Overall, nutritional support plays a critical role in clinical management of SAP, although the optimal timing remains unclear. Predicting the nutritional tolerance of patients with acute pancreatitis remains challenging as the current evaluation system needs to be improved. Various nutritional supplement(s) together with PN or EN with currently mixed clinical outcomes is a subject of interest for future evaluation and may lead to promising outcomes (48). Another meta-analysis compare early enteral nutrition (EEN) with delayed ones (DEN) and conclude that EEN within 48 hours is superior to DEN beyond 48 hours for patients with SAP; however, more studies are required to verify this conclusion (49). Otherwise, nutrient requirements for patients with SAP can be found in ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines: a) energy 25–35 kcal/kg body weight/day; b) protein 1.2–1.5 g/kg body weight/day; c) carbohydrates 3–6 g/kg body weight/day corresponding to blood glucose concentration between

6 and 10 mmol/L); d) lipids up to 2 g/kg body weight/day corresponding to blood triglyceride concentration below 12 mmol/L (50).

Pain control

Pain is the main feature of acute pancreatitis and is the main reason for admission of majority of patients (51–53). There are no extensive studies on the pharmacological control of pain in acute pancreatitis which is quite surprising given the importance of this symptom during the disease. There is also lack of evidence regarding degree of efficacy of the various pharmacological substances used to treat different forms of acute pancreatitis. On the other hand, there are several reports concerning the possibility that non-steroidal anti-inflammatory drugs (NSAIDs) may actually induce acute pancreatitis (54–57). On the other hand, NSAIDs have also been used to prevent ERCP-induced acute pancreatitis (58). In meta-analysis by Pezzilli et al., authors attempted to answer the questions whether NSAIDs may induce acute pancreatitis, whether their prophylactic use can prevent post-ERCP pancreatitis, and whether they are capable of controlling pain in acute pancreatitis. They concluded that: 1) there is a risk for acute pancreatitis associated with the use of NSAIDs and, in clinical practice, it seems that naproxen should be the preferred analgesic in limiting the risk of development of acute pancreatitis; 2) both diclofenac and indomethacin may significantly reduce the risk of acute pancreatitis after ERCP resulting in major clinical and economic benefits and, finally, 3) NSAIDs are able to control the pain in patients with acute pancreatitis. However, further clinical studies on the best NSAID to be used in clinical practice are needed. An example comes from the use of diclofenac; this is a drug largely used to treat pain in acute pancreatitis. It is useful in preventing post-ERCP pancreatitis, but it is considered as major NSAID responsible for inducing acute pancreatitis in general population (59).

Acute pancreatitis is always very painful. There is some drug options for treating pain, and stronger analgesics (opioids) are often needed. Analgesics are

usually given as infusion therapy or through epidural catheter. Sometimes it is possible to adjust the dose of the analgesics by patient himself (so-called patient-controlled analgesia) where overdosing is less possible.

Opioids may be an appropriate choice for treatment of acute pancreatitis pain. Compared with other analgesic options, opioids may decrease requirement for supplementary analgesia. There is currently no difference regarding risk of pancreatitis complications or clinically serious adverse events between opioids and other analgesia options. Recently published meta-analysis on acute pancreatitis pain included five RCTs with a total of 227 participants (age range 23–76 years; 65% men) (60). Opioids assessed were intravenous and intramuscular buprenorphine, intramuscular pethidine, intravenous pentazocine, transdermal fentanyl and subcutaneous morphine. Buprenorphine is non-narcotic analgesic with effect superior to procaine which, unlike procaine, does not exacerbate acute pancreatitis by inducing contraction of the sphincter of Oddi (61). Buprenorphine has an analgesic effect similar to that of pethidine. One RCT, comparing subcutaneous morphine with intravenous metamizole reported non-significant reduction in improvement of pain intensity (primary outcome) (risk ratio 0.50, 95% CI 0.19–1.33). Three studies compared analgesia using opioids with non-opioid treatments. After excluding one study in which opioids were used through continuous intravenous infusion, there was a decrease in the number of patients requiring supplementary analgesia (risk ratio 0.53, 95% CI 0.30–0.93). In a single study, there were no differences regarding the need of supplementary analgesia between patients who received buprenorphine or pethidine (risk ratio 0.82, 95% CI 0.61–1.10). There were no differences in pancreatitis complications between the drugs tested. No clinically serious or life-threatening adverse events occurred related to treatment. No differences for this outcome were found between opioid and non-opioid treatments, or for type of adverse event (nausea-vomiting and somnolence-sedation). One death in the procaine group was reported across all trials. One RCT comparing pethidine with intramuscular buprenorphine reported non-significant differences of supplementary analgesic,

adverse events, and survival. One RCT comparing fentanyl with placebo found no difference in adverse events. Findings of this review are limited by the lack of information to allow full appraisal of the risk of bias, measurement of relevant outcomes and small numbers of participants and events covered by the trials.

Epidural anesthesia (EA) is widely used to induce analgesia in the perioperative period and has been used to decrease pain in patients with SAP (62). Also, experimental studies have shown a specific beneficial effect of EA in SAP attributed to a sympathetic nerve blockade that redistributes splanchnic blood flow to non-perfused pancreatic regions (63, 64). First RCT on the use of EA for treatment of acute pancreatitis showed that there were no complications of epidural procedure, no catheter-related infections, and no hemodynamic complications during median time of EA of 5.7 days (65). Authors were able to show a significant improvement in arterial perfusion of the pancreas which was observed in 13/30 (43%) measurements in the EA group, and in 2/27 (7%) measurements in the control group. In the EA group, none of the patients developed clinical sepsis and only one needed intubation, whereas, in control group, six patients needed intubation for acute respiratory distress (7.7% versus 27.3% were intubated, respectively, $p=0.22$). Furthermore, the use of antibiotics was not different between two groups (61.5% of patients of EA group and 68.2% of control group, $p=0.689$), nor was the duration of therapy. During hospitalization, EA group developed nine cases of loco-regional complications and 10 cases of systemic complications compared to controls with 12 cases of loco-regional complications and 13 systemic complications. Visual Analogue Scale evaluation showed improvement in subjective pain during the first 12 days in the EA group compared to the control group, with a significant difference on day of EA implementation and at ten days. The results for the mean pain score on a scale 1–10 were before randomization 6.55 versus 7.31, $p=0.57$; after EA implementation 1.6 versus 3.5, $p=0.02$; at day one 0.57 versus 2, $p=0.06$; at day five 1.86 versus 1.38, $p=0.69$; at day ten 0.2 versus 2.33, $p=0.034$; at day twelve 0 versus 2.8, $p=0.071$. Conclusion of the study was that EA is a safe

procedure which significantly increased blood flow to the pancreatic gland with consequent lower development of necrosis and suggest a trend towards improvement of clinical outcome for patients with SAP.

CONCLUSION

In intensive care medicine, SAP remains to be a challenging clinical disorder with multiple complications and high mortality. Main pathophysiological mechanisms with impact on outcome are uncontrolled systemic inflammatory response from the beginning and infection of pancreatic necrosis in late phase of the disease. Pre- and postoperative management of SAP patients must offer intensive care monitoring and supportive therapy. Timely recognition of potential complications, especially infections, improves outcome of SAP.

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