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Severe Acute Pancreatitis: A Review*

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Abstract

Background: Severe acute pancreatitis continues to be a difficult problem in clinical management. This paper provides a contemporary definition of the condition and explores the controversial issues that surround its diagnosis and management.
Methods: Review of pertinent English language literature.
Results: The use of various imaging techniques is discussed, with particular emphasis on the assessment of pancreatic necrosis and the evaluation of choledocholithiasis as a cause of the pancreatitis. Prophylactic antibiotics generally are discouraged and early and aggressive nutritional support is advocated. Delayed surgical intervention is recommended to avoid the severe consequences associated with prematurely early attempts at resection of the infarcted pancreas and adjacent retroperitoneal fat.
Conclusions: Better quality evidence, especially regarding the utility or lack thereof of antibiotic prophylaxis, is beginning to inform optimal management of patients with severe acute pancreatitis.

Acute pancreatitis is a challenge in clinical management. Whereas the majority of patients are discharged from the hospital within days, acute pancreatitis remains an unpredictable disease with a high mortality rate (10%–15%) among a defined proportion of those affected. Recent work has brought additional insights into the pathophysiology of the condition and new directions for treatment, with much of the new information challenging established dogma. This is of particular interest for intensivists or surgeons taking care of these critically ill patients.

This review highlights several of the controversies, with a particular focus on patients with severe acute pancreatitis (SAP). Consistent with international consensus guidelines, SAP is defined as pancreatitis in the context of acute organ dysfunction [1]. We hope to advance the implementation of new evidence into practice through a focus on risk assessment, infection prophylaxis, nutrition, issues of concern regarding biliary pancreatitis in particular, timing of surgery, and the surgical approach [2].

Identification of the Patient at Risk

To guide decision making about appropriate monitoring and resuscitation, it is crucial to identify the patients at risk for either local or systemic complications. Whereas many metrics have been used to estimate risk, they may be classified broadly into general or pancreatitis-specific (e.g., Glasgow or Ranson criteria). Review of the literature suggests that general measures of disease severity that quantify either the degree of acute physiologic derangement or organ dysfunction are more accurate at identifying patients who might benefit from monitoring in a critical care environment [3,4]. Apart from the general criteria for intensive care unit (ICU) admission, there is evidence to suggest, for example, that patients with a Acute Physiology and Chronic Health Evaluation (APACHE) II score > 8 points or a high hematocrit ($> 44\%$) should be admitted to a critical care unit (Table 1). These relatively simple criteria might help operationalize protocols for decision making. Biological markers (C-reactive protein, interleukin-6, trypsinogen activation peptide) have not been validated sufficiently for identifying patients at risk; however, of those studied, procalcitonin appears to offer the greatest promise, with concentrations of > 3.8 ng/mL predictive with high accuracy (sensitivity 79%, specificity 93%) of later organ dysfunction [5].

The extent of pancreatic necrosis has been used to identify patients at risk for the development of SAP. Whereas the extent of necrosis is accurate for the prediction of local complications, there also is a strong association between the presence of extensive necrosis ($> 50\%$) and greater degrees of organ dysfunction [6]. The extent of pancreatic necrosis is estimated by dynamic computed tomography (CT) using intravenous contrast medium. To lessen the risk of contrast nephropathy, it is crucial to assure that patients are resusci-

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Table 1. Predictors of Adverse Outcomes in Severe Acute Pancreatitis

Prediction of organ dysfunction
Acute Physiology and Chronic Health Evaluation II score ≥ 8
Multiple organ dysfunction score > 3 at 72 h
Sequential organ failure assessment score > 4 at 48 h
Ranson score ≥ 3 at 48 h
Modified Glasgow score ≥ 3
Prediction of local complications
Balthazar C, D, E CT grade at one week[a]
Hematocrit > 44%
Body mass index > 30

[a]C = Inflammation of pancreas or peripancreatic fat; D = single fluid collection; E = two or more fluid collections and/or retroperitoneal air.

