ENDOSCOPIC DRAINAGE WITH LOCAL INFUSION OF ANTIBIOTICS TO AVOID NECROSECTOMY OF INFECTED WALL-OFF NECROSIS

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SHORT TITLE: Local infusion of antibiotics for infected pancreatic necrosis.

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ABSTRACT:

Background/Objectives: Current treatment of infected pancreatic necrosis (IPN) follows a step-up approach. Our group designed a step-up protocol that associates endoscopic drainage with local infusion of antibiotics through transmural nasocystic catheter. Aim of the study was to evaluate that step-up protocol for IPN in terms of proportion of patients avoiding necrosectomy. M**ethods:** Retrospective analysis of patients admitted with acute pancreatitis (AP) between January 2015 and December 2018. The number of patients who responded to each therapeutic step was analysed: step 1, systemic antibiotics; step 2, endoscopic transmural drainage and local infusion of antibiotics; step 3, endoscopic necrosectomy. **Results**: 1158 patients with AP were included. 110 patients (8.4%) had documented necrotising pancreatitis; 48 of them had IPN (42.6% of necrotising pancreatitis) and were treated with systemic antibiotics. Nineteen patients (39.6% of IPN) responded well and did not required any invasive therapy. Six patients with IPN on systemic antibiotics died within the first four weeks of disease before step 2 could be applied. Urgent surgical therapy in the first 4 weeks was performed in three additional patients. Endoscopic drainage and local antibiotic therapy was performed in the remaining 20 patients; 9 (45% of them) did well and 9 patients underwent necrosectomy (18.7% of IPN). Two patients died on drainage. Overall mortality of AP was 2.53%. **Conclusions:** Endoscopic drainage with local infusion of antibiotics avoids the need of necrosectomy in half of patients with IPN not responding to systemic antibiotics.

INTRODUCTION

Acute pancreatitis (AP) is a frequent and life threatening disease with increasing incidence worldwide [1]. Pancreatic and extrapancreatic necrosis, mainly if infected, is a major determinant of organ failure and mortality in AP [2]. Treatment of sterile necrosis is usually not needed, except in case of clinically significant gastroduodenal, biliary or vascular compression. Infected pancreatic necrosis, however, should be always treated [3].

Infected pancreatic necrosis was a classical indication for open surgical necrosectomy [4,5]. This approach was associated with long hospital stay and high mortality rate [6]. Management of infected necrosis changed importantly over the last decade, mainly due to the results of a series of clinical trials carried out by the Dutch Pancreatitis Study Group. They first showed that a minimally invasive step-up approach, consisting on percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy was superior to open necrosectomy in terms of major complications and death [7]. Interestingly, about one third of the patients in the step-up arm did well with drainage and did not require necrosectomy; this supposed a marked change in the understanding of the management of infected pancreatic necrosis.

An endoscopic transmural approach to drain and to debride walled-off necrosis (WON) has been developed over the last years [8]. This endoscopic approach can be used in a step-up fashion as well, consisting on endoscopic transmural drainage (ETD) followed, if necessary, by endoscopic necrosectomy. The endoscopic step-up approach is equally effective as the minimally invasive surgical step-up approach in terms of major complications and deaths [9]. The endoscopic approach is however associated with a lower risk of pancreatic fistula and a shorter hospital stay than the surgical approach. Based on these results, the endoscopic and the minimally invasive surgical step-up treatment of infected WON have been included in recent clinical guidelines [10-12].

Whether the efficacy of endoscopic drainage of infected WON can be improved by continuous irrigation and lavage of the necrotic cavity is a matter of discussion [13]. In addition, whether the efficacy of the systemic antibiotic therapy can be improved by local infusion of antibiotics into the infected WON is unknown. As a hypothesis, this combined approach of local infusion of antibiotics associated with endoscopic drainage could

improve the efficacy of this therapy by increasing the antibiotic concentration into the necrotic tissue; this could further reduce the number of patients with infected WON requiring necrosectomy.

