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Research Article

Diagnosis and Management of Pancreatic Necrosis Infection

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Abstract

Introduction: Acute Necrotizing pancreatitis (ANP) represents the severe form of human acute pancreatitis (15% of cases). Infection of pancreatic necrosis occurs in 40– 70% of patients with ANP and have mortality rate about 80% of cases. Therefore, early diagnosis of infection in ANP is extremely important. We aimed to describe the diagnostic criteria(clinical, biological and radiological data) and the different modalities of treatment of this complication (medical, percutaneous drainage or surgery).

Methods: One hundred and nineteen patients with ANP were enrolled, among them, 50 (42%) were found to have pancreatic infection. Demographic and clinical characteristics, laboratory examination results, complications and treatment modalities of these patients were collected from their medical records.

Results: Infection of pancreatic necrosis was observed in 42% of cases. Positive diagnosis of infection is kept to a set of clinical data, which are fever (95.9%), signs of peritoneal irritation (81.6%); Biological which are elevation of CRP rate (98%) and white blood cells (93.9%); positive blood cultures (18%) and radiological which are collections with peripheral enhancement (98%); peri-pancreatic air bubbles (18.8%). The treatment was based on an antibiotic therapy alone in 16 patients, and associated with collection drainage in the remaining cases. The drainage was percutaneous in 12 patients with a success rate of 16.66%. The need for surgical necrosectomy was required in 32 patients. The necrosectomy was associated in 15 cases with a gesture of the biliary tract (cholecystectomy with or without external biliary drainage). Bacteriological examination found a predominance of BGN and anaerobes. The mortality rate was high at 42%.

Conclusion: Infection of pancreatic necrosis is a serious complication of ANP. Its diagnosis is based on a set of clinical, biological and imaging data. The treatment is, essentially, medical based in an adequate antibiotic therapy witch can be associated with percutaneous drainage or surgery. This complication has a high rate of mortality.

Keywords: Acute Pancreatitis; Infection; Treatment; Prognostic

Introduction

Acute pancreatitis (AP) is defined, according to the consensus of Atlanta in 1992 [1], as an acute inflammatory process affecting the pancreas with participation of peri-pancreatic tissues or remote organs.

In practice, there are two distinct varieties: edematous pancreatitis and necrotizing pancreatitis. The edematous form usually results in spontaneous recovery; however necrotizing form is the severe form of acute pancreatitis (15% to 20% of cases) whose natural evolution can be divided into two phases [2]. The first 14 days characterized by the presence of systemic inflammatory response syndrome (SIRS) secondary to the release of inflammatory mediators that are responsible for the failure of multiple organs (lung, kidneys, and heart, etc....). The second phase occurs after two weeks of evolution and is dominated by septic complications associated with infection of the pancreatic necrosis, which is seen in 40% to 70% of patients [2]. In front of clinical, biological and radiological data, positive diagnosis is held but only germ isolation in the culture of pancreatic necrosis can confirm this diagnosis. The treatment is multimodal; it can be medical based in an adequate antibiotic therapy witch can be associated with percutaneous drainage or surgery. This complication has a high rate of mortality. The purpose of this article is to describe the diagnostic criteria (clinical, biological and radiological data) and the different modalities of treatment of this complication (medical, percutaneous drainage and surgery).

Patients and Methods

This is a retrospective, single center study conducted on 126 months from January 2004 to June 2014 in the service of Anesthesiology and General Surgery of the Hospital Sahloul Sousse.

Patients

We included in the study all patients hospitalized in the services of Anesthesiology and general surgery and transferred from

another hospital for necrotizing pancreatitis acute (Steps D and E of the classification of Balthazar) whose developed infection of pancreatic necrosis.

Were excluded from the study

- Outbreaks of calcifying chronic pancreatitis
- The unusable files for lack of clinical and laboratory information

Data collection

Demographic and clinical characteristics of the patients, their laboratory results, complications and treatment modalities were collected by reviewing the medical records of the patients.