tated appropriately with crystalloid prior to administration of contrast medium. Unfortunately, imaging might not provide a true picture of the extent of pancreatic necrosis at the time of presentation, and might be most informative 48–72 h later. Using the Balthazar classification scheme for estimating prognosis, the accuracy appears to be greatest at one week [7]. The Extra-Pancreatic Inflammation on CT (EPIC) score might provide prognostic information within the first 24 h, and focuses on the surrounding inflammation (e.g., pleural effusion, ascites, retroperitoneal and mesenteric inflammation) rather than necrosis and might predict systemic complications better [8]. It is important to weigh the benefits of early imaging with the risk of contrast-induced acute kidney injury. Ideally, imaging should be deferred until the yield is the highest. Earlier imaging is indicated, however, if the diagnosis is in doubt or there is a high suspicion of complications that might mandate surgical intervention.

Patients should be assessed for subtle degrees of organ dysfunction and physiologic assessment with the goal of identifying the need for admission to an ICU. Additionally, patients with limited reserve (e.g., elderly patients), obese patients, and those with hypovolemia should be admitted to a unit with the capacity for frequent monitoring, given their potential for rapid decompensation.

Role of Prophylactic Antibiotics

Infection frequently complicates the course of SAP and might manifest as infected pancreatic necrosis, pancreatic abscess, or an infected peripancreatic fluid collection. Infected pancreatic necrosis is the most challenging to manage. This complication occurs in 3–7% of all cases of pancreatitis, and is highly correlated with the extent of necrosis. In patients with necrosis involving more than one-half of the pancreas, the incidence of subsequent infection is as high as 40–70%. Infection typically occurs in the second or third week after presentation [9]. The underlying pathophysiology believed to be responsible is increased intestinal permeability, with translocation of bacteria and bacterial proliferation within necrotic tissue [10]. The predominant bacteria are enteric gram-negative bacilli such as *Escherichia coli* and *Klebsiella* spp., along with *Enterococcus* spp., but recently, the microbiologic pattern has shifted toward more resistant gram-negative bacilli, gram-positive cocci, and yeast, a reflection of exposure to broad-spectrum antimicrobial agents [11]. Given the morbidity associated with infection, many commentators have advocated prophylactic antimicrobial therapy in patients with necrosis to the point that this measure has been incorporated into routine practice. However, there is controversy over the risks and potential benefit.

The debate has been fueled by several randomized controlled trials, with differing methodologic quality, regimens, and outcome measures (Table 2) [12]. Recent meta-analyses have demonstrated a lack of benefit [13,14]. The most recent randomized controlled trial, which is of high methodologic quality, strengthens the observation that there is no benefit of prophylaxis [14]. Dellinger et al. assessed the utility of early antibiotic treatment with meropenem vs. placebo for severe acute necrotizing pancreatitis. The endpoints were pancreatic/peripancreatic infection within 42 days of presentation, the requirement for surgical intervention, and death. No statistical difference could be found for any endpoint, adding further to the argument for withholding of antimicrobial therapy until the presence of infection is proved.

As in other clinical settings, antimicrobial agents are best utilized when directed against a particular pathogen at a particular site. However, the diagnosis of infection in the context of critical illness with SAP is problematic. Many patients have fever and leukocytosis as a result of the retroperitoneal inflammation, which in most cases is sterile. Additionally, instrumentation (e.g., central venous catheters, endotracheal tubes) increases substantially the risk of infection outside the pancreatic bed. As a result, it is crucial to identify using fine needle aspiration (FNA) whether pancreatic necrosis might be causal in the manifestations of sepsis. Whereas many patients with pancreatic necrosis have risk factors for fungal sepsis, there are no data supporting routine administration of antifungal prophylaxis [15].

Antimicrobial prophylaxis using non-absorbable, oral antibiotics (selective digestive decontamination; SDD) has been examined given the underlying pathophysiology of bacterial translocation. Luiten et al. showed a reduction in the risk of infected pancreatic necrosis and a lower mortality rate in patients receiving SDD in a randomized controlled trial [16]. In a report by Sawa et al. [17], the combination of SDD and enteral nutrition was associated with lower rates of organ dysfunction (70% vs. 59%) and death (40% vs. 28%).