We have recently reported on the rationale of a protocol of local infusion of antibiotics for infected WON that takes the physicochemical properties, diffusion ability and minimal inhibitory concentration of different antibiotics into account [14]. Aim of our study was to evaluate that step-up protocol for infected WON in terms of proportion of patients avoiding necrosectomy.

METHODS

A retrospective, single-centre cohort study of patients with AP, who were admitted at the Department of Gastroenterology or the Intensive Care Unit of the University Hospital of Santiago de Compostela, Spain, from January 2015 to December 2018 was carried out. Demographic data, procedure details, clinical outcomes, microbiological data, adverse events, and follow-up data were collected.

Patients

Acute pancreatitis was diagnosed by the presence of at least two out of the following three findings: symptoms consistent with the disease, serum amylase and/or lipase levels higher than threefold the upper limit of normal, and presence of computed tomographic (CT) findings of the disease [15]. Severity of AP and local complications were defined according to the revised Atlanta Classification [15]. A contrast-enhanced computed tomography (CT) scan was performed in patients failing to improve after 5-7 days of initial treatment.

Infected pancreatic necrosis was suspected in patients with necrotising pancreatitis by the presence of persistent clinical signs of sepsis or clinical deterioration despite adequate support. The diagnosis was confirmed by a positive culture of the fluid obtained by endoscopic ultrasound (EUS)-guided fine-needle aspiration and/or the presence of gas within the collection on contrast-enhanced CT scan.

Endoscopic step-up approach for infected WON

Patients diagnosed with infected WON were treated by intravenous administration of imipenem/cilastatin or meropenem at standard dose of 1 g every 8 hours. Patients showing no clinical improvement after 5 to 7 days of systemic antibiotics underwent EUS-guided drainage together with continuous lavage and local infusion of antibiotics, while keeping them on systemic antibiotics. Local imipenem/cilastatin was continuously infused at a dose of 250/250 mg diluted in 260 mL of saline every 6 hours (infusion rate of 43.3 mL/h) through a transmural nasocystic catheter (TNC) placed as described below. Imipenem/cilastatin was the initial antibiotic chosen for local infusion to increase antibiotic concentration within the necrotic tissue based on previously reported studies [16]. Local and systemic antibiotic therapy was then modified if needed according to antibiotic susceptibility of cultured germs from the infected WON. Fluid content of the WON was aspirated thorough the TNC four times daily, at the time of changing the infusion bag, to avoid accumulation of fluids into the cavity.

All endoscopic procedures were performed under deep sedation with propofol or general anaesthesia, and under EUS and fluoroscopic control. EUS was performed with a therapeutic linear echoendoscope (3780 UTK Pentax Europe GmbH Hamburg, Germany) attached to an ultrasound equipment (Ascendus, HITACHI, Medical Systems Europe, Zug, Switzerland). Double-pigtail 10 Fr plastic stents (from January to October 2015) and lumen apposing metal stents (Nagi, Taewoong, and Hot Axios, Boston Scientific; from October 2015 to December 2018) were used for ETD. After stent placement, a 7-8.5Fr nasocystic single pigtail catheter was inserted deep in the infected necrotic cavity under fluoroscopic guidance, either in parallel to plastic stents or through the lumen of the metal stent, for continuous lavage and local infusion of antibiotics as described above (*Figure 1*).

Patients showing no significant clinical improvement after 3 to 5 days of ETD and local antibiotic infusion associated with systemic antibiotics underwent endoscopic or surgical necrosectomy as decided by a multidisciplinary team of gastroenterologists, endoscopists and surgeons.

Main outcomes

Primary outcome was the percentage of patients requiring necrosectomy. Proportion of patients responding to systemic antibiotics (first step) and to ETD and local antibiotic

infusion associated with systemic antibiotics (second step) was calculated as secondary variable. Additional outcomes included feasibility of the procedure, technical and clinical success, and microbiological profile of the infected WON.

Statistical analysis

Data are shown as percentages, mean ± standard deviation, or median with interquartile range as appropriate. A descriptive analysis was performed.