Entry and data analysis

They were carried out by means of the SPSS 19.0 software. Continuous variables are shown as mean ± standard deviation (SD). We used absolute and relative frequencies for qualitative variables express.

Results

Demographic and clinical characteristics of the patients

A total of 119 patients with SAP were enrolled, among them, 50 (42%) were found to have pancreatic infection. The demographic and clinical characteristics of the patients with pancreatic infection are summarized in table 1.

	Pancreatic infection (n = 50)
Gender, n (%)	
Male	20 (40)
Female	30 (60)
Age, years (mean ± SD)	55 ± 16
Etiology of pancreatitis n (%)	
Biliary disease	28(56)
Dyslipidemia	9 (18)
Unknown	13(26)
Past history n (%)	4(8)
Diabetes	12(24)
Hypertension	16(32)
Obesity	
Severity (mean ± SD)	
Ranson's score	3,4 ± 1,47
CTSI	6,26 ± 1,92
Hospital stay, days (mean ± SD)	39 ± 28
Mortality, n (%)	21(42)

Table 1: Demographics and Clinical Characteristics of Patients.

Positive diagnosis of pancreatic necrosis infection

The diagnosis of pancreatic necrosis infection was held in front of a beam of clinical, biological and radiological data. Diagnostic confirmation is through the germ isolation in the culture of pancreatic necrosis.

This infection was observed during the second week of evolution of the PA in 48% (n = 24) of the case and in the third week in 24% (n = 12) case. Early infection, during the first week was observed in 18% (n = 9) of the case. In 10% (n = 5) of cases the infection was later observed during the 4th week.

Clinical data

Classically, the clinical picture is due to increase abdominal pain associated with vomiting and fever evolving. Abdominal examination may reveal signs of peritoneal irritation, sometimes with an abdominal mass.

In our series, the fever was observed in 95.9% of patients. Abdominal pain was expressed by patients in 91.8% of cases. Vomiting was seen in 38.8% of patients. Physical examination revealed signs of peritoneal irritation in 81.6% of cases and an abdominal mass in 34.7% of cases.

Biological data

An inflammatory syndrome with new increase of the rate of white blood cells and CRP is most often observed. In our series, the new increase leukocytosis was observed in 93.9% of cases and CRP in 98% of cases. Blood cultures were positive in 18% of cases.

Imagery data

All patients, in whom infection of pancreatic necrosis was suspected, were explored by abdominal CT scan. In 98% of cases, abdominal CT scan showed the presence of intra-abdominal collections with peripheral enhancement and in 18, 8% of cases the presence of air bubbles within the collection in favor of pancreatic necrosis infection or pancreatico-digestive fistula.

Bacteriological proof

Three types of sampling were sent for bacteriological examination: blood cultures, percutaneous drainage of fluid and surgical drainage fluid. Thirty-seven samples were sent but only 31 results were recovered. All these samples were taken after turning on antibiotics for patients.

The organisms isolated were, in most cases, Gram-negative bacilli of intestinal origin with a polymorphic flora in four cases. The culture was negative in four cases.

Treatment

Antibiotics

All patients, in whom there was a high probability of infection of pancreatic necrosis, were put under antibiotic therapy. This antibiotic was probabilistic in 42% of cases, broad spectrum, covering the seeds of the digestive tract (GNB and anaerobic). Antibiotics alone was sufficient in 32% (n = 16) of patients with an average duration of 11.4 days (6-20 days).

Isolated organisms	Effective
Klebsiella	4
Escherichia coli	4
Enterobacter	4
Acinetobacter	3
Providencia	2
Enterococcus	2
Candidas	1
Stenotrophomonas	1
Clostridium	1
Pseudomonas	1
Polymorph	4
Negative	4

Table a

In 68% (n = 34) cases antibiotic therapy was associated with percutaneous drainage and/or surgical drainage. The average duration of antibiotic therapy, in all patients, was 18.12 days (2-90 days).

