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Natural history of acute pancreatitis and the role of infection

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Bacterial infection of pancreatic necrotic tissue is a frequent complication of severe acute pancreatitis. Infected pancreatic necrotic tissue is observed in 30–70% of all patients suffering from necrotizing pancreatitis. It is the leading cause of deaths in severe acute pancreatitis, with mortality rates ranging from 15 to 30%. The incidence of infection increases with the extent of the necrotic areas and with the time after onset of pancreatitis. Compared to patients with sterile necrosis, those with infection of the necrotic areas have an increased mortality, and systemic complications occur more frequently. Standard treatment for infected pancreatic necrotic tissue is surgical debridement, whereas conservative management is feasible in approximately 30% of the patients with sterile necrosis.

As bacterial infection of pancreatic necrotic tissue has a tremendous impact on the prognosis of the disease and on the patient's clinical course, efforts have been made to prevent it. Although clinical and experimental data provide evidence that prophylactic antibiotics have beneficial effects on the outcome and course of patients with severe acute pancreatitis, this topic has to be investigated further. General recommendations concerning the early use of antibiotics have to await the results of larger, double-blind studies.

Key words: severe acute pancreatitis; bacterial infection; infected pancreatic necrosis, systemic complications; surgical treatment.

The natural history of acute pancreatitis is characterized by a variable clinical picture ranging from a mild and self-limiting disease to a potentially lethal one. The overwhelming majority of patients suffer from mild pancreatitis. Systemic complications and a fatal course are rare. Pain relief, parenteral nutrition and fluid replacement are the basis of clinical management. These patients recover after an uneventful course without further complications.

Ten to twenty percent of all patients with acute pancreatitis develop severe disease, morphologically characterized by intra- or extrapancreatic necrosis (Beger, 1989; Widdison and Karanjia, 1993). Complicated courses are common in severe acute pancreatitis. Although considerable improvements in clinical management have led to a decrease in mortality during the past decade, the rate of fatalities associated with the disease is still unacceptably high. Even in specialized centres, 15–20% of patients with necrotizing pancreatitis die. A lethal course of severe acute pancreatitis is

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characterized by the occurence of systemic complications. If death occurs in the course of severe acute pancreatitis, it occurs in patients with necrotizing pancreatitis and is commonly associated with failure of at least one organ system (Karimgani et al, 1992; de Beaux et al, 1995; Tenner et al, 1997).

Although our knowledge of the pathogenesis of the disease is still limited, progress has been made in our understanding of factors which are responsible for a fatal course. Bacterial infection of pancreatic necrotic tissue is accepted as the most important prognostic factor for severity and outcome in severe cases of acute pancreatitis (Beger et al, 1986; Widdison and Karanjia, 1993; Isenmann and Büchler, 1994).

BACTERIAL INFECTION

Almost a century ago, bacterial infection was regarded as the underlying cause of acute pancreatitis. According to the observations of Fitz, the disease was caused 'by the extension of a gastroduodenal inflammation along the pancreatic duct' (Fitz, 1889). Today, we know that bacteria do not play a role in the initial pathogenesis. Nevertheless, infection is a well known later phenomenon in this disease. Our current definition of acute pancreatitis and its complications includes three different patterns of pancreatic infection (Bradley, 1993; Frey and Reber, 1993).

Infected pancreatic necrotic tissue is found in 1–10% of all patients suffering from acute pancreatitis and in 40–70% of those with necrotizing pancreatitis (Bittner et al, 1987; Beger et al, 1988; Fedorak et al, 1992; Widdison and Karanjia, 1993), bacteria being present in diffuse or focal areas of non-viable pancreatic parenchyma. It is the most frequent pattern of pancreatic infection, becoming relevant during the second to third week after onset of pancreatitis. Moreover, among all infectious complications of severe pancreatitis, infected necrotic tissue has the most striking impact on the patient's course and prognosis.

