ORIGINAL ARTICLE

Pancreatic Infection in Severe Pancreatitis

The Role of Fungus and Multiresistant Organisms

Beat Gloor, MD; Christophe A. Müller, MD; Matthias Worni, MS; Philip F. Stahel, MD; Claudio Redaelli, MD; Waldemar Uhl, MD; Markus W. Büchler, MD

Hypothesis: Recent controlled clinical studies suggest a positive effect of early antibiotic treatment on late morbidity and mortality in severe acute pancreatitis. However, widespread use of antibiotics may lead to an increased number of fungal infections and multiresistant bacteria, thereby worsening the outcome of the disease.

Design: Single-center prospective study.

Setting: University hospital, gastrointestinal surgical service.

Patients: One hundred three patients with necrotizing pancreatitis seen consecutively in our service.

Interventions: In addition to standard treatment, patients with proven necrotizing pancreatitis received a prophylactic intravenous antibiotic treatment. Pancreatic infection was regarded as an indication for surgery.

Main Outcome Measures: Pancreatic infection, microbiological findings, drug resistance, fungal infections.

Results: Thirty-three patients (32%) had infected necrosis. Gram-negative organisms were isolated from 19 patients (58%), Gram-positive organisms were isolated from 18 patients (55%), fungal organisms were isolated from 8 patients (24%), and multiresistant organisms were isolated from 3 patients (9%). In 7 patients (21%), the organisms cultured from the pancreatic tissue were resistant to the antibiotics given in for prophylaxis. Infection with multiresistant organisms or organisms resistant to the antibiotic used for prophylaxis, but not with fungal infection or Gram-positive or Gram-negative infection, was correlated with a negative outcome.

Conclusions: Fungal infection under adequate treatment is not associated with a negative outcome. The occurrence of multiresistant organisms seems to be a rare finding (3 of 103 patients). Antibiotic prophylaxis is effective in preventing infection in necrotizing pancreatitis, but optimal choice and duration of administration of the antibiotic agent(s) need to be carefully determined to avoid the sequelae of multiresistant organisms.

Arch Surg. 2001;136:592-596

From the Department of Visceral and Transplantation Surgery, University of Bern, Bern, Switzerland.

SEVERE ACUTE pancreatitis is still a life-threatening disease. Most advances in the management of severe acute pancreatitis have arisen from general improvements in intensive care and organ system support.[1,2] Septic complications occurring after the first 10 to 14 days of the disease are the most frequent cause of death in patients with pancreatic necrosis.[3-5] Thus, infection of pancreatic or peripancreatic tissue is recognized as the single most important determinant of morbidity and mortality associated with severe necrotizing pancreatitis.[4,6-8] During the natural course of acute pancreatitis, bacterial infection is reported to develop in 40% to 70% of all patients with necrotizing disease.[9-11] Therefore, special interest has been focused on prophylactic administration of antibiotics, based on the hypothesis that reduction of late pancreatic infection will decrease morbidity and mortality. Early studies on prophylactic intravenous antibiotic treatment failed to show any favorable effect on the outcome of patients with acute pancreatitis, either because patients with mild disease were included or ineffective antibiotic regimens were used.[12-14] On the other hand, recent controlled clinical studies support the use of early antibiotic treatment in patients with severe disease.[15-19] A meta-analysis of these studies showed a positive benefit for antibiotics in reducing mortality when broad-spectrum antibiotics with proven pancreatic tissue penetration were used.[20] Hence, routine early antibiotic treatment in all patients with necrotizing acute pancreatitis was recommended.[21] However, widespread use of antibiotics may lead to an increased num-

