Management of the critically ill patient with severe acute pancreatitis

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Objective: **Acute pancreatitis represents a spectrum of disease ranging from a mild, self-limited course requiring only brief hospitalization to a rapidly progressive, fulminant illness resulting in the multiple organ dysfunction syndrome (MODS), with or without accompanying sepsis. The goal of this consensus statement is to provide recommendations regarding the management of the critically ill patient with severe acute pancreatitis (SAP).**

Data Sources and Methods: **An international consensus conference was held in April 2004 to develop recommendations for the management of the critically ill patient with SAP. Evidence-based recommendations were developed by a jury of ten persons representing surgery, internal medicine, and critical care after conferring with experts and reviewing the pertinent literature to address specific questions concerning the management of patients with severe acute pancreatitis.**

Data Synthesis: **There were a total of 23 recommendations developed to provide guidance to critical care clinicians caring for the patient with SAP. Topics addressed were as follows. 1) When should the patient admitted with acute pancreatitis be monitored in an ICU or stepdown unit? 2) Should patients with severe acute pancreatitis receive prophylactic antibiotics? 3) What is the optimal mode and timing of nutritional support for the patient with SAP? 4) What are the indications for surgery in acute pancreatitis, what is the optimal timing for intervention, and what are the roles for less invasive approaches including percutaneous drainage and laparoscopy? 5) Under what circumstances should patients with gallstone pancreatitis undergo interventions for clearance of the bile duct? 6) Is there a role for therapy targeting the inflammatory response in the patient with SAP? Some of the recommendations included a recommendation against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pancreatitis. The jury also recommended against pancreatic debridement or drainage for sterile necrosis, limiting debridement or drainage to those with infected pancreatic necrosis and/or abscess confirmed by radiologic evidence of gas or results or fine needle aspirate. Furthermore, the jury recommended that whenever possible, operative necrosectomy and/or drainage be delayed at least 2–3 wk to allow for demarcation of the necrotic pancreas.**

Conclusions: **This consensus statement provides 23 different recommendations concerning the management of patients with SAP. These recommendations differ in several ways from previous recommendations because of the release of recent data concerning the management of these patients and also because of the focus on the critically ill patient. There are a number of important questions that could not be answered using an evidence-based approach, and areas in need of further research were identified. (Crit Care Med 2004; 32:2524–2536)**

KEY WORDS: acute pancreatitis; multiple organ dysfunction syndrome; sepsis; critically ill patient; evidence-based recommendations

Acute pancreatitis represents a spectrum of disease ranging from a mild, self-limited course requiring only brief hospitalization to a rapidly progressive, fulminant illness resulting in the multiple organ dysfunction syndrome with or without accompanying sepsis. This consensus statement focuses on the management of the critically ill patient with severe acute pancreatitis (SAP). Only a minority of patients with pancreatitis have disease severe enough to require admission to an intensive care unit (ICU). These patients have mortality rates in the range of 30–50% and a mean hospital length of stay >1 month, attesting to the severity of pancreatitis at this end of the spectrum (1).

An established definition of SAP was developed by consensus in 1992 and is widely used throughout the literature. Using this definition, SAP is acute pancreatitis associated with complications that are either local (e.g., peripancreatic fluid collection, necrosis, abscess, pseudocyst) or systemic (e.g., organ dysfunction). However, the definitions used previously for organ dysfunction are not consistent with current criteria that necessitate organ support or ICU admission today. To better identify patients who have severe systemic manifestations of pancreatitis from a critical care perspective, we use the term severe acute pancreatitis to represent pancreatitis in the context of true organ dysfunction, irrespective of the local complications. In this regard, SAP is to pancreatitis as severe sepsis is to sepsis (2).

An international consensus conference was held in April 2004 to develop guidelines for the management of the critically ill patient with SAP. These guidelines differ from those previously published by focusing on the challenges of caring for the patient with severe pancreatitis in the critical care environment. A jury of ten persons representing surgery, internal medicine, and critical care

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attended the presentations of 24 experts in the field of pancreatitis. Experts were asked to address several specific questions posed by the conference organizers and scientific advisors. These questions included the following: a) When should the patient admitted with acute pancreatitis be monitored in an ICU or step-down unit? b) Should patients with SAP receive prophylactic antibiotics? c) What are the optimal mode and timing of nutritional support for the patient with SAP? d) What are the indications for surgery in acute pancreatitis, what is the optimal timing for intervention, and what are the roles for less invasive approaches including percutaneous drainage and laparoscopy? e) Under what circumstances should patients with gallstone pancreatitis undergo interventions for clearance of the bile duct? and f) Is there a role for therapy targeting the inflammatory response in the patient with SAP?

Following the formal presentations, the jury met to review the pertinent literature. One pair of jury members addressed each question, summarizing the level of evidence and making recommendations for consideration and discussion among all jury members using the approach promulgated by the Center for Evidence Based Medicine, Oxford, United Kingdom (3). Since the focus on this consensus conference was critically ill patients with SAP and since a number of recent studies address some of these questions, some statements in this document vary from previously published recommendations (4).

QUESTION 1: WHEN SHOULD THE PATIENT ADMITTED WITH ACUTE PANCREATITIS BE MONITORED IN AN ICU OR STEP-DOWN UNIT?

Rationale

Patients with SAP may benefit from an environment with more intensive monitoring given their potential for progressive organ dysfunction and/or life-threatening local complications. Since the availability of critical care beds is limited, it is important to identify appropriate patients for ICU admission. Additionally, avoiding unnecessary ICU admission may limit the risk of nosocomial infections and iatrogenic complications.

Evidence

One of the most important determinants of poor outcome in SAP is the early development and persistence of organ dysfunction. Although a variety of scoring systems, biomarkers, and radiological findings can help to identify patients at risk of organ dysfunction, these do not substitute for frequent clinical assessment and monitoring. Therefore, the cornerstone of management in early pancreatitis is fluid resuscitation and close monitoring for early manifestations of organ dysfunction. In addition to frequent assessment of vital signs, monitoring should be directed toward the repeated evaluation of intravascular volume status by means of physical examination and monitoring of urine output and the early identification of hypoxemia through either pulse oximetry or arterial blood gas analysis.