Ethical aspects

Local antibiotic infusion associated with ETD is our institutional policy since January 2015. Due to the retrospective design, clinical practice was not influenced in any way by the study. Data were coded for analysis and anonymized once the analysis was finished.

RESULTS

A total of 1324 episodes of AP in 1158 patients (age 66.3±18.0, 697 male) fulfilled inclusion criteria and were analysed. 110 patients (8.42%) had demonstrated necrotising pancreatitis at contrast-enhanced CT scan, which became infected in 48 of them (42.6%) (*Figure 2*). Baseline features of the 48 patients with infected pancreatic necrosis are shown in *Table 1*.

All 48 patients with infected pancreatic necrosis were on systemic antibiotics (imipenem/cilastatin or meropenem), with an appropriate clinical response in 19 of them (39.6% of treated patients). These patients could be discharged without any further therapy and were followed up in our outpatient clinic. Six patients on antibiotics (12.5%) died early at the Intensive Care Unit due to multi-organ failure before any drainage procedure could be performed. Three additional patients on antibiotics at the Intensive Care Unit (6.2%) underwent urgent surgical intervention within the first 4 weeks of disease due to compartmental syndrome and finally died.

EUS-guided transmural drainage with local antibiotic infusion (step 2) was added to systemic antibiotics in the remaining 20 patients (41.7% of patients with infected pancreatic necrosis), who failed to show any relevant clinical improvement after 5-7 days

of systemic antibiotics. Double pigtail 10Fr plastic stents were used for WON drainage in 4 patients, whereas a fully covered lumen apposing stent was placed in the remaining 16 patients. Placing of the TNC was feasible in all cases (technical success rate of 100%). Imipenem/cilastatin was the antibiotic infused locally in all cases as described above. Local gentamicin was added in three patients according to the antibiotic susceptibility test. Clinical features of these patients are shown in table 2.

Infection was initially polymicrobial in fourteen patients and monomicrobial in five. Culture was not successful in the remaining patient. In total, 38 germs could be isolated. Most frequent antibiotic resistance was to penicillin. A second culture after one-week therapy was successful in 14 patients; it was negative in six and monomicrobial in eight patients. Microbiological information is shown in Table 3.

Out of the 20 patients undergoing ETD and local infusion of antibiotics, nine (45%) responded well and no further therapy was required (a percutaneous drainage had to be associated in two patients due to the location and extension of the necrosis). Nine patients (45%) did not improve, and endoscopic (n=6) or surgical (n=3) necrosectomy was carried out. Two patients died due to multi-organ failure on drainage before necrosectomy could be performed. Necrosectomy was therefore carried out in 18.7% of patients with infected pancreatic necrosis.

No complication related to the ETD and the local antibiotic infusion and lavage was recorded. Out of the total cohort of 1158 patients with AP, 33 patients died (global mortality 2.85%); 22 of them died early, within the first two weeks of disease due to multi-organ failure (early mortality 1.90%). Eleven patients with documented infected pancreatic necrosis died due to deteriorating organ failure (mortality of patients with infected pancreatic necrosis 22.92%).

DISCUSSION

The present study shows that endoscopic drainage with local infusion of antibiotics avoids the need of necrosectomy in half of patients with infected WON, who failed to show any significant clinical improvement after 5 to 7 days of systemic antibiotic therapy. By

applying this step-up approach, less than one fifth of the patients with infected pancreatic necrosis who survived underwent pancreatic necrosectomy.

Management of infected WON has evolved over the last decade from the traditional open surgical approach to minimally invasive methods. The PANTER trial supports a step-up approach based on percutaneous drainage followed by minimally invasive surgery over open necrosectomy [7]. An endoscopic step-up approach defined by transgastric drainage followed by endoscopic necrosectomy is a potentially less invasive alternative. This approach has shown promising results in observational and randomized trials [8,17]. The TENSION trial [9] reported similar results for endoscopic and surgical step-up approaches in terms of major complications or death, though the endoscopic approach was superior in terms of lower rate of pancreatic fistulas and shorter hospital stay. Compared with minimally invasive surgery, an endoscopic transmural approach for infected WON, significantly reduced major complications (11.8% *vs* 40.6%), lowered costs ($75,830 *vs* $117,492), and increased quality of life in a recent single-centre, randomized clinical trial [18].

