

Management of infected pancreatic necrosis: state of the art

Necrose pancreática com infecção: estado atual do tratamento

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A B S T R A C T

Pancreatic necrosis occurs in 15% of acute pancreatitis. The presence of infection is the most important factor in the evolution of pancreatitis. The diagnosis of infection is still challenging. Mortality in infected necrosis is 20%; in the presence of organic dysfunction, mortality reaches 60%. In the last three decades, there has been a real revolution in the treatment of infected pancreatic necrosis. However, the challenges persist and there are many unsolved questions: antibiotic treatment alone, tomography-guided percutaneous drainage, endoscopic drainage, video-assisted extraperitoneal debridement, extraperitoneal access, open necrosectomy? A step up approach has been proposed, beginning with less invasive procedures and reserving the operative intervention for patients in which the previous procedure did not solve the problem definitively. Indication and timing of the intervention should be determined by the clinical course. Ideally, the intervention should be done only after the fourth week of evolution, when it is observed a better delimitation of necrosis. Treatment should be individualized. There is no procedure that should be the first and best option for all patients. The objective of this work is to critically review the current state of the art of the treatment of infected pancreatic necrosis.

Keywords: Pancreatitis. Pancreatitis, Acute Necrotizing. Infection. Drainage.

INTRODUCTION

Acute pancreatitis is one of the main causes of hospitalization among benign diseases of digestive system, with an annual cost of two billion dollars in the US^{1,2}. In the last ten years, it has been observed an increase of incidence and 20% of hospitalization. Severity of disease is associated to pancreatic or peri-pancreatic tissue necrosis, and the presence of infection is the most important factor for pancreatitis evolution³. Twenty per cent of patients present pancreatic necrosis and one third of this group have infection. In spite of modern intensive care treatments, mortality of infected pancreatic necrosis is almost 30% (12% to 39%), and, in the presence of multiple organ failure, may reach 70%³⁻⁵. Therefore, infected pancreatic necrosis should not be considered a benign disease.

Infected pancreatic necrosis treatment experienced a great revolution in the past two decades⁶. At first, all patients with infected necrosis will need an invasive procedure that may be performed by endosco-

py, percutaneous access or surgery. In the past, surgery was the first or only option, but recent studies advocate the step up approach, a stepwise treatment, beginning with minimally invasive measures and surgical intervention when initial procedure fails⁷⁻¹⁰. Indication and moment of intervention, choice of procedure and step up approach modified considerably the treatment of severe acute pancreatitis.

Infection of pancreatic necrosis generates a series of doubts, such as etiology, diagnosis, clinical presentation, role of tomography and use of fine needle puncture, and prophylactic use of antibiotics. The objective of the present work is to critically analyze the current status of treatment of infected acute pancreatitis.

How to diagnose infection?

Pancreatic necrosis infection usually occurs in the second or third weeks of evolution. Systemic and laboratory alterations before that period usually are caused by the inflammatory response or infection elsewhere. If these manifestations persist after the first seven

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or ten days, maybe infection is present^{5,11}. One of the great challenges of the treatment of a patient with severe acute pancreatitis is the definition of the presence of infection of pancreatic necrosis.

Occasionally, severity of the disease is only local, without severe systemic manifestations, even in the presence of infection. On the other hand, critical patient at intensive care unit, under mechanic ventilation, with deep vein access and catheters, may have other sources of infection. Many times, definition of infection etiology is difficult. It is fundamental to stress that collection of blood and urine cultures must always be performed in the presence of suspected infection before administration of antibiotics. Finding the agent in the blood culture is valuable, since it may guide which local is infected according to identified agent, and which antibiotics to use. Abdominal tomography is an indispensable resource for evaluation of a patient with worsening of clinical and infectious status. Presence of gas in the pancreatic collection suggests necrosis infection, observed in 40% of patients, and there is also alteration of the tomographic image when compared to the initial exam^{4,12-14}.