Several disease-specific scoring systems have been developed to help identify the patient at risk for adverse outcomes, such as the Ranson criteria (5) and the Glasgow Score (6). Of the 11 Ranson criteria, four are directly related to fluid resuscitation (urea, net fluid sequestration, base deficit, and decreased hematocrit) and are independent predictors of mortality (7). In a report of 49 patients with acute pancreatitis, generic measures of disease severity such as the Acute Physiology and Chronic Health Evaluation II or Simplified Acute Physiology Score II score were superior to disease-specific scoring systems in predicting mortality (8). These scoring systems describe patients in the first 24–48 hrs after their presentation. However, evolving organ dysfunction appears to be a better predictor of outcome than a one-time assessment, suggesting that dynamic scores might be more useful (9).

A variety of serum biomarkers are associated with the severity and prognosis of acute pancreatitis (10). C-reactive protein (CRP), an acute phase reactant, is most widely used. Although high levels of CRP have been associated with pancreatic necrosis (11, 12), there is a 24- to 48-hr latency before CRP increases, limiting its utility as an early predictor (10). Of the many cytokines evaluated, interleukin (IL)-6 appears to hold the most promise as an early predictor of severe disease, but more definitive studies are needed (10). Trypsinogen activation peptide is a pancreatic protease that is released early in acute pancreatitis. In a study of 172 patients designed to evaluate the utility of trypsinogen activation peptide and CRP in identifying patients with severe disease, the discriminatory ability of either was poor. The area under the receiver operating curve at 24 hrs from symptom onset for trypsinogen activation peptide and CRP was only 0.69 and 0.40, respectively. At 24 hrs following hospital admission, their ability to discriminate mild from severe disease was only slightly better, with the area under the receiver operating curve of 0.78 and 0.65 for trypsinogen activation peptide and CRP, respectively (13). Procalcitonin (14) and numerous other markers also have been studied in small groups of patients (10). In general, although some of these markers are used to follow patients with pancreatitis, they are of limited clinical utility in predicting outcome or to triage patients for admission to an ICU.

Radiographic imaging frequently is necessary to both diagnose and stage the severity of acute pancreatitis. In patients with abdominal pain of unclear etiology, computed tomography (CT) of the abdomen can confirm the diagnosis of pancreatitis and identify other causes of pain. When intravenous radiocontrast media are contraindicated, the diagnosis of acute pancreatitis can be inferred from homogeneous glandular enlargement and the presence of peripancreatic fluid collections (15). CT with nonionic intravenous radiocontrast is preferred. The radiocontrast is necessary to identify pancreatic necrosis, which appears as focal or diffuse zones of nonenhanced parenchyma. Necrosis may not be evident until 48–72 hrs after presentation. If the patient is clinically stable, magnetic resonance imaging is an alternative to CT when contrast dye is contraindicated and an assessment of the presence of necrosis is necessary. The extent of pancreatic necrosis appears to be a useful determinant of prognosis, with mortality increasing markedly in patients with necrosis involving >30% of the gland (16–19).

The availability of critical care services may ensure optimal fluid resuscitation in order to prevent, reverse, or attenuate organ dysfunction and facilitate timely use of advanced life support. Thresholds for admission to an ICU vary widely and are dependent on the availability of beds, alternative venues (such as step-down units), and whether frequent monitoring and appropriate management can occur on the ward. Patients with SAP who fulfill conventional criteria for ICU admission (20) should be admitted if possible, as

well as those patients at high risk of rapid deterioration such as the elderly (21), those with significant obesity (e.g., body mass index >30 kg/m^2) (22), patients requiring ongoing volume resuscitation, and patients with evidence of substantial pancreatic necrosis (>30%).

There are no studies evaluating the relationship between different models of critical care delivery and outcomes in patients with SAP. However, a systematic review of 26 observational studies showed that a heterogeneous group of critically ill patients cared for by an intensivist or using an intensivist consultant model in a closed ICU had a shorter duration of ICU stay and lower mortality than similar patients cared for in units without such staffing patterns (23).

Jury Recommendations

Recommendation 1. We recommend ICU admission for patients meeting conventional criteria for admission to a critical care unit. In addition, a step-down unit or ICU should be considered for patients who are at high risk of rapid deterioration such as the elderly, the obese, patients requiring ongoing volume resuscitation, and patients with substantial pancreatic necrosis (level 5 evidence, grade D recommendation).

Recommendation 2. We recommend that when feasible, critically ill patients with pancreatitis be cared for by an intensivist-led multidisciplinary team with ready access to physicians skilled in endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), surgery, and interventional radiology (level 3a evidence, grade B recommendation).

Recommendation 3. We recommend close clinical observation of patients with pancreatitis regardless of their venue of care. These patients usually require early and aggressive fluid resuscitation. They are at risk for the early development of organ dysfunction as a result of inadequate resuscitation and the systemic and local complications of pancreatitis. Clinical monitoring should focus on intravascular volume assessment (e.g., physical examination, urine output, and acid-base status) and pulmonary function (e.g., hypoxemia). Disease-specific scoring systems and global illness severity scores may be useful adjuncts to identify patients at high risk of complications; however, these models should not replace frequent serial clinical assessments (level 5 evidence, grade D recommendation).

Recommendation 4. We recommend against the routine use of markers such as CRP or procalcitonin to guide clinical decision making, predict the clinical course of pancreatitis, or triage patients (level 5 evidence, grade D recommendation).

Recommendation 5. We recommend that in the presence of diagnostic uncertainty at the time of initial presentation, a CT scan of the abdomen (with intravenous contrast in the absence of contraindications) be performed after adequate fluid resuscitation to confirm the diagnosis of pancreatitis and to rule out alternate diagnoses. An admission CT scan may also serve as a baseline for future scans (level 5 evidence, grade D recommendation).

