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Acute Infected Necrotizing pancreatitis: Have we really found a solution - A single centre experience

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ABSTRACT: Acute infected pancreatic necrosis (AIPN) is the most feared outcomeof acute pancreatitis frequently requiring surgical inventions for its management.Recent years have witnessed a paradigm shift from upfront open surgery to a step-upapproach in the management of AIPN. We have studied the outcomes of patients ofAIPN over a period from Dec 2016 to Nov 2019 at our center
Methods: Retrospective analysis of the database of patients withAIPN at a tertiary care hospital. Clinical aspects, interventions and outcomes were evaluated.
Result :31 cases patients fulfilled the inclusion criteria,one patient had refused further treatment and was excluded from the study. Among 30 cases in the study group, common etiology for AIPN was alcohol in15 (48.4%) cases;gallstone in 12 (28.7%) cases, Post ERCP in 02 cases, Idiopathic in 01 patient and one case was drug-induced (Tab Ramipril). The male to female ratio was found to be 3.4:1and the average age was 44yrs. The mortality rate in patients managed withPercutaneous drain(PCD) was 25.92% (7/27) and those who underwent upfrontsurgery, 57.14% (4/7). Mortality was found to be 67% in patients with age >50yr ascompared to 16%(n=19) in age < 50yrs. Mortality with organ failure was significantlyhigh at 53.8% (7/13) compared to patients who did not have organ failure 22% (4/18).
Conclusion: In AIPN, mortality rates were lower in patients managed by the step-up
approach compared to upfront open necrosectomy. The mortality was also higher inpatients who undergo open necrosectomy after initial management with PCD; inpatients with organ failure and age > 50yrs. However upfront open necrosectomy was done as an emergency procedure and outcomes may not be comparable to the patients who underwent percutaneous drain placement. The mortality in this group was high(57.14%), but the subgroup size was too small for making any recommendations. Further studies may be necessary to address the outcomes in this subgroup

Key words : Acute Infective Pancreatic Necrosis; Acute necrotizing pancreatitis, necrosectomy,

I. INTRODUCTION

Acute pancreatitis has plagued mankind since the early years, and even has been debated to have even conquered powerful men like Alexander the Great.[1]However it took more than 2200 yrs since then to understand the disease better, when, Reginald Huber Fitz in 1889 published his detailed treatise on acute pancreatitis in the Boston Medical and Surgical Journal.[2]Over the next century better understanding of the etiopathogenesis of the disease, led to a gradual improvement in the mortality rates. Data of the last few decades have shown a two-fold increase in the diagnosis of acute pancreatitis, in the corresponding period the case fatality reduced by more than half, even though the population mortality due to Acute Pancreatitis(AP) remained the same.[3] The mortality is seen to correlate with the severity of pancreatitis; and its severe form, necrotizing pancreatitis being fatal in as high as one-fourth of the cases.[4,5] The necrosum gets infected in as much as 40-70% of patient with pancreatic necrosis,[6-8] and the mortality further increases in the presence of infected necrosis.[4,5] Before 2010, open necrosectomy was the primary modality to manage this infected necrosum. The PANTER trial in 2010, lead to a paradigm shift in the management of Infected pancreatic necrosis from a more aggressive upfront surgery to a “step-up approach” where the initial management was by percutaneous drain followed by other lesser invasive procedures like Video assisted retroperitonial debridement (VARD) before attempting surgery only when the patient failed to improve.[9] We have adopted the same practice at our center and in this article brought out an audit of the cases of Acute infected

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pancreatic necrosis and reviwed the available literature.

II. MATERIALS AND METHOD

Retrospective analysis of the hospital database of patients treated foracute infected necrotizing pancreatitis (AIPN)from Dec 2016 to Nov 2019 was done. The data collected from the records were tabulated by demography, clinical course,laboratory parameters,Computed tomography(CT) findings, and interventions.Only patients who were found to have infected necrosis on cross-sectional imaging or bacterial growth on aspirated fluid form necrotic collection, were included in the study. The clinical course,interventions done andthe outcome of the management of AIPN was studied. Perioperative follow up of upto 3 months was done from the hodpital data base, long term follow up of the outcomes was not done.

