REVIEW Article

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Acute Pancreatitis : Evidence Base Management

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EXTRACT

This review will summarize the concepts, recent knowledge and advances in the diagnosis, investigation and management of AP. In some issues, particularly those are very controversial, the author's personal opinions will be noted.

Key words : acute pancreatitis, management

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Acute pancreatitis (AP) is an acute inflammatory process of the pancreas, with variable involvement of other regional tissues or remote organ systems.[1] Its overall mortality is approximately 10-20%. There is a wide variation of the disease severity, ranging from mild, self-limiting disease, which is recovered within 3-5 days without morbidity to severe, life-threatening disease which carries mortality rate up to 30-40%. There have been many progresses in the diagnosis, severity staging and management of AP over the last decade and several guidelines have been published over the last few years.[2-6] However, there are still many controversial issues left that need to be addressed and standardized. This review will summarize the concepts, recent knowledge and advances in the diagnosis, investigation and management of AP. In some issues, particularly those are very controversial, the author's personal opinions will be noted.

Etiology

Important etiologies of AP include:

1. Gallstones or common bile duct stones 30-40%
2. Alcohol 30-40%
3. Others (5-10%)

- *Hypertriglyceridemia:* hyperlipidemia type I, IV, V with serum TG >1,000 mg/dL
- *Hypercalcemia:* particularly from hyperparathyroidism
- *Drugs:* azathioprine, 6-MP, sulfonamide, furosemide, thiazide, tetracycline, estrogen, pentamidine, valproic acid, ddI, L-asparaginase
- *Toxins:* organophosphate, scorpion stings
- *Infectious diseases:* mumps, coxsackie, echovirus, CMV, DHF, leptospirosis, salmonellosis, mycoplasma and mycobacterium avium complexes
- *Obstruction:* congenital anomalies i.e. pancreas divisum, annular pancreas, choledochol cyst, or acquired disorders i.e. pancreatic head cancer, intraductal papillary mucinous neoplasm (IPMN), sphincter of Oddi dysfunction (SOD), duodenal diverticulum, ascariasis, etc.
- *Post-ERCP*
- *Post-operative*
- *Abdominal trauma*

4. Idiopathic AP occurred approximately 10% from overall causes.

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DIAGNOSIS OF ACUTE PANCREATITIS

Symptoms and Signs

Abdominal pain

Abdominal pain is present in >95% of patients with AP. Pain is acute in onset, increasing over 10-30 minutes to the maximum and persists for several hours to days. Pain is usually moderate to severe and located at epigastrium, upper abdomen, left abdomen or the whole abdomen. Only half of patients have pain that radiates to the back[7], which is the characteristic of referred pain from retroperiteum. This pain is usually improved by sitting forward, lying on one side with knees flexed position. One pitfall is physicians do not suspect AP when referred back pain is absent. Majority of patients have abdominal distention with marked nausea and vomiting.

Painless AP occurs in ~5% of AP. However, in the series of fatal AP that were first diagnosed postmortem, over 90% had no abdominal pain[8,9] and diagnoses were missed because physicians did not aware of the disease and serum amylase or lipase was not checked. Painless AP should be considered in the setting of post-operative and ICU patients[8,9], organophosphate poisoning[10], dialysis patients and Legionnaires disease[11]. Clinical clues to suspect painless AP are unexplained shock, fluid loss, systemic inflammatory response syndrome and patient deterioration without any explanation.

Systemic inflammatory response syndrome (SIRS) or organ dysfunction

Signs of SIRS including fever, tachycardia, tachypnea, hypotension, acute renal failure and adult respiratory distress syndrome (ARDS) are commonly found in AP, particularly in severe AP.

Cutaneous signs

Periumbilical ecchymosis (Cullen's sign) or flank ecchymosis (Grey-Turner's sign) are rare findings, found in only ~3% of patients. However, their presence is strongly associated with necrotizing pancreatitis (87%)and a high mortality (37%)[12].

Serum amylase and lipase

Critical analysis of the use of serum amylase and lipase[13,14] conclude that:

1. Serum lipase is more sensitive and more specific than serum amylase in diagnosis of AP. Serum amylase has sensitivity 83%, specificity 88% compared to serum lipase which has sensitivity 94% and specificity 96%[13].

