

Adherence to Step-Up Approach in Pancreatic Necrosis in Tertiary Hospital: A Retrospective Study

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Conflict of interest: Nil

Abstract:

Background: Acute pancreatitis is a diverse condition that can be potentially life-threatening. The management of infected necrotizing pancreatitis has changed dramatically during the last two decades and continues to evolve with growing experience, new technologies and ongoing research.

Aims and Objectives: The aim of this study was to evaluate the practical adoption of the step-up approach in a tertiary hospital setting and to assess the short- and long-term outcomes associated with this approach.

Methods: This was a retrospective study done in 146 patients who have met the inclusion and exclusion criteria and was divided into two distinct groups: the 'adherence group' who followed the 'step-up approach,' and the 'non-adherence to step-up approach' group. A thorough comparison and analysis was performed between these to identify the success rate, complication rate, survival rate and potential predictors of mortality.

Results: Out of 146 patients, 134 managed with a step-up approach, while 12 patients underwent up front surgery. The study showed an adherence rate of 91.8%. Adherence to step group had a mortality of 22 (16.42%) and nonadherence group had 2 (16.67%) mortality with no statistical difference. The adherence group had a low incidence of new-onset multiorgan failure (9.7%), compared to 25% of the nonadherence group, which was statistically significant. The complication rate (12.66%) was lower in the adherence group as compared to the non-adherence group (50%).

Conclusion: The step-up approach can be utilized in the management of IPN with reasonably good adherence in a vast majority of patients. Future research should focus on the development of novel therapeutic strategies aimed at modulating the disease course in IPN.

Keywords: PANTER Trial, Step-up Approach, Severe Acute Pancreatitis.

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Introduction

Acute pancreatitis is an inflammatory condition that can progress to a severe form known as SAP (Severe Acute Pancreatitis), posing a significant risk of mortality. AP (Acute Pancreatitis) is characterized by the aberrant activation of trypsinogen, infiltration of inflammatory cells, and destruction of secretory cells. Multiple factors contribute to the pathogenesis of AP, including calcium (Ca²⁺) overload, mitochondrial dysfunction, impaired autophagy, and endoplasmic reticulum stress. Furthermore, emerging evidence suggests that exosomes, small extracellular vesicles, may play a role in the pathophysiological processes of various human diseases, including AP. [1] The majority of cases of acute pancreatitis follow a mild, self-limited course without complications. To successfully manage these patients, a multidisciplinary approach involving gastroenterologists, surgeons, interventional radiologists, critical care specialists, infectious disease specialists, and nutritionists is crucial. [2]

The management of these patients involves various critical considerations, including appropriate use of imaging, intravenous fluids, antibiotics, and nutritional support, as well as the type and timing of endoscopic, radiologic, and surgical interventions. [3] The "step-up" approach has gained prominence, shifting surgical procedures from traditional open surgery to less invasive techniques such as PCD (Percutaneous Catheter Drainage), endoscopy, small incision surgery, and video-assisted surgery. These advancements in surgical approaches have been accompanied by updates and revisions to the management guidelines for AP. [4] The prospective randomized controlled PANTER trial in 2010 tested the paradigm shift from surgical open necrosectomy to the "Step-Up Approach." The results demonstrated that the step-up approach is superior to surgical open necrosectomy, as it leads to fewer complications. Notably, a significant proportion of patients can be effectively treated without the need for surgery when using the step-up approach.^[5] Evaluating the practical adoption of the step-up

approach in a tertiary care setting is essential since adherence to this approach requires multi-modal management, specialized expertise, and ample resources that may not be readily available in many healthcare centres. Therefore, the objective of this study is to assess the practical feasibility and implementation of the step-up approach in a real-world tertiary care setting.

Aims and Objectives

In this study we wanted to evaluate the practical adoption of the step-up approach in a tertiary hospital setting and to assess the short- and long-term outcomes associated with this approach.

Materials and Methods

This study was a retrospective observational study conducted at the Department of Surgical Gastroenterology, Asian Institute of Gastroenterology, and Hyderabad from January 1, 2018 to December 31, 2020. The study included patients with proven or suspected pancreatic necrosis.