In summary, antimicrobial agents should be restricted to patients with proved infection. The sole exception is a decompensating patient in whom infection is strongly suspected but not yet proved. Whereas there is some evidence

Table 2. Randomized Controlled Trials of Efficacy of Antibiotic Prophylaxis

Study	*Blinded?*	*Results in favor of prophylaxis*	*Comments*
Pederzoli et al., 1993	No	Significantly lower rate of pancreatic infection	No difference in other outcomes[a]
Saino et al., 1995	No	Lower mortality rate	Excess early deaths in control group, but unbalanced randomization
Delcenserie et al., 1996	No	Lower rate of pancreatic infection	Underpowered
Schwarz et al., 1997	No	Tendency toward benefit	Underpowered
Nordback et al., 2001	No	Less organ failure, fewer pancreatic infections	>40% of control patients converted to imipenem
Isenmann et al., 2004	Double[b]	No difference in any outcome[c]	Good method; few patients with necrosis
Dellinger et al., 2007	Double[b]	No difference in any outcome[d]	—

[a]Endpoints were reduced rate of pancreatic infection, number of operation, organ failure, or death.
[b]Tested against placebo.
[c]Endpoints were rate of infected pancreatic necrosis, systemic complications, or death.
[d]Endpoints were pancreatic or peripancreatic infection, death, or requirement for surgical intervention.

of the utility of SDD, the strength of the evidence is insufficient to incorporate this modality into routine practice.

Nutritional Support

Conventional dogma dictated that "total rest" of the pancreas was necessary during the support of patients with SAP. The rationale was that enteral nutrition (EN) would stimulate the secretion of pancreatic enzymes that might aggravate the retroperitoneal inflammation further. However, several lines of evidence suggest that EN is without harm and might even be beneficial, especially if delivered directly into the jejunum via feeding tube [18]. A prospective, non-randomized six-year sequential study (three years of use of parenteral nutrition, then three years of enteral nutrition) demonstrated lower rates of organ failure, infected necrosis, and mortality for those fed enterally [19]. These data are further supported by a randomized, controlled trial comparing parenteral with enteral nutrition in SAP, with clear evidence of a mortality benefit among those receiving EN [20]. A meta-analysis preceding this report provided further confirmation of the superiority of EN over parenteral nutrition (PN), with an attenuated inflammatory response, fewer infectious complications, fewer surgical interventions, shorter hospital stay, and better survival [21].

Whereas there is a suggestion of benefit with jejunal compared with intragastric feeding, the evidence evaluating the utility and safety of intragastric feeding is less clear. It is clear that jejunal feeding results in less exocrine stimulation than does gastric feeding. One report suggests an increase in complications among those receiving gastric compared with jejunal feeding; however, these complications were relatively minor (e.g., atelectasis) [22]. A small randomized, controlled trial suggested good tolerance and equivalent outcomes in those receiving nasogastric and nasojejunal feeding [23].

Taken together, these data suggest that early EN is safe and indeed preferable to PN. The evidence is strongest for nutrition delivered into the jejunum. If jejunal access is not possible, intragastric feeding should be considered. If enteral feeding is not tolerated after five days, PN should be used to meet caloric and protein requirements [24].

Biliary Pancreatitis and Utility of Endoscopic Retrograde Cholangiopancreatography

Gallstones play a suspected causal role in 40–60% of all cases of pancreatitis. Although the precise mechanism whereby stones cause pancreatitis is not understood despite more than a century of study, it generally is believed that stones obstruct the pancreatic duct of those patients with a common biliopancreatic duct channel within the ampulla of Vater. Ductal obstruction usually is transient, with the stone passing spontaneously within 48 h in the majority of cases [25]. High pancreatic ductal pressure and extravasation of pancreatic juice with subsequent activation of proteolytic enzymes begins the process of autodigestion of the pancreas and surrounding tissues. Digestive enzyme release is amplified with lysis of acinar cells, leading to a vicious cycle of inflammation and necrosis.