Fine needle puncture was very used and widespread in the past. Its use nowadays is restrict and controversial¹². One of the reasons for this change is the modern conservative treatment of infected pancreatic necrosis. The presence of a microorganism in the aspirate of fine needle puncture does not mean immediate change of treatment. On the other hand, definition of etiologic agent helps choosing the correct antibiotics, in special in patients at intensive unit care for more than two weeks; in that scenario, it is not rare the presence of resistant germs to antibiotics. In this context, the advocated treatment is the use of carbapenemic drugs that usually are efficient to control infection. Rodriguez *et al.*¹³ reported 25% of false negative results of fine needle puncture and that this could be explained by previous use of antibiotics. A recent study evaluated the opinion of specialists about the use of fine needle puncture and showed that among 118 interviewees, none use routinely the method and 85% only use it in selected patients¹⁴. This current approach is based on the fact that invasive procedures must be performed usually after four weeks. In the presence of suspicion of infection or

image of infected pancreatic necrosis, initial treatment is the use of antibiotics. In the nineties, infection diagnosis after fine needle puncture lead to immediate surgical procedure, what is not done nowadays.

Van Baal *et al.*¹² retrospectively evaluated 208 patients submitted to drainage of pancreatic necrosis and divided them into three groups: those with presence of clinical signs of infection, with gas in the collection at tomography, and those with positive fine needle puncture. Result of culture of pancreatic necrosis, obtained by necrosectomy or external drainage, showed the presence of microorganisms in 80% of patients with clinical signs of infection, in 94% of patients with gas at tomography, and in 88% of patients with positive fine needle puncture. The authors suggested that infection diagnosis may be based on clinical evolution and image exam, and that fine needle puncture should be reserved to situations when the procedure will change treatment. This is observed in patients with multiple organ failure and signs of infection, which origin is not safely determined.

Prophylactic antibiotics: are they still used?

The use of antibiotic prophylaxis is being studied and discussed in literature. The first studies in the nineties suggested that prophylactic use of antibiotics lowered the incidence of pancreatic necrosis infection and mortality. However, the methodology quality of those studies are questionable^{15,16}. More recent randomized studies did not confirm the initial data. Dellinger *et al.*¹⁷ conducted a multicenter study and evaluated 100 patients with severe acute pancreatitis that were divided into two groups: placebo and use of meropenem. Infection was observed in 18% of patients of treated group, and in 12% of patients that received placebo. Surgery was necessary in 26% of those treated with antibiotics and in 20% of those treated with placebo. There was no difference of mortality. Garcia-Barrasa *et al.*¹⁸ evaluated the use of ciprofloxacin for infection prophylaxis of pancreatic necrosis and also did not observe difference of mortality or of necrosis infection.

Therefore, the use of antibiotics in pancreatic necrosis must be restricted to patients with diagnosed infection, that usually occurs after the third week. Most used antibiotics are those with good penetration in the

pancreatic tissue, such as carbapenemic, quinolones and metronidazol.

Percutaneous Drainage

Open pancreatic necrosectomy is a significant surgical trauma for many critically ill patients. Since morbidity (34% to 95%), mortality (13% to 39%) and pancreatic insufficiency due to the procedure are high, in the last two decades some authors proposed a less invasive treatment^{13,19,20}. Freeny *et al.*²¹ advocated in the end of the nineties the percutaneous drainage of infected pancreatic necrosis. They evaluated 34 patients: in 47% drainage was the only intervention. In 74% of patients infection was controlled, allowing postponement of surgical treatment. In the beginning of this century, other authors also observed that minimally invasive access is associated to lower activation of inflammatory response, when compared to surgical treatment.

These initial studies encouraged the PANTER trial (Pancreatitis, Necrosectomy versus step up approach), a multicenter randomized study performed at the Netherlands⁸. Open necrosectomy was compared to step up approach, that consists in a stepwise treatment with initial percutaneous drainage, and, in the persistence of infection, open necrosectomy by laparotomy or via retroperitoneal. From that moment on, the concept of set up approach widespread, being the first option percutaneous drainage, and necrosectomy only performed in failed treatment.

Van Santvoort *et al.*¹⁰ evaluated 88 patients, 45 submitted to surgery and 43 to step up approach. There was no difference of mortality between both groups (19% of step up group vs. 16% of surgery group), but only 12% of patients of the minimally invasive group progressed to multiple organ failure versus 40% of the other group. Percutaneous drainage was the only necessary treatment in 35% of patients. It is important to highlight the necessity of more than one percutaneous puncture in 44% of patients submitted to the step up approach. On the other hand, the group submitted to open necrosectomy needed a new surgery in 42%. Incidence of diabetes was also lower in the group treated by the step up approach (16% versus 38%).