III. RESULT:

Thirty-one patients with AIPN were included in our study. One patient refused any intervention and was excluded from the study. This study showed male preponderance, with a 24:7 male to female ratio with a median age of 44yrs.Alcohol (n=15) was the most common etiological factor, followed by Gall stone (n=12 patients)(Table I).However, the etiology for AIPD in all 07 female patients wasCholelithiasis. Two cases were Post Endoscopic retrograde cholangiopancreaticography(ERCP)pancreatitis while drug-induced(Ramipril) AIPN was attributed as etiology in one patient; one case the cause could not be determined inspite of extensive investigation and was documented as idiopathic etiology.

The initial investigations revealed that 51.6%(n=16) patients had anemia, 61.3%(n=19) patients had leucocytosis and 58.97%(n=18) patients had hyperbilirubinemia. Contrast enhanced CT abdomen was done between 3-5 days in all the cases from the onset of symptoms. On imaging 64.5%(n=20) of patients were found to have pancreatic necrosis> 30% and 68% (n= 21) patient had CT severity index >6. (Table II)

Most of the patients with AIPN were managed by the step-up approach(n=24), however, 7 patients underwent upfront surgery.

Among 24 patients managed by step-up approach,diagnosis of infected necrosis was made in 15 patients due to air in the pancreatic collection, while the remaining 09 cases did not have imaging evidence of infected necrosis and suspicion was raised due to fever and elevated procalcitonin level. All 24 patients were managed by percutaneous drains(PCD), placed under CT or ultrasonographic guidance. The culture of the necrosum revealedpolymicrobial infection(n=18;75%) in most of the case; only 7 cultures (25%) had monomicrobial infection. Common organisms grown were E. coli, Proteus mirabilis, Pseudomonas, and klebsiella(Table-1).

Out of 24 patients managed with PCD, 16patients(66.7%) recovered.The median time for PCD insertion was 64.54days from the day of onset of symptoms. Eighteen patients required multiple pigtail insertion or upsizing of the PCD catheter while six patients were managed with single pigtail insertion.

In the setting of clinical deterioration, despite upsizing eight patients continued to deteriorate. Among these 08 patients, five (21%) underwent surgical exploration with necrosectomy. The median interval for exploration was 53.4days from the onset of pancreatitis (min 27days, max 78 days from onset of symptoms). There were 04(80%)cases of post-op mortality in patients who underwent open necrosectomy(Table III). The general condition of remaining 03 (12.5%) patients, had deteriorated to a state which precluded them fromsurgical exploration, and therefore they continued to be managed by PCD drainage and culture directed antibiotics. Two of these three patients died of persistent sepsis and organ failure. One patient died because of aggravation of underlying coronary artery disease.

In our study, overallmortality in the patients managed with PCD was 25.92%(n=7).
Seven patients had AIPN associated complicationsand therefore underwent upfront surgery.Among these 07 cases, two had perforation peritonitis, two had an intra-abdominal bleed and one had persistent gastric outlet obstruction. There was 04mortality in these patients who underwent upfront exploration and necrosectomy.

IV. DISCUSSION

The demographics, etiology, mortality, morbidity, and outcomes have not been uniformly comparable in various series previously reported. The inability to predict the onset and outcome, in addition to the lack of uniformity of guidelines in the management of these cases, have only compounded the diversity in the reported outcomes.