Among the isolated bacteria, 60.4% of germs were sensitive to imipenem + amikacin. This antibiotic had necessitated the addition of a third antibiotic in 6 cases (Vancomycin in 5 cases and Teicoplanin in one case) and an antifungal (Fluconazole) in one case. The combination Cefixime + metronidazole + gentamicin has shown efficacy in 12.5% of cases. Ertapenem was use in 8.3% of cases and in 4.2% of cases we had recourse to fosfomycin.

Percutaneous drainage

Percutaneous drainage was performed in 12 patients. Sixteen drains were used. Percutaneous drainage was indicated at an average of 22.45 days of evolution of the acute pancreatitis (8-40 days).

The average duration of percutaneous drainage was 16.36 days (3 to 35 days). The percutaneous drainage allowed complete resolution of the collection in 2 cases giving a success rate of 16.66%.

Surgery

Surgical drainage was required in 64% (n = 32) of cases. In 10 cases, surgery was indicated after percutaneous drainage failure.

The average delay of surgery was 26.64 days (9-54 days) of evolution of the acute pancreatitis.

The incision was, in more than half of the cases, a midline incision. In almost 20% of cases, a bi-subcostal transversal incision was performed. Elective extra-peritoneal route was preferred in only one case.

Surgery has achieved a necrosectomy with setting up a collection drainage system. The necrosectomy was associated in 48.4% (n = 15) of cases in a gesture of the biliary tract (cholecystectomy with or without external biliary drainage).

Morbidity and mortality

Surgery was complicated by duodenal fistula and external pancreatic fistula in the same patient. This patient was reoperated on 2 times; she had a directed fistulisation of his fistulas with good evolution.

A residual collection was observed in 14 patients of whom 13 were operated (9 patients for once and 4 patients for 2 times).

An infection of the wall was observed in one case with favorable evolution in local treatment.

The average hospital stay was 39 days (12-120 days). The mortality rate was 42% with an average delay of 41.57 days (12-70 days).

Discussion

Positive diagnosis of pancreatic necrosis infection

Clinical and biological data

There are no reliable clinical criteria for distinguishing between infected and sterile pancreatic necrosis. The signs of systemic inflammation, such as fever and hyper leukocytosis are usually seen in infected necrosis, but can be increased to the same extent in the sterile necrosis. Organ failure is more common in the infected necrosis than in sterile necrosis, but it has not been validated to predict the likelihood of infection [2,3]. CRP rate is correlated with the occurrence of pancreatic necrosis infection. CRP can be used as a marker of differentiation between infected necrosis and sterile necrosis in severe acute pancreatitis [4]. Procalcitonin, which is released by the thyroid gland during bacterial infections, has been proposed as a potential marker of infection in a wide range of disease states [5]. A high value of procalcitonin can be used as pancreatic necrosis infection marker with a sensitivity of 75 to 94% and a specificity of 83 to 91% [6,7].

From a practical standpoint, pancreatic necrosis infection usually occurs from the end of the first week of evolution. It should be suspected in front of fever, abdominal pain or recurrence of organ failure. This clinical picture may appear early during evolution or late after several weeks of apparent improvement [8]. In our study, the main symptoms are fever and abdominal pain associated with vomiting with the new increase in rates of white blood cells and CRP.

However, keep in mind that this clinical picture is not always synonymous with pancreatic necrosis infection. This consideration may help avoid unnecessary surgery.

Imagery data

Contrast-enhanced CT-scan is the diagnostic method of choice for identifying pancreatic necrosis and its extension. It is the first exam to be completed when we suspected pancreatic necrosis infection. It may show the presence of air bubbles within the pancre-

atic necrosis. His sensitivity was 50% and specificity was 92% [9]. This finding is rarely seen in the infected pancreatic necrosis, so its absence does not exclude infection. In our study, the air bubbles were observed in 18.8% of cases. The role of other imaging methods is much more limited. The usefulness of ultrasound is limited in patients with severe acute pancreatitis. The magnetic resonance imaging could be used in selected cases, for example, to search the pancreatic necrosis when the use of contrast media is against-indicated [8].