The first step, percutaneous drainage, is performed to control infection, postpone surgery, and, in

some cases, to avoid surgery. In literature, success of percutaneous drainage to avoid necrosectomy is variable, from 30% to 100%^{9,19,21}. The objective of the drainage is to remove the liquid that surrounds pancreatic necrosis. Drains do not remove pancreatic necrosis, but the removal of liquid under pressure may control infection. Therefore, drainage must be indicated for patients with evidence of pancreatic necrosis infection and performed usually at third or fourth weeks of evolution^{11,22}. A recent study observed that 88% of surgeons perform drainage before fourth week¹⁴.

It is discussed the role of rinsing after percutaneous drainage, the size of the drain and the possible advantage to change to progressively larger drains. Percutaneous drainage modified the evolution of pancreatitis, due to its capacity to resolve infection and multiple organ failure.

Predictive factors of success of percutaneous drainage

Success of percutaneous drainage is directly related to volume, local and distribution of the liquid collection and peri-pancreatic necrosis, aside from the clinical condition of the patient^{9,23,24}. The presence of debris is one of the most important factors related to the success of drainage. Literature does not characterize subgroups of patients with predictive factors that should be exclusively treated by percutaneous drainage. This information is important, since when drainage is insufficient, necrosectomy must be performed right after control of sepsis and improvement of organic dysfunction, if possible.

Babu *et al.*²³ showed that percutaneous drainage reverted sepsis in 62% of patients and 48% did not need necrosectomy. These authors described a high rate of success with only drainage, in relation to others in literature. They believe that the reason is the extensive rinsing of abdominal cavity with saline to remove debris. They indicate as predictive factors for success of drainage: sepsis resolution, APACHE II levels at the procedure and multiple organ failure in the first week of pancreatitis.

Hollemans *et al.*²⁴ evaluated 113 patients and showed that male sex, presence of multiple organ failure, extension of pancreatitis necrosis and heterogeneity

of collection are predictive of failure of drainage, indicating the necessity of necrosectomy. These authors proposed a nomogram. When all factors are present, success of exclusive drainage is 2%. However, it must be pointed out that regardless the chance of success of percutaneous drainage, treatment of infected pancreatic necrosis must be initiated with drainage. The change for a higher caliber drain must be encouraged to postpone and avoid necrosectomy, but there are no studies showing this treatment as definitive to avoid surgery²⁴.

When endoscopic treatment must be indicated?

Endoscopy may be used in two procedures for infected pancreatic necrosis: drainage and necrosectomy. Some authors advocate endoscopic necrosectomy when endoscopic drainage fails^{7,11,25,26}. Studies that analyze endoscopic necrosectomy efficiency are still rare. A systematic review of literature evaluated 14 series with 455 patients. It was necessary an average of four procedures per patient, and exclusive endoscopic treatment was observed in 81%. Mortality was 6% and morbidity 36%, and bleeding was the main complication. The quality of these studies is questionable, since most do not indicate the severity of disease and only 57% involved infected pancreatic necrosis²⁵. Indication for this type of treatment must be restricted to delimited pancreatic necrosis.

Bakker *et al.*²⁷ performed the first randomized study comparing transgastric endoscopic necrosectomy with video-assisted retroperitoneal necrosectomy (PENGUIN trial - Pancreatitis, Endoscopy Transgastric vs Primary Necrosectomy in Patients with Infected Necrosis). They evaluated 20 patients, ten in each group: in the group treated endoscopically, interleukin-6 levels following the procedure were lower, patients did not present multiple organ failure and pancreatic fistula was observed in only 10% of patients, versus 70% in patients submitted to video-assisted procedure. It was necessary an average of three endoscopic procedures and two patients needed surgery. However, in spite of promising results with endoscopy, it must be stressed the low number of patients, and that, in the surgical group, necrosectomy was the first procedure, while in the endoscopic group endoscopic drainage preceded

necrosectomy.