Recommendation 6. We recommend that CT to identify local complications be delayed for 48–72 hrs when possible, as necrosis might not be visualized earlier (level 5 evidence, grade D recommendation).

QUESTION 2: SHOULD PATIENTS WITH SEVERE ACUTE PANCREATITIS RECEIVE PROPHYLACTIC ANTIBIOTICS?

Rationale

Infection of the necrotic pancreas develops in 30–50% of patients with necrosis documented by CT or operation (24–27). Although infection might occur within the first week following initial presentation, its incidence tends to peak in the third week of the disease (28). Rates of organ failure and mortality appear to be highest among patients with infected pancreatic necrosis.

The mechanism by which the necrotic pancreas becomes infected is unclear, but experimental and clinical data suggest that the gastrointestinal tract is the likely source of organisms, since intestinal colonization by pathogens often precedes pancreatic infection (29–33). These data, combined with the adverse outcomes associated with the development of infected pancreatic necrosis, underlie the rationale for the use of either prophylactic intravenous or oral, nonabsorbable antimicrobials. Different regimens have been proposed, but most have a spectrum of activity that includes Gram-negative organisms. There is no justification for an-

Table 1. Summary of randomized trials examining routine prophylactic antibiotics for necrotizing pancreatitis

Study	Blinded	Intervention	n	Ranson Score, Mean	Infected Pancreatic Necrosis, %	Surgery, %	Mean Length of Stay, Days	Mortality, %
Pederzoli et al. (37)	No	None	33	3.6	30	33	NA	12
		Imipenem	41	3.7	12[a]	29		7
Sainio et al. (38)	No	None	30	5.7	40	47	44	23
		Cefuroxime	30	5.3	30	23[a]	33	3[a]
Delcenserie et al. (39)	No	None	12	2.1	33[b]	25	28	25
		Ceftazidime and amikacin and metronidazole	11	2.5	0	0	22	9
Schwarz et al. (41)	No	None	13	4.5	54	NA	NA	15
		Ofloxacin and metronidazole	13	5.0	62			0
Nordback et al. (42)	No	None	33	NA	18	15	21	15
		Imipenem	25		4	8	17	8
Isenmann et al. (40)	Double	Placebo	35	2.0	9	17	23	4
		Ciprofloxacin and metronidazole	41	3.0	12	24	22	3

NA, not applicable.
[a] $p < .05$; [b] end point is severe sepsis or infected pancreatic necrosis.

timicrobial prophylaxis in patients without necrosis, given the relatively low incidence of infectious complications in this setting.

Evidence

Intravenous Antimicrobial Prophylaxis. Three randomized controlled studies tested the efficacy of parenteral ampicillin (1 g every 6 hrs for 5–7 days) in unselected patients with acute pancreatitis. There were no differences in outcomes (infectious complications, deaths, or hospital length of stay) between treatment and control groups in all three studies. However, there were no major pancreatic complications and only one death in these trials, indicating that the majority of these patients had mild pancreatitis (34–36).

More recent studies have targeted patients at greater risk of pancreatic infection, using high levels of CRP and/or evidence of pancreatic necrosis on CT as inclusion criteria. Six randomized controlled trials have tested the efficacy of prophylactic systemic antibiotics in this higher risk group (37–42) (Table 1). These trials differ in their inclusion criteria and the choice of antimicrobials. Two studies demonstrated reduced rates of pancreatic infection (37, 39). Only one of these trials was adequately powered to demonstrate a statistically significant decrease in this end point, and in this study the reduction in infection rates was not associated with a reduction in the number of operations, organ failure, or mortality (37). The other four studies did not demonstrate a significant reduction in rates of pancreatic infection with prophylaxis (38, 40–42). The report by Sainio and colleagues (38) is the sole study demonstrating a reduction in mortality in the treatment arm, but an excess of early deaths in the control group, unrelated to infection, suggests an imbalance in randomization. In this study, prophylaxis was associated with fewer urinary tract infections and fewer operative interventions; however, many of the operations were directed toward the debridement of noninfected pancreatic necrosis. In the Schwarz et al. (41) trial, there was a trend toward benefit but the study was underpowered to derive definitive conclusions. In the trial by Nordback et al. (42), in which patients with CRP >150 and pancreatic necrosis by CT were randomized to prophylaxis or standard care, there was less organ failure with a trend toward fewer pancreatic infections in the treatment arm, without significant effects on operative interventions or mortality. However, >40% of the patients in the control arm of this study were converted to imipenem therapy because of suspicion of infection (42). The fourth study, with the highest methodological quality, yet with a relatively small proportion of patients with necrosis, demonstrated no differences in outcome (40).

Three meta-analyses have been published (43–45), none of which included the most recently published randomized controlled trial by Isenmann. All of these analyses have concluded that prophylactic antimicrobial therapy is beneficial in necrotizing pancreatitis with either trends or statistically significant reductions in mortality, rates of infection, or surgical intervention. In each of these meta-analyses, the results were influenced by the inclusion of the trial with a high early mortality in the control arm by Sainio and colleagues (38), described previously. After excluding this report, one meta-analysis showed no beneficial effect to prophylactic antimicrobial therapy (44). Another meta-analysis was limited to the three studies in which acute necrotizing pancreatitis was an entry criterion (45). In this analysis, the pooled estimates suggested a trend toward a decrease in the risk of local pancreatic infections. However, a significant reduction in mortality was evident. The improvement in mortality without a reduction in rates of pancreatic infection suggests that the antimicrobials might have exerted their beneficial effects through other mechanisms, the most likely of which is earlier treatment of other nosocomial infections.

The lack of any consistent benefit across studies, their variable inclusion criteria, variable methodological quality, different antimicrobial regimens, and the significant potential for harm preclude a recommendation for routine intravenous prophylactic antimicrobial therapy in patients with SAP with or without necrosis. Furthermore, prophylactic antimicrobials have been associated with a change in the spectrum of pancreatic isolates from enteric Gram-negatives to fungi and Gram-positive organisms (46, 47). A large, multiple-center, double-blind, randomized controlled trial of meropenem vs. placebo is underway and might provide additional insight into the risks and benefits of systemic antimicrobial prophylaxis.