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 10/13/2015

PATIENTS AND METHODS

Between January 1994 and May 2000, 254 consecutive patients with acute pancreatitis were seen at the Department of Visceral and Transplantation Surgery at the University of Bern, Bern, Switzerland. Of those, 151 and 103 patients suffered from mild edematous and acute necrotizing pancreatitis, respectively. Only the latter group will be discussed in this article because at our institution these patients routinely receive antibiotic prophylaxis. Inclusion criteria were an elevation of the serum amylase level to more than 3 times the upper normal limit, a typical clinical picture[22] including abdominal pain,[23] and the appearance of pancreatic and/or extrapancreatic necrosis[24] on contrast-enhanced computed tomography (CT) together with a serum C-reactive protein value of more than 150 mg/L.[25] Computed tomography was performed within 48 to 96 hours of admission and was repeated weekly in patients whose clinical condition did not improve. On admission, all patients were treated medically according to generally accepted principles consisting of withholding oral intake, providing pain relief, and restoring fluid and electrolyte losses intravenously.[26] If vomiting had been a prominent part of the clinical picture, a nasogastric tube was inserted. A proton pump inhibitor was given to prevent stress ulcers, and low-molecular-weight heparin (3000 U/d) was given to prevent thrombosis. Pain relief included the use of peridural anesthesia and/or intravenous narcotic analgesics. Clinical severity staging of acute pancreatitis was carried out using the Ranson prognostic signs and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system. Initially, patients were hospitalized in an intermediate care unit or, in case of organ failure, in the intensive care unit. In all patients antibiotic treatment was applied soon (≤4 hours) after CT findings of necrosis. In Bern we used imipenem/cilastatine (3-4 doses of 500 mg/d, intravenously) according to the study protocol. In some patients initially cared for in other hospitals, other antibiotic substances were prescribed.

Fine-needle aspiration guided by CT with Gram stain and microbiological culture was carried out if pancreatic infection was clinically suspected. Newly developed signs of metabolic disorders and deterioration of lung, kidney, or the circulatory system and/or a newly developed rise in the number of blood leukocytes and/or fever (temperature >38.5°C) after an initial response to conservative treatment were reasons for performing fine-needle aspiration. Necrotizing pancreatitis as proven by fine-needle aspiration was regarded as an indication for surgical treatment and resulted in operative intervention (necrosectomy and continuous postoperative lavage of the necrotic cavities) within 24 hours. Intraoperatively, smears for microbiological culture were taken (≥2) from the area of pancreatic necrosis as well as from the adjacent necrotic cavities in the retroperitoneum. Postoperative antibiotic treatment, including antimycotic treatment, was adapted according to the bacteriological findings and microbiological testing of resistance.

Patients without signs of pancreatic infection were treated nonoperatively.

Microbiological studies were performed by the microbiology laboratory of the University of Bern according to standard clinical practice.

All data were collected prospectively and entered into a statistical package program (SPSS Statistical Software, Chicago, Ill) on a personal computer. Differences were analyzed using the Fisher exact test or χ^2 test where appropriate. Quantitative variables were analyzed using the Wilcoxon test. A total of 12 factors potentially influencing outcome (time of infection, Gram-positive infection, Gram-negative infection, multiresistant organisms, resistance to antibiotic prophylaxis, duration of antibiotic treatment, secondary infection, APACHE II and Ranson score, preoperative intensive care unit treatment, preoperative ventilation, and parenteral nutrition) were analyzed using a log-rank test. $P<.05$ was considered statistically significant.

ber of multiresistant bacterial and fungal infections, thereby worsening the course of the disease and the outcome. In this study, we report microbiological findings in patients who received prophylactic antibiotic treatment and analyze the influence of antibiotic treatment on the time point of infection, the type of organisms cultured from these patients, and the patient's outcome.

RESULTS

One hundred three patients had necrotizing pancreatitis according to CT findings and C-reactive protein levels and were included in this study. Sixty-four (62%) of them were men and 39 (38%) were women. The mean age was 56.8 years (range, 28-87 years). The cause of the pancreatitis was biliary in 47 patients (46%), alcoholism in 35 patients (34%), and another cause or undefined in 21 patients (20%). There was no difference in age or cause of pancreatitis between survivors and nonsurvivors.