The term 'pancreatic abscess' describes a localized and encapsulated collection of purulent material with little or no necrosis in the pancreas or peripancreatic region. In contrast, infected pancreatic pseudocysts are defined as localized and encapsulated collections of infected pancreatic juice, not containing pus or necrotic material. Both, pancreatic abscess and infected pseudocysts, are a late sequel of severe acute pancreatitis. In comparison with infected necrotic tissue, they are characterized by a mild to moderate clinical picture with significantly lower APACHE II and Ranson scores. Systemic complications and a fatal course are less frequent in these patients (Bittner et al, 1987).

INCIDENCE OF INFECTED NECROTIC TISSUE

In the literature, there are considerable differences concerning the incidence of infected pancreatic necrotic tissue, ranging from 1 to 10% of the patients with acute pancreatitis and from 30 to more than 70% of those with pancreatic necrosis (Beger et al, 1986; Gerzof et al, 1987; Bassi et al, 1989; Bradley et al, 1991). These wide ranges are most probably caused by differences in patient selection and the assessment of

bacterial infection. In our series of more than 1400 cases of acute pancreatitis and 300 patients with necrotizing pancreatitis, the incidence of infected necrotic tissue was 6.8% of all cases of acute pancreatitis and 33% among those patients with pancreatic necrosis (Table 1).

Table 1. Incidence of infected pancreatic necrotic tissue and pancreatic abscess in 1442 patients suffering from acute pancreatitis at the University of Ulm, Department of General Surgery, 1982–1996.

	Patients	% of NP	% of AP
Infected necrotic tissue	99	33.0	6.8
Pancreatic abscess	40	13.3	2.8

NP = necrotizing pancreatitis; AP = acute pancreatitis.

TIMING OF PANCREATIC INFECTION AND FACTORS INFLUENCING THE INCIDENCE

Pancreatic infection is closely associated with the presence of intra- and/or extra-pancreatic necrosis. The time of presentation is variable. By the use of fine-needle aspiration, bacteria can be detected at a median of 6 days after the onset of acute pancreatitis (Gerzof et al, 1987; Isenmann et al, 1992). On the other hand, most patients with infected necrotic tissue are operated on in the third week after the onset of symptoms of pancreatitis. These figures are obviously contradictory. They are influenced by two major factors. First, the results of bacterial cultures taken at laparotomy show a time-dependent increase in the incidence of infected necrotic tissue (Figure 1). Twenty-four percent of the patients undergoing operation during the first week after onset of pancreatitis had a positive bacterial culture. The rate increased to 36 and 71% of the patients operated in the second and third week respectively. Second, based on the data obtained from contrast-enhanced CT scan, pancreatic infection depends on the extent of necrosis. Samples from pancreatic necrosis taken during surgery showed bacterial infection in 26.8% of our patients with

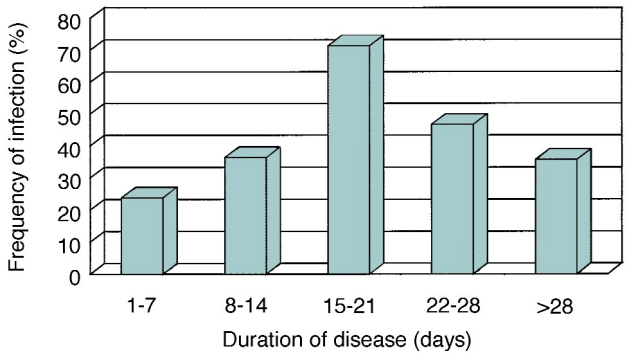

Figure 1. Timing of bacterial infection based on tissue sampling during laparotomy in 45 patients with infected pancreatic necrosis. Reproduced from Beger (1989, *Surgical Clinics of North America* **69:** 529–549) with permission.

an extent of necrosis of less than 30% according to CT findings. This proportion increased to 38.2% if more than 50% of the gland was found to be necrotic (Figure 2). Thus, pancreatic infection is a variable process, influenced by both the extent of necrosis and time. These facts may explain the wide range in the reported incidence of pancreatic infection as well as confusing data concerning the time of infection.