Inclusion and Exclusion Criteria

Patients who met the following criteria such as proven or suspected pancreatic necrosis as determined by medical records based on clinical presentation with fever, tachycardia, increased total leukocyte count, imaging evidence of walled-off pancreatic collection with the presence of air pockets on CT (Computed Tomography), positive culture of pancreatic or peripancreatic necrotic tissue obtained through FNAC (Fine-Needle Aspiration Cytology), drainage procedure, or operation were included in the study. Patients who do not meet the inclusion criteria, specifically those with necrosis but no signs of infection based on the absence of air on CT or negative culture from the collection were excluded from the study.

Study Procedure

This single-centre retrospective observational study commenced after receiving approval from the Institutional Ethical Committee. Data was collected from medical records, including demographic information, detailed history of illness, duration of symptoms, previous treatments, past medical and surgical histories, physical examination findings, blood tests, imaging tests, and details of medical, radiological, endoscopic, and surgical interventions. The outcomes, results, and any complications were recorded. Additionally, the duration of hospital stay and ICU (Intensive Care Unit) requirements are documented. The step-up approach is defined by the sequence of interventions for infected necrotizing pancreatitis. A treatment sequence that began with medical management and went on to minimal invasive interventions to a percutaneous drain and/or endoscopic intervention was classified as a step-up approach, including

patients who received additional subsequent drains, endoscopic drainage, or any surgical debridement. Operative debridement includes open/minimal invasive necrosectomy, minimally, and VARD (Video-Assisted Retroperitoneal Debridement).

In this retrospective study, the aim was to analyze the adherence and the outcomes of the 'step-up approach' in managing pancreatic necrosis. Patients were treated with medical management, endoscopic intervention, percutaneous intervention, and surgical intervention. The study population was divided into two distinct groups: the 'adherence group' who followed the 'step-up approach,' and the 'non-adherence to step-up approach' group. A thorough comparison and analysis was performed between these to identify the success rate, complication rate, survival rate, and potential predictors of mortality. Treatments that excluded an initial drain and/or endoscopic interventions and went directly to surgical intervention were deemed non-adherence to the step-up approach.

Statistical Analysis

Statistical analysis was performed to analyze and interpret the data. All responses were tabulated in a Microsoft Excel 2019 spreadsheet. Graphical representations were made whenever necessary using Microsoft Excel 2019. The means were compared using the t test or Mann-Whitney U test when appropriate. The proportions were compared by Fisher's exact test or chi-square test when appropriate. All tests were two-tailed, and p value $\leq .05$, differences were deemed statistically significant. Data were analyzed using the IBM-SPSS statistics application, version 25.

Results

The majority of the study population belonged to the 4th and 5th decade. The mean of the study population was 35.84 with a standard deviation of 12.33. There was a male gender preponderance in our study. They contributed 80.0%, while females were 19.2%. A total of 16 out of 146 patients had at least one comorbidity. The most common comorbidity was diabetes (13, 8.9%), followed by hypertension. (7, 4.8%) The mean duration of stay on first admission was 17.73 days with a standard deviation of 15.261 days (ranging from 3 to 88 days). There were a total of 44 patients who required readmissions. Among them, 5 patients got readmission twice, and 2 patients got readmission thrice. The average duration of the total stay was 27.10 days with a standard deviation of 17.38 days. The duration between the onset of acute pancreatitis and the first intervention was analyzed. 97.9% (143) patients intervened more than 4 weeks, and 2.1% (3) patients intervened less than 4 weeks.

The most common aetiology for acute pancreatitis in our study population was alcoholism, followed

by biliary pathology. Idiopathic was the next most common aetiology. The least common were hypertriglyceridemia, hypercalcemia, and pancreas divisum. The majority of patients presented with moderately severe pancreatitis followed by severe pancreatitis in our study population. The most common presentation was pain (78.8%) and fever (79.5%) in our study participants. All of them were febrile and had tachycardia on examination. 4 patients had respiratory failure and renal failure in our study group. The incidence of multi-organ failure was 11%. 51 patients (34.9%) had normal leukocyte counts. 94 patients (64.4%) had leukocytosis. One patient (0.7%) had leukopenia. 77 patients (52.7%) had normal platelet counts. Among 146 patients, 69 patients (47.3%) had thrombocytosis. Hypoalbuminemia was seen in 106 patients (72.6%), whereas only 40 patients had normal serum albumin levels.