Prophylactic Antifungal Therapy. The practice of routine antibacterial prophylaxis for SAP is associated with an increasing number of reports of pancreatic necrosis infected with *Candida* species (24, 46, 48). These infections are associated with a higher mortality than bacterial infections, although this finding is not consistent across all studies (48–52). One observational study with historical controls suggested that prophylaxis or early preemptive treatment (in the setting of *Candida* colonization) with fluconazole might prevent fungal pancreatic infections (51). However, given the limited data available, there is insufficient evidence to support a recommendation of routine antifungal prophylaxis in patients with SAP.

Selective Decontamination of the Digestive Tract. Another strategy for infection prophylaxis is the use of selective decontamination of the digestive tract. Given that the source of pathogens is thought to be the gastrointestinal tract, this approach offers a sound biological rationale. In a multiple-center, randomized controlled trial, Luiten et al. (53) studied 102 patients with severe pancreatitis defined by an Imrie (Glasgow) score ≥3 and/or one or more peripancreatic fluid collections on CT. The treatment group received an oral and rectal regimen of colistin, amphotericin, and norfloxacin. In addition, intravenous cefotaxime was administered until Gram-negative bacteria were eliminated from oral and rectal cultures. The prophylaxis regimen was associated with a significant reduction in pancreatic infections, particularly those due to Gram-negative organisms (54). The number of patients requiring surgical intervention was no different, but the number of operations per patient was reduced in the treatment arm. Overall mortality and length of stay were not affected by the prophylaxis regimen, but *post hoc* analysis suggested a mortality benefit among patients with the highest severity scores. This study suggests that selective decontamination of the digestive tract is a promising modality worthy of further study, but the data are insufficient to warrant a specific recommendation.

Jury Recommendations

Recommendation 7. We recommend against the routine use of prophylactic systemic antibacterial or antifungal agents in patients with necrotizing pan-

creatitis in light of inconclusive evidence and divided expert opinion. Subsets of patients who benefit from prophylactic antibiotics may be identified by further investigation (level 2b evidence, grade B recommendation).

Recommendation 8. We recommend against the routine use of selective decontamination of the digestive tract in the management of necrotizing pancreatitis. Further investigation of this promising strategy in SAP is warranted.

QUESTION 3: WHAT IS THE OPTIMAL MODE AND TIMING OF NUTRITIONAL SUPPORT FOR THE PATIENT WITH SEVERE ACUTE PANCREATITIS?

Rationale

Patients with SAP are frequently hypercatabolic; timely institution of feeding is important if malnutrition is to be avoided or treated. Local complications of pancreatitis might cause upper gastrointestinal tract obstruction, making enteral nutrition problematic. There are also concerns that enteral nutrition may exacerbate the severity of SAP through further pancreatic stimulation and enzyme release. These considerations have led to a widespread reliance on parenteral nutrition as the main nutritional support modality in SAP.

A large body of evidence suggests that there are several potential benefits to enteral nutrition compared with parenteral nutrition including a reduction in microbial translocation, improvements in gut blood flow, and preservation of gut mucosal surface immunity. Furthermore, since altered gut microbiological flora and barrier function may contribute to the development of infected pancreatic necrosis, there are theoretical advantages to enteral feeding in SAP. Prior guidelines advocate jejunal rather than gastric administration of enteral nutrition in patients with acute pancreatitis to limit the potential for pancreatic stimulation, although this requires either endoscopic or radiological feeding tube placement (55).

Evidence

Role of Feeding in Exacerbation of SAP. In 20% of patients with resolving pancreatitis, abdominal symptoms recur following the introduction of oral intake (56). The likelihood of relapse appears greatest in patients with pancreatic necrosis or those with longer periods of pain before the reintroduction of enteral nutrition. Observations such as these have led to a belief that enteral nutrition might exacerbate SAP by stimulating the inflamed pancreas and that recovery could be hastened with pancreatic rest achieved through the cessation of enteral intake. Studies in healthy volunteers confirm that pancreatic secretions are stimulated by feeding directly into the stomach, duodenum, and jejunum (57). The effects on pancreatic secretion are mitigated when feeding occurs significantly beyond the ligament of Treitz (58).

The benefits of enteral nutrition vs. parenteral nutrition in the general critically ill population have encouraged an increasing number of investigators to use enteral nutrition as the preferred mode of nutritional support in SAP. Data from relatively small case series suggest that jejunal feeds are relatively well tolerated without adverse effects (59, 60). Pupelis and colleagues (61) randomized 60 patients undergoing laparotomy for management of peritonitis or SAP (n = 42 patients) to receive early jejunal feeding with a standard formula via a nasojejunal tube or intravenous fluids alone. Patients in the jejunal feeding group required fewer laparotomies and had more rapid recovery of bowel transit and a lower mortality rate (61). This is a very select population of patients with SAP, making extrapolation to all those with SAP difficult, but there was no suggestion of harm associated with the use of enteral nutrition.

The limited evidence suggests that jejunal feeding is not likely to be harmful in patients with SAP. However, placing a feeding tube into this position is often difficult or impractical, raising the question whether more proximal feeding is feasible. In a small case series without controls, Eatock et al. (62) found that nasogastric feeding was tolerated and did not appear to exacerbate pancreatitis. In a randomized controlled trial (n = 50) available only in abstract form, investigators reported similar CRP levels and pain scores after the introduction of nasogastric compared with nasojejunal feeds (63).