2. Serum amylase 3 x ULN has sensitivity 60%, specificity 75-100% for AP, which is comparable to serum lipase 2 x ULN[14]

3. Combination of both serum amylase and lipase may not be better than each enzyme alone for diagnosis of AP[14]

Consensus document on diagnosis, objective assessment of severity and management of AP from Santorini Consensus 19993 concluded that serum lipase has slightly higher sensitivity and specificity than amylase (evidence category A).

Conditions that may have AP without hyperamylasemia are patients with late presentation (i.e. >3-5 days), hypertriglyceridemic pancreatitis (normal amylase in ~50%[15]) and alcoholic pancreatitis (normoamylasemia in ~20%[16]). Serum lipase may be preferred in these conditions.

Urine amylase

Urine amylase is commonly used in practice to adjunct serum amylase for diagnosis AP. It can be elevated longer than serum amylase. However, very few studies have verified the accuracy of urine amylase in the diagnosis of AP. One prospective study using a cut-off of 2,000 IU/ml showed the sensitivity 83% and specificity 88% for urine amylase[17]. In the author's opinion, urine amylase may be helpful when patient presented late and serum lipase is not available.

Plain abdominal X-ray

Common radiographic findings from plain abdominal X-ray are shown in Table 1. Considered more specific findings in AP are localized segmental small bowel ileus (sentinel loop) or dilatation of transverse colon ("colon cut-off sign") (Figure 1).

Table 1 Radiographic findings of acute pancreatitis[18]

Radiographic findings	Incidence (%)
Segmental small bowel ileus	41
Colonic dilatation	22
Obscure psoas margin	19
Increased epigastric soft tissue margin	19
Increased gastrocolic separation	15
Gastric greater curvature distortion	14
Duodenal ileus	11
Pleural effusion	4
Pancreatic calcifications	3
One or more of the above signs	79

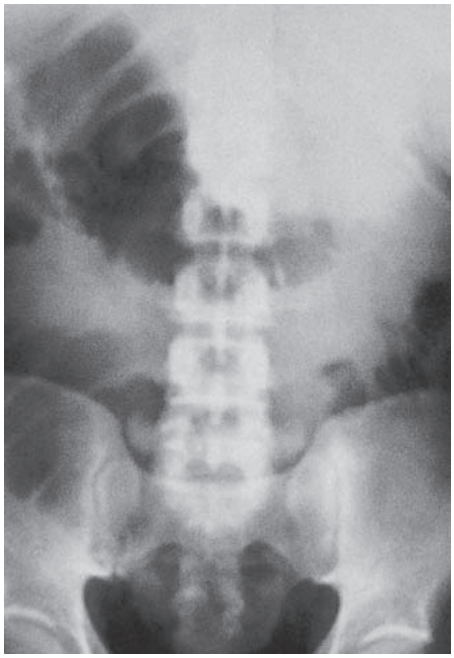

Figure 1 Plain radiography of abdomen showing "colon cut-off sign" (From the American Gastroenterological Association: clinical teaching slides, unit 5, Pancreatitis)

Computed tomography

Computed tomography (CT) is very helpful to diagnose AP when the presentation is not clear and other abdominal emergencies are possible. CT can be normal in about 10% of AP[19]. The advantage of CT is it can predict severity of AP[20]. (See "Predicting severity of acute pancreatitis")

Diagnosis of "Gallstone" as a Cause of Acute Pancreatitis

Diagnosis of gallstone as a cause of AP is important, since in severe gallstone (GS) pancreatitis with or without cholangitis, urgent ERCP within 72 hours may have a role to improve morbidity and mortality (see "Role of ERCP in acute GS pancreatitis"). Meta-analysis by Tenner[21] showed that the best parameter for predicting stone as a cause of AP is serum ALT ≥3x ULN, which had PPV of 95%, but sensitivity is only 48%. Therefore, its presence predicts GS as the cause of AP with confidence but its absence cannot rule out GS pancreatitis. Ultrasonography should be done in all patients in adjunct to serum ALT to view gallbladder stone that is presumed to be the cause. However, sensitivity of US for GS is only 70-80% in an acute phase of AP due to the overlying bowel ileus that may obscure the viewing of US. Thus, both serum ALT and US are essential and should be performed at admission and US may need to be repeated later if the initial result is negative and the cause of AP is still undetermined.