In our series, the average age of patients with acute necrotizing pancreatitis was 44yrs (n= 31).The age group of the patient varied from 21 – 67 yrs.This studies done by W.Uhl[10] and Raghu M G et al[11], have also show that the contion is more common in the 4th and 5 th decade. The male

to female ratio was 3.4:1 in our study.The proportion of male patients was higher in our study compared to similar studies by W.Uhl[10](male to female ratio of 1.85:1) and Van Santvoort HC et al[4] (male to female ratio -1.6:1). The common etiology for AIPN was alcohol in 48.38%(n=15) cases and gall stone in 38.7% (n=12) cases.However, western data differed from our findings, wherethe most common etiology of necrotizing pancreatitis was gallstones (46%–48%), followed by alcohol consumption (24%).[4] In the Indian population,while fewstudies have shown that alcohol is a more common etiological factor, this has not been uniformly observed in other studies from the subcontinent .[12,13]

In our study, etiology in all female patients (n=7, 100%)was gall stone; whereas in males, 62.5% (n=15)were due to alcohol intake. (Table IV) This could be explained, because ofethnic and cultural practices in India, women indulge less in alcohol as compared to men. Two cases (5.12%) were ERCP inducedAIPN. In one patient,etiology could not be ascertained despite detailed evaluation, and wasdeemed to have idiopathic cause for AIPN. One case had drug-induced pancreatitis following the use of Tab Ramipril.Drug-induced pancreatitis (DIP) is a relatively rare entity, and its incidence is reported between 0.1 and 2% of acute pancreatitis cases.[14] Only a few case reports have been published regarding ramipril induced acute pancreatitis.[15]Pathophysiology for development of pancreatitis due to ramipril is not very well understood, though Pancreatitis associated with Angiotensin Converting enzyme (ACE) inhibitors(like Ramipril) is thought to be a result of localized angioedema of the gland.[16]

In our series of the 24 (77%) patients who underwent treatment with PCD, 16 (67%) cases recovered without any further intervention.The common indications for multiple pigtails were undrained/inadequatly drained collection and new localized collection. The first pigtail insertion was done at an average of 50.75 days from the onset of symptoms (min 24 days and max 108 days from onset of symptoms). In a study by Deshpande A et al, the average time to first intervention for infected necrosis was 19.21 days, with the earliest intervention being on12th day of onset of symptoms.[17] However delay in the intervention (of approximately 3-5 weeks) allows liquefaction of necrotic tissue andallows the necrosum to become better defined (walled-off). This makes drainage/necrosectomy easier and more complete.[18]

In our study,PCD was found to be successful in avoiding open necrosectomy in 67 % of cases. The mortality in patients managed with PCD was 25.92%(n=7) which was higher as compared to other studies.A systemic review of 11 studies(384 patients), showed that surgical necrosectomy could be avoided in 56% of the patients. The overall mortality rate in the study was 17%.[19] Another systematic review showed that the percutaneous approach alone was successful in 50.8% of patients without the need for another surgical intervention, with a mortality of 13.6% in cases managed by the step-up approach.[20]

Overall, 35% (11/31) of the patient died in the hospital or within 3months of the onset of pancreatitis.The Overall mortality reported in various studies varied from 13.6% to up to 30%.[20,21]This wide variation and heterogeneity in the outcome, refects the relative difficultly in the management and diversity of outcome at various centers. The mortality rate in patients managed with PCD was 25.92% (7/27). Among the 07 patients who underwent upfront necrosectomy, surgery was performed in an emergency/urgent setting with the patient in compromised physiological state; consequently resulting in poorer postoperative outcome andhighermortality(57.14%; n=4).Previous studies, including the PANTER trial, failed to demonstrate a difference in mortality between the surgical and step-up group.[9]However the PANTER trial, the patients in both groups were relatively stable and surgery was conducted electively.The mortality in patients managed with PCD in our study was found to be comparable to other studies(25.92% vs18-27%).[9,18,19]However, the mortality in upfront surgery patients was found to be higher in our study(57% vs 30%)compared to other studies.[19,22]In our series, patients underwent upfront surgery, in an emergency setting in 4 patients, with stormy post-operative recovery and high mortality. Higher mortality among the cohort of patients who underwent emergency surgery is likely due to surgical insult in a physiologically compromised state. Pancreatitis and its complications are known to be associated with cytokine storm leading to SIRS; infected pancreatic necrosis further complicates the condition due to the progression to sepsis and organ failure.[23]

