A Multimodal Approach for the First-Line Treatment of Infected Pancreatic Necrosis

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Objectives: Because infected pancreatic necrosis (IPN) has multiple presentations, not all patients are likely to benefit from the same first-line treatment. Our objective was to evaluate morbidity and mortality in a series of patients treated with a multimodal therapeutic approach.

Methods: Between May 2012 and May 2019, 51 patients diagnosed with IPN were treated. The 5 initial treatment alternatives were as follows: percutaneous drainage, minimally invasive necrosectomy, antibiotics alone, transgastric necrosectomy, and temporizing percutaneous/endoscopic drainage. Initial treatment selection depended on evolution, clinical condition, and extension of pancreatic necrosis. Success, morbidity, and mortality rates were determined.

Results: In terms of determinant-based classification, 37 were classified as severe, and 14 as critical. Percutaneous, temporizing drainage, minimally invasive necrosectomy, antibiotics alone and transgastric necrosectomy approaches were used in 21, 10, 11, 4, and 5 patients, respectively. Necrosectomy was not required in 18 patients (35%). There were no significant differences in mortality among the different treatment approaches ($P < 0.45$). Overall success, morbidity, and mortality rates were 68.6%, 52.9%, and 7.8%, respectively.

Conclusions: The multimodal approach seems to be a rational and efficient strategy for the initial treatment of IPN.

Key Words: infected pancreatic necrosis, acute pancreatitis, necrosectomy, multimodal approach, step-up approach, pancreatic necrosis

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Infected pancreatic necrosis (IPN) is a complication of acute pancreatitis, which results in high morbidity and mortality. Because it can present different clinical and morphological features, not all patients are likely to benefit from the same treatment approach. In the last years, however, most patients with IPN have received percutaneous drainage as first-line treatment.[1,2]

The use of percutaneous drainage (step-up approach) as initial treatment of pancreatic necrosis has become widespread, although evidence shows that its resolution rate ranges between 30% and 40%.[1,3] When initial percutaneous drainage fails, patients require additional necrosectomy with conventional or minimally invasive surgery. Retrospective studies[4] and the only randomized prospective trial[5] in the literature show that patients requiring necrosectomy after initial percutaneous drainage have higher mortality rates than those treated only with percutaneous drainage. Thus, some patients may probably benefit from initial necrosectomy (versus initial percutaneous drainage).

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Given the different presentations and available treatments, patient and treatment selection pose a serious challenge to IPN management. Local lesions and clinical conditions call for a patient-centered approach. To optimize patient management, we have developed a multimodal approach considering all available alternatives for initial treatment of IPN, as opposed to the step-up approach, which consists only percutaneous or endoscopic drainage as initial treatment.

The objective of this study was to assess morbidity and mortality in a series of consecutive patients with IPN treated with a multimodal approach.

MATERIALS AND METHODS

Between May 2012 and May 2019, all patients diagnosed with IPN were treated using the multimodal approach. Necrosis was defined as presence of focal or diffuse well-marginated zones of unenhanced pancreatic parenchyma with contrast density less than 50 HU on contrast computed tomography (CT). We excluded patients with infected acute fluid collections and infected pseudocysts, according to the definitions provided by the International Symposium on Acute Pancreatitis. In suspected cases of infected necrosis (ie, persistent fever, medically uncontrolled multiorgan failure, and increased white blood cell count or C-reactive protein level), patients underwent a contrast-enhanced CT scan to exclude any other cause of instability or infection and so that fine-needle aspiration of all the necrotic collections could be performed using an 18-gauge needle under CT or ultrasound guidance. The infection was confirmed in presence of purulent material on fluid inspection or for positive bacteriologic studies. If the sample was negative, another needle aspiration was performed according to the clinical evolution.

Once IPN was confirmed, the modality of the first-line treatment was decided according to our multimodal approach. In this approach, the selection of the initial treatment alternative depends on the various clinical situations in the context of IPN. Selection is based on evolution at diagnosis of pancreatic infection (early, less than 14 days of evolution; or late, more than 14 days of evolution), clinical condition (severity of inflammatory response at intervention, presence or absence of organic dysfunctions), and local conditions (extent and topography of necrosis and safety of percutaneous access).