Predicting Severity of Acute Pancreatitis

Approximately 80% of AP patients had mild severity with uneventful courses. They recovered in 3-5 days by only supportive treatment with mortality rates closed to zero. However, 20% of patients had severe AP complicated with multiple organ failure, pancreatic necrosis, infected pancreatic necrosis and their mortality rates were up to 10-30%. Early prediction for which patient will have severe AP will help management plan e.g., admission to ICU, performing CT scan to look for pancreatic necrosis and considering antibiotic prophylaxis if pancreatic necrosis is present. In case of severe GS pancreatitis, there may be a role for urgent ERCP and sphincterotomy.

It should be emphasized that there is no good correlation between the presence of systemic organ failure and the presence of pancreatic necrosis[22,23]. Assessment tools that can predict systemic organ dysfunction or severe clinical outcomes may not accurately predict the presence of pancreatic necrosis[24]. Thus, both aspects must be considered simultaneously.

Predicting the "severe outcome" of AP

1. Clinical assessment e.g., presence of organ failure (Table 2)[1], SIRS or cutaneous signs e.g. Cullen's and Grey-Turner's signs.
2. Body mass index (BMI) >30 kg/m^2[25]
3. Chest X-ray: findings of bilateral or left pleural effusion[26]
4. Initial hematocrit >44% or <44% but fail to decrease after 24 hours of resuscitation[27]
5. Multiple prognostic scoring system e.g., Ranson score (3, modified Glasgow score ≥3 (Table 3) or APACHE II score ≥8[3]
6. C-reactive protein (CRP) ≥150 mg/dL[3]

Predicting the presence of pancreatic necrosis

1. Contrast-enhanced CT scan (CECT), i.e. Balthazar CT Severity Index (CTSI) ≥4 (Table 4)[28].
2. C-reactive protein ≥150 mg/dL[29]

Ranson Score

Ranson score is the first scoring system using multiple clinical and laboratory parameters to predict severe outcome of AP and is still the most popular severity assessment tool[33]. Original Ranson score,

Table 3 Ranson Score for acute alcoholic pancreatitis[30], acute GS pancreatitis[31] and Modified Glasgow Score[32]

Ranson Score	
For Alcoholic Pancreatitis	**For GS Pancreatitis**
At admission	*At admission*
Age >55 years	Age >70 years
WC >16,000 /mm^3	WC >18,000 /mm^3
Blood glucose >200 mg/dL	Blood glucose >220 mg/dL
LDH >350 IU/L	LDH >400 IU/L
AST >120 IU/L (>250 S.F. units)	AST >210 IU/L (>440 S.F. units)
During 48 hours	*During 48 hours*
Fall in hematocrit >10%	Fall in hematocrit >10%
Serum calcium <8 mg/dL	Serum calcium <8 mg/dL
Increase in BUN >5 mg/dL	Increase in BUN >5 mg/dL
Base deficit >4 mmol/L	Base deficit >2 mmol/L
Fluid sequestration >4 L	Fluid sequestration >6 L
Arterial PO_2 <60 mmHg	-
Modified Glasgow Score	
During 48 hours	
WBC >15,000/mm^3	
PaO_2 <60 mmHg	
Glucose >180 mg/dL	
Serum BUN >45 mg/dL	
Serum calcium <8 mg/dL	
Serum albumin <3.2 g/dL	
LDH >600 IU/L	
AST >200 IU/L	

Table 4 Balthazar CT Severity Index (CTSI)[28]

Staging	Score
Extent of involvement	
A - Normal pancreas	0
B - Focal or diffuse enlargement of pancreas, including contour irregularities, non-homogeneous attenuation of the gland, dilatation of PD, foci of small fluid collections within the gland	1
C - Same as B plus involvement of peripancreatic fat (stranding)	2
D - Same as B and C plus single, ill-defined fluid collection	3
E - Same as B and C plus ≥2 ill-defined fluid collections and/or intra- or peripancreatic gas	4
Necrosis (%)	
0%	0
<33%	2
33% - <50%	4
≥50%	6
Total	**10**

which was made from retrospective analysis of patients mainly (70-80%) alcoholic AP was shown to have excellent accuracy to predict severe AP using a cutoff of ≥3[34]. However, this excellent result was not reproducible by others when GS was prevalent. Later, the second version of Ranson score for GS pancreatitis was published[31]. This causes difficulty and confusion to clinicians to remember 18 parameters for both versions rather than only the original 11 parameters and in case the etiology of AP is unclear at admission. The common pitfall found in most surveys is most clinicians used the original Ranson score (for alcoholic AP) for AP of any causes. This causes many patients with mild GS pancreatitis to be "over" stratified as severe AP. Another limitation of Ranson score is it needs 48 hours to complete the score.

