

## Delayed surgical therapy reduces mortality in patients with acute necrotizing pancreatitis

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### Abstract

**Objective:** To review the trends in management and analyze the factors influencing outcomes of acute necrotizing pancreatitis.

**Methods:** It was a retrospective analytical study. All adult patients with computed tomography with proven necrotizing pancreatitis managed at the department of surgery, Aga Khan University Hospital, Karachi were included in this study extending from January 1998 to January 2008. Outcome variables were hospital stay, complication rate and in-hospital mortality. Data analysis was carried out using SPSS version 16. For comparison, Pearson chi-square test, Fisher's exact test, t-test and ANOVA were used, where applicable. A p-value less than 0.05 was considered statistically significant.

**Results:** Of 1479 patients, 47 patients were included. Median age was 48 (range: 38-56) years with 31(66%) males and 16(34%) females. Overall out of 18(38%) that underwent necrosectomy, 16 had infected acute necrotizing pancreatitis while the rest were negative. Computed Tomography and/or FNAC identified 18 infective acute necrotizing pancreatitis patients, 16 underwent necrosectomy, one patient expired without surgery and the other was managed conservatively. Enteral nutrition was widely used with rising trend of oral feeding from 2006 onwards. Complication rate was 63%. Overall mortality remained 9/47(19.7%), where in infected ANP as well as in postoperative patients, mortality was 7/18 (38.9%). The patients with early pancreatic necrosectomy had prolonged hospital stay, more complications and statistically significant increase in in-hospital mortality.

**Conclusion:** Better outcomes were achieved in infected acute necrotizing pancreatitis with delayed pancreatic necrosectomy and the other contributing factor could be early enteral nutritional therapy.

**Keywords:** Acute necrotizing pancreatitis, Mortality, Karachi (JPMA 61:973; 2011).

### Introduction

Acute pancreatitis has been considered as a disease of obscure pathogenesis, with numerous causes, few effective remedies and an unpredictable outcome.<sup>1</sup> Necrosis, one of its grave complications, occurs in up to 20% of patients with mortality rates of 10-25%. Superimposed infection on necrosis occurs in 40-70% of patients and may increase mortality rate up to 40%. In the last two decades, the mortality due to acute necrotizing pancreatitis (ANP) has

decreased significantly because of; better understanding of pathophysiology, improved health care systems and sophisticated diagnostic techniques.

Simple schematic flow chart showing the pathophysiology of ANP<sup>2</sup> is depicted in Figure. This flow chart highlights few important implications: (1) The disease has early toxic and late septic phase, so the management and prognosis depends on the time of arrival in the hospital, (2) early 72 hours are critical for management specially the fluid resuscitation, (3) severity stratified care based on Ranson's or

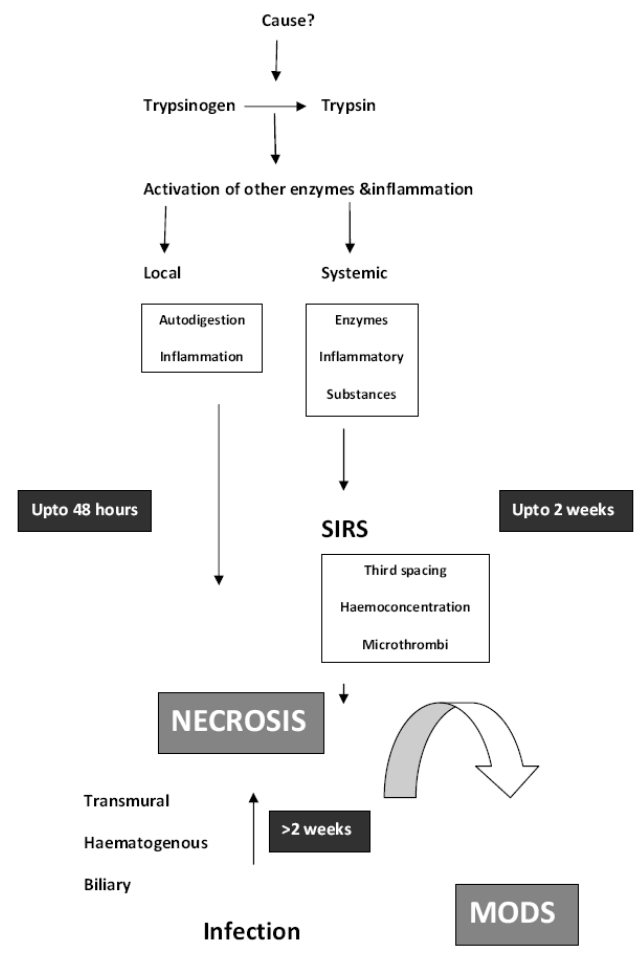


Figure: Flow chart showing Pathophysiology of Acute Necrotizing Pancreatitis.

