CHEST Postgraduate Education Corner

CONTEMPORARY REVIEWS IN CRITICAL CARE MEDICINE

Acute Pancreatitis and Critical Illness

A Pancreatic Tale of Hypoperfusion and Inflammation

Sarah E. Greer, MD, MPH; and Kenneth W. Burchard, MD

Since it was first widely recognized at the end of the 19th century, acute pancreatitis has proven a formidable clinical challenge, frequently resulting in management within critical care settings. Because the early assessment of severity is difficult, the recognition of severe acute pancreatitis (SAP) and the implementation of critical care treatment precepts often are delayed. Although different management strategies for life-threatening features of SAP have been debated for decades, there has been little recent reduction in mortality rates, which can be as high as 30%. This article discusses severity designation at the time of diagnosis, reviews the pathophysiologic mechanisms so well characterized by the noxious combination of severe systemic inflammation and hypoperfusion, and provides a management algorithm that parallels current critical care strategies. ***(CHEST 2009; 136:1413–1419)***

Abbreviations: ACS = abdominal compartment syndrome; APACHE = acute physiology and chronic health evaluation; IAP = intraabdominal pressure; SAP = severe acute pancreatitis

Acute pancreatitis is an inflammation of the pancreas that is characterized by clinical features that include abdominal pain with radiation to the back, nausea, and vomiting. Patients are classified with severe acute pancreatitis (SAP) if they display organ failure as manifested by shock, pulmonary insufficiency, renal failure, or GI bleeding; local complications such as necrosis, pseudocyst, or abscess; or other defined criteria.[1,2]

Critical care services are most appropriate for patients with SAP, but delineating the patients in whom severe disease develops and, therefore, might benefit from critical care strategies that limit the progression of pancreatic inflammation is challenging. Unfortunately, no highly sensitive and specific test or system exists that can accurately measure prognosis at the time of hospital admission.

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Affiliations: From the Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH.

Correspondence to: Kenneth W. Burchard, MD, Dartmouth-Hitchcock Medical Center, Department of General Surgery, One Medical Center Dr, Lebanon, NH 03756; e-mail: Kenneth.W.Burchard@Hitchcock.org

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Determination of Severity

Ranson et al[3] originally described a scoring system to determine the severity of pancreatitis, which has been widely used since 1974. However, a metaanalysis[4] of studies using the criteria Ranson et al[3] reported a sensitivity for predicting SAP of 75%, a specificity of 77%, a positive predictive value of 49%, and a negative predictive value of 91%. A major drawback of this system, as well as the Glasgow criteria,[5] is that they can only be determined after 48 h, which is well past the critical window with respect to early resuscitation and improvement of pancreatic perfusion and microcirculatory defects. The Atlanta criteria[2] define severe disease in patients with acute pancreatitis but have not been applied consistently either in the clinical setting or in studies. The acute physiology and chronic health evaluation (APACHE) II score also is widely used and has the advantage of being calculated at the time of diagnosis or hospital admission. Still, the sensitivity of an APACHE II score of > 7 to predict SAP was found[4] to be 65%, with a specificity of 76%, a positive

predictive value of 43%, and a negative predictive value of 89%. Clinician judgment that takes into account multiple factors has a sensitivity of predicting severe disease at hospital admission of 39%, a specificity of 93%, a positive predictive value of 66%, and a negative predictive value of 82%.[4]

The clinical diagnosis of pancreatitis typically is confirmed with serum amylase and lipase levels. However, the magnitude of elevation of these levels does not correlate well with the severity of pancreatitis.[6,7] Other biomarkers, such as levels of C-reactive protein, neutrophil elastase, interleukin-1, interleukin-6, procalcitonin, and α_1-antitrypsin, tend to correlate better with disease severity[7–9] but have been of limited clinical utility in triaging patients or predicting outcome. C-reactive protein values at hospital admission are not predictive of outcome,[8] but at 48 h they have sensitivity and specificity values that are similar to those using the Ranson et al[3] criteria and APACHE II scores.[4,7]

The inference from all these studies is that early severity prediction is difficult and often inaccurate; thus, all patients with pancreatitis initially should be managed as if the disease is severe.[10] Table 1 lists clinical variables that should raise the suspicion that pancreatitis is severe.