Endoscopic drainage of infected WON in the present study was carried out by transgastric double-pigtail plastic stents or lumen-apposing metal stents (LAMS). Metal stents are usually preferred in this setting [19,20], but a recent randomised controlled trial was not able to demonstrate superiority of LAMS for WON drainage [21]. It is therefore unlikely that the stents used for drainage have had an impact on the results of the present study. From a practical point of view, however, LAMS provide a larger diameter for drainage, which may become important if continuous lavage is applied, and an easier placement of the TNC. In addition, LAMS facilitate necrosectomy when needed.

Several studies and recent guidelines support the use of systemic antibiotics as the first step in the management of infected pancreatic necrosis [10,22,23]. In fact, a relevant proportion of patients with IPN (about 40% in the present study) responds well to this therapy and can be discharged without any further treatment. Failure of systemic antibiotics to eliminate infection in pancreatic necrosis can be at least partly explained by the poor penetration of antibiotics into the necrotic tissue [24]. Antibiotic concentrations within the infected WON could be increased by additional local administration, and thus the same antibiotic given intravenously was used for local infusion.

The addition of a TNC to the ETD to provide irrigation as a method to treat infected WON was firstly described in 1996 [25]. From then, several authors have published their experience in both infected WON and pseudocysts [13,26,27]. Local administration of antibiotics into the infected WON through TNC have been recently reported by Werge et al [28]. The eradication rate of germs infecting the necrosis was increased by infusing vancomycin, gentamicin and amphotericin B locally, suggesting that this may be an additional therapy to systemic antibiotics for infected WON. Based on the analysis of the scientific evidence, carbapenems were preferred in the present study rather than a combination of different antibiotics [14].

Local administration of antibiotics and lavage through a TNC associated with systemic antibiotics allowed avoiding necrosectomy in the present study in about half of the patients with infected WON, who did not respond to systemic antibiotics alone. Globally, the conservative treatment (systemic antibiotics –step 1- and endoscopic drainage with local antibiotics –step 2- without necrosectomy) in the present study was successful in about 60% of the patients with infected pancreatic necrosis, which is in line with previously reported data [29].

An important strength of our protocol is that the microbiological profile infecting the necrosis can be evaluated as often as needed by lavage and aspiration through the TNC. This allows for personalized antibiotic therapy even though few cases are expected to benefit from cultures and antibiotic sensitivity testing. In line with previous reports [30], we found a polymicrobial infection in the majority of patients with infected WON, which becomes monomicrobial or sterile after local and systemic antibiotic administration.

The observational retrospective design, the limited number of patients with IPN and the lack of a control group are the main limitations of the present study. Even though more than eleven hundreds of patients with AP were evaluated, only 48 had confirmed infected pancreatic necrosis. This reflects however real clinical practice in our setting. To what extent the improvement of patients was related to local antibiotic administration or only to endoscopic drainage remains uncertain. However, this is an explorative evaluation of a previously reported protocol for the treatment of infected WON [14]. The results here reported are therefore the basis for controlled trials to evaluate the impact of local infusion of antibiotics in patients with infected pancreatic necrosis.

In conclusion, endoscopic transmural drainage with local infusion of antibiotics through TNC could be an adequate approach in the step-up management of infected pancreatic necrosis. By applying this approach in clinical practice, less than half of the patients with infected WON, who did not respond to systemic antibiotics, required necrosectomy. Whether this approach is superior to drainage alone deserves further investigations in controlled trials.