After the promising results of PENGUIN trial, it was proposed the TENSION trial that introduced stepwise treatment for endoscopy and surgery. The study will compare the surgical step up approach (initial percutaneous drainage and eventually surgical procedure in cases of failure) with endoscopic step up approach (endoscopic drainage followed by endoscopic necrosectomy in case of initial treatment failure)²⁸.

Which is the best moment for drainage or necrosectomy?

The timing of surgical intervention in pancreatic necrosis has changed over the last two decades. Göttinger *et al.*²⁹ showed mortality of 46% of patients submitted to surgery during the first three weeks of the beginning of the disease, versus 25% after this period. Rodriguez *et al.*¹³ also stated that postponing surgical treatment is associated to lowering of mortality. This study evaluated 167 patients submitted to necrosectomy. The group operated with less than four weeks of evolution had a mortality rate of 20.3%, while the group when the procedure was performed after four weeks, mortality was 5.3%. Present consensus advocate that any invasive procedure must be postponed until pancreatic necrosis is delimited, that usually is observed after four weeks of symptoms^{5,11,30,31}. A Dutch group proposed a clinical randomized study in 2015 (POINTER trial) with the objective to compare the results of early drainage versus late drainage in infected pancreatic necrosis²².

Grinsven *et al.*¹⁴ proposed a question form about the best moment for drainage in infected pancreatic necrosis. They observed that 55% of interviewees postpone drainage after the diagnosis of infection, but 45% adopt immediate drainage. In this study, 87% of interviewees advocate the use of step up approach. Percutaneous drainage was indicated by 12% of interviewees only in the presence of delimited pancreatic necrosis, by 44% in some situations before delimitation, and other 44% performed drainage in any possible moment. This work showed that the presence of gas at abdominal tomography and signs of infection are associated to earlier drainage in relation to only clinical signs. The higher discrepancy of opinion of specialists is

observed in the first three weeks of disease. After this period, when pancreatic necrosis is delimited, most indicate drainage.

Open or minimally invasive necrosectomy

Open necrosectomy was considered the main treatment for decades, but with therapeutic minimally invasive improvements, it was observed a change of concepts. The reason was the need to reduce morbidity of procedure, that is performed in already frail patients^{6,32,33}. Blunt dissection must be performed, avoiding resection to prevent bleeding, enteric fistula and removal of viable pancreatic tissue^{10,34}. After debridement, in the past, abdominal cavity was maintained open for scheduled reoperations, what was abandoned. Nowadays, it is advocated abdominal closure with extensive drainage of retroperitoneum and reintervention on demand^{13,30}. Open necrosectomy usually is associated to higher mortality, that varies from 20% to 60%, although some studies report mortality lower than 10%^{34,35}. Madenci *et al.*³⁴ reported mortality of 8.8% in 68 patients submitted to open necrosectomy. In spite of low mortality, 41% of patients needed drainage of abdominal collections during post-operative and 15% were reoperated. Doctor *et al.*³⁵ evaluated 59 patients submitted to necrosectomy, with promising results, mortality of 10% and reoperation in only 8%. In that study, incidence of pancreatic fistula was 50.8%.

Minimally invasive retroperitoneal access is been widespread and becoming popular in the last 20 years. Main options are percutaneous necrosectomy and video-assisted debridement of pancreatic necrosis (VARD)³⁶. These techniques are variations of retroperitoneal access via subcostal incision, proposed by Fagniez *et al.*³⁷ in the eighties. This access is accompanied by a high morbidity rate: enteric fistula in 45%, bleeding in 40% and colon necrosis in 15% of patients.

Percutaneous necrosectomy was widespread by the group of Liverpool³⁸. Technique includes passage of a 12Fr drain by interventionist radiology guided by image, and, posteriorly the path is dilated to allow placement of a nephroscope, and, with the aid of forceps, removal and irrigation of necrosis. In general, several approaches are needed. This access is not adequate to patients with necrosis of head and uncinata process

of pancreas³⁸⁻⁴¹. Rarity *et al.*⁴¹ analyzed retrospectively patients submitted to open necrosectomy in relation to this access. Authors followed up 394 patients. 69.5% were treated by percutaneous necrosectomy. Mortality was 15.3% in 274 patients that used minimally invasive access versus 23.3% in 120 patients submitted to open necrosectomy. It was also observed less organ dysfunction and less complication following the minimally invasive procedure.