APACHE-II (Acute Physiology And Chronic Health Evaluation) score may defer or impede the complications.<sup>2,3</sup>

Although early aggressive but clinically appropriate resuscitation has been proved to be of prime importance in initial three days, however, there are other issues which are still controversial i.e. nutrition, timing of surgery and prophylactic antibiotics.

Enteral route of nutrition is now widely accepted due to better septic and metabolic profile than parenteral; but whether to use nasogastric or nasojejunal feeding is still controversial. Early surgery has been shown to be associated with increased mortality; therefore, it is now a widely accepted practice to delay the surgery. The issue of prophylactic antibiotics in severe acute pancreatitis is still controversial; although to date available systemic reviews conclude that prophylactic antibiotics decrease mortality, but significant difference on pancreatic infection, operative treatment rate or fungal infection has not yet been established.<sup>4</sup>

The current study was undertaken with the aim of

reviewing the management and outcomes of ANP patients presenting over a period of ten years at a tertiary care hospital in Karachi. We have tried to analyze the current controversies regarding the management of ANP in the light of ten year data from our center.

## Patients and Methods

We conducted a retrospective analytical study based on case note review of patients admitted under care of Department of Surgery at a tertiary care hospital in Karachi from January 1998 to January 2008.

The hospital's computerized data base with ICD - 9 - CM (International classification of diseases, Ninth revision, Clinical modification) coding system was queried for code-577<sup>3</sup> to identify patients with acute pancreatitis admitted during the 10 years study period. CT scan reports were reviewed for necrosis and patients with CT proven necrotizing pancreatitis were included in the review. Patients with acute on chronic pancreatitis, less than 14 years at age, incomplete records and those who were operated outside our hospital were excluded.

Data was collected for the following variables: demographic status, co-morbid, clinical presentation, laboratory data, radiology and microbiology reports, surgical details and outcomes. Outcome variables were length of stay, complication rate and in-hospital mortality.

Diagnosis of Etiology was made after complete review of patient's records. It was labeled as non-alcoholic, no-gallstone if no clue was found. Severity stratification was done using computerized software for APACHE-II (Acute Physiology and Chronic Health Evaluation) score. Surgery was considered early if it was done within 15 days of disease onset. Indications of surgery were clinical suspicion of infected ANP, radiological signs of infected ANP, fine needle aspiration (FNAC) of the pancreatic necrosis and any other life threatening conditions like bowel perforation. In contrast to enhanced CT scan, unenhanced areas in pancreas with background signs of pancreatitis were labeled as necrosis and presence of blebs of air inside these unenhanced areas were considered as sign of infected necrosis. Condition of the patient at the time of admission was considered in systemic inflammatory response syndrome (SIRS) or organ failure using the criteria from the Atlanta Symposium.<sup>5</sup>

All data was collected on a proforma specifically designed for the purpose. The data was entered twice by two different data entry operators in EPIDATA (version 3.1). The data entry was considered as valid if the error rate was less than 0.3 %. The final data was converted to Statistical Package for Social Sciences (SPSS) version 16.0 (Copyright SPSS Inc., 1989 - 2007) for analysis. All data analysis was carried out using SPSS version 16.0. For quantitative data,

means  $\pm$ Standard deviation were calculated. For quantitative data with skewed distributions, medians and inter quartile ranges (IQR) were obtained. We used the Pearson chi - square test and Fischer's exact test to assess differences in categorical data between the groups. Quantitative normally distributed data was assessed by independent sample t - test and ANOVA if assumptions were fulfilled, otherwise Mann - Whitney U test or Kruskal Wallis test was used. For the difference of hospital stay, among the groups pairwise comparison with Turkey test was done. For all purposes, P-value less than 0.05 were considered statistically significant.

## Results

After evaluating the CT scan reports of 1479 patients, 47 patients were included in the study according to the inclusion and exclusion criteria. Age of patients (median with IQR) was 48 (range: 38-56) years with 31 (66%) males and 16 (34%) females. Fifteen patients presented directly at our hospital, where 32 (68%) were either referred to or shifted from other hospitals. Etiology and sources of nutrition are summarized in Table-1. Complication rate was 63%. Overall mortality remained 9/47 (19.7%), where infected pancreatic necrosis and postoperative patients, mortality was 7/18 (38.9%).

Necrosectomy was done in 18/47 (38%) patients. Out of these 18, sixteen had infected necrosis. Six patients were operated early and surgery was delayed in 12 patients. The outcomes of these patients are compared and summarized in

**Table 1: Clinical Data of Patients.**

Characteristics	n (%)
<b>Etiology:</b>	
Gallstones	22 (46%)
Alcohol	4 (9%)
Post ERCP	1 (2%)
Idiopathic	20 (43%)
<b>Source of Nutrition:</b>	
Nasojejunal	30 (64%)
NJ+Parenteral	8 (17%)
Oral	8 (17%)
Nasogastric	1 (2%)
<b>Condition on Admission:</b>	
SIRS	19 (40%)
Single Organ Failure	7 (14%)
Multi Organ Failure	4 (8%)

Abbreviations: NJ= nasojejunal, SIRS= severe inflammatory response syndrome.