Our multimodal approach consists of 5 therapeutic modalities: (1) percutaneous—initial percutaneous drainage followed by minimally invasive necrosectomy if necessary; (2) minimally invasive necrosectomy—initial necrosectomy without previous percutaneous or endoscopic drainage (Necrosectomy is performed transperitoneally using minimally incisions guided by images or retroperitoneal guided by video. This treatment is followed by percutaneous drainage of satellite collections if necessary, or minimally invasive necrosectomy through another incision); (3) antibiotics alone—initial treatment with a broad-spectrum antibiotic alone without intention of percutaneous or endoscopic drainage, if necessary, is followed by percutaneous drainage or minimally

TABLE 1. Clinical and Local Condition for the Election of Therapeutic Modalities

Modality	Percutaneous	Minimally Invasive Necrosectomy	Transgastric Necrosectomy	Antibiotics Alone	Temporizing Drainage
Time of infection	Any	Late	Late	Early	Early
Organic dysfunction	No	Any	No	No	Yes
Safety of percutaneous access	Yes	No	Any	No	Any
Pancreatic necrosis	<50%	>50%	>50%	<50%	Any
Extrapancreatic necrosis—spaces	≤2	≥2	≤2	≤1	Any
Dominant fluid component	Yes	No	Yes	No	Any
Others	No head necrosis	Transperitoneal or retroperitoneal	Walled off necrosis in lesser sac	Without liquid collection	Percutaneous or endoscopic drainage

invasive necrosectomy depending on lesion size; (4) transgastric necrosectomy—performed by endoscopic guidance or by video through an open or laparoscopic cystogastroanastomosis followed by percutaneous drainage or minimally invasive necrosectomy if necessary; and (5) temporizing drainage—initial percutaneous or endoscopic drainage followed by minimally invasive necrosectomy. A temporizing drainage approach is followed in patients with early infection and single or multiple organ failure (sepsis), to stabilize them, control sepsis, and defer an eventual necrosectomy.

Table 1 shows the clinical and local conditions for the election of the different therapeutic modalities, and Figure 1 shows the therapeutic algorithm. Taking as an example the classic denomination of "step-up," in Table 2, we show the names chosen for the different modalities of our multimodal approach.

The following are the types of minimally invasive necrosectomy used: (*a*) image-guided open necrosectomy (A small transperitoneal or retroperitoneal incision is made in the affected area based on CT or perioperatory ultrasound findings); (*b*) video-guided retroperitoneoscopy performed by dilating the previously established percutaneous drainage tract or through minimal lumbotomy (After tract dilation, video laparoscopic trocars are placed to introduce optics and instruments for removal of necrotic tissue. The working cavity can be improved with a low-pressure retropneumoperitoneum); and (*c*) transgastric necrosectomy—when there was a significant bulge to the stomach, it was performed endoscopically; otherwise, a cystogastroanastomosis was performed by a mini incision in the epigastrium guide by imaging or by laparoscopy. In case of endoscopic necrosectomy, in the first session, an internal connection is created between the stomach and the walled-off necrotic cavity, and a cystogastric prosthesis is placed for tract preservation after balloon dilation. Endoscopic necrosectomy is performed in subsequent sessions.

The following data were collected from all patients: epidemiology, severity classification by Determinant-Based Classification of Acute Pancreatitis, computed tomography severity index (CTSI), Sequential Organ Failure Assessment (SOFA) score, interval between onset and treatment, number of catheters used, and treatment duration. Study physicians determined both general and procedure-related morbidity and mortality. General morbidity referred to worsening or new organic dysfunction. Procedure-related morbidity was described as bleeding, pancreatic fistula, gastrointestinal (GI) fistula, intra-abdominal abscesses, and wound infection. Success in each modality was defined when the following parameters were achieved: control of the infection, resolution of the necrotic cavities on imaging, and no requirement for another modality. In temporizing drainage, the success was defined as clinical improvement (reduction in SOFA score and/or inotropic requirement) after drainage. Mortality included deaths between admission and 60 days postdischarge.