Modified Glasgow Score

Like Ranson score, the 8 parameter Glasgow (Imrie) score was introduced and widely used in UK and Europe. It uses a cutoff of ≥3 and needs 48 hours to complete like Ranson score. The last version,

"Modified Glasgow score" has been verified in a large prospective study and showed its accuracy for both alcoholic and GS pancreatitis[32]. Modified Glasgow score is simpler than Ranson score and more convenient for clinician to remember only 1 system for AP of any cause.

APACHE II Score

APACHE II, although more complicated, was found to be the best scoring system for AP, since it can be used within the first 24 hours, supporting the role in "early" severity prediction of AP. Various cutoff points have been used varied from 6-13, based on the appropriate need of sensitivity and specificity. Conclusion from Santorini Consensus recommended using a cutoff of ≥8[3].

C-reactive protein

CRP is the most available single prognostic parameter for predicting severe AP. It is as accurate as any scoring system and also needs 48 hours to precisely separate mild from severe AP. Interestingly, CRP was also found to be very accurate (86% accuracy) in predicting the presence of pancreatic necrosis[29]. At presence, many centers use CRP routinely to predict pancreatic necrosis and performing CT scan when CRP is elevated. The cutoff point from each study varies from 120-210 mg/dL. Finally, Santorini Consensus recommended using a cutoff of ≥150 mg/dL[3].

Meta-analysis of the values of each severity assessment of AP is shown in Table 5. It should be noticed that on admission or during the first 24 hours, APACHE II score is the best and as accurate as other scoring systems done at 48 hours. Unfortunately, clinical assessment on admission is not sensitive and can miss about 60% of severe AP. At 48 hours, every scoring systems, clinical assessment and CRP are equally effective. However, the PPV of any scoring systems are about 60% implying that about 40% of predicted "severe AP" by scoring systems will turn out to be mild. In contrast, clinical assessment by specialists at 48 hours is as sensitive as others but the PPV is highest (89%). This means patients with predicted clinical çsevere APé will eventually be severe, hence, emphasizing that any scoring systems cannot replaced the thoroughly assessment by clinicians.

The conclusions of the use of severity assessment from Santorini Consensus 19993 are:

1. During the first 24 hours, APACHE II Score has the best performance and as good as other assessment at 48 hours. BMI, initial CXR or hematocrit are optional and have been used by some centers.

2. At 48 hours, clinical assessment, Ranson Score, Modified Glasgow Score, APACHE II Score and CRP are equally effective.

Contrast-enhanced CT scan

CT scan is considered the gold standard for diagnosis of pancreatic necrosis and the extent of peripancreatic inflammation. Most guidelines recommend performing CT in only patients with predicted severe AP[2,4] since the probability of having pancreatic necrosis in these groups are very high. However, some authorities recommended performing CT in every patient with AP[24], because there is no good correlation between the presence of systemic organ failure and the presence of pancreatic necrosis[22,23] as mention earlier. Thus, clinical assessment or any scoring systems, though can predict systemic organ dysfunc-

Table 5 Meta-analysis of the values of each severity assessment of AP[35,36]

System	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
On Admission				
Clinical	39	93	66	82
APACHE II	65	76	43	89
48 hr				
Clinical	68	97	89	90
APACHE II	76	84	54	93
Ranson	75	77	49	91
Glasgow	69	84	57	90
CRP	80	76	67	86

tion and severe clinical outcomes quite well, they do not accurately predict the presence of pancreatic necrosis[24].