**Table-2: Outcomes of patients.**

Outcome	Early Surgery (N=6)	Delayed Surgery (N=12)	No Surgery (N=29)	P-Value
Hospital stay $\text{¥}$	38 (60)	32 (25)	10 (11)	0.0071
Complication rate	5 (83%)	11 (91%)	14 (48%)	0.0182
In hospital mortality	3 (50%)	4 (33%)	2 (6.9%)	0.0503

$\text{¥}$  (Mean $\pm$ CI), 1 ANOVA, 2 Chi-square test, 3 Fisher's Exact Test.

**Table-3: Comparison of variables & outcomes in initials vs referrals.**

	Initials (n=15)	Referrals (n=32)	P-Value
APACHE-II $\text{¥}$	6 (6)	8 (7)	0.252 <sup>1</sup>
Balthazar Score $\text{¥}$	6 (4)	6(4)	0.636 <sup>1</sup>
Condition on Admission			
SIRS -	6 (40%)	13 (40%)	0.114 <sup>2</sup>
Single organ failure-	-	7 (21%)	
M.O.D.S -	-		
Pancreatic Infection	3	15	0.072 <sup>3</sup>
Extra Pancreatic Infection	2	11	0.123 <sup>3</sup>
Necrosectomy	4 (26%)	14 (43%)	0.343 <sup>3</sup>
Outcomes			
Hospital stay $\text{¥}$	9 (9)	17 (26)	0.258 <sup>1</sup>
Complication rate	7 (46%)	23 (71%)	0.089 <sup>2</sup>
In hospital Mortality	1 (6.7%)	8 (25%)	0.136 <sup>3</sup>

$\text{¥}$  Median(IQR), 1 Mann Whitney U test, 2 Chi-square test, 3 Fisher's Exact Test.

Table-2. Indication of surgery was based on >2 of clinical, radiological or FNA evidence of infection; where one patient was operated due to upper GI bleeding and was found to have duodenal pseudo aneurysm secondary to erosion. In four patients abdominal wall was not closed, whereas in 14 (29.8%) patients abdominal wall was closed over drains.

We found infective necrosis in 18 (38%) patients, based on CT scan criteria and/or FNAC. Necrosectomy was done in 16 (89%) patients with infected necrosis; one died without surgical intervention and one clinically stable patient with signs of infection on CT scan was managed conservatively. The frequencies of cultured organisms were 8 (E.coli), 5 (Acinetobacter), 4 (klebsiella), 3 (Staphylococci aureus, B.cepacia), 2 (Streptococci-D), 1 (S.saprophyticus, Enterococcus, Enterobacter, Pseudomonas, Stenorophomona, Fungal growth) and in two patients culture report was not found.

In six (33%) patients single organism was detected, whereas in ten (56%) >1 organism was cultured. Extra pancreatic infection was diagnosed in 13(27.7%) patients. Fungal growth was found in four (8.5%), one in pancreatic necrosis and rest in urine.

Table-3 summarizes the comparison in profiles of patients who were admitted initially at our hospital versus those who were referred from other centers.

## Discussion

In this study, we compared the outcomes (hospital stay, complications and in-hospital mortality) among patients with acute necrotizing pancreatitis managed with early surgery, delayed surgery or conservatively. We found increased hospital stay, complications and in-hospital mortality in operated patients versus conservatively managed patients.

This study includes data of a large sample of patients

with ANP managed at single centre. There are certain limitations in our study mainly due to its retrospective nature; and the results need to be interpreted in a prudent manner. We experienced major difficulty in getting the severity scores (incomplete Ranson's score in most patients before year 2003), documentation of critical decisions, determining the baseline comparability of groups at the time of intervention, the information about the type and choice of antibiotics whether they were used prophylactically, empirically or therapeutically. We could not find etiology in 20 (46%) patients; which might be due to slippage of stone from common bile duct (CBD), concealed history of alcohol use by the patients, other causes of acute pancreatitis or due to idiopathic nature of the disease.