In our series mortality was found to be 67% in patients with age >50yr which was higher comparedto patients of age <50yrs (16%; n=19)(Table IV). In a study from Bristol, the death rate for those patients over the age of 60 years was 28% compared with 9% in younger patients.[24]Similarly, a Hong Kong study revealed

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a mortality of 5.9% in those under 50yrs, which was significantly lower compared to the mortality of21.3% in thoseaged over 75 yrs.[25]

The mortality in cases due to Alcohol-induced pancreatitis was found to be higher i.e.33% (n= 5) compared to 25%(n=3) in cases of gall stone induced AIPN.

A review of 14 observational studies by Petrov et al found that, when organ failure is associated with infected pancreatic necrosis, the mortality was higher compared to patients who did not have infected necrosis (30% vs 32%, p=0.0007).[5]In our series, among patients with organ failure, the mortality rate was significantly high 53.8% (7/13) compared to patients who did not have organ failure 22% (4/18). In a meta-analysis by Werge et al, the mortality in patients with organ failure was found to be 40% which was lower compared to our study, however, mortality in patients without organ failure was between 20-30% which was comparable to our studies.[4,5]

In this series, efforts were to manage all cases by the step-up approach as per established protocols and upfront surgery was mainly reserved for emergency cases. Therefore the cohort of cases managed by the step-up approach and by upfront surgery cannot be compared in terms of outcomes and mortality. Also as our center is a referral center for multiple peripheral hospitals, most of the cases presented after 5-15 days of onset of symptoms. Standardization in management, in terms of aggressive fluid resuscitation, prophylactic use of antibiotics, management of early complications, and organ could therefore not be ensured, and subsequent outcome variation by early manipulation of these factors cannot be commented upon.

V. CONCLUSION

Thestep-up approach has already been accecpted as the established line of management in uncomplicated cases of acute pancreatitis with infected pancreatic necrosis. The patients treated with the step-up approach are more stable, have lesser complications, lesser organ failure, and mortality compared to open necrosectomy. With this present management algorithm, patients who require open necrosectomy are those with complications of acute necrotizing pancreatitis or followngfailure of step-up approach. Such patients havehigher morbidity/mortality due to compromised clinical status and organ failure.We have not been able to significantly improve outcomes in these patients. Our study did not have adequate number patients in this sub group to draw conclusions or make recommendations to address this problem. Further research may be necessary to address this difficult problem.

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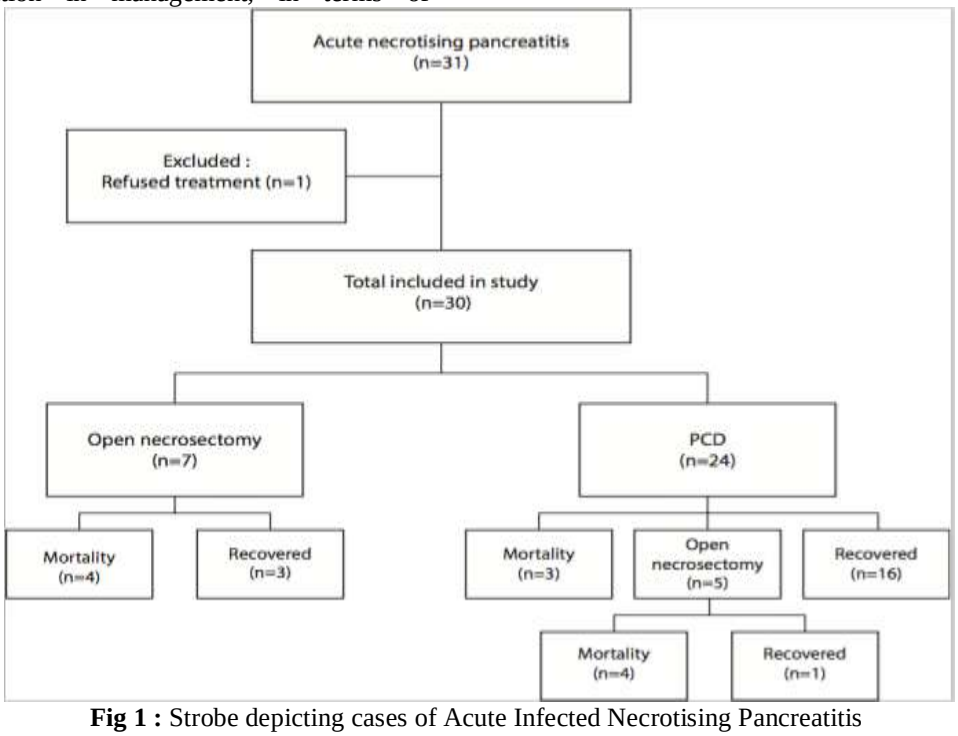