Imaging

The detection of pancreatic necrosis is achieved most commonly with contrast-enhanced CT scanning[11,12] after circulatory resuscitation, and, typically, at least 48 to 72 h after diagnosis, with the Balthazar score used to define the extent of necrosis based on enlargement, inhomogeneities of attenuation, and the presence of fluid collections.[13–15] The CT severity index then can be calculated, which has been shown[16] to correlate with prolonged hospital stay, the need for necrosectomy, and death. A new scoring system, the extra-pancreatic inflammation on CT scan, is based on the presence of pleural effusion, ascites, and retroperitoneal fluid collection, and has been shown[17] to be superior to both the Balthazar score and the CT severity index in predicting outcome. An extra-pancreatic inflammation on CT score of ≥ 4 had 100% sensitivity and 70.8% specificity for predicting SAP. Gadolinium-enhanced MRI has been shown to be equivalent to contrast-enhanced CT scanning for assessing the severity of acute pancreatitis and the presence of necrosis,[18–20] but Gadolinium-enhanced MRI is more difficult to perform than CT scanning and, therefore, is used less frequently.

Pathophysiology of Systemic Manifestations

The principal systemic complications from SAP relate to alterations in circulation, pulmonary physiology, and renal function.

Circulatory Threats

Hypoperfusion from pancreatitis can result from mechanisms that are very similar to those of any severe inflammatory state, including sepsis.[21] Therefore, it is not unreasonable to consider parameters recently used[22–24] to evaluate sepsis resuscitation as also being useful for evaluating SAP (early goal-directed therapy and the assessment of adrenocortical function), with an understanding that more rapid restoration of the circulation is likely to be an advantage. Table 2 lists the common mechanisms for circulatory threat from pancreatitis.

In keeping with the principal pathophysiologic processes engendered by SAP and the dictum that "inflammation begets hypoperfusion, and hypoperfusion begets inflammation," early critical care management focuses on the attainment of an adequate circulation while supporting other vital organ function. Because hypovolemia is the principal etiology of hypoperfusion in patients with SAP, the rapid restoration of intravascular volume must be the first

Table 1—*Clinical Clues That Pancreatitis May Be Severe*

Description
Hypotension
Oxygen saturation < 90% breathing room air
Generalized peritonitis
Elevated hemoglobin level
Elevated BUN/creatinine level
Metabolic acidosis
Decreased ionized calcium level
Elevated lactate dehydrogenase level

Table 2—*Mechanisms of Circulatory Threat in SAP*

Description
Plasma volume depletion
Exudation of plasma at site of inflammation and general abdominal cavity
Exudation of plasma at sites of systemic capillary alterations
Depletion of interstitial and plasma volume from intestinal fluid accumulation
Migration of interstitial fluid into the intracellular space
Blood loss from hemorrhage
Myocardial depression
ACS

therapeutic strategy.[25,26] Isotonic crystalloid should be administered according to resuscitation principles, rather than to maintenance volumes, and repeated measures of patient response (BP, pulse, respiratory status, mental status, urine output through a bladder catheter, repetitive blood tests) should be obtained. Adequate intravascular volume resuscitation improves the perfusion of pancreatic tissue and can mitigate the progression of pancreatitis, reducing its associated morbidity and mortality.[27–29] However, volume replacement targets have not been studied in prospective randomized trials.[30]

One prospective cohort study[31] has reported that a hospital admission hematocrit of $>44\%$ and its failure to decrease within 24 h were good indicators of pancreatic necrosis and predictors of organ failure. In a separate retrospective analysis,[32] necrotizing pancreatitis developed in all patients in whom hemoconcentration worsened within 24 h of hospital admission, suggesting that early, aggressive expansion and maintenance of plasma volume, as evidenced by reaching the patient's usual hematocrit, are imperative. More recent evidence,[33] using a technique to measure intrathoracic blood volume index, confirmed the specificity of an elevated hematocrit as an index of plasma volume depletion in patients with necrotizing pancreatitis. Unfortunately, neither a normal hematocrit nor a normal central venous pressure proved to be sufficiently sensitive to rule out deficits in plasma volume.

Hemodynamic dysfunction in SAP patients has been shown[25,26] to result principally from decreased preload rather than from intrinsic cardiac dysfunction, but myocardial depression is possible. Myocardial dysfunction from depressants in the bloodstream can be present even in younger patients with previously normal hearts but is more evident in patients with underlying heart disease. Distinguishing between cardiogenic and hypovolemic hypoperfusion can be difficult but is extremely important because the therapeutic strategies for each are distinctly different. Using such surrogates for hemodynamic assessment as body weight, input and output calculations, pulmonary function, and chest radiographs can be particularly misleading in patients with any severe systemic inflammation condition, and these difficulties only are augmented in SAP patients, in whom even measures such as central venous pressure can be confounded by increased thoracic and abdominal pressure. Other techniques to evaluate cardiac performance (ECG or measurement of cardiac output) may be necessary to provide an accurate hemodynamic diagnosis to guide therapeutic decisions, such as the use of inotropic drugs.