Given the pathogenesis of biliary pancreatitis, the use of endoscopic retrograde cholangiopancreatography (ERCP) has been considered for decompression of the pancreatic ductal system through the removal of retained stones. However, it is crucial to identify those patients in whom an impacted gallstone is likely to be responsible for the inflammation. Unfortunately, abdominal ultrasonography has limited sensitivity for detecting gallstones in the context of acute pancreatitis: 80% for detecting cholelithiasis and only 50% for identification of choledocholithiasis. Magnetic resonance cholangiopancreatography (MRCP), a non-invasive radiologic investigation, appears to be as accurate as ERCP for the identification of choledocholithiasis and bile duct obstruction, while avoiding the potential complications of ERCP. However, the role of MRCP in those with SAP, and the cumbersome logistics of performing MRI on a critically ill, unstable patient preclude its routine use in this context [26].

Endoscopic retrograde cholangiopancreatography with ductal clearance is clearly indicated in acute pancreatitis when there is evidence of biliary obstruction (e.g., hyper-

bilirubinemia) or cholangitis. However, absent these indications, its role is less clear, with several experts arguing that a great proportion of stones will pass spontaneously and that ERCP-related complications might outweigh any benefits.

Two randomized trials [27,28] suggested benefit from early ERCP only in those patients with predicted SAP, whereas a third trial reported no benefit [29]. However, a systematic review confirmed a lower rate of complications among patients with severe disease [30]. More recently, a randomized, controlled trial demonstrated the superiority of a strategy leading to early ERCP ($\leq$ 48 h) in patients with persistent ductal obstruction evidenced by pain, quality of nasogastric aspirate, and serum bilirubin concentration [31].

The use of endoscopic ultrasonography, coupled with ERCP when choledocholithiasis is detected, might allow more appropriate selection of patients who need a sphincterotomy, and may prevent further ERCP-related morbidity [32].

Indications for Surgery

There are several clear indications for operative intervention in the context of SAP. Patients with an acute abdomen in whom the diagnosis is unclear or those who develop a catastrophic complication of pancreatitis (e.g., hemorrhage, bowel infarction, or perforation) will benefit from surgical management. Similarly, those patients who develop abdominal compartment syndrome may derive substantial improvement after abdominal decompression.

More controversial is the utility of surgical intervention in those with SAP without any of the above indications. Sufficient evidence exists to argue against a role for operative debridement in patients with sterile pancreatic necrosis, as most patients will incur all the risks of operation (open abdomen, fistula, hemorrhage, infection) without any potential for benefit [33]. Thus, the focus should be directed first to identifying patients with infected pancreatic necrosis. Whereas attempts to differentiate patients with and without infected pancreatic necrosis using biological markers such as C-reactive protein or procalcitonin have been described, CT-guided fine needle aspiration (FNA) of the area of necrosis remains the gold standard. Aspiration, guided by ultrasound or CT scan, is a safe and reliable investigative tool to look for evidence of infected necrosis or a collection of pus [33–35]. Gram stain and culture of the aspirate is accurate for the diagnosis of infection, with both a positive predictive value and negative predictive value around 90% and most inaccuracies occurring during the first week [34]. It is important that the intervention be limited to aspiration, as attempts to drain what might be a sterile collection may lead to bacterial contamination and subsequent infection [36]. In case of suspected infected necrosis, FNA should be performed before any antibiotic treatment is instituted. Once the diagnosis has been made, the results of cultures can direct antimicrobial therapy.

Once infected necrosis has been proved, the next area of controversy is the means and timing of intervention [37]. There is little doubt that antimicrobial therapy alone is associated with a high mortality rate [38]. However, there are some advantages to temporizing until the area of infected necrosis is sufficiently demarcated that debridement is facilitated. When intervention can be delayed, the process of sequestration and demarcation is accompanied by liquefaction such that the "necrosis" becomes a pancreatic abscess that might be amenable to percutaneous rather than operative drainage, or perhaps to laparoscopy rather than celiotomy.

Historical series suggest that early surgical intervention often results in unnecessary procedures, with an increase in the number of deaths [39]. One randomized controlled trial comparing early (48–72 h) to late ($>$ 12 days) intervention showed a trend toward a better survival rate with delayed intervention; interestingly, 20% of the patients randomized to late surgery improved without operation [40]. A recent abstract reported a clear association between death and the timing of surgery after the onset of symptoms, especially if surgery was postponed beyond 30 days [41]. The clinical status of the patient will dictate whether temporizing is prudent, but a deteriorating patient will require intervention irrespective of clinical complexity, even in the presence of sterile necrosis. The extension of the necrosis ($>$ 50%) and development or worsening of multiple organ dysfunction syndrome are strong arguments favoring operative intervention in the presence of clinical deterioration [42].