In the author's opinion, the strategy to perform CT scan only in patients with predicted severe AP by clinical staging systems is probably appropriate for our country. Although with this strategy, some patients with pancreatic necrosis but having good clinical status will be missed. So far the current treatment options we have for pancreatic necrosis i.e. antibiotics prophylaxis or fine needle aspiration (FNA) may not influence the outcomes of these patients because treatments are probably beneficial only in patients with pancreatic necrosis with systemic organ failure. (See "Antibiotic prophylaxis in pancreatic necrosis" and "Fine needle aspiration of pancreatic necrosis")

Timing of CT scan to look for pancreatic necrosis is another debatable issue. Data from animal studies suggested that "too early" CT scan (i.e. before 72 hours) may initiate pancreatic necrosis by impairing the microcirculation from contrast media, though data in human is yet unknown. Pancreatic necrosis may occur as early as 3-4 days[37] but infection usually does not happen until 2nd or 3rd week[38]. Thus, early CT scan within the first 72 hours is rarely indicated because it may not influence the treatment plan. In addition, pancreatic infection is unusual at this period. Therfore CT scan is not recommended unless the diagnosis is in doubt or other abdominal catastrophe is suspected. Instead, physicians should rather pay attention to the patient with vigilance for organ failures than worry for the infection during this period. Thus, whether early CT aggravates pancreatic necrosis should not be the issue. Therefore most guidelines suggest timing of CT scan during day 3rd-10th.

Treatment

Mild acute pancreatitis

1. Supportive and symptomatic treatments
2. Analgesics, opioids or opioid derivatives: Morphine is not contraindicated, although theoretically, morphine can cause sphincter of Oddi spasm and may worsening the AP, however there has never been reported in human.
3. Resuscitation with intravenous fluid and/or colloids
4. In patients with significant ileus, nothing by mouth, and/or nasogastric tube decompression should be established

Severe acute pancreatitis

1. Early enteral feeding with nasojejunal tube or total parenteral nutrition
2. Urgent ERCP within 72 hours in case of severe GS pancreatitis
3. Perform contrast-enhanced CT scan to evaluate the presence of pancreatic necrosis between day 3rd-10th.
4. Consider antibiotics prophylaxis in selected case of pancreatic necrosis and re-evaluate within 7-10 days.
5. Consider fine needle aspiration (FNA) of pancreatic necrosis to differentiate sterile from infected pancreatic necrosis if patients fail to improve or worse after conservative treatments with or without antibiotic prophylaxis.
6. Surgical debridement in case of documented infected pancreatic necrosis either by positive FNA or presence of gas in the area of necrosis (Figure 2), and selected case of unimproved sterile necrosis with organ failure.

Recommendations of management of AP from various current guidelines are summarized as an algorithm in Figure 3[2,4-6].

Nutritional Management

In mild AP, patients usually improved rapidly and were able to eat after 3-5 days, hence, parenteral nutrition is usually unnecessary. In contrast, patients with severe AP were usually placed on total parenteral nutrition (TPN) due to the fear of pancreatic stimulation

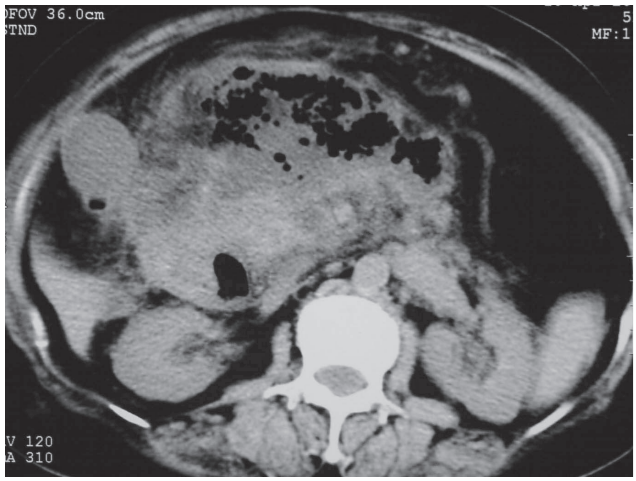

Figure 2 Computed tomography demonstrating gas in the area of pancreatic necrosis indicating infected pancreatic necrosis