Pulmonary Failure

SAP is almost universally associated with pulmonary dysfunction, which is often manifested as a decreased PaO_2 in the first hours to days of illness without radiographic abnormalities.[34] Later, alterations such as atelectasis and pleural effusions may become apparent, but the principal threat to pulmonary function is ARDS from systemic inflammation and the associated endocrine, paracrine, and autocrine molecular mechanisms.[34,35] Recognition that the pathophysiologic mechanisms responsible for the poor oxygenation in ARDS patients are distinctly different from those characteristic in hydrostatic pulmonary edema (*ie*, congestive heart failure) is essential to the appropriate early management of SAP.[36]

ARDS respiratory failure that is not cardiac in origin develops in at least one-third of patients with SAP.[35] Early management includes support of the lungs with current ventilator modalities and an understanding that the respiratory alterations are driven by the inflammatory illness (SAP) and not by the fluid used to resuscitate the circulation.[35] Depleting intravascular volume for the pulmonary alterations in the midst of circulatory embarrassment will not ameliorate the underlying condition unless true cardiogenic hypoperfusion has been identified. After restoration of the circulation, a more cautious fluid management strategy may improve short-term lung recovery.[36,37]

Renal Failure

Table 3 lists the potential causes of acute renal failure in patients with pancreatitis. In the setting of SAP, acute renal failure is associated with a mortality risk as high as 50%.[38]

Renal impairment is first subject to the distinction between prerenal and renal etiologies. Prerenal oliguria and increasing creatinine concentrations are managed by the enhancement of global circulation. Renal injury sufficient to cause acute tubular necrosis also is managed by assuring that the circulation meets global oxygen demand as well as by avoiding renal toxins (*eg*, IV contrast agents).

Table 3—*Etiologies of Acute Renal Failure in SAP*

Description
Global hypoperfusion
Microcirculatory hypoperfusion
Inflammatory mediators
ACS
Rhabdomyolysis

Prevention of Infection

The emergence of infected pancreatic necrosis from both local and systemic processes, including pseudoaneurysm formation and massive hemorrhage, as well as from recurrent or progressive multisystem organ failure, can be lethal. A necrotic pancreas is at high risk for infection, usually from organisms contained in the nearby bacterial and fungal reservoirs of the colon and the acid-suppressed stomach. This typically happens without a gross opening in the GI tract, presumably through translocation, and can reflect the microflora alterations (*eg*, prevalence of Enterococcus, coagulase-negative Staphylococcus, hospital Gram-negative flora, and Candida species) associated with a critical care setting.[39]

Antibiotic Prophylaxis

The infection of necrotic pancreatic tissue represents a morbid and often fatal late complication of acute pancreatitis. Because outcomes are significantly worse,[40] many efforts[23,41–46] have focused on reducing the rates of infection either through the use of prophylactic antibiotics or by selective digestive decontamination.[47] Early studies[48,49] used antibiotic regimens that later were shown to have poor penetration into infected pancreatic tissue. Antibiotic prophylaxis has been a controversial topic and the subject of several metaanalyses.[50–54] The Cochrane Collaboration[54] examined the effectiveness and safety of therapy with prophylactic antibiotics in patients with acute pancreatitis complicated by pancreatic necrosis and noted an association with significantly decreased mortality but not with infected pancreatic necrosis. However, previous metaanalyses did not include the two most recent studies[23,46] that were double blinded, neither of which showed any benefit for prophylactic antibiotics with respect to development of infected pancreatic necrosis, requirement for surgical intervention, or mortality.

Enteral Feeding

Although it has long been part of the traditional approach to the treatment of acute pancreatitis, bowel rest, in an effort to reduce stimulation of exocrine pancreatic secretion, has not shown improved outcomes. In fact, enteral nutrition offers several theoretical advantages over total parenteral nutrition, including maintaining the integrity of the GI barrier and preventing bacterial overgrowth and translocation. It also limits complications associated with total parenteral nutrition, such as hyperglycemia and catheter sepsis. When delivered into the mid-jejunum or distal jejunum, elemental enteral nutrition does not stimulate pancreatic secretion.[55,56] A metaanalysis[57] of six randomized trials of total parenteral nutrition compared with enteral nutrition delivered by a nasojejunal tube placed beyond the ligament of Treitz noted an overall reduction in the number of infections in patients receiving enteral nutrition and a reduction in the need for pancreatic surgery, but no reduction in organ failure or mortality.