Starting between days 2 and 4 after onset of symptoms, patients received a prophylactic antibiotic treatment for a median of 14 days (range, 4-23 days). Necrotic tissue remained sterile for organisms in 70 patients (68%). In the remainder (33 patients [32%]), infection occurred after a median of 26 days (range, 10-49 days) after onset of symptoms. Patients received a median of 2 antibiotic drugs (range, 2-5 drugs) either simultaneously or subsequently. The different prophylactic antibiotic treatments used in patients with necrotizing pancreatitis are listed in **Table 1**.

Pancreatic infection was polymicrobial in 19 patients (58%) and monomicrobial in 14 (42%) with a total of 61 positive cultures. Gram-negative organisms were identified in 19 patients (58%), Gram-positive organisms in 18 (55%), and fungal organisms in 8 (24%).

PATIENTS WITH COMPLICATED PANCREATIC INFECTION

Twenty-three patients (70%) were transferred to our institution from other hospitals, including 2 patients who were transferred from abroad. One of the latter was infected with a methicillin-resistant *Staphylococcus aureus* and finally died of septic multiorgan failure. Overall, multiresistant organisms were found in 3 (9%) of the patients with infection (n=33) and in 3% of all patients

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 10/13/2015

Table 1. Antibiotics Administered for Prophylaxis in 103 Patients With Necrotizing Pancreatitis*

Antibiotic	No. (%) of Patients
Imipenem/cilastatin only	53 (51)
Imipenem/cilastatin in combination with or followed by another antibiotic substance	44 (43)
Other antibiotic substances (referral patients)	6 (6)

**In those patients with infected necrosis only antibiotics given for prophylaxis are listed. A total of 12 different antibiotics were prescribed. Of 103 patients, 97 (94%) received imipenem/cilastatin.*

Table 2. Summary of Nonsurvivors and All Patients With Complicated Pancreatic Infection Caused by Resistant Organisms or Fungus

Patient No.	Organism Resistant to Antibiotic Prophylaxis	Multiresistant Organism	Fungal Infection	Death
2			Yes	
3			Yes	
5	Yes		Yes	
7				Yes
9	Yes			Yes
13			Yes	Yes
15	Yes	Yes	Yes	Yes
16	Yes			
17	Yes			
18			Yes	
22				Yes
24	Yes	Yes		Yes
26	Yes	Yes		
29			Yes	
31			Yes	
33				Yes
Total	**7**	**3**	**8**	**7**

receiving antibiotics (n=103). All 3 patients with multiresistant organisms were infected with Gram-positive bacteria (methicillin-resistant *S aureus*, n=2; multiresistant coagulase-negative *Staphylococcus*, n=1). These 3 patients each were treated with 3 different antibiotics for 15, 23, and 25 days, respectively. Two of them died. In 7 patients (21%), including the 3 infected with multiresistant organisms, the organisms cultured from the pancreatic tissue harvested during surgery were resistant to the antibiotic substance given previously for prophylaxis. Three of those 7 patients with such resistant organisms died. Univariate analysis revealed infection with multiresistant organisms and organisms resistant to the antibiotic prophylaxis as significant risk factors for a fatal outcome ($P=.02$ and $P=.007$, respectively; Fisher exact test). **Table 2** provides an overview of nonsurvivors and patients with complicated pancreatic infection caused by organisms resistant to the antibiotic prophylaxis, multiresistant organisms, or fungal infection.

In 2 patients, extrapancreatic *Candida* infection (one in the urine and one in the tracheobroncheal lavage fluid) was diagnosed before pancreatic infection was demonstrated, and was treated with fluconazole for 5 and 10 days, respectively. Nevertheless, in both these patients and 6 other patients, pancreatic necrotic tissue harvested during surgery was found to be infected with *Candida* species. Patient characteristics and risk factors for fungal infection of these 8 patients are listed in **Table 3**. Fungal infection was not correlated with a negative outcome ($P=.13$; Fisher exact test).