The most common organism encountered by our study participants is *E. coli*, followed by *Klebsiella pneumoniae*. However, the majority of the patients' culture report revealed no growth. Out of 146 patients, 113 patients had necrosis extent between 30-50%, whereas 21 patients had <30% necrosis. 12 patients (8.2%) had necrosis >50%. Out of 146 patients, 97.9% had walled off necrosis, whereas only 2.1% patients had acute necrotic collection. The majority of the study participants had two collections followed by a single collection. 26 patients (17.8%) had 3 collections, and 6 patients (4.1%) had 4 collections.

Other features, such as air pockets, were seen in 67 patients; bowel communication was seen in 10 patients; and bleeding/aneurysm was seen in 3 patients. 96 Out of 146 patients managed with oral nutrition, 49 patients required NJ (Nasojejunal Feeding) or FJ (Feeding Jejunostomy). Only 3 patients managed with the TPN (Total Parenteral Nutrition). All patients were administered antibiotics. 12 patients were managed with medical management alone. Among 143 patients who required ICU care, the mean number of days the ICU care needed for the patients was 7.48 days with a standard deviation of 6.328.

Apart from medical management, percutaneous, endoscopic, and surgical interventions were performed in our study participants. A total of 61 patients had undergone percutaneous interventions. Among which 16 patients had undergone both surgical and percutaneous interventions, 19 patients had undergone percutaneous and endoscopic interventions. A total of 51 patients underwent endoscopic interventions. Of 51 patients, 19 patients underwent percutaneous as well as endoscopic interventions, whereas 3 patients underwent both endoscopic and surgical interventions. 2 patients underwent all three interventions. Only 12 patients had undergone

surgical intervention alone where 'step-up approach' was not adhered to and followed. 61 out of 146 patients were managed with percutaneous catheter drainage. Of 61, 28 patients required a second session.

Among 28, 7 patients required a third session. Eventually, 2 patients were treated with a fourth session. 9 out of 146 patients were managed with percutaneous necrosectomy. Among them, 5 patients required a second session. Of which 4 patients required a third session. The technical success of percutaneous intervention was 81.25%, whereas the clinical success was 51.61%. The most common complication encountered in patients who underwent percutaneous interventions was residual collection (23.07%) and pancreatic duct leak (15.38%). No complications were encountered in 53.85% of the study participants. 27 patients had undergone endoscopic drainage, whereas 25 patients had undergone endoscopic necrosectomy. Endoscopic cysto-gastrostomy was performed using SEM (Self-Expanding Metallic) stents in 26 patients and using DPS (Double Pigtail Plastic Stent) in 10 patients. The technical success rate of endoscopic interventions was 95.65%, whereas the clinical success rate was 20%.

The most common complication encountered in endoscopic interventions was residual collection formation (42.86%). One patient each developed fistula, stent migration, and fistula plus residual collection, respectively. 4 patients underwent a minimally invasive approach, whereas 30 patients underwent an open approach. Among them, the most common procedure performed was necrosectomy and necrosectomy with diversion ileostomy with feeding jejunostomy in 33.33% of patients, respectively. The most common complication encountered was wound dehiscence (33.33%). Bleeding, fistula formation, residual collection formation, and incisional hernia were the other complications. Of 146 patients, 91.8% (134) were managed with a step-up approach. The rest of the patients (12, 8.2%) did not adhere to the step-up approach (Figure 1). The mortality rate in our study population was 16.4%, whereas 122 patients (83.6%) were ultimately recovered.

The comparison of variables between the step-up adherence group and non-step-up adherence is analyzed below (Table 1). The continuous variables are mentioned as mean with standard deviation, whereas the categorical variables are mentioned as frequencies. The predictors of mortality are analyzed below (Table 2). The continuous variables are mentioned as mean with standard deviation, whereas the categorical variables are mentioned as frequencies. The extent of necrosis, hypoalbuminemia, and multi-organ failure are significant predictors of mortality in the study.