Indications for Intervention

Infected Pancreatic Necrosis

When the infection of pancreatic necrosis occurs, intervention that includes surgical debridement and image-guided drainage is indicated.[40] Infection should be suspected based on clinical findings of fever, leukocytosis, and hypotension, usually 1 to 2 weeks after diagnosis.[58] Confirmation of infected peripancreatic material should be performed using fine-needle aspiration of pancreatic tissue and necrosis or fluid collections.[40] Infected necrosis demands debridement, with the probability that multiple interventions over days to weeks will be necessary to provide effective mechanical clearance of the infected material. Sterile pancreatic fluid collections typically will resolve within 6 weeks, but up to 15% will persist as encapsulated pseudocysts.[59,60] Although small (< 6 cm) and asymptomatic pseudocysts may be managed conservatively, large, symptomatic, infected, or rapidly expanding pseudocysts require intervention and drainage.[58] There also is a role for surgery in patients with sterile necrosis whose conditions do not improve despite maximal supportive care.[61]

Abdominal Compartment Syndrome

The progression of edema in the abdominal cavity and retroperitoneal space attendant to SAP as well as intravascular volume restoration can result in a sufficient increase in intraabdominal pressure (IAP) to cause abdominal compartment syndrome (ACS), which, in turn, can lead to further hypoperfusion in both a regional fashion (high venous resistance) and a global fashion (decreased venous return) and, thus, increase the risk of tissue injury. IAP elevation has been associated with an increased risk of multisystem organ failure, peripancreatic infection, and death.[62,63]

Definitions of ACS vary and can include an absolute pressure of > 25 mm Hg with organ malfunction and abdominal perfusion pressure (mean arterial pressure-IAP) of < 50 mm Hg in some reports or < 60 mm Hg in others with organ malfunction.[64,65] An elevated IAP can cause thoracic alterations that result in high peak and plateau pressures from decreased thoracic compliance, and high ventilator

Table 4—*Summary of Recommendations*

Description
Management of all pancreatitis as severe until proven otherwise
Aggressive restoration of intravascular volume
No use of prophylactic antibiotics
Enteral feeding
Surgical intervention for limited indications of ACS and infected pancreatic necrosis

settings can further threaten venous return. The release of abdominal pressure, however, can result in sudden, striking improvement in cardiopulmonary and renal function. The techniques used, ranging from draining ascites to a xiphoid-to-pubis incision, depend on individual patient circumstances.

Summary

The impact of medical care on mortality from SAP appears to have reached a plateau. Optimal management includes early and aggressive circulatory resuscitation starting at the time of diagnosis and the support of pulmonary and renal function as necessary. Therapy with systemic antibiotics will not prevent infected pancreatic necrosis, but enteral feeding does reduce infection risk. Monitoring IAP and anticipating ACS are as significant as measuring BP, pulse, and urine output in the critical care management of patients with SAP. Early surgical intervention is indicated only for the treatment of ACS. Late indications for surgery most often include drainage and debridement of infected pancreatic necrosis (Table 4).

As an illness driven by the consequences of severe systemic inflammation, further reductions in mortality from SAP may be realized by applying evaluation and management strategies that have been successful for the treatment of severe sepsis. Because the pancreas is suffering from the combined effects of severe inflammation and hypoperfusion, the systemic amelioration of these noxious processes may prove to not only protect the patient, but also to diminish the damage at the inciting location.[66]