Table 3. Characteristics of 8 Patients With Fungal Infection of Pancreatic Necrosis vs 25 Patients With Bacterial Infection Only*

	Fungal Infection (n = 8)	Bacterial Infection (n = 25)
Male	3 (37)	18 (72)
Female	5 (63)	7 (28)
Biliary pancreatitis	5 (63)	15 (60)
Post-ERCP pancreatitis	0	1 (4)
Alcohol-induced pancreatitis	1 (12)	8 (32)
Other or unknown etiology	2 (25)	1 (4)
Total parenteral nutrition	4 (50)	16 (56)
Antibiotic treatment for <7 d	0	5 (20)
Antibiotic treatment for 7-14 d	3 (37)	8 (32)
Antibiotic treatment for >14 d	5 (63)	12 (48)
Necrosis of >50% of the gland	8 (100)	18 (72)
Mortality	2 (25)	5 (20)
APACHE II score during first week of the disease (range)	12.7 (7-21)	11.8 (6-22)
Mean ± SEM preoperative ICU stay, d	27.6 ± 17.9	16 ± 14.8
Mean ± SEM preoperative mechanical ventilation, d	18.5 ± 17.9	11 ± 9

**Data are presented as number (percentage) unless otherwise indicated. ERCP indicates endoscopic retrograde cholangiopancreatography; APACHE II, Acute Physiology and Chronic Health Evaluation II; and ICU, intensive care unit. None of the characteristics or parameters was statistically different between the 2 groups.*

Infection of the necrotic tissue with organisms (bacteria or fungus) previously cultured from sites other than the pancreas occurred in 14 patients (2 fungal and 12 bacterial infections) with infected necrosis (14/33; 42%). These organisms were isolated between 2 and 10 days prior to the diagnosis of pancreatic infection and they were the same as the ones grown later from the pancreas. The primary source was the bile in 7 patients, the tracheal mucosa in 3, venous catheters in 2, the urinary tract in 1, and both the tracheal mucosa and the urinary tract in 1. Four of the 12 patients with a bacterial infection are included in the 7 patients infected with organisms resistant to the prophylactic antibiotic. Endoscopic retrograde cholangiopancreatography (ERCP) (always with administration of an antibiotic prophylaxis) was performed in all patients with a biliary cause for their pancreatitis (n=47) and in 31 patients with a cause other than gallstones. Of the 33 patients with infected necrosis, 20 (61%) had undergone an ERCP procedure. Five of the 7 patients with a biliary origin of the (subsequent) pancreatic infection had a previous ERCP. These 5 were not different from the remaining 15 in terms of organisms cultured from the pancreatic tissue, extent of necrosis, and interval between onset of symptoms and occurrence of pancreatic infection. None of the 33 patients with infected necrosis had post-ERCP pancreatitis. For all patients undergoing ERCP, the procedure was done for treatment of already established pancreatitis.

Overall mortality was 9% (9/103). The mortality rate in patients with infected necrosis was 21% (7/33).

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 10/13/2015

COMMENT

The patterns of morbidity and mortality in acute necrotizing pancreatitis have changed during the last 2 decades. Except for a minority of early fatalities due to so-called fulminant acute pancreatitis, most deaths today occur after the first 7 to 10 days owing to infective complications, particularly infected necrotic tissue.[4,27-31] Therefore, antibiotic treatment aimed at preventing or delaying the onset of infection of necrotic tissue seems to be a major step forward in the management of these severely ill patients. Indeed, results of contemporary randomized clinical trials restricted to patients with severe acute pancreatitis have demonstrated improvement in outcome associated with antibiotic treatment.[20,21] The other side of the coin, however, is the fact that routine antibiotic treatment is expensive and may be associated with an increased risk of fungal infections or the selection of multiresistant organisms. In the present study, we found a predominance of polymicrobial infections and this is in accordance with other studies.[3,32-34] Gram-negative and Gram-positive species were found in 19 and 18 patients, respectively, indicating an increase of Gram-positive germs (mainly enterococci and staphylococci) as compared with studies from the 1980s, when patients did not receive prophylactic antibiotic treatment.[9-11] This was documented in a previous report from our institution[6] and in an Italian study by Bassi et al.[15] They found 8 Gram-negative and 6 Gram-positive isolates in 13 patients with infected necrosis after 14 days of antibiotic treatment.[15] In contrast to these results, Luiten et al[35] did not see a shift toward more Gram-positive infections after selective gut decontamination combined with short-term intravenous antibiotic treatment.

