

Outcome of severe acute pancreatitis: Is there a role for conservative management of infected pancreatic necrosis?

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BACKGROUND: Infected pancreatic necrosis is associated with high morbidity and mortality and is mandatory for surgical or radiological intervention. A selected group of patients with CT evidence of infected pancreatic necrosis and a comparatively lower APACHE score may be clinically stable throughout the course of their illness.

METHODS: Case records of 52 patients with severe acute pancreatitis admitted from October 2000 to September 2005 were retrospectively analysed to assess the feasibility of conservative management of infected pancreatic necrosis. CT evidence of retroperitoneal air pockets, deteriorated clinical condition, sepsis and positive blood culture were used to diagnose infected pancreatic necrosis.

RESULTS: In the 52 male patients reviewed, 24 patients had infected pancreatic necrosis. Eighteen patients who had progressively deteriorated clinical conditions required surgical intervention; five patients of whom (27.8%) died. Six patients with transient end organ dysfunction and stable clinical conditions were treated with prolonged administration of antibiotics and ICU support. All these patients recovered and discharged from the hospital, and no symptoms or readmission happened during follow-up of 6-44 months.

CONCLUSIONS: Selected patients with infected pancreatic necrosis who are clinically stable with transient end organ dysfunction can be treated conservatively with a favourable outcome. Necrosectomy associated with high morbidity

and mortality in these patients can be avoided. The need for intervention should be individualized and based on clinical conditions of the patients.

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KEY WORDS: acute necrotizing pancreatitis; APACHE II; multiple organ dysfunction syndrome; mortality; antibiotics

Introduction

Patients with significant pancreatic necrosis are at high risk of developing infection of necrotic tissue and peripancreatic collection^[1] and infected pancreatic necrosis is the most important risk factor of death from necrotizing pancreatitis.^[2] The presence of retroperitoneal gas bubbles surrounding the necrosis produced by gas forming organisms is considered an absolute indication for urgent surgical intervention.^[3] Under these circumstances, surgery is associated with high morbidity and mortality.^[4, 5] However, not all air collection is necessarily infected.^[6] Aggressive conservative management with prolonged use of antibiotics and supportive measures can delay or avoid surgery in selected situations.^[7] Surgery is optimal in most of patients with infected pancreatic necrosis, and a few patients recover after conservative treatment. In this study, we analyzed the outcome of patients with infected pancreatic necrosis treated conservatively or surgically as well as the determinants of a successful conservative treatment.

Methods

Case records were retrospectively reviewed of 52 male patients with severe acute pancreatitis treated at our

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centre between October 2000 and September 2005. These patients were diagnosed with an APACHE II score ≥ 8 and treated according to the standard management protocol in the intensive care unit (ICU). Fluid, electrolytes and albumin were replaced after the measurement of hematocrit (30%-35%), urinary excretion, and electrolytes. Assisted ventilation was begun if the partial pressure of oxygen could not be maintained with an oxygen mask for ≥ 60 mmHg. In patients with progressive renal failure (serum creatinine >3.0 mg/dl), hemodialysis was performed. All patients received prophylactic antibiotics within 48 to 72 hours after the presence of pancreatic necrosis. Ciprofloxacin (2 \times 0.5 g iv) combined with metronidazole (3 \times 0.5 g iv) was given to the majority of the patients. Contrast enhanced computed tomography (CECT) was performed to stage the disease after the first week of illness and repeated when patient's clinical status deteriorated or continued improvement failed and before discharge to detect the asymptomatic complications. Magnetic resonance cholangiopancreatography (MRCP) was performed in appropriate patients to rule out ductal anomalies. Pancreatic infection was suspected clinically in the presence of following indicators: leukocytosis $>10\,000/\mu\text{l}$, fever >38.5 °C, abdominal pain combined with local peritonitis, and positive blood culture. The diagnosis of the infection was based on the presence of gas bubbles within pancreatic or extra pancreatic necroses on CECT. In these patients, clinical conditions deteriorated. The antibiotic regimen was

changed to imipenem 3 \times 0.5 g iv in combination with metronidazole 3 \times 0.5 g iv, until clinical recovery. In addition, circulatory, ventilatory and renal support was adopted and intensified as necessary. Clinical development was monitored closely. Surgery was indicated for patients with end organ dysfunction and/or progressive clinical deterioration despite ICU support and antibiotics. Descriptive statistical methods were used for the analysis of the data.