The conventional surgical approach typically involves a midline laparotomy and often necessitates open-abdomen management with some form of temporary closure, particularly if performed early in the course of disease. However, many surgeons are advocating less extensive procedures in the form of a minimally invasive retroperitoneal pancreatic necrosectomy [43] or video-assisted retroperitoneal debridement (VARD) through flank incisions [44]. Whereas it is difficult to establish if one technique offers benefit over another, these alternate approaches argue against a "one size fits all" strategy, and emphasize the importance of careful patient selection. One limitation of these minimally invasive debridement techniques is the observation that a higher reoperation rate may result, with potentially greater morbidity than is seen with open surgery [45]. The ability to delay interventions to allow better demarcation and liquefaction of pancreatic necrosis offers greater opportunity for success of minimally invasive techniques, and might become the standard of care in the future. Investigators are now comparing the step-up approach with standard open necrosectomy. This approach involves an attempt at percutaneous drainage, followed by VARD, among those who fail percutaneous drainage [46], prior to celiotomy.

Conclusions

Severe acute pancreatitis carries with it substantial morbidity and mortality rates. Several changes in surgical and ICU management have reduced the mortality rate in recent years, many of which have challenged surgical dogma. Less antimicrobial use, early enteral feeding, and delayed operation are all counterintuitive, but appear to offer benefit in this critically ill patient population.

Author Disclosure Statement

No competing financial interests exist.