The infection rate in our study was 32%. Of note is the fact that 26 (79%) of those with infected necrosis had extended necrosis; ie, necrosis of more than 50% of the gland, which has been identified by others to be a risk factor for infection.[36,37] In patients who did not receive antibiotic prophylaxis, infection rates as low as 40% and as high as 76% have been reported.[9-11,38] Also, in more recent studies, infection rates varied widely between 30% and 58% in control patients and between 0% and 61% in patients receiving antibiotic prophylaxis.[16-19,34] Ho and Frey[38] reported an infection rate of 27% in a group of 50 patients receiving imipenem/cilastatin for 4 weeks.

Another important finding in our study is the fact that infection occurred as late as 26 days after onset of symptoms. Taking into account that antibiotic treatment was started 2 to 4 days after onset of symptoms and that antibiotics were given for a median of 14 days, patients were without antibiotic treatment for 8 to 10 days before infection was diagnosed. This may be one explanation why in as many as 26 patients (79%) the bacteria cultured from the necrotic tissue were susceptible to the antibiotic substance given initially as prophylaxis. However, statistical analysis revealed resistance to antibiotic prophylaxis was an independent risk factor for a fatal outcome.

Among the 7 patients who died, 2 died of infection with multiresistant organisms. Multiresistance was a rare finding in this study. However, once infection with multiresistant organisms occurred (n=3), the mortality rate was 67% (2/3). Accordingly, looking at all patients with necrotizing pancreatitis, infection with multiresistant organisms was another negative risk factor. Because there were only 3 patients with multiresistant organisms, we omitted further statistical analysis. Nevertheless, it needs to be mentioned that they all were treated with prophylactic antibiotics for more than 2 weeks with 3 different drugs, a pattern that is known to bear an increased risk for the selection of multiresistant organisms.

Fungal infection of pancreatic necrosis was found in less than 10% of all patients who did not receive antibiotic prophylaxis.[9,10] Today, several risk factors for fungal infection, such as routine use of antibiotics, long-term central venous access for parenteral nutrition, and prolonged intensive care treatment, all seem to contribute to the increase in the prevalence of fungal infection. However, as seen in Table 3, none of the listed risk factors was significantly associated with fungal infection. Overall, we found a 24% infection rate for fungal infection and univariate analysis showed no correlation with outcome. Hoerauf et al[39] diagnosed 13 fungal infections in their retrospective series of 37 patients and *Candida* infection was found to be an independent risk factor for mortality if not treated adequately. Bassi et al[15] found 4 *Candida* isolates in their controlled study of 13 patients treated with imipenem or pefloxacin. On the other hand, Grewe et al,[40] in a group of 57 patients with necrotizing pancreatitis, found an incidence of fungal infections of only 12%, despite the fact that their patients had been treated with a mean of 4 different antibiotics for a mean of 23 days.

The microbiological profile (predominantly *Enterobacteriaceae*) of infected pancreatic necrosis in patients who did not receive antibiotic prophylaxis suggests an enteric source. Our study confirms that routine antibiotic treatment effectively suppresses and delays the transfer from bacteria from the gut, thereby leading to a relative increase of extra-enteric pancreatic infections. Indeed, 42% of the infections in our patients presumably did not originate from the gut but from infected venous catheters (n=2), the urinary tract (n=2), the tracheal mucosa (n=3), or the biliary system (n=7). Others have previously documented these same sources of organisms and routes of spread of bacteria in experimental acute pancreatitis.[41,42] Such "secondary" (hospital-acquired) infections are very difficult to suppress and are well known in critically ill patients.