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References

1 Forsmark CE, Baillie J. AGA Institute technical review of acute pancreatitis. Gastroenterology 2007; 132:2022–2044
2 Bradley EL 3rd. A clinically based classification system for acute pancreatitis: summary of the International Symposium on Acute Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg 1993; 128:586–590
3 Ranson JH, Rifkind KM, Roses DF, et al. Prognostic signs and the role of operative management in acute pancreatitis. Surg Gynecol Obstet 1974; 139:69–81
4 Larvin M. Assessment of clinical severity and prognosis. In: Beger HG, Warshaw AL, Buchler MW, et al, eds. The pancreas. Oxford, UK: Blackwell Science, 1998; 489–502
5 Blamey SL, Imrie CW, O'Neill J, et al. Prognostic factors in acute pancreatitis. Gut 1984; 25:1340–1346
6 Gumaste VV, Roditis N, Mehta D, et al. Serum lipase levels in nonpancreatic abdominal pain versus acute pancreatitis. Am J Gastroenterol 1993; 88:2051–2055
7 Rettally C, Skarda S, Garza MA, et al. The usefulness of laboratory tests in the early assessment of severity of acute pancreatitis. Crit Rev Clin Lab Sci 2003; 40:117–149
8 Mofidi R, Duff MD, Wigmore SJ, et al. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006; 93:738–744
9 Yadav D, Agarwal N, Pitchumoni CS. A critical evaluation of laboratory tests in acute pancreatitis. Am J Gastroenterol 2002; 97:1309–1318
10 Pandol SJ, Saluja AK, Imrie CW, et al. Acute pancreatitis: bench to the bedside. Gastroenterology 2007; 132:1127–1151
11 London NJ, Neoptolemos JP, Lavelle J, et al. Contrast-enhanced abdominal computed tomography scanning and prediction of severity of acute pancreatitis: a prospective study. Br J Surg 1989; 76:268–272
12 Clavien PA, Hauser H, Meyer P, et al. Value of contrast-enhanced computerized tomography in the early diagnosis and prognosis of acute pancreatitis: a prospective study of 202 patients. Am J Surg 1988; 155:457–466
13 Balthazar EJ, Ranson JH, Naidich DP, et al. Acute pancreatitis: prognostic value of CT. Radiology 1985; 156:767–772
14 Ranson JH, Balthazar E, Caccavale R, et al. Computed tomography and the prediction of pancreatic abscess in acute pancreatitis. Ann Surg 1985; 201:656–665
15 Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med 1999; 340:1412–1417
16 Simchuk EJ, Traverso LW, Nukui YM, et al. Computed tomography severity index is a predictor of outcomes for severe pancreatitis. Am J Surg 2000; 179:352–355
17 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
18 Pamuklar E, Semelka RC. MR imaging of the pancreas. Magn Reson Imaging Clin N Am 2005; 13:313–330
19 Matos C, Bali MA, Delhaye M, et al. Magnetic resonance imaging in the detection of pancreatitis and pancreatic neoplasms. Best Pract Res Clin Gastroenterol 2006; 20:157–178
20 Arvanitakis M, Delhaye M, De Maertelaere V, et al. Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. Gastroenterology 2004; 126:715–723
21 Beger HG, Bittner R, Buchler M, et al. Hemodynamic data pattern in patients with acute pancreatitis. Gastroenterology 1986; 90:74–79
22 Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001; 345:1368–1377
23 Dellinger RP, 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
24 Rivers EP, Kruse JA, Jacobsen G, et al. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. Crit Care Med 2007; 35:2016–2024
25 Altimari AF, Prinz RA, Leutz DW, et al. Myocardial depression during acute pancreatitis: fact or fiction? Surgery 1986; 100:724–731
26 Horton JW, Burnweit CA. Hemodynamic function in acute pancreatitis. Surgery 1988; 103:538–546
27 Knol JA, Inman MG, Strodel WE, et al. Pancreatic response to crystalloid resuscitation in experimental pancreatitis. J Surg Res 1987; 43:387–392
28 Niederau C, Crass RA, Silver G, et al. Therapeutic regimens in acute experimental hemorrhagic pancreatitis: effects of hydration, oxygenation, peritoneal lavage, and a potent protease inhibitor. Gastroenterology 1988; 95:1648–1657
29 Bassi D, Kollias N, Fernandez-del Castillo C, et al. Impairment of pancreatic microcirculation correlates with the severity of acute experimental pancreatitis. J Am Coll Surg 1994; 179:257–263
30 Tellado JM. Prevention of infection following severe acute pancreatitis. Curr Opin Crit Care 2007; 13:416–420
31 Brown A, Orav J, Banks PA. Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. Pancreas 2000; 20:367–372
32 Brown A, Baillargeon JD, Hughes MD, et al. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? Pancreatology 2002; 2:104–107