References

1. Bradley EL 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11–13, 1992. Arch Surg 1993;128:586–590.

2. Nathens AB, Curtis JR, Beale RJ, et al. Management of the critically ill patient with severe acute pancreatitis. Crit Care Med 2004;32:2524–2536.
3. Buter A, Imrie CW, Carter CR, et al. Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis. Br J Surg 2002;89:298–302.
4. Rau BM, Bothe A, Kron M, et al. Role of early multisystem organ failure as major risk factor for pancreatic infections and death in severe acute pancreatitis. Clin Gastroenterol Hepatol 2006;4:1053–1061.
5. Rau BM, Kemppainen EA, Gumbs AA, et al. Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): A prospective international multicenter study. Ann Surg 2007;245: 745–754.
6. Karimgani I, Porter KA, Langevin RE, et al. Prognostic factors in sterile pancreatic necrosis. Gastroenterology 1992;103: 1636–1640.
7. Balthazar EJ, Ranson JH, Naidich DP, et al. Acute pancreatitis: Prognostic value of CT. Radiology 1985;156:767–772.
8. De Waele JJ, Delrue L, Hoste EA, et al. Extrapancreatic inflammation on abdominal computed tomography as an early predictor of disease severity in acute pancreatitis: Evaluation of a new scoring system. Pancreas 2007;34:185–190.
9. Beger HG, Bittner R, Block S, et al. Bacterial contamination of pancreatic necrosis: A prospective clinical study. Gastroenterology 1986;91:433–438.
10. Ammori BJ. Role of the gut in the course of severe acute pancreatitis. Pancreas 2003;26:122–129.
11. Gloor B, Muller CA, Worni M, et al. Pancreatic infection in severe pancreatitis: The role of fungus and multiresistant organisms. Arch Surg 2001;136:592–596.
12. de Vries AC, Besselink MG, Buskens E, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: Relationship between methodological quality and outcome. Pancreatology 2007;7:531–538.
13. Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg 2006;93:674–684.
14. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: A randomized, double-blind, placebo-controlled study. Ann Surg 2007;245:674–683.
15. Eggimann P, Jamdar S, Siriwardena AK. Pro/con debate: Antifungal prophylaxis is important to prevent fungal infection in patients with acute necrotizing pancreatitis receiving broad-spectrum antibiotics. Crit Care 2006;10:229–233.
16. Luiten EJ, Hop WC, Lange JF, et al. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995;222:57–65.
17. Sawa H, Ueda T, Takeyama Y, et al. Treatment outcome of selective digestive decontamination and enteral nutrition in patients with severe acute pancreatitis. J Hepatobiliary Pancreat Surg 2007;14:503–508.
18. Windsor AC, Kanwar S, Li AG, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. Gut 1998;42:431–435.
19. Targarona Modena J, Barreda Cevasco L, Arroyo Basto C, et al. Total enteral nutrition as prophylactic therapy for pancreatic necrosis infection in severe acute pancreatitis. Pancreatology 2006;6:58–64.
20. Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. Dig Surg 2006;23:336–344.
21. Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 2004;328:1407–1410.
22. Eckerwall GE, Axelsson JB, Andersson RG. Early nasogastric feeding in predicted severe acute pancreatitis: A clinical, randomized study. Ann Surg 2006;244:959–965.
23. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol 2005;100:432–439.
24. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 2005;24:502–509.
25. Winslet MC, Imray C, Neoptolemos JP. Biliary acute pancreatitis. Hepatogastroenterology 1991;38:120–123
26. Makary MA, Duncan MD, Harmon JW, et al. The role of magnetic resonance cholangiography in the management of patients with gallstone pancreatitis. Ann Surg 2005;241:119–124.
27. Fan ST, Lai EC, Mok FP, et al. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med 1993;328:228–232.
28. Neoptolemos JP, Carr-Locke DL, London NJ, et al. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979–983.
29. Folsch UR, Nitsche R, Ludtke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. N Engl J Med 1997;336:237–242.
30. Ayub K, Imada R, Slavin J. Endoscopic retrograde cholangiopancreatography in gallstone-associated acute pancreatitis. Cochrane Database Syst Rev 2004:CD003630.
31. Acosta JM, Katkhouda N, Debian KA, et al. Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: A prospective randomized clinical trial. Ann Surg 2006;243:33–40.
32. Liu CL, Fan ST, Lo CM, et al. Comparison of early endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the management of acute biliary pancreatitis: A prospective randomized study. Clin Gastroenterol Hepatol 2005;3:1238–1244.
33. Buchler MW, Gloor B, Muller CA, et al. Acute necrotizing pancreatitis: Treatment strategy according to the status of infection. Ann Surg 2000;232:619–626.
34. Rau B, Pralle U, Mayer JM, et al. Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis. Br J Surg 1998;85:179–184.
35. Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology 1987;93:1315–1320.
36. Walser EM, Nealon WH, Marroquin S, et al. Sterile fluid collections in acute pancreatitis: Catheter drainage versus simple aspiration. Cardiovasc Intervent Radiol 2006;29:102–107.
37. Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2002;2:565–573.
38. Widdison AL, Karanjia ND. Pancreatic infection complicating acute pancreatitis. Br J Surg 1993;80:148–154.
39. Hartwig W, Maksan SM, Foitzik T, et al. Reduction in mortality with delayed surgical therapy of severe pancreatitis. J Gastrointest Surg 2002;6:481–487.

40. Mier J, Leon EL, Castillo A, et al. Early versus late necrosectomy in severe necrotizing pancreatitis. Am J Surg 1997; 173:71–75.
41. Besselink MGH, Schoenmaeckers EJP, Buskens E, et al. timing of surgical intervention in necrotizing pancreatitis: A 10 year consecutive case series and systematic review. Pancreatology 2006;6:395–396.
42. Rau B, Pralle U, Uhl W, et al. Management of sterile necrosis in instances of severe acute pancreatitis. J Am Coll Surg 1995;181:279–288.
43. Connor S, Ghaneh P, Raraty M, et al. Minimally invasive retroperitoneal pancreatic necrosectomy. Dig Surg 2003;20: 270–277.
44. Horvath KD, Kao LS, Wherry KL, et al. A technique for laparoscopic-assisted percutaneous drainage of infected pancreatic necrosis and pancreatic abscess. Surg Endosc 2001;15: 1221–1225.
45. Connor S, Raraty MG, Howes N, et al. Surgery in the treatment of acute pancreatitis: Minimal access pancreatic necrosectomy. Scand J Surg 2005;94:135–142.
46. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al. Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): Design and rationale of a randomised controlled multicenter trial [ISRCTN38327949]. BMC Surg 2006; 6:6–10.

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