In summary, the contemporary literature provides convincing evidence that early antibiotic prophylaxis is beneficial and this should form part of the standard treatment of patients identified as having severe acute pancreatitis.[2,20,21] However, several issues remain that have not been addressed by any controlled study.[43] The proper duration of prophylactic antibiotic treatment remains unknown. The selection of multiresistant (Gram-positive) organisms and fungal infections is always an issue, and this is more likely when antibiotics are given for longer periods. Since there is evidence that the incidence of Gram-positive and fungal infections increases with routine antibiotic prophylaxis, substances that specifically deal with these organisms may need to be added to the prophylactic treatment.[44] These issues need to be carefully controlled to prevent a major setback in the treatment of severe necrotizing pancreatitis.

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 10/13/2015

Corresponding author: Markus W. Büchler, MD, Department of Visceral and Transplantation Surgery, Inselspital, University of Bern, CH-3010 Bern, Switzerland (e-mail: markus.buechler@insel.ch).

REFERENCES

1. Sigurdsson GH. Intensive care management of acute pancreatitis. *Dig Surg.* 1994; 11:231-241.
2. Johnson CD. Antibiotic prophylaxis in severe acute pancreatitis. *Br J Surg.* 1996; 83:883-884.
3. Widdison AL, Karanjia ND. Pancreatic infection complicating acute pancreatitis. *Br J Surg.* 1993;80:148-154.
4. Bradley EL. Antibiotics in acute pancreatitis: current status and future directions. *Am J Surg.* 1989;158:472-478.
5. Takeda K, Matsuno S, Sunamura M, Kobari M. Surgical aspects and management of acute necrotizing pancreatitis: recent results of a cooperative national survey in Japan. *Pancreas.* 1998;16:316-322.
6. Büchler MW, Gloor B, Müller CA, et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann Surg.* 2000;232:619-626.
7. Hotz HG, Reber HA. Acute pancreatitis. *Curr Opin Gastroenterol.* 1999;15:392-397.
8. Ratschko M, Fenner T, Lankisch PG. The role of antibiotic prophylaxis in the treatment of acute pancreatitis. *Gastroenterol Clin North Am.* 1999;28:641-659.
9. Beger HG, Bittner R, Block S, Büchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. *Gastroenterology.* 1986;91:433-438.
10. Bassi C, Falconi M, Girelli F, et al. Microbiological findings in severe pancreatitis. *Surg Res Commun.* 1989;5:1-4.
11. Gerzof SG, Banks PA, Robbins AH, et al. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology.* 1987;93:1315-1320.
12. Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. *J Surg Res.* 1975;18:197-200.
13. Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. *Ann Surg.* 1976;183:667-671.
14. Craig RM, Dordal E, Myles L. The use of ampicillin in acute pancreatitis [letter]. *Ann Intern Med.* 1975;83:831-832.
15. Bassi C, Falconi M, Talamini G, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. *Gastroenterology.* 1998;115:1513-1517.
16. Sainio V, Kemppainen E, Puolakkainen P, et al. Early antibiotic treatment in acute necrotising pancreatitis. *Lancet.* 1995;346:663-667.
17. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. *Ann Surg.* 1995; 222:57-65.
18. Schwarz M, Isenmann R, Meyer H, Beger HG. Antibiotika bei nekrotisierender Pankreatitis: Ergebnisse einer kontrollierten Studie. *Dtsch Med Wochenschr.* 1997; 122:356-361.
19. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. *Pancreas.* 1996;13:198-201.
20. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: a meta-analysis. *J Gastrointest Surg.* 1998;2:496-503.
21. Powell JJ, Miles R, Siriwardena AK. Antibiotic prophylaxis in the initial management of severe acute pancreatitis. *Br J Surg.* 1998;85:582-587.