Results

Twenty-four patients had infected pancreatic necrosis based on the computed tomography (CT) findings of gas bubbles in the retroperitoneum. In 11 patients who had initially refused surgery and been treated conservatively 5 patients were later subjected to surgery because of progressive deterioration and/or failure to recover from illness.

Blood culture was done in the patients who underwent surgery and in those who were treated conservatively. The results of blood culture were positive in 21 patients and negative in 3. Gram positive culture was obtained in 9 patients and negative culture in 12. In gram positive culture, *Staphylococcus* coagulase positive organisms were isolated in 7 patients and *Staphylococcus* coagulase negative organisms in 2 patients. In gram negative culture, *Pseudomonas* were isolated in 6 patients, *Klebsiella* in 4, and *Escherichia Coli* in 2.

Eighteen (75%) of the 24 patients underwent

Table 1. Demographic characteristics, etiology, severity scores and outcome in 18 patients in the surgical group

Number of patients	Age (y)	Sex	Etiology	APACHE II	Gas detected by CECT	CTSI	Outcome
1	29	Male	Alcohol	16	+	10	Died
2	44	Male	Alcohol	18	+	10	Died
3	32	Male	Alcohol	18	+	7	Recovery
4	39	Male	Alcohol	13	+	5	Recovery
5	32	Male	Alcohol	14	+	6	Recovery
6	66	Male	Unknown	15	+	9	Recovery
7	59	Male	Unknown	17	+	7	Recovery
8	42	Male	Biliary	13	+	6	Recovery
9	32	Male	Alcohol	12	+	10	Recovery
10	54	Male	Biliary	15	+	10	Recovery
11	51	Male	Unknown	14	+	10	Died
12	33	Male	Alcohol	20	+	10	Died
13	38	Male	Alcohol	19	+	10	Died
14	23	Male	Alcohol	14	+	8	Recovery
15	64	Male	Unknown	19	+	7	Recovery
16	40	Male	Trauma	14	+	8	Recovery
17	40	Male	Alcohol	13	+	8	Recovery
18	26	Male	Alcohol	12	+	8	Recovery

surgery within 35 days on average. Their mean age was 41.3 ± 12.8 years. Etiological factors included alcohol consumption (11 patients), biliary microlithiasis (2), blunt abdominal trauma (1), and unknown cause (4). The mean APACHE II score was 15.3 ± 2.6 . Four patients showed 30%-50% necrosis and the remaining 14 patients >50% necrosis. The mean CT severity index (CTSI) was 7.7 ± 1.7 . Fifteen of the 18 patients underwent necrosectomy with local retroperitoneal

lavage. Three patients had necrosectomy and drainage with laparostomy combined with re-exploration. Five of the 18 patients died (27.8% mortality), 2 after intervention within 3 weeks after onset of the illness and the remaining 3 patients after delayed intervention. In the latter group, 2 died from multiorgan dysfunction and 1 from duodenal fistula. The demographic characteristics, etiology, severity scores and outcome in the 18 patients are shown in Tables 1-3.