The bacteriological proof

The confirmation of the positive diagnosis of pancreatic necrosis infection requires bacteriological evidence. The scanno-guided percutaneous fine needle puncture has become the gold standard [8]. When it is performed by an experienced interventional radiologist, is a safe and accurate procedure, even in patients with multiple organ failure [10]. Sensitivity and specificity exceed respectively 88% and 90% [11]. Any time the percutaneous fine needle puncture presents a risk of contamination of an initially sterile collection [12]. In our study, bacteriological evidence was obtained using percutaneous or surgical drainage performed for therapeutic purposes in the absence of adequate technical facilities.

Treatment

Antibiotics

Antibiotic therapy is indicated for the treatment of infected pancreatic necrosis, it can be used alone or in combination with drainage of a collection. Antibiotics used should cover the suspected bacterial flora and have a good diffusion in the pancreatic tissue. The Carbapenems, quinolones and nitroimidazoles have all these characteristics [13]. More recent data have shown that imipenem-cilastatin exceeds pefloxacine [14] and that fluoroquinolone-metronidazole combination often used in patients with a penicillin allergy is insufficient [15] because of the emergence of Gram-positive bacteria such as Staphylococci, which represent 30% of isolated bacteria [16], so adequate coverage of these microorganisms, including resistant strains, is of great importance. Antibiotic therapy should be tailored to the culture results and antibiotic sensitivity. In our study, imipenem was used in 72.9% of patients (in association with amikacin in 60.4% of cases). An antibiotic covering methi-resistant staphylococci was used in 12.5% of cases.

The duration of antibiotics after drainage is usually determined depending on the clinical course of patients.

Instead of antibiotic therapy in the treatment of sterile pancreatic necrosis remains long been a subject of several controversies, it showed no benefits in terms of pancreatic necrosis infection rate reduction. This was demonstrated by two large controlled clinical trials and double-blind [15,17].

In our series, antibiotics, introduced for strong presumption of pancreatic necrosis infection but undocumented showed no benefit in reducing the rate of secondary infection.

The abuse and prolonged antibiotic therapy can promote fungal infections occurred that may interest 8-15% of patients [18]. The role of antifungal therapy in this setting has not been elucidated and could be indicated for persistent infection of necrosis symptoms.

Percutaneous drainage

Literature data on the efficacy of percutaneous drainage are very heterogeneous. The first series have generally disappointing results with a success rate of less than 30% [18-24]. In our series the success rate was 16.66%. Many authors agree that the yet liquefied necrosis is responsible for the failure. In the series of Delattre., *et al*. [25]. The success rate was 100% in localized abscess where necrosis is scarce; the rate was 54% in cases of pancreatitis Stage D of Balthazar and only 6% for stages E. The real question is whether it is possible to eradicate necrosis by the only percutaneous drainage. Four work provides an affirmative answer [26-29]. Gouzi., *et al.* [27] reported a series of 32 patients, drained with large caliber drains (24 Fr) in which washing was instituted (2-3 l/d): 81% of these patients had infected necrosis proven by culture and 78% healed without surgery with an overall mortality of 15.5%. Whole., *et al.* [28] reported a series of 41 patients, the technical conditions for carrying out drainage is not specified, the success rate was 73% and mortality by 14%. Some go even further by performing a true percutaneous necrosectomy [26,29]. Shonnard., et al. [29] reported the observation of a cured patient after the removal of the necrosis by instrumental maneuvers through the drain. Echenique., *et al.* [26] in 20 selected patients achieved 100% success rate with zero mortality by performing every 2 days sessions washing and extraction of necrosis by large caliber drains; the number of sessions ranged from 7 to 32 per patient. It is therefore possible, after certain technical requirements such as the use of large-bore drains, regular washing keeping permeable drains, changing of excluded or clogged drains and installing additional drains if necessary, to obtain appreciable results by percutaneous drainage.