Statistical Analyses

Univariate statistical comparisons were performed by using the Student *t* test or Mann-Whitney *U* test for continuous

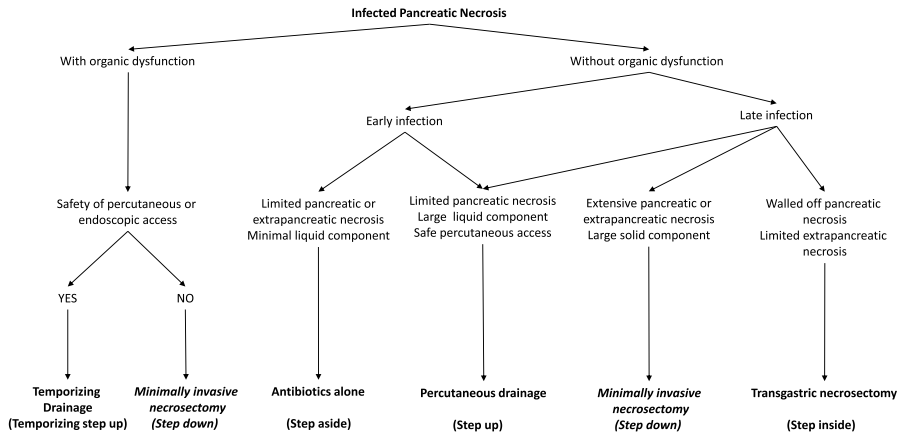

FIGURE 1. Multimodal approach algorithm for the initial treatment of IPN.

TABLE 2. Denomination of Our Therapeutic Modality

Modality	Denomination	Characteristic
Percutaneous	Step up	Increasing order
Minimally invasive necrosectomy	Step down	Decreasing order
Transgastric necrosectomy	Step inside	Endocavitary drainage
Antibiotic alone	Step aside	No invasive treatment
Temporizing drainage	Temporizing step up	Stabilize and control sepsis

TABLE 3. Epidemiological Data From 51 Patients With IPN

Age, mean (range), y	53.5 (23–79)
Sex, female, n (%)	29 (57)
Biliary etiology, n (%)	45 (88)
Severity, n (%)*	
Critical	14 (27)
Severe	37 (73)

*Severity criteria according to Determinant Based Classification.

or ordinal variables and by the χ^2 test or Fisher exact test for categorical variables.

RESULTS

Fifty-one consecutive patients with final diagnosis of IPN were treated between May 2012 and May 2019. Table 3 presents overall epidemiological data. Table 4 shows detailed information on age, sex, and severity for the 51 patients grouped by treatment approach. Patients treated with a temporizing drainage and minimally invasive necrosectomy approach had a significantly higher proportion of critical attacks ($P < 0.01$).

Table 5 presents SOFA score, CTSI, and percentage of pancreatic necrosis, and Table 6 presents SOFA score, CTSI, and percentage of pancreatic necrosis per treatment approach. Patients treated with the temporizing drainage approach had significantly higher SOFA scores ($P < 0.01$). On the contrary, those treated with a percutaneous and transgastric approach presented significantly lower SOFA scores ($P < 0.01$). When the temporizing drainage and minimally invasive necrosectomy approach were used, patients had higher CTSIs ($P < 0.01$). Necrosis <30% was significantly more frequent ($P < 0.05$) in patients treated with a percutaneous approach, and necrosis >50% prevailed in those

TABLE 5. SOFA Score, CTSI, and Percentage of Pancreatic Necrosis in 38 Patients With IPN

SOFA, mean (SD)	3.3 (5.6)
CTSI, mean (SD)	7.43 (1.87)
Pancreatic necrosis, n (%)	
<30%	19 (37.3)
30%–50%	13 (25.4)
>50%	19 (37.3)

treated with the temporizing drainage and minimally invasive necrosectomy approach ($P < 0.05$).

Table 7 presents the interval between onset of attack and delivery of selected treatment, number of percutaneous catheters placed, and treatment duration. The longest interval between onset of attack and treatment was for patients treated with a transgastric necrosectomy ($P < 0.01$). The shortest interval was for the group treated with the temporizing drainage and antibiotics alone approach ($P < 0.01$). There were no significant intergroup differences regarding number of catheters per patient ($P = 0.09$) or treatment duration ($P = 0.24$).