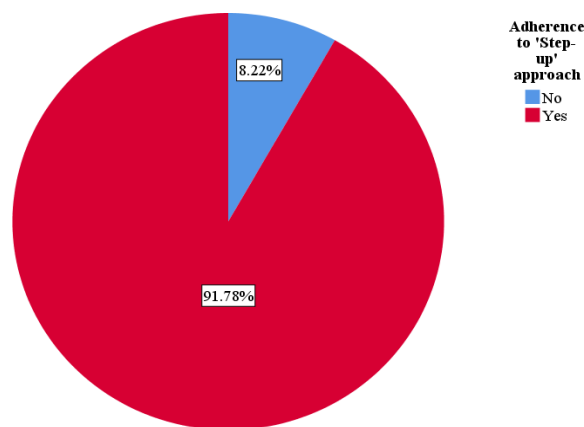


Figure 1: Pie Chart Representing the Adherence to 'Step-Up Approach' in Our Study Population

Table 1. Comparison of Adherence to Step-Up Approach with Non-Adherence to Step-Up Approach

Variables	Adherence to Step-Up Approach (N=134)	Non-Adherence to Step-Up Approach (N=12)	P-Value	Odds Ratio [95% Confidence Interval]	
Age (in years)	35.90 ± 12.260	35.17 ± 13.730	0.845	0.448 [0.189 – 0.653]	
Gender	Male	109 (81.34%)	9 (75%)	0.701	0.688 [0.174 – 1.727]
	Female	25 (18.66%)	3 (25%)		
Comorbidities	Diabetes	12 (8.96%)	1 (8.33%)	0.855	0.734 [0.456 – 0.931]
	Hypertension	7 (5.22%)	0		
	No Comorbidities	115 (85.82%)	11 (91.67%)		
Aetiology	Ethanol	62 (46.3%)	6 (50%)	0.852	0.453 [0.129 – 0.734]
	Biliary	35 (26.1%)	5 (41.7%)		
Total Leucocyte Count (cu.mm)	<4000	1 (0.75%)	0	0.846	0.927 [0.367 – 1.435]
	4000-11000	46 (34.33%)	5 (41.67%)		
	>11000	87 (64.92%)	7 (58.33%)		
Extent of Necrosis	30-50%	101 (75.37%)	12 (100%)	0.148	0.44 [0.336 – 0.589]
	>50%	12 (8.96%)	0		
	<30%	21 (15.67%)	0		
Severity	Moderately Severe	118 (88.06%)	8 (66.67%)	0.079	0.317 [0.059 – 1.700]
	Severe	16 (11.94%)	4 (33.33%)		
Culture Reports	E. coli	25 (18.66%)	3 (25%)	0.518	0.546 [0.335 – 0.712]
	Candida	1 (0.75%)	1 (8.33%)		
	K. Pneumoniae	16 (11.94%)	0		
	Enterococci	1 (0.75%)	0		
	Gram Negative Bacilli	2 (1.5%)	0		
	Serratia Marcescens	1 (0.75%)	0		
	Not available	43 (32.84%)	3 (25%)		
	No growth	44 (32.1%)	5 (41.67%)		
	Pandorae spp.	1 (0.75%)	0		
Serum Albumin (g/dl)	<3.5	102 (76.12%)	7 (58.33%)	0.181	0.439 [0.130-1.479]
	3.5-5.5	32 (23.89%)	5 (41.67%)		
Mortality	22 (16.42%)	2 (16.67%)	0.673	0.316 [0.11 – 0.779]	
Total Hospital Stays (days)	27.07 ± 17.589	27.33 ± 15.646	0.961	0.457 [0.128 – 0.624]	
ICU Stay (days)	7.27 ± 6.334	10.09 ± 5.907	0.155	0.377 [0.226 – 0.567]	
Organ Failure	Single-Organ Failure	6 (4.77%)	2 (16.67%)	0.646	0.558 [0.264 – 0.831]
	Multi-Organ Failure	13 (9.7%)	3 (25%)	0.042	1.387 [0.767 – 1.51]