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Table 1. Characteristics of patients with infected pancreatic necrosis

Characteristic	**n= 48**
Age, median (IQ range), years	63.6 (55-71)
Gender, n (%)	
Male	31 (64.6)
Female	17 (35.4)
Aetiology of pancreatitis, n (%)	
Gallstone disease	25 (52.4)
Alcohol	16 (33.3)
Others	7 (14.6)
Necrotic collection size, median (IQ range), cm	14.5 (11.5-20)
Pancreatic necrosis, n (%), <30% of the gland 30%-50% of the gland >50% of the gland	 15 (31.3) 22 (45.8) 11 (22.9)
Mortality, n (%)	11 (22.9)
Hospital stay, median (IQ range), days	43.5 (27.5-73.0)

IQ range: Interquartile range

Table 2. Characteristics of patients undergoing endoscopic drainage and local infusion of antibiotics.

Characteristic	**n=20**
Age, median (IQ range),years	60 (55-68)
Gender, n (%) Male Female	 16 (80) 4 (20)
Aetiology of pancreatitis, n (%) Gallstone disease Alcohol Others	 11 (55.0) 2 (10.0) 7 (35.0)
Pancreatic collection size, median (IQ range), cm	16.2 (13.0-19.0)
Pancreatic necrosis, n (%), <30% of the gland 30%-50% of the gland >50% of the gland	 5 (25.0) 11 (55.0) 4 (20.0)
Time from onset of pancreatitis to endoscopic drainage, median (IQ range), weeks	6 (4.3-8.0)
Type of stent used for drainage, n (%) Pigtail 10Fr Nagi stent 14-16 mms Hanaro 12 mms Hot Axios 10-15 mms	 4 (20) 6 (30) 1 (5) 9 (45)
Necrosectomy, n (%)	9 (45.0)
Mortality, n (%)	2 (10.0)
Hospital stay, median (IQ range), days	54.2 (32.5-65.5)

IQ range: Interquartile range

Table 3. Individual microbiological profile of infected pancreatic necrosis at different time points before (first culture) and during (second and third cultures) local antibiotic therapy. Antibiotic resistance is shown in parenthesis. Culture was unsuccessful in one patient.

Patient number	**First culture (Resistance)**	**Second culture (Resistance)**	**Third culture (Resistance)**
Patient 1	*Escherichia coli*	*Candida albicans*	*Candida albicans*
Patient 2	*Enterococus faecalis, Staphylococcus haemolyticus* (Penicillin)	*Candida glabatra*	*Serratia marcesens*
Patient 3	*Streptococcus mitis, Candida albicans* (Fluconazole)		
Patient 4	*Enterococus faecali, Klebsiella pneumoniae* (Carbapenem)	*Staphylococcus haemolyticus* (Penicillin)	
Patient 5	*Escherichia coli*	*Escherichia coli*	*Escherichia Coli, Stenotrophomona maltophila* (Carbapenem)
Patient 6	*Haemophylus parainfluenzae*	*Enterococus faecium* (Penicillin)	*Enterococus faecium* (Penicillin)
Patient 7	*Stenotrophomona maltophila* (Penicillin), *Streptococcus mitis*		
Patient 8	*Enterococus faecium* (Penicillin), *Staphylococcus epidermidis, Geotrichum*	*Geotrichum, Stenotrophomona maltophila* (Carbapenem), *Enterococus faecium* (Penicillin), *Staphylococcus epidermidis*	*Candida krusei*
Patient 9	*Escherichia coli*	*Proteus mirabilis*	*Proteus mirabilis, Candida albicans*
Patient 10	*Klebsiella pneumoniae, Staphylococcus aureus, Candida albicans*	*Enterococus faecium* (Penicillin), *Candida albicans*	