Percutaneous (n = 21)

In 15 patients (71.4%), infection resolved successfully with percutaneous drainage alone. The other 6 patients required minimally invasive necrosectomy; retroperitoneal approach was used in 2, and retroperitoneoscopy in 4. Four patients presented 5 complications (19%) (Table 8). No deaths were recorded.

Temporizing Drainage (n = 10)

Seven patients improved their clinical condition after initial percutaneous drainage. All patients required minimally invasive necrosectomy. Transperitoneal approach was used in 7, and retroperitoneal in 3. Eight patients suffered 15 complications (Table 8), and 3 died from sepsis and multiple organic dysfunction.

Minimally Invasive Necrosectomy (n = 11)

Five patients received minimally invasive transperitoneal necrosectomy, and 6 underwent minimally invasive retroperitoneal necrosectomy. In 7 cases, there was no need for additional treatment. Four developed collections distant from the site of initial necrosectomy, 3 received percutaneous drainage, and 1 retroperitoneoscopic necrosectomy. Six patients experienced 8 complications (Table 8), and 1 died from sepsis and multiple organic dysfunction.

Antibiotic Alone (n = 4)

In 2 patients, infection resolved successfully with antibiotic treatment alone. The other 2 patients required minimally invasive

TABLE 4. Epidemiological Data for the 51 Patients Grouped by Treatment Approach

	Percutaneous	Temporizing Drainage	Minimally Necrosectomy	Antibiotics Alone	Transgastric Necrosectomy
n	21	10	11	4	5
Age, mean (range), y	54.3 (32–78)	60.5 (34–79)	52.4 (23–72)	47.5 (32–62)	44 (28–68)
Sex, female, n	12	6	6	2	3
Severity criteria, n					
Severe	21	2	5	4	5
Critical		8	6		

TABLE 6. SOFA Score, CTSI, and Percentage of Pancreatic Necrosis in the 51 Patients Grouped by Treatment Approach

	Percutaneous	Temporizing Drainage	Minimally Necrosectomy	Antibiotics Alone	Transgastric Necrosectomy
n	21	10	11	4	5
SOFA, mean (SD)	0.16 (0.38)	13.6 (7.2)	2.12 (1.45)	0.75 (0.5)	0
CTSI, mean (SD)	5.2 (1.13)	9.45 (1.64)	8.7 (1.09)	5.50 (0.57)	6.08 (1.09)
Pancreatic necrosis, n					
<30%	16			3	
30%–50%	4	4	2	1	2
>50%	1	6	9		3

TABLE 7. Interval Between Onset of Attack and Treatment, Number of Percutaneous Catheters Placed, and Treatment Duration

	Percutaneous	Temporizing Drainage	Minimally Necrosectomy	Antibiotics Alone	Transgastric Necrosectomy
Time to delivery of treatment, mean (SD), d	42.1 (13.8)	13.22 (4.1)	47.76 (6.1)	11.5 (2.2)	52.16 (4.7)
No. catheters per patient, mean (SD)	2.25 (1.06)	1.37 (0.5)	1.5 (0.7)		0.2 (0.4)
Treatment duration, mean (SD), d	41.6 (17.2)	46.3 (19.51)	35.78 (9.3)	24.5 (12.7)	38.5 (3.8)

TABLE 8. Morbidity in 51 Patients With IPN

	Local Bleeding	Intestinal Fistula	Pancreatic Fistula	Worsening or New Organic Dysfunction
n	5	5	12	7
Percutaneous, n	1	1	2	1
Temporizing drainage, n	3	2	6	3
Minimally necrosectomy, n	0	2	4	2
Antibiotic alone, n	0	0	0	0
Transgastric necrosectomy, n	1	0	0	1

necrosectomy (1 transperitoneal and 1 retroperitoneal). No morbidity or mortality was recorded under this approach.

Transgastric Necrosectomy (n = 5)

Four patients treated with this approach achieved resolution without additional treatment. The other patient required retroperitoneoscopic necrosectomy. One patient suffered from GI bleeding, which was resolved by endoscopic treatment. No deaths were recorded.