Table 2. Outcome of surgical intervention in 18 patients with infected pancreatic necrosis

Duration of illness onset to intervention (days)	Necrosectomy with local lavage	Necrosectomy and drainage with laparostomy
<21	2	1
22-45	10	2
46-90	2	-
>90	1	-
Outcome		
Alive	12	1
Death	3	2

The remaining 6 of the 24 patients recovered without surgery. These patients had a stable clinical course and were given a prolonged treatment with antibiotics and ICU support. The cause of the disease was alcohol related in 1 patient, biliary calculus related in 1, and unknown in 4. All these patients were men, aged 45.3 ± 13.4 years. Combined use of quinolones, imipenem and metronidazole was prescribed to all patients. Two patients with multiple organ dysfunction were given additional fluconazole. The duration of antibiotic therapy ranged from 20 to 43 days, averaging 36.2 ± 8.8 days. The mean duration of ICU stay ranged from 7 to 17 days (mean 14.2 ± 3.8 days). APACHE

Table 3. Characteristics of patients undergoing conservative management

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yr)	31	53	51	49	61	27
Sex	Male	Male	Male	Male	Male	Male
Dur. of history (wk)	3	3	3	3	2	3
BMI	20.5	25.8	27.4	24.2	26.4	23.8
APACHE II score	8	9	8	9	11	10
Fever	+	+	+	+	+	+
Organ dysfunction (duration)	CVS (72 h)	Renal (48h)	Renal (24 h)	Renal (72 h)	MODS (7 days)	MODS (72 h)
Hematocrit (%)	32	34	33	29	46	32
WBC (mm^3)	16 200	11 600	13 100	12 460	17 500	12 600
H/o alcohol intake	No	No	No	No	Occasional	Regular
Triglyceride levels	Normal	Normal	Normal	Normal	Normal	Normal
Calcium	Normal	Normal	Normal	Normal	Normal	Normal
Etiology	Idiopathic	Idiopathic	Idiopathic	Idiopathic	Biliary	Idiopathic
Jaundice	Nil	Nil	Nil	Nil	Nil	Nil
CT e/o air pockets	+	+	+	+	+	+
Extent of necrosis (%)	30-50	30-50	30-50	30-50	>50	>50
CTSI	7	6	8	7	10	9
ICU stay (d)	7	16	14	17	17	14
Total Hospital stay (d)	30	45	46	28	40	42
Antibiotic agents used	Ci+I+M	I+Cef+Ci+M	I+Cef+Ci+M	Cef+Ci+M+I	Cef+Ci+M+I	I+Ci+M
Dur. of antibiotic therapy (d)	20	43	40	42	40	32
Follow-up period (mon)	16	25	36	44	6	6
CT scan resolution (mon)	3	3	2.5	2	-	1.5

APACHE: acute physiological and chronic health evaluation; BMI: body mass index; Cef: cefotaxime, Ci: ciprofloxacin, CT: computed tomography; CTSI: CT severity index; CVS: cardiovascular system, Dur: duration; I: imipenem; ICU: intensive care unit; M: metronidazole; MODS: multiple organ dysfunction syndrome; WBC: white blood cells.