Enteral Nutrition Vs. Parenteral Nutrition. Eight trials have directly compared enteral nutrition and parenteral nutrition in patients with pancreatitis. Two of these studies demonstrated an attenuated inflammatory response in enterally fed patients as measured by resolution of systemic inflammatory response syndrome or reduction in circulating levels of CRP, tumor necrosis factor (TNF)-α, or IL-6 (64, 65). In all the remaining studies, the majority of which compared total parenteral nutrition with jejunal feeds, outcomes related to infections, organ failure, and mortality were either similar (66) or lower in enterally fed patients (67–71). Results of a meta-analysis of six trials in which patients (n = 263) were randomized to receive either nasojejunal enteral feeds or parenteral nutrition within 48 hrs of admission suggested significant benefit for those fed enterally (72). In this analysis, infection rates, rates of surgical intervention, and length of stay were significantly lower in this group, whereas a mortality benefit did not reach statistical significance.

These studies of enteral vs. parenteral nutrition were performed before the understanding of the merits of strict glycemic control for critically ill patients in reducing infectious complications and mortality (73). As parenteral nutrition is often accompanied by some degree of hyperglycemia, it is likely that the results of many of these studies are confounded by the higher glucose levels in the parenterally supported patients. Consequently, all critically ill patients with SAP, and particularly those receiving parenteral nutrition, should be managed using protocols for strict glycemic control.

Role of Glutamine Supplementation, Immunonutrition, or Probiotics. Experimental data in animal models of SAP suggest that glutamine-enriched parenteral nutrition reduces bacterial translocation (74, 75). The data available in patients with SAP are limited. De Beaux et al. (76) randomized 14 patients with SAP to receive either standard parenteral nutrition or isonitrogenous parenteral nutrition enriched with glutamine and reported less monocyte IL-8 production in the glutamine group. In a similar study, Ockenga et al. (77) reported an increase in albumin with a reduction in CRP levels in patients receiving glutamine-enriched parenteral nutrition. These studies, although small and inconclusive, are consistent with the larger body of literature suggesting that glutamine supplementation of parenteral nutrition is beneficial in the critically ill.

There is a single study of glutamine-enriched enteral nutrition in SAP (78). Sixteen patients with SAP were randomized to receive standard enteral nutrition or a glutamine-enriched "immune-

enhancing" enteral nutrition preparation. Patients in the latter group experienced significant elevations in serum immunoglobulin G and retinol binding protein and significantly more rapid recovery than those receiving standard enteral feeds.

The use of probiotics in SAP has also been studied. Treatment with specific fiber-fermenting lactobacillus and fermentable fiber is designed to modify potentially pathogenic bacterial overgrowth in the gut, reduce bacterial translocation, and improve immune function. This approach is conceptually sound given the mechanism by which it is believed the necrotic pancreas becomes infected, but the approach is supported by very limited experimental data (79). In the only available clinical trial evaluating this approach, 45 patients with pancreatitis were randomized to receive either the probiotic regimen delivered via a nasojejunal tube or a similar preparation in which the lactobacillus had been heat-inactivated (80). There were no differences in mortality rate, yet infected pancreatic necrosis was significantly less frequent in patients receiving the probiotic preparation. These results suggest that probiotics are worthy of further study in SAP, but current data are not strong enough support their use.

Jury Recommendations

Recommendation 9. We recommend that enteral nutrition be used in preference to parenteral nutrition in patients with SAP. Enteral nutrition should be initiated after initial resuscitation. The jejunal route should be used if possible (level 1a evidence, grade A recommendation).

Recommendation 10. We recommend parenteral nutrition only be used when attempts at enteral nutrition have failed after a 5- to 7-day trial (level 5 evidence, grade D recommendation).

Recommendation 11. We recommend that, when used, parenteral nutrition should be enriched with glutamine (level 5 evidence, grade D recommendation).

Recommendation 12. We recommend that patients, both enterally and parenterally fed, be managed with protocols ensuring strict glycemic control (level 1b evidence, grade A recommendation).

Recommendation 13. We recommend against the routine use of immune-enhancing enteral feed formulas or probiotics (level 5 evidence, grade D recommendation).

QUESTION 4: WHAT ARE THE INDICATIONS FOR SURGERY IN ACUTE PANCREATITIS AND WHAT IS THE OPTIMAL TIMING FOR INTERVENTION? WHAT ARE THE ROLES FOR LESS INVASIVE APPROACHES INCLUDING PERCUTANEOUS DRAINAGE AND LAPAROSCOPY?

Rationale

There are several incontrovertible indications for operative intervention in patients with SAP: suspected or confirmed intra-abdominal catastrophe including intestinal infarction or perforation, exsanguinating hemorrhage, or abdominal compartment syndrome. The patient with SAP must be assessed daily for deterioration with these possibilities in mind since timely operative intervention is essential.

In acute pancreatitis, the extensive inflammatory process in the retroperitoneum leads to the development of peripancreatic fluid collections and pancreatic necrosis (81). Routine operative or percutaneous drainage of the former is not necessary and may infect otherwise sterile tissues. Necrosis develops in approximately 10–20% of patients with acute pancreatitis and in a significantly greater proportion of those with severe clinical disease (16). Putatively, the presence of tissue necrosis further exacerbates or impairs the resolution of the local and systemic inflammatory response. Nonviable tissue also might be seeded by enteric organisms, resulting in infected pancreatic necrosis.

Necrosis in the context of severe clinical disease mandates repeated assessment of the need for intervention, which in many cases involves operative debridement of the pancreas and peripancreatic tissues. Later in the disease, the necrotic pancreas demarcates from viable tissue, leading to an easier and safer debridement with a greater likelihood of sparing pancreatic tissue. Over time, this area of necrosis undergoes liquefaction, resulting in a pancreatic abscess that might be more amenable to percutaneous, rather than operative drainage. Thus, the optimal type of the intervention depends on the clinical course of the patient and the precise timing of the intervention. In the review of evidence that follows, we use the terms debridement and/or drainage to reflect this continuum.