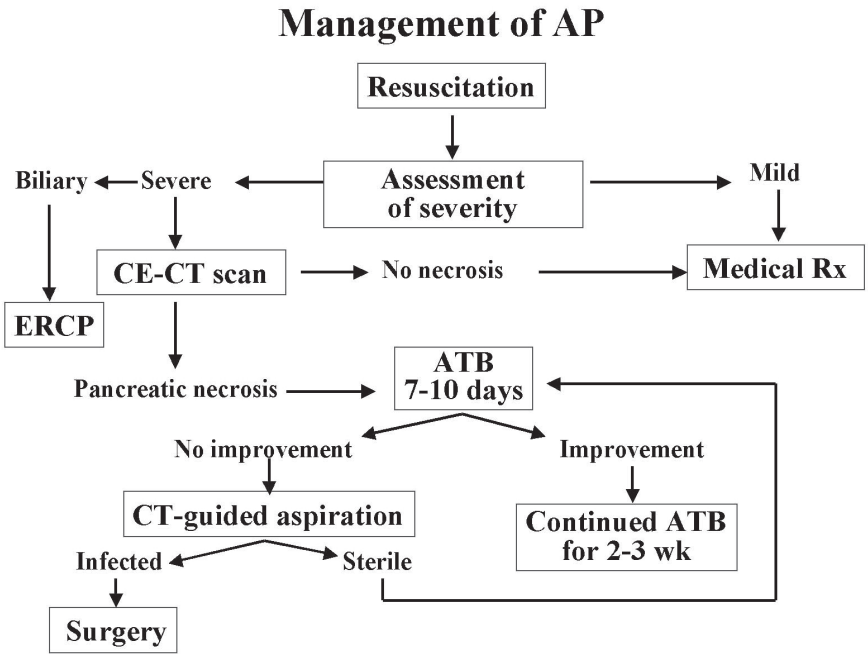

Figure 3 Algorithm for the management of acute pancreatitis

by enteral feeding. However, there has been growing body of evidence that early enteral feeding via nasojejunal tube is safe and significantly reduces cost. It also may reduce septic complications and various inflammatory mediators by maintaining the gut barrier and preventing bacterial translocation from intestine, even though the mortality rate is not decreased compared to the parenteral route[39-41]. Recently, nasogastric feeding in patients with severe AP has been studied compared with nasojejunal tube[42]. Overall morbidity and mortality of both groups were similar, suggestive that nasogastric feeding may also be feasible.

Antiprotease, Antisecretory Drugs and Cytokine Antagonist

Gabexate mesilate

Results from meta-analysis[43] conclude that antiprotease gabexate mesylate can reduce complication rate of AP (OR 0.7, 95%CI 0.56-0.88). However, the benefit is modest (NNT = 26) and not decreased the mortality rate.

Somatostatin and Octreotide

In the meta-analysis by Andriulli[43], somatostatin and octreotide can reduce mortality of severe AP (OR 0.39, 95%CI 0.18-0.86, NNT = 14) for unclear reason because it does not reduce the complication rate of AP. Furthermore, recent large multicenter RCT of 302 patients fails to show any benefit of octreotide[44]. At presence, somatostatin or octreotide are not recommended in severe AP.

Platelet-activating factor (PAF) antagonist

Although initial study with PAF antagonist, lexipafant seemed to be promising[45], later multicenter study failed to show any benefit of lexipafant[46]. Thus, its use is not recommended.

Antibiotic Prophylaxis in Pancreatic Necrosis

Strategy of antibiotic prophylaxis in patients with pancreatic necrosis was proposed based on the facts that incidence of infected pancreatic necrosis varies from 30-70% of pancreatic necrosis and mortality rate of infected pancreatic necrosis is ~30% or ~3 fold increase from sterile necrosis (~10%). Differentiation between sterile and infected necrosis is usually difficult. Moreover, fine needle aspiration (FNA), which is the most accurate tool is not widely available. Thus, strategy of prophylaxis with broad-spectrum antibiotics that act on gut flora has been used in order to reduce the incidence of infected pancreatic necrosis (Table 6).

Results from the controlled trials above[47-51,54] and 3 meta-analyses[57-59] concluded that prophylactic antibiotics reduce the incidence of infected pancreatic

Table 6 Controlled trials of antibiotic prophylaxis in patients with pancreatic necrosis

