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REVIEW

Current treatment of infections in acute pancreatitis

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Abstract. Infection of pancreatic and peripancreatic necrosis frequently complicates the course of severe acute pancreatitis and accounts for the majority of morbidity and mortality in these patients. Late infectious complications such as pancreatic abscesses appear less dangerous to the patient, but should be treated aggressively. The use of prophylactic broad spectrum antibiotics can no longer be supported, as in two recent controlled trials no benefit was found, and antibiotic resistance and fungal infections have increasingly been described. Enteral nutrition is a simple and effective manner to reduce infectious complications, and strategies to reduce the risk for infection should be further refined. The treatment of established infection is based on source control and appropriate antibiotic treatment.

Introduction

Acute pancreatitis is an inflammatory disease of the pancreas, which may be either localized, or affect the whole pancreas. Clinical manifestations consist of acute epigastric pain, often associated with referred pain in the back, nausea and vomiting.

The condition is mainly caused by alcohol abuse or biliary tract stones. Other causes include trauma (including endoscopic retrograde cholangiopancreaticography [ERCP]), drugs, hyperlipaemia, and viral infections. In up to 20% of patients , no clear cause can be identified.

Pancreatitis is a disease with a typically unpredictable course, which according to the Atlanta criteria, can be classified as either mild or severe[1]. Most patients develop only mild pancreatitis, which is self-limiting and carries a low morbidity and mortality rate. Signs and symptoms usually resolve within 3 to 5 days. There is no necrosis , only pancreatic oedema, and systemic effects are limited. These may include one or more symptoms of systemic inflammation, such as fever, tachycardia, tachypnoea or leucocytosis.

Some of these patients may progress to severe acute pancreatitis (SAP), which is associated with organ failure and /or local complications such as necrosis, abscess formation or pseudocysts. Typically, the Ranson score is 3 or higher, and on admission, the APACHE II score is 8 or higher. Patients with the fulminant variant of the disease develop multiple organ dysfunction syndrome (MODS) within 24-72 hours after admission due to an intense systemic inflammatory response syndrome (SIRS). In these patients, contrast enhanced computed tomography scan is the gold standard to confirm the presence of pancreatitis, and more importantly, the presence of necrosis of the gland [2]. It is not useful to perform a CT scan within the first 4 to 6 days after the start of symptoms, except to exclude alternative diagnoses or to look for complications other than pancreatic necrosis such as bleeding or perforation, as pancreatic necrosis usually only develops after this time frame. In these patients infectious and other complications frequently arise and determine the further course of the disease. Common local complications include peripancreatic fluid collections, which may compress adjacent organs and cause biliary obstruction or ileus, pseudocysts with associated problems such as bleeding or rupture, and thrombosis of peripancreatic veins.

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Necrosis of the pancreatic tissue is the main risk factor for the development of infected pancreatic necrosis, which typically develops 1-3 weeks after onset of an attack of acute pancreatitis. Necrosis and especially infection of the necrosis, have been identified as important risk factors for mortality [3-5], although recent investigations suggest that the degree of organ dysfunction may be even more important [6, 7].

Late infectious complications occur 4 to 8 weeks after the first attack of pancreatitis. As their nature and associated mortality seem to be different, these late complications should be considered as separate entities.

In this review, we will give an overview of common infectious complications of SAP, with the focus on infected pancreatic necrosis.

Definitions. Not all infections are equal ...

Pancreatic infections are often synonymous with infected pancreatic necrosis. However, as rarer conditions such as pancreatic abscess and infected pancreatic pseudocysts differ considerably in terms of management and outcome, it is important to differentiate between them.

Infected pancreatic necrosis is an infection of non-viable pancreatic tissue that results from ischaemia during an episode of acute pancreatitis. Also peripancreatic necrotic tissues may become infected, and the term "infected pancreatic necrosis" is used interchangeably for both conditions. It is not clear whether making a distinction between those conditions is clinically relevant.

Pancreatic abscess is defined as a contained, peripancreatic collection of purulent material. It does not contain any necrotic material, which makes it different from infected pancreatic necrosis, and although it is often the result of an episode of acute pancreatitis, it mostly occurs later in the course of the disease or after a surgical procedure. Pancreatic abscess will be addressed in a separate chapter at the end of this manuscript; the focus will first be on infected pancreatic necrosis.

Impact of infection of pancreatic necrosis

Mortality in SAP has a biphasic distribution. Forty to fifty percent of the patients that die do so in the first 2 weeks, and this is related to the severity of organ dysfunction. An intense systemic inflammatory response syndrome is responsible for this, and as in patients with severe sepsis, this may lead to MODS, which in this setting has been designated as "fulminant" or "early" SAP. Most of these patients do not have documented infected pancreatic necrosis at this stage.

Table 1. Pooled microbiological data from the two controlled randomized trials comparing antibiotic prophylaxis with placebo.