33 Huber W, Umgelter A, Reindl W, et al. Volume assessment in patients with necrotizing pancreatitis: a comparison of intrathoracic blood volume index, central venous pressure, and hematocrit, and their correlation to cardiac index and extravascular lung water index. Crit Care Med 2008; 36:2348–2354
34 Browne GW, Pitchumoni CS. Pathophysiology of pulmonary complications of acute pancreatitis. World J Gastroenterol 2006; 12:7087–7096
35 De Campos T, Deree J, Coimbra R. From acute pancreatitis to end-organ injury: mechanisms of acute lung injury. Surg Infect (Larchmt) 2007; 8:107–120
36 Rivers EP. Fluid-management strategies in acute lung injury: liberal, conservative, or both [comment]? N Engl J Med 2006; 354:2598–2600
37 The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006; 354:2564–2575
38 Zhang XP, Wang L, Zhou YF. The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. Dig Dis Sci 2008; 53:297–306
39 Besselink MGH, Verwer TJ, Schoenmaeckers EJP, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg 2007; 142:1194–1201
40 Uhl W, Warshaw A, Imrie C, et al. IAP guidelines for the surgical management of acute pancreatitis. Pancreatology 2002; 2:565–573
41 Pederzoli P, Bassi C, Vesentini S, et al. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993; 176:480–483
42 Saino V, Kemppainen E, Puolakkainen P, et al. Early antibiotic treatment in acute necrotizing pancreatitis. Lancet 1995; 346:663–667
43 Delcenserie R, Yzet T, Ducrois JP. Prophylactic antibiotics in treatment of severe acute pancreatitis. Pancreas 1996; 13: 198–201
44 Schwarz M, Isenmann R, Meyer H, et al. Antibiotic use in necrotizing pancreatitis: results of a controlled study. Dtsch Med Wochenschr 1997; 122:356–361
45 Nordback I, Sand J, Saaristo R, et al. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis: a single-center randomized study. J Gastrointest Surg 2001; 5:113–118
46 Isenmann R, Runzi M, Kron M, et al. German Antibiotics in Severe Acute Pancreatitis Study Group: prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology 2004; 126:997–1004
47 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
48 Bassi C, Pederzoli P, Vesentini S, et al. Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob Agents Chemother 1994; 38:830–836
49 Buchler M, Malfertheiner P, Frieb H, et al. Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 1992; 103:1902–1908
50 Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: a meta-analysis. J Gastrointest Surg 1998; 2:496–503
51 Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. Pancreas 2001; 22:28–31
52 Heinrich S, Schafer M, Rousson V, et al. Evidence-based treatment of acute pancreatitis. Ann Surg 2006; 243:154–168
53 Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg 2006; 93:674–684
54 Villatoro E, Bassi C, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev (database online). Issue 4, 2006
55 Kaushik N, Pietraszewski M, Holst JJ, et al. Enteral feeding without pancreatic stimulation. Pancreas 2005; 31:353–359
56 Vu MK, van der Veek PP, Frolich M, et al. Does jejunal feeding activate exocrine pancreatic secretion? Eur J Clin Invest 1999; 29:1053–1059
57 Marik PE, Zaloga GP. Meta-analysis of parenteral nutrition versus enteral nutrition in patients with acute pancreatitis. BMJ 2004; 328:1407
58 American Gastroenterological Association (AGA) Institute on "Management of Acute Pancreatits" Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA Institute medical position statement on acute pancreatitis. Gastroenterology 2007; 132:2019–2021
59 Baillie J. Pancreatic pseudocyts (part II). Gastrointest Endosc 2004; 60:105–113
60 Baillie J. Pancreatic pseudocysts (part I). Gastrointest Endosc 2004; 59:873–879
61 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
62 Keskinen P, Leppaniemi A, Pettila V, et al. Intra-abdominal pressure in severe acute pancreatitis. World J Emerg Surg 2007; 2:2
63 Rosas JM, Soto SN, Aracil JS, et al. Intra-abdominal pressure as a marker of severity in acute pancreatitis. Surgery 2007; 141:173–178
64 Malbrain MLNG, Cheatham ML, Kirkpatrick ML, et al. Results from the International Conference of Experts on

Intra-abdominal Hypertension and Abdominal Compartment Syndrome: I. definitions. Intensive Care Med 2006; 32:1722–1732
65 Wong K, Summerhays CF. Abdominal compartment syndrome: a new indication for operative intervention in severe acute pancreatitis. Int J Clin Pract 2005; 59:1479–1481
66 De Waele JJ, Hoste EA, Baert D, et al. Relative adrenal insufficiency in patients with severe acute pancreatitis. Intensive Care Med 2007; 33:1754–1760