Fig 1 : Strobe depicting cases of Acute Infected Necrotising Pancreatitis

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Table I – Demographic distribution of cases

No	Parameters	Observation
1	Avg Age	44yrs
2	Male: female ratio	24:7
3	Etiology (n=31)	
	a) Alcohol induced	15(48.38%)
	b) Gall stone induced	12(38.7%)
	c) Post ERCP	2(6.45%)
	d) Drug induced	1(3.22%)
	e) Idiopathic	1(3.22%)
4	Per cutaneous drainage	
	a) Earliest percutaneous drainage	02 days
	b) Late percutaneous drainage	90 days
5	Route of Drainage	
	a) Retro peritoneal	04
	b) Trans abdominal	20
6	Number of pigtail insertion	
	a) One	06
	b) Two/ more than two	18
7	Culture positivity	
	Number	24
8	Bacteria grown	
	a) Proteus mirabilis	4
	b) E Coli	13
	c) Pseudomonas	15
	d) Klebsiella pneumoniae	14

Table II : Evaluation of cases of acute necrotising pancreatitis

Sl No	Investigation	Range	
1.	Hb	>10gm%	<10gm%
		15	16
2.	TLC	Normal	Raised
		12	19
3.	Bil	Normal	Raised
		13	18
4.	SGOT	Normal	Raised
		24	07
5.	SGPT	Normal	Raised
		24	07
6.	Alk Phosphate	Normal	Raised
		18	13
7.	CECT		
	a. Necrosis	<30%	>30%
		11	20
	b. Modified CT Severity index	<6	>6
		10	21

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Table III : Data of cases managed with Surgery

Sl No	Procedure details	PCD group (n = 24)	Upfront surgery (n= 7)
1.	No of cases operated	5	7
2.	Indication		
	a) Failure of Step up approach	5	0
	b) Bleed / perforation/ acute event	0	4
	c) Unresolving WOPN	0	3
3.	Timing of Surgery	53.4 days (27-78 days)	66.6 days (31 – 120 days)
4.	Total death after surgery	04(80%)	04 (57.14%)

Table IV : Distribution of mortality

Sl no	Parameter	Range		P Value
1.	Age	<50yrs(n=19)	>50yrs (n= 12)	0.003
		03(15.78%)	08 (66.66%)	
2.	Sex	Male (n= 24)	Female(n=7)	0.663
		09 (37.5%)	02(28.57%)	
3.	Co morbidity	Absent(n=22)	Present(n=09)	0.534
		10 (45.45%)	3(33.33%)	
4.	Etiology	Alcohol(n=15)	Gall stone(n=12)	0.637
		05(33.33%)	03(25%)	
5.	Organ failure	Present(n=13)	Absent(n=18)	0.069
		07(53.8%)	04(22.22%)	
6.	Modified CT Severity Index	>6(n=10)	<6(n=21)	0.025
		06(60%)	05(23.8%)	
7.	Surgery	PCD group (n=24)	Open necrosectomy (n=07)	0.173
		07(29.16%)	04(57.14%)	

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