Patient 11	*Candida dubliniensis* *Streptococcus species,* *Staphylococcus epidermidis*		
Patient 12	*Enterobacter aerogenes,* *Staphylococcus epidermidis* (Penicillin), *Candida lusitaniae* (Amphotericin B)	*Candida lusitaniae*	
Patient 13	*Staphylococcus aureus* (Meticillin), *Candida albicans*	*Staphylococcus aureus* (Meticillin)	
Patient 14	*Staphylococcus epidermidis* (Penicillin)	*Staphylococcus epidermidis* (Penicillin), *Klebsiella oxytoca*	
Patient 15	*Enterococcus faecium* (Penicillin), *Saccharomyces cerevisiae*	*Escherichia coli,* *Saccharomyces cerevisiae,* *Staphylococcus epidermidis* (Penicillin)	
Patient 16	*Staphylococcus haemolyticus* (Penicillin) *Candida tropicalis*		
Patient 17	*Stenotrophomomnas maltophilia,* *Enterococcus faecium* (Penicillin), *Candida albicans*		
Patient 18	*Enterococcus faecium* (Penicillin), *Candida albicans*		
Patient 19	*Klebsiella pneumoniae* (Carbapenem), *Candida glabrata*	*Enterococcus faecium* (Penicillin), *Staphylococcus haemolyticus,* *Candida glabrata* (Fluconazole)	

Figure legends

Figure 1. Nasocystic catheter (white arrow) through a transgastric metal stent (arrow heads) in a patient with infected walled-off necrosis.

Figure 2. Flow chart of patients with acute pancreatitis included in the study.