A multicenter randomized recent study [30] compared, in 88 patients, open surgery with a minimally invasive approach (percutaneous drainage or endoscopic trans-gastric followed by retroperitoneal laparoscopic debridement for non-improvement after 72 hours). The primary endpoint was the occurrence of major complications (occurrence of perforation of hollow organs, bleeding, organ failure or death). The risk of major complications was statistically higher in the open surgery group compared to the minimally invasive approach group (69% vs 40%, p <0.006) and the risk of recurrence of a new multiple organ failure, a new hospital in intensive care unit and the occurrence of sequelae diabe-

tes was also statistically lower in the minimally invasive approach group (12% vs 42%, p = .0001; 16% vs 40%, p <0.01; 16% vs 38%, p <0.02 respectively). However, the difference in terms of overall mortality was not statistically significant (19% for open surgery vs 16% for the minimally invasive approach) and the length of stay in intensive care unit or the total duration of hospitalization.

A recent international consensus conference [31] emphasized various minimally invasive approaches and their potential combinations depending on the anatomical location of the infected necrosis and solid nature or otherwise of the latter based on the detailed analysis of literature since 1996 in a series of more than five patients.

Table 2 summarizes, based on different approaches in patients with all infected necrosis, the overall morbidity, the reoperation rate and overall mortality.

	Number of patients (1996-2012)	Global Morbidity	Surgical re-intervention rate	Global Mortality
Open surgery	511	36%	39%	20%
Retroperitoneal Surgical Approach	72	34%	7%	15%
Percutaneous Drainage	306	27%	34%	13%
Endoscopic Drainage	125	21%	9%	3,4%

Table 2: Complications of minimally invasive approaches for drainage of infected necrotizing pancreatitis.

Minimally invasive techniques have the major advantage of reducing mortality and morbidity. It can be combined and not to oppose the surgery, witch keeps indications in case of diffuse and ill-defined infected necrosis, or failure of minimally invasive strategy. It is essential to choose the path of optimal drainage, take into account the anatomical distribution of necrosis in the peritoneum or the retroperitoneal spaces [32].

Expression of results of percutaneous drainage only in terms of healing is a restrictive view of this treatment. Indeed, percutaneous drainage can have a timer role, mostly for precarious patients with multiple organ failure [20,23,33,34].

In our series, percutaneous drainage has to postpone surgical drainage on average 16 days in 10 patients, and 7 of them were operated during the 6th week of evolution of the PA. Some authors now agree to wait for that period [35]. The role of percutaneous drainage timer makes it possible to necrosis to delineate. It allows necrosectomy easier and more complete.

Related morbidity percutaneous drainage is difficult to establish in terms of secondary infection, hemorrhage and fistula, as these complications are also part of the natural evolution of necrotizing pancreatitis. In our series, we did not observe any of these complications.

Surgical drainage

Access routes and Gestures

Traditionally, surgery includes necrosectomy via laparotomy associated with drainage of peripancreatic collections. During laparotomy, a large intra-abdominal mobilization is performed, all necrotic areas are unrestrained by the finger with collapse of pancreatic necrosis and peripancreatic cubicles semi-solid, with implementation of several drains. A recent CT scan would be important to guide safe dissection and localize small collections partitioned away from the pancreatic area. Drainage is necessary for the continuous removal of necrotic or infected material [36]. The choice of surgical debridement technique is variable between surgical centers. Some advocate a necrosectomy-pancreatostomy or "open drainage" allowing repetitive debridement; this approach is based on the presumption of adaptive pursuit of the inflammatory process, even after the initial surgery and thus new areas of necrosis or infection probably appear [36]. Louis., et al. showed, in their series with 18 patients necrosectomy-pancreatostomy, that this technique is effective treatment of acute pancreatitis with infected necrosis at the cost of repeated and complementary gestures and residual hernia [37]. Others recommend the necrosectomy-washing or "closed drainage" very currently used [38-42] which ensures progressive debridement of devitalized tissue but the rapid formation of preferential channels often allows the creation of new infected collections requiring complementary surgical or radiological procedures. Finally, others argue the necrosectomy with conventional drainage without irrigation [43,44]. It requires action from the outset as complete as possible and possible reoperation is more complex and dangerous. No prospective randomized study has compared these procedures, but generally all three procedures have favorable results [45,46].