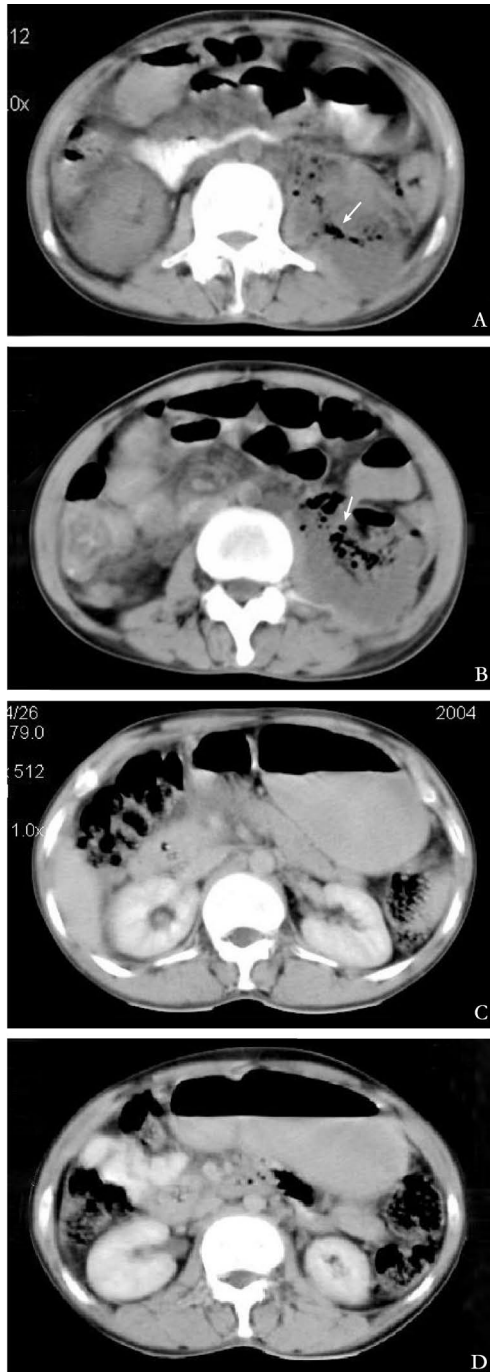


Fig. 1. CECT showing gas bubbles (arrow) in left para renal region with infected pancreatic necrosis (A, B); CECT showing complete resolution of pancreatic necrosis with minimal gas bubbles after medical treatment alone. The patient was completely asymptomatic at the time of CECT (C, D).

II score in these patients ranged from 8 to 11 with a mean value of 9.2 ± 1.8 . Balthazar's grading was D with 30%-50% pancreatic necrosis in 4 patients and >50% pancreatic necrosis in 2 patients. The mean CTSI was 7.8 ± 1.5 . The duration of illness before admission (i.e. time lag between onset of the illness and the diagnosis

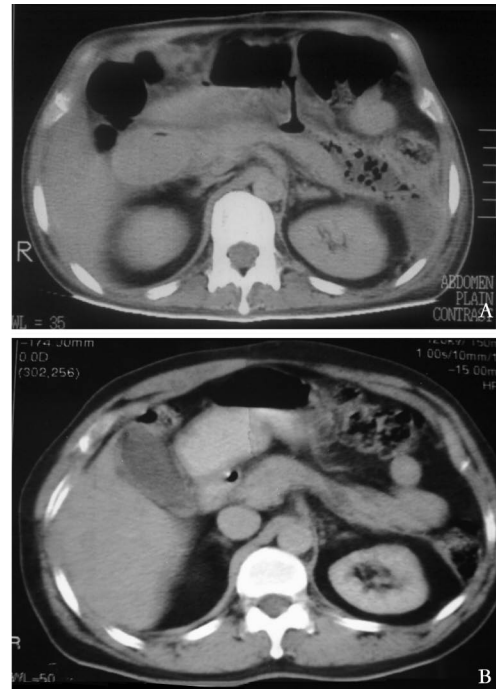


Fig. 2. CECT showing multiple gas bubbles in tail region of pancreas and left para renal region with infected pancreatic necrosis (A); CECT showing complete resolution of infected pancreatic necrosis after medical treatment alone (B).

of infection) was less than 2 weeks in 1 patient and 3 weeks in the remaining 5 patients. Transient organ dysfunction of 24- to 72-hour duration was noticed in 4 patients: renal dysfunction in 3 and cardiovascular compromise in 1. Two patients had multiple organ dysfunction, one for 72 hours and the other for 7 days. The mean hospital stay was 38.5 ± 7.7 days (range 28-46 days). The six patients recovered without sequelae and discharged from the hospital. They were asymptomatic on regular follow-up at outpatient clinic (mean 22.2 ± 15.7 months). These patients had a lower APACHE II score compared to the surgical group. CECT showed infected pancreatic necrosis with gas bubbles in the left para renal region (Fig.1A, B). Contrast medium was seen in the duodenum and colon but no bowel communication. CECT showed resolution of infected pancreatic necrosis with minimal gas bubbles after conservative treatment (Fig. 1C, D). There was infected pancreatic necrosis with gas bubbles in the tail of the pancreas and the left para renal region as well as complete resolution after conservative treatment (Fig. 2A, B).