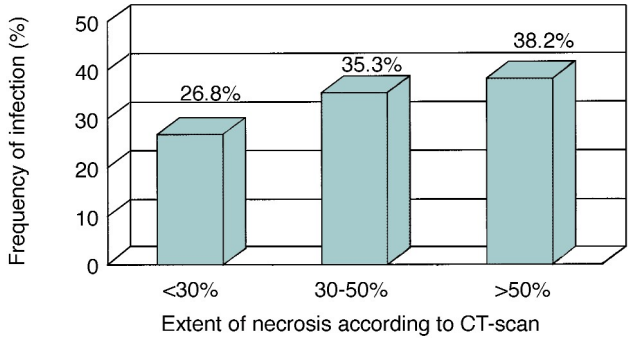

Figure 2. Correlation between the extent of necrosis (as shown by contrast-enhanced CT) and bacterial infection.

SPECTRUM OF BACTERIA AND PATHWAY OF PANCREATIC INFECTION

The spectrum of bacteria in infected pancreatic necrotic tissue has been examined in a number of clinical (Beger et al, 1986; Gerzof et al, 1987; Bassi et al, 1989) and experimental (Mithöfer et al, 1996) series. Clinical data have been obtained either from intraoperative smears (Beger et al, 1986; Bassi et al, 1989) or from samples taken by fine-needle aspiration (Gerzof et al, 1987). The spectrum of interest is characterized by two important characteristics: in most cases, infected necrotic tissue is a monomicrobial infection, caused by enteric bacteria. It is dominated by Gram-negative bacteria and also includes anaerobes and fungi. *Escherichia coli* is the species most commonly found in infected necrotic tissue, but there are also Gram-positive bacteria such as enterococci and *Staphylococcus aureus* (Table 2).

There has been some speculation whether the spectrum of bacteria is influenced by the therapeutic use of antibiotic drugs during the course of severe acute pancreatitis. This obviously has been supported by data showing a selection of Gram-positive bacteria after the use of broad-spectrum antibiotics during experimental pancreatitis (Mithöfer et al, 1996). As the spectrum of bacteria affects the choice of antibiotics used to prevent infectious complications, this has received considerable attention. Recent clinical data seem to indicate an increase in the frequency of detection of Gram-positive bacteria in pancreatic necrosis, and this has been linked to the use of antibiotics during the early course of severe pancreatitis (Sainio et al, 1995). In the absence of controlled data, interpretation of these findings is more than difficult. Until now, there has been no conclusive answer for this observation.

As the spectrum of bacteria of interest resembles that of the intestinal flora, it seems most likely that the bacteria originate from the gastrointestinal tract. Various routes have been considered as presumptive pathways of bacterial translocation into the pancreatic and peripancreatic region. The colon contains the greatest variety and

Table 2. Spectrum of bacteria and frequency in infected pancreatic necrotic tissue: 105 patients at the Department of General Surgery, University of Ulm, May 1982 to December 1993.

Monomicrobial	69%
Escherichia coli	23%
Staphylococcus aureus	14%
Enterococcus	6%
Klebsiella	5%
Polymicrobial	31%
Escherichia coli	22%
Enterococcus	16%
Staphylococcus aureus	3%
Klebsiella	4%
Pseudomonas	1%
Proteus	4%
Candida	5%

number of bacteria anywhere in the body, and the transverse colon is located in close proximity to the pancreas. Therefore, the large bowel has been suspected as a source of the bacteria complicating necrotizing pancreatitis; bacteria could enter the necrotic areas either by translocation through the colonic wall or via the lymphatics. (Wells et al, 1986; Medich et al, 1993; Kazantesev et al, 1994; Widdison et al, 1994). Haematogenous seeding via the circulation, ascending infection from the duodenum via the main pancreatic duct and seeding from the hepatic portal vein, liver and biliary system are other routes of bacterial infection that have been implicated. Although a number of experimental studies have addressed this topic, none of the proposed pathways has been conclusively confirmed or excluded (Widdison et al, 1994). Most probably, pancreatic infection is a result of the combination of bacterial translocation from the transverse colon, haematogenous and/or lymphatic seeding as well as ascending colonization of the biliopancreatic ductal system.