Author	Year	Antibiotics	Dose	No. of Patients	Mortality	Pancreatic Infection
Systemic antibiotics vs Placebo						
Pederzoli[47]	1993	Imipenem	500 mg IV q 8 hr	41	7%	12%*
		None		33	12%	30%
Sainio[48]	1995	Cefuroxime	1.5 g IV q 8 hr	30	3%*	30%
		None		30	23%	40%
Delcenserie[49]	1996	Ceftazidime +	2 g IV q 8 hr	11	9%	0
		Amikacin +	7.5 mg/kg IV q 12 hr			
		Metronidazole	500 mg IV q 8 hr			
		None		12	25%	58%
Schwarz[50]	1997	Ofloxacin +	200 mg IV q 12 hr	13	0	62%
		Metronidazole	500 mg IV q 12 hr			
		None		13	15%	54%
Nordback[51]	2001	Early Imipenem	1 g IV q 8 hr	25	8%	8%* (Surg)
		Late Imipenem	1 g IV q 8 hr	33	15%	36% (Surg)
Spicak[52]	2003	Prophylactic meropenam	500 mg IV q 8 hr x 10 days	20	20%	25% (Infect rate)
		Treated meropenam	500 mg IV q 8 hr	21	24%	33% (infect rate)
Isenmann[53]	2004	Ciprofloxacin +	400 mg IV q 12 hr	41	7%	17%
		Metronidazole	500 mg IV q 12 hr			
		None		35	11%	14%
Selective intestinal decontamination of the gut vs Placebo						
Luiten[54]	1995	Norfloxacin	50 mg PO × 4	50	22%*	18%*
		Colistin	200 mg PO × 4			
		Amphotericin	500 mg PO × 4			
		Cefotaxime	500 mg IV q 8 hr			
		None		52	35%	38%
Comparison between antibiotics						
Bassi[55]	1998	Imipenem	500 mg IV q 8 hr	30	10%	10%*
		Pefloxacin	400 mg IV q 12 hr	30	24%	34%
Manes[56]	2003	Meropenem	500 mg IV q 8 hr	88	14%	11%
		Imipenem	500 mg IV q 6 hr	88	11%	14%

**Statistically significant versus control groups*

necrosis as well as mortality rate. The most recent Cochrane review concluded that antibiotics reduce the incidence of infected pancreatic necrosis with OR = 0.51 (95%CI 0.26-0.98) and also the mortality (OR 0.32, 95%CI 0.12-0.81)[59]. Most current recommendation guidelines support the use of systemic antibiotics that have high pancreatic tissue level i.e. imipenem, meropenem, or quinolone plus metronidazole for at least 2-3 weeks in patients with documented pancreatic necrosis[4-6].

Recently, there have been 2 RCTs, which are the first 2 "double blind" trials of antibiotic prophylaxis in AP so far. Both studies could not demonstrate benefit of prophylactic antibiotics, meropenem[52] or ofloxacine plus metronidazole[53] compared to "on demand" antibiotics (administered only when infection was clearly documents, i.e. clinical septicemia or positive FNA)[52, 53]. Reason for the lack of benefit in these 2 studies is unknown, but some proposed that in the study by Isenmann[53], most patients had pancreatic necrosis <30%. Incidence of infected pancreatic necrosis is known to be higher with the more extent of necrotic area, particularly necrotic area >50%[38]. In addition, patients in this study were also not very sick as reflected by the mean Ranson score of only 2-3. The effects of enteral nutrition, which has gained popu-

larity during the last few years may also be a factor. Enteral nutrition was found to be able to prevent bacterial translocation in AP, thus, theoretically, may decrease the incidence of pancreatic infection. Although most studies in the past[47-51,54] did not report how many of their patients received TPN, however they possibly did. Early enteral feeding may contribute to the low rate of pancreatic sepsis in the recent studies. At present, though the role of antibiotic prophylaxis in pancreatic necrosis is still controversial, in practice, it may be used in selected cases, e.g. area of necrosis >50%, associated with organ failure, or in case whose enteral feeding cannot be initiated.

In some instance, patients with severe AP may be too sick or have renal failure, that prohibit contrast-enhanced CT. MRI with gadolinium injection has recently shown to be an alternative to CT scan although it should be further verified[60]. Elevated CRP is also accurate to predict pancreatic necrosis, particularly for exclusion due to its high negative predictive value for pancreatic necrosis[29]. In case all the above options are unavailable, antibiotic prophylaxis may be reasonably initiated in patients with clinically severe AP[59].

After initiating prophylactic antibiotics, clinical response should be evaluated daily. If gradual clinical improvement continues, antibiotic should be continued for at least 2 weeks. However, if no improvement was seen after 7-10 days or whenever patients get worse, prompt FNA is indicated.