VARD retroperitoneal access is performed by a 5cm incision of left flank, and the percutaneous drain path is used to access the pancreatic necrosis. Laparoscopic optics is introduced and CO₂ is inflated by the percutaneous drain. Necrosis is removed by forceps that are used in open surgery. In case of necrosis of head or central region of pancreas, percutaneous necrosectomy and VARD have technical limitations and these methods should not be used as first option. Some authors propose laparoscopic debridement, but experience is still limited³⁰. Paresch⁴² published in 2006 the largest casuistic in literature of video-assisted transperitoneal access. Eighteen patients were treated, and only half had pancreatic necrosis infection. Mortality was 2% and 11% needed reintervention.

Is there a role for non-surgical treatment?

Exclusive clinical treatment or with minimally invasive procedures avoids surgical complications, such as worsening of multiple organ failure, pancreatic insufficiency and incisional hernia³⁴. Runzi *et al.*⁴³ published the first big series of non-surgical treatment of infected pancreatic necrosis. They evaluated 28 patients, and, among these, 16 were not operated. The others presented multiple organ failure. Mortality was 12.5%. it must be pointed out that in that work, only three patients were submitted to percutaneous drainage, although ten presented worsening of clinical condition. Lee *et al.*⁴⁴ also described non-surgical treatment. They treated eight patients exclusively with antibiotics. Rasslan *et al.*⁴⁵ presented a series of six patients with necrosis and gas in the retroperitoneum treated exclusively with antibiotics.

We believe that, in the beginning of disease, treatment must be made only with antibiotics, but in the presence of worsening of clinical conditions, some intervention must be made.

CONCLUSIONS

Infected pancreatic necrosis treatment must be made by a multidisciplinary team including surgeon, intensive care specialist, radiologist and endoscopic surgeon. Only referral centers have conditions to treat this disease. When we review the treatment of infected acute pancreatitis in the last two decades, it is observed an extraordinary evolution. We do not operate as many times as before, scheduled reoperations are no longer used, new resources are available, as those here described, and a significant reduction of morbidity and mortality rates

was achieved. There is no mandatory procedure to be made initially or as best option. The use of the step-up approach and postponing the drainage must be adopted in all patients. In those with infection, even with gas in retroperitoneum, it is possible to use only antibiotics with good results, in patients without multiple organ failure. Minimally invasive treatment with drainage may be the first alternative, but evolution, clinical condition and pancreatic necrosis characteristics will define the best technique to be used. Literature presents high rates of success with minimally invasive drainage, but, when infection is not reverted, open necrosectomy must be considered.

RESUMO

A necrose pancreática ocorre em 15% das pancreatites agudas. A presença de infecção é o fator mais importante na evolução da pancreatite. Confirmar o diagnóstico de infecção ainda é um desafio. A mortalidade na necrose infectada é de 30% e na vigência de disfunção orgânica, chega a 70%. Nas últimas décadas, ocorreu uma verdadeira revolução no tratamento da necrose pancreática infectada. Mesmo assim, persiste o desafio e há múltiplas questões ainda não resolvidas: tratamento exclusivo com antibiótico, drenagem percutânea guiada por tomografia, drenagem por via endoscópica, desbridamento extra-peritoneal vídeo-assistido, acesso extra-peritoneal, necrosectomia por via aberta? Foi proposto o tratamento por etapas, "step up approach", iniciando-se com as medidas menos invasivas e reservando-se a intervenção operatória para os casos em que o procedimento anterior não resolver definitivamente o problema. A indicação e o momento da intervenção devem ser determinados pela evolução clínica. O ideal é que a intervenção seja feita apenas depois da quarta semana de evolução, quando já existe melhor delimitação da necrose. O tratamento deve ser individualizado. Não existe um procedimento que deva ser o primeiro e a melhor opção para todos os doentes. O objetivo deste trabalho é fazer uma análise crítica do estado atual do tratamento da necrose pancreática infectada.

Descritores: Pancreatite. Pancreatite Necrosante Aguda. Infecção. Drenagem.

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