22. Levitt MD, Eckfeldt JH. Diagnosis of acute pancreatitis. In: Go VLW, Dimagno EP, Gardner JD, Lebenthal E, Reber HA, Scheele GA, eds. *The Pancreas: Biology, Pathobiology, and Disease.* 2nd ed. New York, NY: Raven Press; 1993:613-635.
23. Uhl W, Büchler MW, Malfertheiner P, et al. A randomized, double blind, multicenter trial of octreotide in moderate to severe acute pancreatitis. *Gut.* 1999;45: 97-104.
24. Sakorafas GH, Tsiotos GG, Sarr MG. Extrapancreatic necrotizing pancreatitis with viable pancreas: a previously under-appreciated entity. *J Am Coll Surg.* 1999; 188:643-648.
25. Büchler M, Malfertheiner P, Schoetensack C, Uhl W, Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis: results of a prospective clinical study. *Int J Pancreatol.* 1986;1:227-235.
26. Banks PA. Medical management of acute pancreatitis and complications. In: Go VLW, Dimagno EP, Gardner JD, Lebenthal E, Reber HA, Scheele GA, eds. *The Pancreas: Biology, Pathobiology, and Disease.* 2nd ed. New York, NY: Raven Press; 1993:593-612.
27. Schmid SW, Uhl W, Friess H, Malfertheiner P, Büchler MW. The role of infection in acute pancreatitis. *Gut.* 1999;45:311-316.
28. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *Br J Surg.* 1999;86:1020-1024.
29. Allardyce D. Incidence of necrotizing pancreatitis and factors related to mortality. *Am J Surg.* 1987;154:295-299.
30. Renner I, Savage W, Pantoja J, Renner V. Death due to acute pancreatitis: a retrospective analysis of 405 autopsy cases. *Dig Dis Sci.* 1985;10:1005-1008.
31. de Beaux AC, Palmer KR, Carter DC. Factors influencing morbidity and mortality in acute pancreatitis: an analysis of 279 cases. *Gut.* 1995;37:121-126.
32. Bradley ELd, Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg.* 1991; 161:19-24.
33. Bittner R, Block S, Büchler M, Beger HG. Pancreatic abscess and infected pancreatic necrosis: different local septic complications in acute pancreatitis. *Dig Dis Sci.* 1987;32:1082-1087.
34. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute pancreatitis. *Surg Gynecol Obstet.* 1993;176:480-483.
35. Luiten EJ, Hop WC, Lange JF, Bruining HA. Differential prognosis of gram-negative versus gram-positive infected and sterile pancreatic necrosis: results of a randomized trial in patients with severe acute pancreatitis treated with adjuvant selective decontamination. *Clin Infect Dis.* 1997;25:811-816.
36. Beger HG, Krautzberger W, Bittner R, Block S, Büchler MW. Results of surgical treatment of necrotizing pancreatitis. *World J Surg.* 1985;9:972-979.
37. Vesentini S, Bassi C, Talamini G, et al. Prospective comparison of C-reactive protein level, Ranson score and contrast-enhanced computed tomography in the prediction of septic complications of acute pancreatitis. *Br J Surg.* 1993;80:755-757.
38. Ho HS, Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. *Arch Surg.* 1997;132:487-493.
39. Hoerauf A, Hammer S, Muller-Myhsok B, Rupprecht H. Intra-abdominal Candida infection during acute necrotizing pancreatitis has a high prevalence and is associated with increased mortality. *Crit Care Med.* 1998;26:2010-2015.
40. Grewe M, Tsiotos GG, Luque de-Leon E, Sarr MG. Fungal infection in acute necrotizing pancreatitis. *J Am Coll Surg.* 1999;188:408-414.
41. Widdison AL, Karanjia ND, Reber HA. Routes of spread of pathogens into the pancreas in a feline model of acute pancreatitis. *Gut.* 1994;35:1306-1310.
42. Widdison AL, Alvarez C, Chang YB, Karanjia ND, Reber HA. Sources of pancreatic pathogens in acute pancreatitis in cats. *Pancreas.* 1994;9:536-541.
43. Reber HA. Do prophylactic antibiotics influence the course and outcome of acute pancreatitis. Paper presented at: The Society for Surgery of the Alimentary Tract; May 16, 1999; Orlando, Fla.
44. Laws HL, Kent RB. Acute pancreatitis: management of complicating infection. *Am Surg.* 2000;66:145-152.

©2001 American Medical Association. All rights reserved.
Downloaded From: http://archsurg.jamanetwork.com/ on 10/13/2015