Evidence

Discrimination Between Sterile and Infected Pancreatic Necrosis. Severe acute pancreatitis represents one of the archetypical examples of a sterile inflammatory process leading to organ dysfunction (82). The clinical picture is often one of the systemic inflammatory response syndrome and can be indistinguishable from severe sepsis. The potential for development of infected pancreatic necrosis and/or extrapancreatic sites of infection further complicates the management of these patients. A deteriorating clinical picture or the development of new or progressive signs of infection suggests the need for microbial sampling as clinically indicated. The use of empirical antimicrobial therapy while awaiting the results of cultures should be based on the rate of clinical deterioration, with deescalation once results are available and cessation of antimicrobials in the absence of proven infection.

In the critically ill patient with evidence of systemic inflammatory response syndrome or sepsis, it is critical to discriminate between sterile and infected pancreatic necrosis. In this regard, CT is helpful, because the finding of retroperitoneal air is generally indicative of the presence of gas-forming organisms and thus infected necrosis. However, the presence of retroperitoneal air in patients with infected pancreatic necrosis is rare,

Table 2. Diagnostic utility of fine needle aspiration in patients with pancreatic necrosis and clinically suspected infection

	n	Prevalence of Infection, %	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Rau et al. (26)	94	37	83	93	88	90
Gerzof et al. (25)	60	46	100	100	100	100

rendering CT a relatively insensitive diagnostic test. In the absence of retroperitoneal gas, ultrasound- or CT-guided fine needle aspiration (FNA) of the necrotic tissue with Gram-negative stain and culture can discriminate between sterile and infected pancreatic necrosis. In two studies comparing FNA results with the reference standard of tissue cultures obtained following percutaneous or operative intervention among patients with a clinical suspicion of pancreatic infection (25, 26), the positive and negative predictive values of FNA approached or exceeded 90% (Table 2). However, many patients with negative cultures obtained through FNA who had a benign clinical course did not undergo operative or percutaneous intervention and were assumed to have sterile pancreatic necrosis. Acknowledging these limitations and the lack of a blinded, uniformly applied reference standard, the use of cultures obtained through FNA is recommended for the discrimination of sterile and infected pancreatic necrosis.

Management of Sterile Pancreatic Necrosis. Several case series describe the course of patients with SAP and sterile pancreatic necrosis treated without debridement (24, 83–85). From these data, it is clear that patients without evidence of pancreatic infection can be managed without operation with low rates of mortality and morbidity, even in the face of organ dysfunction. Clinical deterioration is not necessarily an indication for operative debridement. The significant risk of iatrogenic bowel injuries, hemorrhage, an open abdomen, and infecting sterile pancreatic necrosis should be considered and balanced against the low probability of a false-negative FNA before proceeding with operative debridement of sterile necrosis.

Management of Infected Pancreatic Necrosis. Several large cases series suggest that the diagnosis of infected pancreatic necrosis warrants consideration of a single or a series of interventions designed to achieve the goal of pancreatic debridement and/or drainage (83, 84, 86–90). There are no reports suggesting that antimicrobial therapy alone is adequate. Percutaneous drainage may be the only intervention necessary if the necrosis has demarcated and liquefied to an extent that the imaging characteristics are more consistent with a pancreatic abscess. Several case series suggest that necrosectomy should be delayed to achieve this end (89, 91, 92). These studies suggest a reduction in the relative risk of death of 37–69% in patients in whom necrosectomy is performed at least 2–3 wks after presentation. However, these results are all confounded by the indication for surgery, since most critically ill patients at highest risk of death undergo operation earlier in the course of their disease.

In a small clinical trial in an era of mandatory operative necrosectomy predating the use of FNA (93), 36 critically ill patients with pancreatic necrosis were randomized to early (<72 hrs) or delayed (>12 days) intervention. There was a trend toward lower mortality and a need for fewer debridements in patients assigned to delayed intervention who underwent an operation (27% vs. 56%). Importantly, a significant minority (20%) of those randomized to late necrosectomy improved without operation. There was an imbalance of randomization such that there was an excess of patients with more severe disease in the early intervention arm. Acknowledging the limitations of the available data, it seems likely that there is some benefit to delaying intervention if the clinical setting permits.

Access to the retroperitoneum via laparotomy or flank incision represents the conventional operative approach and is considered the gold standard for achieving retroperitoneal debridement and drainage. Repeated operative interventions are frequently necessary to accomplish an adequate debridement. There are recent reports of selected, relatively stable patients undergoing laparoscopic retroperitoneal debridement in conjunction with percutaneous drainage (94). Percutaneous drainage, with or without percutaneous debridement, might also offer advantages by minimizing the morbidity of laparotomy or temporizing until the retroperitoneal process has sufficiently demarcated such that operative management, when necessary, is facilitated (95). Case series of percutaneous interventions suggest that as many as 53–100% of highly selected patients might be spared an operative necrosectomy (96–99). Endoscopic transgastric debridement and drainage also have been reported and appear to reduce the need for operative debridement (100). These reports emphasize the need for repeated interventions and imaging studies over a prolonged period of days to weeks to accomplish debridement and retroperitoneal drainage with frequent reassessment of the clinical and radiological response. A delay in achieving definitive control of the infected necrotizing process is not prudent in deteriorating patients with multiple organ failure; thus, the clinical scenario must be considered before embarking on a course of minimally invasive operative or percutaneous interventions.

Jury Recommendations

Recommendation 14. We recommend sonographic- or CT-guided FNA with Gram stain and culture of pancreatic or peripancreatic tissue to discriminate between sterile and infected necrosis in patients with radiological evidence of pancreatic necrosis and clinical features consistent with infection (level 4 evidence, grade C recommendation).

Recommendation 15. We recommend against debridement and/or drainage in patients with sterile necrosis (level 4 evidence, grade C recommendation).

Recommendation 16. We recommend pancreatic debridement or drainage in patients with infected pancreatic necrosis and/or abscess confirmed by radiological evidence of gas or results of FNA. The gold standard for achieving this goal is open operative debridement. Minimally invasive techniques including laparoscopic and/or percutaneous interventions might be effective in selected patients (level 4 evidence, grade C recommendation).