Complications	Bleeding	3 (2.24%)	1 (8.3%)	0.035	1.002 [0.910 – 1.216]
	Enterocutaneous Fistula	1 (0.7%)	1 (8.3%)		
	Pancreatic Fistula	3 (2.24%)	1(8.3%)		
	Residual Collection	4 (2.98%)	2 (16.67%)		
	Stent Block and Migration	3(2.24%)	0(0%)		
	PCD Block	1(0.7%)	0(0%)		
	Hernia	1 (0.7%)	1 (8.3%)		

Multivariate Analysis of Factors Related to Mortality

Table 2. Multivariate Analysis of Factors Related to Mortality

Factors	Mortality	Odds Ratio [95% Confidence Interval]
Age	0.166	0.31 [0.13 – 0.72]
Gender	0.521	0.11 [0.05 – 0.251]
Comorbidities	0.849	0.80 [0.73 – 0.88]
Total Leucocyte Count	0.163	0.87 [0.74 – 1.03]
Extent Of Necrosis	0.983	1.18 [0.58 – 2.40]
Severity	<0.01	2.37 [1.77 – 3.17]
Culture Report	0.469	0.58 [0.48 – 0.69]
Serum Albumin	0.390	0.87 [0.51 – 1.52]
Adherence To Step-Up Approach	0.951	0.98 [0.49 – 1.96]
Total Hospital Stays	0.215	0.50 [0.34 – 0.73]
Total ICU Stays	0.558	0.90 [0.45 – 1.28]
Single Organ Failure	0.430	0.89 [0.78 – 0.89]
Multi Organ Failure	0.199	0.66 [0.32 – 0.81]
Complications	< 0.01	1.90 [1.33 – 2.71]

Discussion

The management of infected necrotizing pancreatitis has changed dramatically during the last two decades and continues to evolve with growing experience, new technologies, and ongoing research. The PANTER trial by Van Santvoort et al., in 2010 has brought a paradigm shift in the management of infected pancreatic necrosis. The study has shown that one-third of patients were spared from an operation with an equal rate of mortality and lower complications. [5]

A total of 146 patients were enrolled in this study. This included 118 male patients (81%) and 28 female patients (19%). This is similar to the higher incidence of acute pancreatitis and pancreatic necrosis in the male gender. Tam and his colleagues performed a retrospective observational study that compared patients treated in the 'early' pre-PANTER trial period and 'late' post-trial period. Similar to our study, they included 73% male patients. [6] The majority of the study participants were in the 4th or 5th decade, and the mean age was 35.84 with a standard deviation of 12.33. The mean age was 35.90 years with a standard deviation of 12.260 years in the adherence group and 35.17 years with a standard deviation of 13.730 years in the non-adherence group. Similarly, Pawar et al., published their experience in 2021, which included 74% of male patients, and the mean age of their study population was 37.66 years with a standard deviation of 14.41 years. [7]

In our study, the majority of the population (97.9%) intervened after 4 weeks of their onset of acute pancreatitis. The most common aetiology being alcohol, followed by biliary and idiopathic. The most common symptoms were pain and fever, and all of them were febrile and tachycardic. The incidence of multi-organ failure in pancreatic necrosis was 11% in our study, whereas single-organ failure was 5.4%. Respiratory failure and renal failure were commonly encountered. Throughout the literature, there is heterogeneity in the incidence of single-organ and multi-organ failure. The PANTER trial reported 46.59% incidence of single organ failure and 31.82% incidence of multi-organ failure. [5] Leukocytosis was seen in 64.4% of patients, and thrombocytosis was seen in 47.3%. Hypoalbuminemia was observed in 72.6% of the study population. The most common organism encountered in the culture report was *E. coli*, followed by *K. pneumoniae*.

Computed tomography imaging was performed in all patients. The extent of necrosis, type of collection, number of collections, and other notable features were analyzed. 77.4% of patients had pancreatic necrosis extent between 30 and 50%. The majority of them had walled off necrosis (97.9%), while the rest had acute necrotic collection. Most of them had two or more per-pancreatic collections. Air pockets, bowel communication, and bleeding aneurysm were observed in 45.9%, 6.8%, and 2.1% of the study participants, respectively. Out of the 143 patients who required ICU care, their average

duration of ICU stay was 7.48 days, with a standard deviation of 6.328 days. The overall average length of total hospital stay for these patients was 27.10 days, with a standard deviation of 17.38 days. The mean duration of hospital stay in the adherence group was 27.07 days, and the non-adherence group was 27.33 days.