The necrosectomy may also be performed by retroperitoneal road [47-49]. This path provides direct access to the posterior collections, but does not allow intraperitoneal exploration witch may detect complications such as colonic necrosis or associated biliary gesture in case of biliary etiology. It is an interesting alternative for posterior collections while the transperitoneal approach, above-described, is well suited to anterior collections, located in the back cavity of the lesser sac, which it provides direct drainage. In our study, most patients were operated by transperitoneal road (median laparotomy, subcostal or transversal laparotomy) with conventional drainage. The retroperitoneal approach via a lombotomy, was preferred in only one patient.

Laparoscopic necrosectomy with the establishment of large-bore drains for irrigation has been suggested by some with low rates of morbidity and mortality [50,51]. The Glasgow group proposed a necrosectomy consisting of debridement with lavage using a cystoscope, which follows a previously radiologically placed guidewire at the collection under general anesthesia [52]. Various modifications of this method have been described. The retroperitoneal necrosectomy involves percutaneous insertion of an operating nephroscope to access the pancreatic necrosis zone, followed by debridement, washing and the establishment of drains for continuous retroperitoneal irrigation [53].

Deadline for intervention

The timing of surgery is of utmost importance. Delayed for 2 or 3 weeks is associated with significant reduction of morbidity and mortality [54,55]. This is due to the fact that liquefaction, demarcation and organization of necrotic tissue facilitate necrosectomy and drainage in one intervention. Equally important, during this period, the systemic inflammatory response usually disappears allowing patients to better tolerate the extra stress of surgery and anesthesia. Currently, delaying surgery of 2 or 3 weeks is a consensus recommendation. Early surgery in this context could be justified only in selected cases, such as for patients who develop acute surgical abdomen in connection with colonic necrosis for example [56]. In our study, the average time of surgery was about 4 weeks.

Postoperative complications

As expected, the morbidity is high. Complications after surgical debridement of the infected pancreatic necrosis are common and include pancreatic and entero-cutaneous fistula, residual collections, infection of the abdominal wall, bleeding, organ failure (usually renal failure), hernia and exocrine and endocrine pancreatic insufficiency, etc. [12]. The complications observed in our study are detailed in the following table.

Bacteriological study

Traditionally, pancreatic necrosis infection-causing germs from essentially digestive flora bacterial translocation but they can reach the pancreas through blood. The first route of contamination was confirmed by the results of several studies [3,57-59] including our showing that 43-86% of isolated organisms are Gram-negative bacilli, 28-36% are *staphylococci* and *streptococci*, 4-11% and 7-37% anaerobic species of Candida. By cons, other studies show that this plant has undergone a change with emergence of Gram-positive microorganisms. Delattre and Gouzi [25,27] found that the seeds in question were made by a majority of *enterococci, staphylococcus* and *Pseudomonas*. Gloor., *et al.* [60] have, the emergence of Gram-positive bacteria and the increased incidence of fungal infection, on behalf of antibiotic prophylaxis. This antibiotic decreases and delays bacterial translocation and promotes contamination through blood. It is observed, increasingly, the emergence of multi-resistant bacteria in pancreatic necrosis infection. These germs are dominated by *Staphylococcus aureus* methi-R, and they are isolated especially in patients receiving antibiotic prophylaxis and those transferred from other services [60,61].

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