The mortality rate in 29 conservatively managed patients was 6.9% as compared to a mortality rate of 19.7% in 18 surgically treated patients. Similar findings with the conservative approach have been demonstrated.<sup>6</sup> In some other studies, early surgery is shown to be associated with increased morbidity and mortality.<sup>3,7</sup> It is now widely accepted to defer the surgery as long as possible to optimizing the SIRS and buy time for demarcation of necrotic from viable tissue for blunt dissection.<sup>2</sup> Therefore, the proposed indications for early surgery are acute compartment syndrome and a subset of patients with fulminant, downhill clinical course despite aggressive ICU care.<sup>2</sup>

Every case of necrotizing pancreatitis does not require surgery; the use of surgical modality is limited to those with infected necrosis or its septic complications and patients with several weeks of unyielding supportive care.<sup>2,6,8,9</sup> Even in infected ANP, few studies have reported successful conservative management of selected patients with transient organ failure;<sup>10,11</sup> but this yet needs to be proved by prospective studies. In our study, mortality of patients with infected necrosis was found to be 38.9% as compared to 6.9% in uninfected necrosis patients.

Although difference in outcomes were statistically significant, but on pair wise comparison with Tukey's test, difference of hospital stay between early and delayed surgery was insignificant. The information about the critical decisions and comparability of the two groups at the time of surgery was incomplete or missing, thus limiting us from drawing any conclusion. However, during the entire study period, the strategy remained to delay surgery or manage conservatively. The difference might be due to the worsening condition of patients, which made them vulnerable to early surgery.

Being a hyper catabolic state, acute pancreatitis demands adequate nutritional support. In our study, we found that enteral nutrition had been preferred over parenteral; although we could not determine exact timings and duration of each. Numerous prospective studies,<sup>12,13</sup> a recent meta

analyses<sup>14,15</sup> and International Association of pancreatology<sup>16</sup> have recommended enteral nutrition owing to better septic, metabolic profile and cost effectiveness. Parenteral nutrition should be administered only when enteral nutrition is not feasible i.e. paralytic ileus and should be switched to enteral feeding as early as possible.

Nasojejunal feeding (NJ) was used during entire study period, while we found increasing tendency towards oral feeding after year 2006. Seven patients with computed tomography severity index (CTSI) <6 received oral feeding; all survived without any pancreatic and extra pancreatic infection. On the basis of this finding, oral or nasogastric route may be considered a viable option especially with CTSI <6; however, prospective evidence is required. Although, few studies have shown nasogastric feeding as equally beneficial to NJ feeding in terms of complications with less expertise and more ease;<sup>17-19</sup> yet most surgeons feel wary to practice it routinely, arguing for gastric outlet obstruction or gastro paresis or intolerance.

Surgical jejunostomy at the time of necrosectomy is another option; its safety and success has been validated in few studies with few or no tube related complications.<sup>20</sup> We performed feeding jejunostomy in seven patients; five died of pancreatitis related complications- and two were successfully continued nutrition through this route. Even one study concluded PEG (Percutaneous Endoscopic Gastrostomy) having almost equal efficacy to nasojejunal (NJ) tube feeding.<sup>21</sup>

The use of prophylactic antibiotics in severe acute pancreatitis is a controversial issue. Earlier, prophylactic antibiotics were proved beneficial in severe pancreatitis.<sup>22,23</sup> However, few studies in recent past<sup>24,25</sup> and inconclusive results on infection rate by a systemic review,<sup>4</sup> have brought a paradigm shift away from use of prophylactic antibiotics in all patients of acute severe pancreatitis to CT proven Acute necrotizing pancreatitis only.<sup>2</sup> In our review, various combinations of antibiotics were used; meropenem/ Imipenim/ Tazocin with ciprofloxacin, amikacin or metronidazole. In few patients, triple antibiotics i.e. ceftriaxone, ampicillin and metronidazole were also used, which are reported to have varying or poor penetration in the pancreas.<sup>22</sup> This might be the reason behind growth of resistant organisms in most fungal infections in a few patients who received these combinations.

We can speculate on the basis of this discussion that antibiotic combinations are associated with increased rate of resistance and fungal infections. Here, we must accept the facts that there was a lack of data regarding the rationales behind this changing roster of antibiotics and most of the patients (68%) were referred from other hospitals after receiving various antibiotics. These factors preclude us from

drawing any conclusions about the prophylactic use of antibiotics.

Initial 48 hours are critical in the management; this fact is further strengthened by our study. The delay in presentation of the patients or those referred from other hospitals (without appropriate management), were associated with SIRS, organ failure, infections (pancreatic and extra pancreatic) as well as poor outcomes. These findings are statistically insignificant, nonetheless they are clinically valuable.

As possible in a retrospective study, there was missing data on key prognostic factors including timing of enteral versus total parental feeding and the follow-up data was also incomplete. The indications for early and delayed surgery were not clearly defined but the trends over the period of time were found to be in favour of delayed surgery in infected acute necrotizing pancreatitis (IANP). Two of the patients with IANP were treated conservatively, by intravenous antibiotics and CT guided drainage. This has opened a new dimension in the management of IANP and could be taken as a multi-institution research project to produce evidence base for future management of IANP.

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