Bakker and his colleagues reported 36 days in the surgical necrosectomy group and 45 days in the endoscopic intervention group. [8] Similarly, Pawar et al. reported 13 days in the endoscopic intervention group and 19 days in the percutaneous intervention group. [7] Tam et al. had an adherence rate of 46%. (6), whereas Ankush Pawar, in their RWON study, only one patient underwent surgical necrosectomy with a 99.6% rate of adherence step-up approach. [7]

Surgical Intervention: A total of 34 patients underwent surgical intervention (4 minimally invasive approach, 30 open approach). The surgical procedures performed are necrosectomy, diversion ileostomy, feeding jejunostomy, abdominal packing, and Video-Assisted Retroperitoneal Debridement (VARD). The complications encountered in the surgical approach group were bleeding, wound dehiscence, residual collection, fistula (enterocutaneous fistula, pancreatic fistula), and hernia. The incidence of multi-organ failure in the adherence group was 9.8% and 25% in non-adherence in our study, whereas single-organ failure was 5.4%. Throughout the literature, there is heterogeneity in the incidence of single-organ and multi-organ failure.

The PANTER trial reported 46.59% incidence of single organ failure and 31.82% incidence of multi-organ failure. [5] A prospective randomized study conducted in 1997 revealed a remarkable reduction in mortality rates with delayed surgical intervention, leading to the early termination of the study. [9] Another study examining different practice patterns over various time periods found that delaying surgical intervention resulted in the lowest mortality rates. [10] Subsequent retrospective reviews and systematic studies further confirmed the benefits of delayed intervention in cases of known infected necrosis, consistently demonstrating lower mortality rates. These findings have been incorporated into national guidelines, which continue to advocate for a delayed intervention approach in the management of necrotizing pancreatitis. [11,12] The successful implementation of the step-up approach has revolutionized the treatment landscape for infected pancreatic necrosis, emphasizing the importance of adopting less invasive interventions to optimize patient care and outcomes. [13] In conclusion, the findings of the study suggest that a significant number of patients with necrotizing pancreatitis can be successfully treated with PCD (Percutaneous Catheter Drainage) without the need for additional

surgical necrosectomy. This highlights the potential effectiveness of PCD as a primary treatment option in managing peripancreatic collections in these patients. [14] In a study conducted by Gomatos IP et al., in 2016, data from patients with necrotizing pancreatitis at the Liverpool Pancreas Centre between 1997 and 2013 were analyzed. In conclusion, advancements in perioperative care and increased experience have contributed to improved outcomes in the treatment of necrotizing pancreatitis. MARPN (Minimally Invasive Retroperitoneal Necrosectomy) plays a significant role in reducing complications and mortality within a multimodality approach, and it should be considered as the initial choice if feasible. [15] In a retrospective study conducted by Wronski et al. in 2017, a total of 70 patients who underwent interventions for necrotizing pancreatitis between January 2007 and December 2014 were included. The study aimed to analyse postoperative morbidity and outcomes associated with minimally invasive intervention or open surgical debridement. Out of the 70 patients, 22 underwent primary open necrosectomy, while 48 were treated using minimally invasive techniques. The findings suggest that minimally invasive treatment should be preferred as the initial management approach for necrotizing pancreatitis over open necrosectomy. [16]

Conclusions

There has been a paradigm shift in the management of IPN (Infected Pancreatic Necrosis) over the last decade, with decreased utilization of upfront open surgical exploration. The step-up approach can be utilized in the management of IPN with reasonably good adherence in a vast majority of patients. Reasons for non-adherence in an experienced institute with multidisciplinary expertise are usually medically justified and, hence, largely unavoidable. Non-adherence to step-up was associated with increased risk of post-procedural complications and multi-organ failure. Patients of IPN with hypoalbuminemia, severe disease > 50% necrosis, and those who develop new-onset multi-organ failure and complications are at a higher risk of mortality. Non-adherence to step-up was not significantly associated with mortality. Future research should focus on the development of novel therapeutic strategies aimed at modulating the disease course in IPN.

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