Fine Needle Aspiration (FNA) of Pancreatic Necrosis

Indications of FNA for differentiating sterile vs. infected pancreatic necrosis are[5]:

1. Patients with pancreatic necrosis and clinical features of sepsis syndrome (Recommendation grade B)

2. Patients with pancreatic necrosis who are deteriorated or fail to improve after antibiotic prophylaxis for 7-10 days

Technically, FNA can be done either by CT-guided[61] or US-guided[62]. Both Gram's stain and culture are equal sensitive and specific to diagnose infected pancreatic necrosis (~90%).

Documented infected pancreatic necrosis is clearly indication for surgery. Patients with negative FNA (or sterile necrosis) eventually almost always respond to conservative treatments. Antibiotic prophylaxis may be continued. CT scan and FNA may be needed to repeat weekly if there is still no clinical improvement after full conservative treatment. Patients with sterile necrosis but fail to improve, for example persistent organ failure, abdominal pain, or intolerable to feeding after full conservative treatment (i.e. >4 weeks) are also considered relative indications for surgery by some recommendations. (See "Indications of surgery in patients with severe acute pancreatitis")

Role of ERCP in acute gallstone pancreatitis

To date, there have been 4 RCTs, 3 in full papers[63-65] and 1 in abstract[66] that study the role of ERCP in acute GS pancreatitis. The conclusions are:

1. In mild acute GS pancreatitis, there is no role of urgent ERCP.

2. In acute GS pancreatitis with concomitant ascending cholangitis, urgent ERCP (within 72 hours) is

Table 7 Results of 4 RCTs on the role of ERCP in acute GS pancreatitis

Authors	Timing of ERCP	N	Severity	Complications (%)		Mortality (%)	
				Control	ERCP	Control	ERCP
Neoptolemos[63]	<72 hr	121	Mild	14	14	0	0
			Severe	54	18	13	0
Fan[64]	<24 hr	127	Mild	17	18	0	0
			Severe	54	13	18	3
Combined 2 Studies[67]		**248**	**Mild**	**16**	**16**	**0**	**0**
			Severe	**54**	**15**	**15**	**2**
Nowak[66]	<24 hr	250	NR	34	13	11	1
Folsch[65]	<72 hr	238	NR	51	46	6	11

NR = Not reported

recommended, since studies showed the significant reduction of local, systemic complications and mortality (Table 7)[63,64].

3. In severe acute GS pancreatitis without ascending cholangitis, role of ERCP is less clear. In the UK study[63], when doing subgroup analysis only severe pancreatitis without jaundice or cholangitis, complication rate was still significantly less in the ERCP group compared to placebo (15% vs 60%)[67]. In contrast, in the German study[65] which excluding patients with cholangitis, ERCP had no benefit and had more complication, particularly respiratory failure. However, this study was widely criticized because it was multicenter study but many centers included only 1-2 patients per year during the study. Thus, the competency of endoscopists was doubted and might result in the high complication rate of ERCP group in this study[67].

Currently, the Japanese Society of Emergency Abdominal Medicine 2002 recommends ERCP in both patients with cholangitis and severe GS pancreatitis (recommendation grade B)[6], similar to the previously released UK guidelines 1998 (recommendation grade A)[2]. However, the most recent guideline to date by the International Association of Pancreatology 2002 recommends ERCP only in patients with cholangitis (recommendation grade B), while in severe GS pancreatitis, the role is inconclusive[5].

Surgery

Indications of surgery in patients with severe acute pancreatitis[5]

1. Patients with documented infected pancreatic necrosis by Gram stain or culture of FNA or the presence of gas in pancreatic necrosis from CT (Recommendation grade B)

2. Selected patients with sterile pancreatic necrosis with unimproved organ failure after receiving full conservative treatment. (Recommendation grade B)

The appropriate timing of surgery should be after the 3rd or 4th week and try to avoid surgery during the first 14 days. (Recommendation grade B)

Surgery for prevention of recurrent GS pancreatitis[5]

In mild GS pancreatitis, cholecystectomy should be done in the same admission whenever the patient is improved (Recommendation grade B). In severe GS pancreatitis, cholecystectomy can be done when patient get improvement and abdominal inflammation is resolved (Recommendation grade B).

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