Figure 1

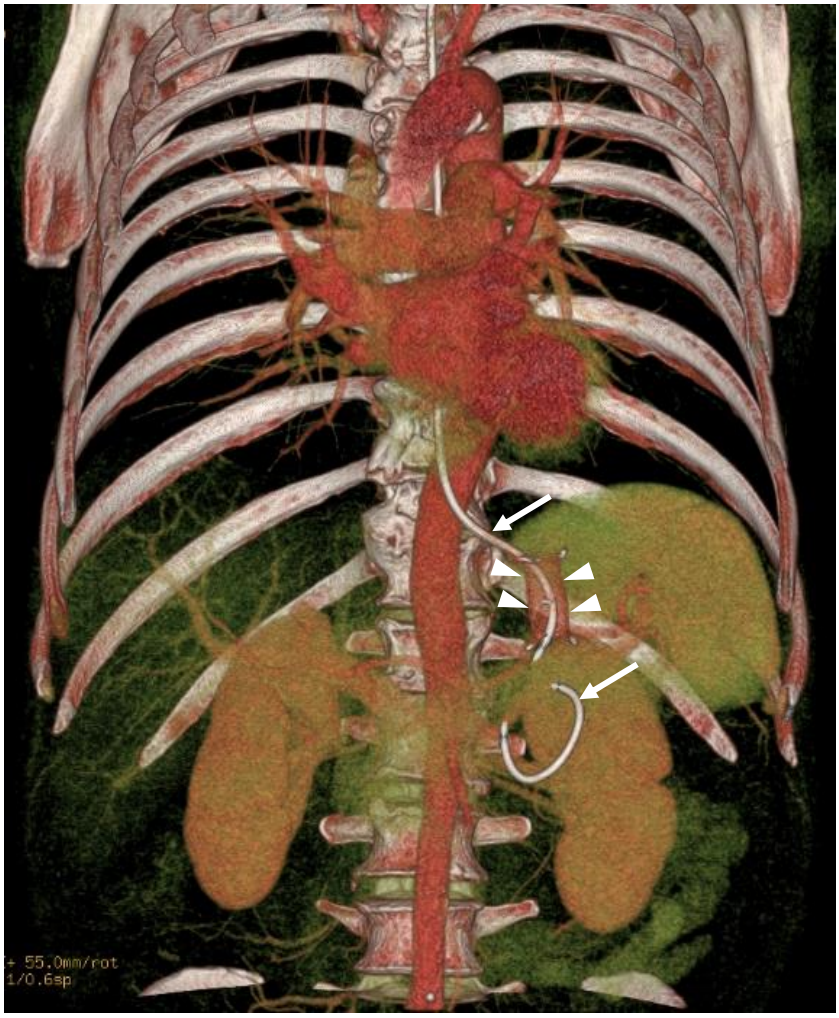
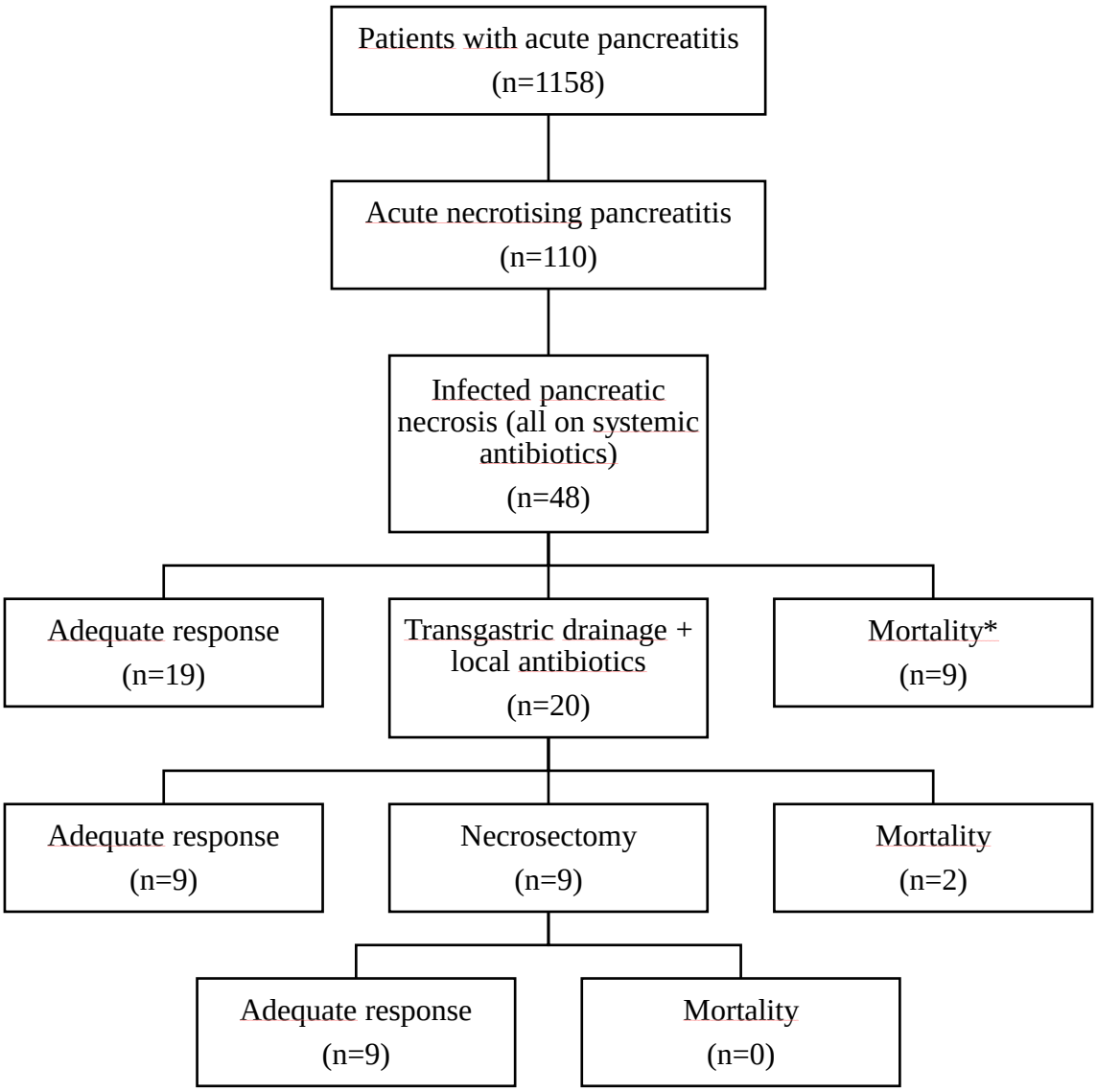


Figure 2.



*Three patients on intensive care died after urgent open necrosectomy.