Discussion

The mainstay therapy for management of infected

pancreatic necrosis has been surgical necrosectomy and debridement. This has been shown to significantly decrease the overall mortality despite compromised nature of the patients.^[8] Percutaneous US/CT guided drainage^[9] or transgastric endoscopic intervention^[10] has been resorted in specific situation. None of the patients in the present series had a percutaneous drainage or any other intervention. Delayed mortality in the setting of acute pancreatitis is generally a consequence of bacterial infection of necrotic pancreas or peripancreatic collection.^[11] Antibiotic therapy with either imipenem or quinolone, which has high degree of penetration, reduces the rate of infection and improves the survival.^[12]

Infection in necrotic pancreas is suspected clinically in the presence of increasing abdominal pain, fever, and leukocytosis and/or organ failure. However, no specific signs or symptoms are available for differentiating sterile from infected necrosis.^[13] Gas bubbles on CECT are almost pathognomonic of infected pancreatic necrosis. CT findings of retroperitoneal air in pancreatic bed could also be the result of fistulization in the absence of an infection which needs to be excluded in all cases of necrotizing pancreatitis.^[6] In our patients, CECT using oral contrast did not reveal any bowel fistula or communication. Fine needle aspiration (FNA) is thought to be ideal for confirming infected pancreatic necrosis. It is not used since FNA is associated with complications like exogenous contamination^[14] and subsequent false positive aspirates up to 10%.^[15] In this study, CT criteria were considered for assessment of infection of necrotic pancreas, and not on FNA.^[16,17] Evidence supports both false positive and false negative results with FNA.^[14] Also, clinical deterioration despite culture negativity would warrant surgical intervention.

The standard protocol for management of infected necrosis complicated with acute pancreatitis is early surgical drainage and debridement regardless of the clinical status of the patients.^[18] Antibiotics with high penetration of the pancreas (imipenem & quinolone agents) are often used to treat infection. There is a concern about the emergence of fungal super infection with the use of broad-spectrum antibiotics, necessitating prophylactic anti-fungal therapy.^[19,20] In this study, we used these antibiotics in two patients who had multiorgan dysfunction in the conservative group. Six of the 24 patients recovered after conservative management. Transient and organ dysfunction lasted for 24 to 72 hours in 4 patients, and multiorgan dysfunction in the other 2 for 72 hours (1 patient) and 7 days (1), who also recovered

without sequelae. All except one in this conservative management group had transient end organ dysfunction for up to 72 hours. Their recovery though delayed was uneventful, and prolonged treatment with antibiotics was necessary. Similar reports supported prolonged conservative management in patients with infected pancreatic necrosis.^[7,16,21] Transient end organ dysfunction is usually associated with good clinical outcome.^[22]

Current guidelines advocate surgical intervention for infected pancreatic necrosis. Studies^[7,15,22] including the present one based on retrospective observations have demonstrated that non-operative management has been associated with a favorable outcome in patients with this dreaded complication. If bacteremia and septic state can be suppressed with prolonged antibiotic therapy along with antifungal agents, the need for necrosectomy associated with high morbidity and mortality in these patients can be avoided.

In conclusion, conservative management is effective in patients with infected pancreatic necrosis when their clinical condition is stable and/or transient end organ dysfunction is shown by a lower APACHE score at ICU. Well-designed prospective studies are needed to throw more light on this issue and can give guidelines in the appropriate selection of patients with infected pancreatic necrosis for conservative management.

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Contributors: SA proposed the study and wrote the first draft. KDG analyzed the data. All authors contributed to the design and interpretation of the study and to further drafts. SR is the guarantor.

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