Recommendation 17. We recommend that when possible, operative necrosectomy and/or drainage be delayed at least 2–3 wks to allow for demarcation of the necrotic pancreas. However, the clinical picture (severity and evolution) should be the primary determinant of the timing of intervention (level 4 evidence, grade C recommendation).

QUESTION 5: UNDER WHAT CIRCUMSTANCES SHOULD PATIENTS WITH GALLSTONE PANCREATITIS UNDERGO INTERVENTIONS FOR CLEARANCE OF THE BILE DUCT?

Rationale

Gallstones represent one of the most common etiologies of acute pancreatitis, accounting for 40–60% of all cases (101). All patients with pancreatitis should be evaluated for the presence of gallstones since this etiology has specific therapeutic implications. The mechanism by

which gallstones initiate the process of pancreatitis is by temporary or persistent obstruction of the sphincter of Oddi, leading to an increase in pancreatic ductal pressure and initiation of the inflammatory cascade through mechanisms that have not been fully elucidated (102–104). Given this purported mechanism, it has been postulated that prompt removal of the impacted stone would attenuate the inflammatory response. However, in most cases the obstruction is only transient; the stone has often spontaneously passed before attempts at removal. Nevertheless, this is the rationale for early biliary clearance in patients with gallstone pancreatitis.

Evidence

Identification of the Patient With Biliary Pancreatitis. Ultrasonography should be performed to assess for gallstones as a potential cause of pancreatitis, and the abdominal CT scan should be reviewed with this in mind. The sensitivity of ultrasound for identification of cholelithiasis in the presence of acute pancreatitis is approximately 85%, whereas the sensitivity for choledocholithiasis is <50% (105, 106). The limited sensitivity is likely due to the obscuration of the biliary tree by bowel gas. Recent reports suggest that endoscopic ultrasound offers significantly greater sensitivity and specificity for the identification of cholelithiasis and offers comparable sensitivity to ERCP for the identification of choledocholithiasis in patients with acute pancreatitis (105, 106). Serum biochemistry also might offer some predictive utility in differentiating biliary pancreatitis from other etiologies. For example, in one meta-analysis, a three-fold or greater increase in alanine aminotransferase had a positive predictive value of 95% in identifying pancreatitis with a biliary etiology (107). Timing of presentation will influence the predictive utility of diagnostic tests; thus, gallstones should be considered the presumptive etiology in those without an alternate diagnosis.

Timing of Biliary Clearance. For patients with severe acute gallstone pancreatitis, urgent biliary drainage and clearance of the bile duct must be considered. There is general consensus that patients with severe acute gallstone pancreatitis with obstructive jaundice should undergo urgent ERCP and, if gallstones are identified, endoscopic sphincterotomy should be performed. The role of urgent ERCP and endoscopic sphincterotomy in the setting of acute pancreatitis due to suspected or proven gallstones but without obstructive jaundice is more controversial. Four randomized trials have been conducted comparing early ERCP (defined as within 24 of admission or within 72 hrs symptom onset) to delayed or no biliary drainage. Three of the four trials have been published (108–110) and the fourth has been presented only in abstract form (111) (Table 3). In addition, a systematic review has been performed on all four trials (112). Two of the published trials suggested that patients benefit from early ERCP with reduced morbidity (108) or reduced mortality (113). The third trial showed no benefit of ERCP and a significant increase in the development of respiratory failure with a trend toward increased mortality (110). The fourth trial suggested a lower mortality in patients undergoing ERCP, but the limited information in the abstract precludes making any definitive conclusions. Taken together in the form of a meta-analysis, these trials suggested a significant reduction in mortality and morbidity in subjects receiving early ERCP (112). In two trials, subjects were stratified by severity of pancreatitis (108, 109). In both of these reports, the benefits were limited to those with severe disease. Importantly, the negative study by Folsch et al. (110) had the lowest proportion of patients with severe pancreatitis, emphasizing the importance of disease severity as an indicator of those likely to benefit from early ERCP.

Based on the preceding evidence, it is recommended that patients with severe acute gallstone pancreatitis undergo early ERCP and, if indicated, endoscopic sphincterotomy. This recommendation differs from prior consensus guidelines (4) because it takes into account the systematic review (112) and unpublished data (111) and because of the focus on this consensus document on critically ill patients with SAP.

Among patients who undergo ERCP with endoscopic sphincterotomy and have subsequently recovered from their critical illness, there are case series to suggest that cholecystectomy should be performed at the earliest possible time due to the relatively high risk of subsequent gallbladder symptoms (114–117). However, one case series suggests that older patients with successful endoscopic sphincterotomy may have a low incidence of further attacks of acute pancreatitis and may not need cholecystectomy (118).

Jury Recommendations

Recommendation 18. We recommend that gallstone pancreatitis be suspected in all patients with SAP and therefore all patients should have evaluation with sonography and biochemical tests (level 4 evidence, grade C recommendation).

Recommendation 19. In the setting of obstructive jaundice (or other evidence of acute obstruction of the biliary and/or pancreatic tract) and acute pancreatitis due to suspected or confirmed gallstones,

Table 3. Summary of randomized controlled trials comparing early ERCP within 72 hrs of presentation or 24 hrs of symptom onset in acute pancreatitis

Study	Intervention	n	Severe Pancreatitis, %	Gallstones Present, %	Complications, %	Mortality, %
Neoptolemos et al. (109)	None	59	44	85	34	8
	ERCP/ES	62			17[a]	2
Fan et al. (108)	None	98	42	66	29	9
	ERCP/ES	97			18	5
Folsch et al. (110)	None	112	14	46	51	6
	ERCP/ES	126			46	11
Nowak et al. (111)	None	102	Not reported	Not reported	36	13
	ERCP/ES	178			17[a]	2

ERCP, endoscopic retrograde cholangiopan creatography; ES, endoscopic sphincterotomy.
[a] $p < .05$.

we recommend that urgent ERCP should be performed within 72 hrs of onset of symptoms. If ERCP cannot be accomplished because it is not technically feasible or available, alternative methods of biliary drainage must be considered (level 5 evidence, grade D recommendation).