CLINICAL SIGNIFICANCE OF PANCREATIC INFECTION

In mild acute pancreatitis, morphologically characterized by oedematous changes of the gland, severe complications such as organ failure and fatal outcome are rare and observed in less than 1% of patients (Beger et al, 1988; Büchler et al, 1991). Severe pancreatitis is closely associated with the presence of necrotic tissue. Therefore, intra- or extrapancreatic necrosis is a major determinant for the development of the severe complications of pancreatitis.

Fatalities during severe acute pancreatitis most frequently occur as a sequel of septic multi-organ failure, and pancreatic infection is accepted to be the leading cause of death in severe acute pancreatitis (Beger et al, 1986; Bradley and Allen, 1991; Widdison and Karanjia, 1993; Isenmann and Büchler, 1994). This finding is based on the observation that there is a significant difference in the incidence of systemic complications between patients with infected and sterile necrosis. Pulmonary insufficiency, renal failure, shock, sepsis and sepsis-like syndrome as well as coagulopathy are common complications in patients with severe acute pancreatitis. In 300 patients with

necrotizing pancreatitis treated at our hospital, failure of one of these organ systems occured in 89.4% of those patients with infected necrotic tissue and in 73.4% of those with sterile necrotic tissue. Pulmonary insufficiency, renal failure, coagulopathy as well as sepsis and a sepsis-like syndrome were more frequent when necrotic tissue was infected (Table 3). Mortality was 12.9% in sterile necrosis compared to 25.2% in infected necrosis. In our patients, as well as in other series, systemic complications are more frequent in patients with pancreatic infection, and the hospital stay of this subgroup as well as their time in ICU is considerably longer.

Table 3. Morbidity and mortality in patients with sterile and infected necrotic tissue: 300 patients at the Department of General Surgery, University of Ulm, May 1982 to December, 1996.

	Sterile necrotic tissue (201 patients)	Infected necrotic tissue (99 patients)
	Systemic complications	
Pulmonary insufficiency*	58.7%	74.7%
Sepsis/sepsis syndrome†	36.3%	54.5%
Coagulopathy‡	42.8%	54.5%
Renal insufficiency§	21.4%	21.2%
Hospitalization (days)¶	45 (2–209)	62 (1–238)
ICU duration (days)¶	21 (1–184)	27 (1–238)
Mortality	26 patients 12.9%	94 patients 25.2%

* pO_2 < 60 mmHg.
† Sepsis: T > 38.5 °C and leukocytes > 12 000/µl and base excess –4 mmol/l for > 48 hours and positive blood culture/aspirate. Sepsis syndrome: T > 38.5 °C and leukocytes > 12 000/µl and base excess –2.5 mmol/l and negative blood culture/aspirate.
‡ Prothrombin time < 70% and/or activated partial thromboplastin time > 45 seconds.
§ Serum creatinine > 180 µmol/l.
¶ 221 patients undergoing surgical treatment.

The treatment of necrotizing pancreatitis has undergone considerable change during recent years. Formerly, early and aggressive surgery was advocated as the treatment of choice in patients with severe acute pancreatitis. The current approach is much more conservative and is based on the observation that a considerable number of patients with pancreatic necrosis will recover without surgical intervention. Today, there is general agreement among most authorities that patients with severe acute pancreatitis should be managed by conservative treatment as long as they respond to therapy (Beger et al, 1988; Wilson et al, 1988; Beger, 1989; Sarr et al, 1991; Rau et al, 1995). As long as the necrotic areas remain sterile, surgery is restricted to patients with progressive clinical deterioration not responsive to ICU treatment for more than 72 hours.

This delayed surgical approach favours the demarcation of necrosis and thus reduces morbidity and mortality formerly observed after early surgical intervention. Following this strategy, 36.3% of our patients with sterile necrotic tissue were treated without operation (Rau et al, 1995).

Whereas a considerable proportion of patients with sterile necrotic tissue recover without surgical intervention, infected necrotic tissue is accepted as a clear-cut

indication for surgical debridement and lavage; in such cases the rationale for surgery is based on the observation that infected debris should be removed from the peritoneal cavity thus removing toxic substances released by bacteria and accounting for remote organ failure. Furthermore, late complications such as pancreatic abscess should be prevented.