Table 8 presents procedure-related complications. There were no significant differences among groups regarding incidence of local bleeding, GI fistula, worsening, or new organic dysfunction. Patients treated with the temporizing drainage and minimally invasive necrosectomy approach had a significantly higher incidence of pancreatic fistula ($P < 0.01$).

Table 9 presents success rate (%) and mortality per approach. There were no significant differences in mortality among the different treatment approaches ($P < 0.45$). Table 10 presents the need for necrosectomy, general morbidity, and mortality for 51 patients.

DISCUSSION

Infection in acute pancreatitis can present differently, and therefore, not all patients are likely to benefit from the same treatment approach. Such situation calls for tailored treatments based on a patient's clinical condition and type of pancreatic necrosis. We developed a strategy that includes all treatment approaches and applied them selectively depending on patient's local and systemic signs. This multimodal approach involves the initial selection of percutaneous drainage, open or endoscopic necrosectomy, or antibiotic treatment. We used this strategy to treat 51 patients with IPN with a success rate of 68.6% and a mortality rate of 7.8%.

During the last few years, the use of percutaneous drainage as initial treatment has been widely used in IPN.[6,7] The first prospective trial PAncreatitis, Necrosectomy versus sTEp up appRoach (PANTER trial),[5] conducted after several retrospective studies, reported that only 88 of 378 patients presented the

TABLE 9. Success Rate and Mortality in the 51 Patients With IPN Grouped by Treatment Approach

	Percutaneous	Temporizing Drainage	Minimally Necrosectomy	Antibiotics Alone	Transgastric Necrosectomy
n	21	10	11	4	5
Success, n (%)	15 (71.4)	7 (70)	7 (63.3)	2 (50)	4 (80)
Mortality, n	0	3	1	0	0

TABLE 10. Need for Necrosectomy, Morbidity, and Mortality in 51 Patients With IPN

Treatment, n (%)	
Without necrosectomy	18 (35)
With necrosectomy	33 (65)
Morbidity, n (%)	
1 or more complications	27 (52.9)
Mortality, n (%)	4 (7.8)

necessary local conditions for percutaneous drainage. These 88 patients with safe retroperitoneal access were randomized to initial percutaneous drainage with or without posterior necrosectomy or conventional necrosectomy through bilateral subcostal incision. No additional necrosectomy was required in 35% of patients treated with initial percutaneous drainage. Mortality was similar in both patient groups. Subgroup analysis, however, showed some differences. In the group treated with initial percutaneous drainage, patients who needed necrosectomy after failure of the initial percutaneous treatment had twice the mortality rate (24%) of those treated with percutaneous drainage alone (12%). The mortality rate of patients who needed necrosectomy after failed percutaneous drainage was also higher than that of patients in the conventional necrosectomy group (16%). The high mortality rate of patients with failed initial percutaneous drainage was also observed in a study by Baudin et al.[8] In this study, 48 patients received initial treatment with percutaneous drainage. Mortality was higher among patients who failed to respond to initial percutaneous drainage than those treated successfully with initial percutaneous drainage (55.6% vs 0). These studies show that initial percutaneous drainage can be detrimental to some patients.

A delayed indication of necrosectomy in patients initially treated with percutaneous drainage can increase morbimortality from inadequate sepsis management. At present, one of the biggest challenges in the treatment of IPN is to identify those patients who would benefit from initial necrosectomy to avoid unnecessary delays (ie, delays resulting from delivering initial percutaneous drainage instead of a more adequate treatment). Various studies have assessed the clinical and tomographic differences between patients who respond and those who do not respond to initial percutaneous drainage. Tong et al[9] and Babu et al,[4] for example, concluded that patients with extensive glandular necrosis, areas of high diffuse density, and a small fluid component are not good candidates for initial percutaneous drainage. Under these conditions, the most appropriate course of action would be initial necrosectomy, rather than percutaneous drainage. In our series, 11 patients presented predictors for the failure of initial percutaneous drainage and, therefore, were successfully treated with initial minimally invasive necrosectomy (step-down approach).