Recommendation 20. In the absence of obstructive jaundice, but with SAP due to suspected or confirmed gallstones, we recommend that ERCP be strongly considered within 72 hrs of onset of symptoms (level 1c evidence, grade B recommendation).

QUESTION 6: IS THERE A ROLE FOR THERAPY TARGETING THE INFLAMMATORY RESPONSE IN THE PATIENT WITH SEVERE ACUTE PANCREATITIS?

Rationale

It is commonly accepted that the physiologic response and many of the complications of SAP occur as a result of an uncontrolled inflammatory response. Potentially, there may be a therapeutic window between onset of symptoms and development of organ failure during which anti-inflammatory therapy may be successful. Recent therapeutic strategies have been directed toward interrupting the systemic inflammatory response to mitigate the development of organ dysfunction. The role of many inflammatory mediators in SAP has been investigated, including TNF-α, IL-1β, IL-6, IL-8, cytokine-induced neutrophil chemoattractant/growth-related oncogen-α, macrophage chemoattractant protein-1, platelet activating factor (PAF), IL-10, CD40L, C5a, intracellular adhesion molecule-1, substance P, and caspase-1 (119). Therapies targeting several of these mediators have been studied in animal models, but there are limited human data. Additionally, recombinant human activated protein C (rh-APC) has been shown in a large multiple-center trial to reduce mortality from severe sepsis (120), leading to the question of its role in SAP.

The host response during SAP is complex and varies during the course of disease. It has been shown that the inflammatory response is likely compartmentalized, with a local proinflammatory response and a systemic anti-inflammatory response (121). If the area of pancreatic necrosis becomes infected, additional host responses triggered by the microorganisms will further alter the inflammatory response. These variations make the targeting of specific mediators during the course of SAP difficult.

Evidence

TNF-α Blockade. TNF-α, derived predominantly from activated macrophages, is thought to be a key mediator in shock and is found in high circulating concentrations in acute pancreatitis (122). In animal models, administration of anti-TNF-α has been shown to attenuate pancreatic injury and reduce mortality (123). Although anti-TNF-α therapy is now a well-accepted treatment modality for both Crohn's disease and rheumatoid arthritis (124), there are no data available on its effectiveness in patients with SAP.

PAF Blockade. PAF, a potent activator of leukocytes and a chemoattractant, is present at high concentrations in the inflamed pancreas, and its systemic administration has been reported to induce pancreatitis in experimental models (125). Furthermore, PAF antagonists have been shown to attenuate the inflammatory response in animal models of pancreatitis (126). Lexipafant is the only PAF antagonist to be evaluated in clinical trials of patients with pancreatitis. Lexipafant appeared to lower the incidence of organ dysfunction in two relatively small trials; both were underpowered to assess mortality (127, 128). In a large European randomized controlled trial (n = 286), patients with SAP (Simplified Acute Physiology component of the Acute Physiology and Chronic Health Evaluation II) scores >6 within 72 hrs of symptom onset receiving lexipafant had lower organ failure scores and a trend toward lower mortality (129). The greatest benefit appeared when patients received treatment within 48 hrs of onset. In a subsequent randomized controlled study (Larvin, unpublished), 1,500 patients with SAP score >5 within 48 hrs of symptom onset were randomized to lexipafant or placebo. However, in contrast to prior trials, lexipafant had no effect on organ failure or mortality.

Modulation of the Coagulation Cascade. Recombinant human activated protein C has proven effectiveness in reducing mortality in patients with severe sepsis (120). Sixty-two patients with pancreatitis were enrolled in this trial; mortality was 24% in the placebo arm and 15% in those receiving rh-APC. All enrolled patients had a known or suspected source of infection, which is not the case in many patients with SAP. There are no studies of rh-APC in patients with SAP who do not have a documented source of infection. Given the absence of available data in SAP without infection, its use in this context is not recommended. Furthermore, even in patients with established infection, rh-APC should be used with caution due to the theoretical potential for significant retroperitoneal bleeding.

Jury Recommendations

Recommendation 21. General supportive measures used in the critically ill should be employed in patients with SAP, as these interventions might play an important role in attenuating the inflammatory response. Thus we recommend the use of early volume resuscitation (130) (level 1b, grade A recommendation) and lung-protective ventilation strategies for patients with acute lung injury (131) (level 1b evidence, grade A recommendation).

Recommendation 22. Once the presence of infection is documented or highly suspected and the patient with SAP meets the definition of severe sepsis (2), we recommend that management according to current sepsis guidelines be initiated (132, 133). These therapies include the use of rh-APC (120) (level 1b, grade A recommendation) and low-dose corticosteroids for vasopressor-dependent shock (134) (level 1b evidence, grade B recommendation). We recommend that careful consideration be used before the administration of rh-APC based on the theoretical but unproven concern of retroperitoneal hemorrhage (level 5 evidence, grade D recommendation).

Recommendation 23. We recommend against the use of other immune-modulating therapies targeting inflammatory mediators in SAP, such as anti-TNF-α therapy and lexipafant (level 1b, grade A recommendation for lexipafant; level 5 evidence, grade D recommendation for all other therapies).

OPPORTUNITIES FOR RESEARCH

Several aspects of care in patients with SAP require further evaluation in the form of well-designed clinical trials. Specifically, the benefits of prophylactic intravenous or oral antimicrobial therapy need to be further assessed. The merits of

enteral over parenteral nutrition require reevaluation in the context of strict glycemic control. The consequences of gastric vs. jejunal feeds should be tested in further randomized trials. Given the many uncertainties about the pathophysiology of pancreatitis and the promising value of novel therapies in animal models, we recommend that research continue in these areas. Application of anti-inflammatory mediator therapy in small human trials before progressing to larger international cooperative trials is paramount to the development of innovative treatment approaches. The formation of collaborative research networks that prioritize clinical questions and collaboratively conduct multiple-center studies would help to generate high-quality evidence in sufficiently powered studies to help improve the management of patients with SAP.

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