DIAGNOSIS OF PANCREATIC INFECTION

As bacterial infection has a striking impact on the prognosis and treatment of patients with necrotizing pancreatitis, it must be diagnosed precisely and treated without delay. Until recently, biochemical markers for the diagnosis of infected pancreatic necrotic tissue were not available. Ongoing multi-organ failure might be reflected in a variey of abnormal non-specific laboratory parameters, including serum C-reactive protein, which is the biochemical gold standard in the detection of pancreatic necrosis (Wilson et al, 1989; Uhl et al, 1991; Isenmann et al, 1993). However, the serum CRP level is not a reliable marker of infected pancreatic necrotic tissue (Rau et al, 1997).

A number of laboratory parameters and different mediators have been tested for their capability to discriminate between sterile and infected pancreatic necrotic tissue. Promising results have been achieved with procalcitonin (PCT), a 116 amino acid propeptide of calcitonin. PCT has been shown to be a potent marker for severe bacterial and fungal infection. In patients with necrotizing pancreatitis this marker correlates closely with the presence and severity of bacterial/fungal infection of pancreatic necrotic tissue (Rau et al, 1997). Although these data need to be confirmed by larger studies, they are promising and corroborate the potential of PCT as a reliable marker of pancreatic infection.

Today, fine-needle aspiration (FNA) with subsequent microbiological examination of the material is the gold standard for detecting infected pancreatic necrotic tissue (Barkin et al, 1982; Gerzof et al, 1987; Hiatt et al, 1987; Stiles et al, 1990; Rau et al, 1998). Indications for FNA are ongoing multi-organ failure, a persistent septic state of the patient, or newly developed signs of sepsis after an initial improvement during the clinical course of an attack. FNA can be performed either using sonographic or computed tomographic guidance. CT-guided fine-needle aspiration was introduced in the 1980s (Gerzof et al, 1987). Due to the fact that the patient has to be positioned in the CT machine, there are problems applying this technique in critically ill patients. Aspiration under ultrasound guidance offers the advantages of a bed-side performance and improved cost-effectiveness. In experienced hands, both methods achieve diagnostic accuracies of around 90% and complications are rare (Barkin et al, 1982; Hiatt et al, 1987; Stiles et al, 1990; Rau et al, 1998). Up to now, FNA is the only reliable method for detecting infected pancreatic necrotic tissue.

PREVENTION OF PANCREATIC INFECTION

As bacterial infection is one of the determinants for the prognosis of severe acute pancreatitis, its prevention by the prophylactic use of antibiotics has been a matter of clinical and experimental investigation for more than two decades. The first clinical series using prophylactic antibiotics in patients with acute pancreatitis failed to show a

benefit (Craig et al, 1975; Howes et al, 1975; Finch et al, 1976). These studies, however, enrolled only those patients with mild pancreatitis, in whom septic complications are rare and who have a mortality of less than 1%. Thus, it is now appreciated that a beneficial effect could have been shown in this group of patients.

With progress in our understanding of the basis of bacterial infection in acute pancreatitis, it became clear that the successful application of a prophylactic antibiotic strategy in this disease must take into account several principles. First, only patients with pancreatic necrosis are at risk from bacterial infection. Second, the antibiotic must be directed against the spectrum of bacteria found in infected pancreatic necrotic tissue and third, it must be able to penetrate into human pancreatic tissue (Büchler et al, 1992). During the past few years, a number of controlled studies have been conducted with these principles in mind. Only patients with necrotizing pancreatitis were enrolled, and the antibiotics of choice were shown to have a favourable pharmacokinetic profile in the human pancreas (Pederzoli et al, 1993; Sainio et al, 1995; Schwarz et al, 1997). Although none of the studies was double-blinded and the study population never exceeded 100 patients in total, they demonstrated variable benefical effects in patients who received prophylactic antibiotic treatment (Table 4). These studies showed either a reduction in the incidence of infected pancreatic necrotic tissue (Pederzoli et al, 1993), a significant reduction in mortality (Sainio et al, 1995) or a reduction of the APACHE II score in patients who received prophylactic antibiotics (Schwarz et al, 1997). On the basis of these clinical data, some have recommended the routine use of prophylactic antibiotics in patients with severe acute pancreatitis (Powell et al, 1998). However, we share the opinion of others (Ho and Frey, 1997) that this topic has to undergo further investigation and that a general recommendation concerning the use of prophylactic antibiotics has to await the results of larger, double-blind studies.