Initial percutaneous drainage is an adequate treatment for cases with a large fluid component and limited glandular necrosis. Table 11 compares patients treated with initial percutaneous drainage in our series with those of the PANTER trial.[5] Our patients presented lower necrosis percentage and SOFA scores. In our series, the success rate was twice as high (71.4% vs PANTER 35%). There were no deaths in our group of patients, whereas PANTER trial reported a mortality rate of 12%. Percutaneous drainage alone has a high success rate when there is adequate patient selection, limited necrosis, and lack of organic dysfunction.

Temporizing drainage is the best indication when early intervention is required in the presence of severe and persistent inflammatory response. In this clinical situation, the goal of percutaneous or endoscopic drainage is to control the inflammatory response. If necessary, drainage catheters serve as a bridge for eventual elective necrosectomy. Unlike the other modalities, local conditions are not taken into account in temporizing drainage because its use is mandatory in patients with organic dysfunctions and early infection. The choice of this modality is based on its mini invasiveness and low morbidity. We used this strategy to treat 11 patients with IPN with a success rate of 70%.

Antibiotic treatment alone has proved effective in patients with limited glandular necrosis, early diagnosis of infection, and no organic dysfunction.[10] In a study by Renzi et al,[11] 12 of 28 patients initially treated with antibiotics required necrosectomy, whereas 14 (50%) did not. We obtained similar results. Of the 4 patients selected for antibiotic treatment, 2 (50%) did not require necrosectomy.

In patients with late infection, transgastric access to walled-off necrosis is feasible when there is contact with the posterior wall of the stomach.[12–15] The endoscopic approach is particularly indicated when the distance between the wall of necrosis and the posterior wall of the stomach is not greater than 2 cm and there is little peripancreatic necrosis. The German multicenter prospective study German multicenter study on Endoscopic PAncreatic Retroperitoneal Debridement,[16] conducted in 6 German centers, showed a success rate of 80%, morbidity of 26%, and mortality of 7.5%. In our series, 4 of the 5 patients selected for this approach were successfully treated by transgastric necrosectomy.

In the multimodal approach, proper selection of initial treatment is based on the onset of infection, clinical condition, and the characteristics of local lesions. Success in each modality was defined when the following parameters were achieved: control of the infection, resolution of the necrotic cavities on imaging, and no requirement for another modality. Our success rate greater than 50% in each modality can be considered as an indicator of the effectiveness of our multimodal strategy. The different clinical and local conditions of patients with NPI prevent a direct comparison between the different therapeutic modalities.

One of the main difficulties in selecting an initial treatment is the lack of a classification covering the broad spectrum of local lesion presentations. The last Atlanta classification only mentions 2 possible forms of evolution for necrosis: acute necrotic collection at an early phase and walled-off necrosis at a late phase. However, in daily clinical practice, not all patients develop walled-off necrosis, and many intermediate stages are not covered by said classification. In fact, local lesions display a spectrum of variable amounts of pancreatic and peripancreatic necrosis. Such situation calls for tailored treatments based on patient's clinical condition and type of pancreatic necrosis. Our multimodal strategy allows

TABLE 11. Comparison of Percutaneous Approach in Our Series and PANTER Patients

	Percutaneous Multimodal	**Step-up PANTER[5]**
CTSI, mean	5.2	8
Pancreatic necrosis, %		
<30%	76	40
30%–50%	19	33
>50%	5	28
SOFA score, mean	0.16	3
Success with percutaneous drainage alone, %	71.4	35
Mortality, %	0	12

us to choose the best therapeutic modality available according to the clinical and local condition of each patient.

CONCLUSIONS

There are multiple options for the initial treatment of IPN. Available treatment alternatives should be adapted to each individual patient instead of using a single approach for all patients. Treatment should be chosen on the basis of organic dysfunction, time of evolution, extension, and localization of pancreatic/peripancreatic necrosis.

This multimodal strategy makes a rational use of the different options for initial treatment of IPN. Its use in 51 consecutive IPN patients resulted in a success rate of 68.6% (ie, successful initial treatment) with an overall mortality of 7.8%. This approach must be validated with future multicenter studies conducted on a larger sample of patients.

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