Table 4. Results of controlled trials concerning prophylactic antibiotic treatment in necrotizing pancreatitis.

		Patients		Incidence of pancreatic infection		Mortality	
	Antibiotic	C	T	C (%)	T (%)	C (%)	T (%)
Pederzoli et al (1993)	Imipenem	33	41	30*	12*	12.1	7.3
Sainio et al (1995)	Cefuroxime	30	30	40	30	23.3*	3.3*
Schwarz et al (1997)	Ofloxacin + metronidazole	13	13	53	61	15.4	0

T = treatment group; C = control group.
* Statistically significant differences.

TREATMENT OF INFECTED PANCREATIC NECROTIC TISSUE

The current principles of treatment of severe acute pancreatitis are based on the observation that a considerable number of patients can be managed without operation. The results of early surgical intervention were disappointing and led to more restrictive approaches (Ranson et al, 1974; Acosta et al, 1978; Nordback and Auvinen, 1985). Today, apart from one exception (Rattner et al, 1991), there is general

agreement that conservative treatment should be continued for as long as the patient responds to it. The main indications for surgery in necrotizing pancreatitis are (1) ongoing multi-organ failure despite maximum intensive medical care over a period of more than 72 hours, and (2) overt or strongly suspected pancreatic infection (Bradley, 1987; Beger et al, 1988; Wilson et al, 1988; Bradley and Allen, 1991). Given these principles, 30–40% of all cases of necrotizing pancreatitis can be managed without operation (Bradley and Allen, 1991; Rau et al, 1995).

Pancreatic infection is regarded as an absolute indication for surgical intervention for several reasons. Infected debris should be removed from the retroperitoneum as it is the source of bacteria and their toxic compounds which are thought to be responsible for remote organ failure. Furthermore, late complications, such as pancreatic abscess, should be prevented and viable pancreatic parenchyma preserved.

The current strategies of surgical treatment of infected necrosis are based on the observation that the aggressive removal of all necrotic material is likely to lead to severe complications such as diffuse bleeding and gastrointestinal fistulas. Some approaches entail the use of open or semi-open techniques in which the necrotic areas are removed by frequent and planned re-operations (Bradley, 1987; Sarr et al, 1991). These procedures, which require repeated intra-abdominal manipulations, bear multiple risks, including mechanical ileus and incisional hernia, and they prolong the intensive care stay of the patient.

At our institution, closed management is preferred, combining careful digital necrosectomy and post-operative lavage of the lesser sac via large-bore single- and double-lumen catheters. Post-operative irrigation of the omental bursa eliminates the remaining necrotic material and biochemically active compounds from the pancreatic region without the necessity of repeated intra-abdominal manipulations. According to our experience, this approach is a safe and successful procedure in patients with necrotizing pancreatitis. In comparison to open or semi-open techniques, it provides similar results with respect to clinical outcome but is superior in terms of the lower demand for repeated complex radiology, ICU therapy and cost (Table 5). In contrast to the established therapeutic algorithm, there have been some recent attempts at prolonged conservative management of patients with infected necrosis (Dubner et al, 1996; Rünzi et al, 1996). This attempt is in complete contrast to the established surgical standards of early removal of infected material. As, up to now, only uncontrolled data and series of selected patients are available, prolonged conservative treatment of infected necrotic tissue is far from being an established therapeutic approach.

Table 5. Results of necrosectomy and local lavage for necrotizing pancreatitis in 140 patients at the University of Ulm, Department of General Surgery, 1982–1996.

			Range
Pre-operative	Ranson	4 points	0–9
	APACHE II	9.0 points	0–28
Post-operative	Hospitalization	53 days	7–192
	ICU	22 days	1–184
	Lavage duration	22 days	1–109
	Lavage fluid	24 l/24h	2–36
	Frequency of re-operation	36.4%	
	Mortality	12.9%	

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