	Placebo groups combined	Intervention groups combined
Total number of patients	**106**	**108**
Patients with infected pancreatic necrosis (%)	11 (10.4%)	16 (14.8%)
Gram positive microorganisms		
Coagulase negative staphylococci	4	5
Enterococci	2	7
Staphylococcus aureus	4	1
Streptococcus viridans	0	1
Total	10	14
Gram negative microorganisms		
E. Coli	4	4
Pseudomonas sp.	0	3
Enterobacter spp.	0	2
Proteus sp.	1	2
Acinetobacter spp.	0	2
Lactobacillus	1	0
Total	**6**	**13**
Anaerobes		
Bacillus	1	0
Fungi		
C Albicans	1	3
C Glabrata	1	0
Total	**2**	**3**

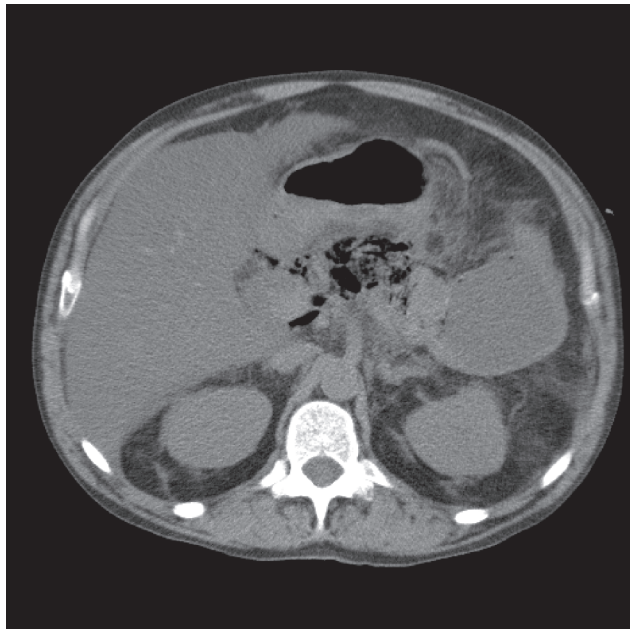

Figure 1. Abdominal CTscan with gas in the retroperitoneum, indicative of pancreatic infection.

Infected pancreatic necrosis and complications related to infected pancreatic necrosis, mostly severe sepsis and septic shock, are the main causes of death once the patient has overcome the early phase of acute pancreatitis. Infection of pancreatic necrosis has long been considered the main determinant of mortality [3, 4], but recently, the severity of organ dysfunction, both early in the course of the disease, and later due to severe sepsis originating from the pancreatic necrosis, is increasingly being recognized as the most important factor in determining mortality [6, 7].

In some patients, pancreatic necrosis and infection of this necrosis may also cause secondary complications such as bleeding or gut ischaemia.

Pathophysiology of infection

Mechanisms involved in infection of pancreatic necrosis are not yet well understood. Although only documented in animal experiments, bacterial translocation from the gut is presumed to be the main threat to patients with SAP. In laboratory experiments, an incidence of bacterial translocation of up to 100% has been found [8]. Factors involved in translocation may be ileus, with increased intestinal wall tension, the use of prophylactic antibiotics (because of the selection of micro-organisms), and intra-abdominal hypertension (IAH), which is increasingly documented in patients with SAP [9]. IAH, defined as intra-abdominal pressures of more than 12 mmHg, and abdominal compartment syndrome (ACS) - the clinical picture that results from prolonged IAH, characterized by hypotension, acute renal failure and pulmonary insufficiency [10] - are associated with an increased translocation rate [11]. Inadequate abdominal perfusion pressures leading to gut barrier failure may be a plausible explanation [12].

Infection of pancreatic necrosis may also be the result of direct contamination due to bowel perforation, or haematogenous dissemination of distant foci of infection such as pneumonia or catheter-related infections. Other factors involved may be reflux from the duodenum, which is illustrated by occasional fulminant deterioration in patients with acute pancreatitis undergoing ERCP. At a later stage, superinfection and persistent inflammation of the pancreatic and peripancreatic tissues may occur, a clinical picture resembling tertiary peritonitis.

Microbiology of infected pancreatic necrosis

The micro-organisms involved in infection of pancreatic necrosis are most often enteric gram-negative bacteria, although an increase in gram-positive infections has been described [13]. This observation and also observations of the organisms described in most series, may have been blurred by the extensive use of antibiotic prophylaxis, often broad spectrum antibiotics, such as carbapenems or quinolones.

The use of these agents may cause a selection of often resistant gram positive and gram negative organisms, and this problem has been increasingly recognized. Previously, we described the incidence of antibiotic resistant infections in infected pancreatic necrosis as being as high as 52%; the majority of these infections were nosocomial superinfection, occurring after surgery and after prolonged exposure to broad spectrum antibiotics.

Interesting data on this topic have emerged from two blinded studies on antibiotic prophylaxis. The study by Isenmann et al, which compared ciprofloxacin and metronidazole with placebo, found that in the intervention group, 78% of the organisms that caused infections (including extrapancreatic infections), were resistant to ciprofloxacin. Dellinger et al found that 5 out of 6 isolates from pancreatic infection that were tested were resistant to the study drug (meropenem). Table 1 summarizes the organisms isolated from the combined placebo and intervention groups of these studies. From this table it is clear that the organisms recovered from patients in the placebo group are different from those recovered from the intervention group: notably, more infections with nosocomial gram negative organisms (such as *Pseudomonas*, *Acinetobacter* and *Enterobacter spp.*) were found, and also more enterococcal infections were present in patients who were given antibiotic prophylaxis. It should also be noted that an important number of patients in the placebo group was switched to antibiotics on suspicion of pan-

Table 2. Overview of placebo controlled trials comparing antibiotic strategies in patient with severe acute pancreatitis.

First author	n	Treatment in intervention group	Blinded	Pancreatic infection rate (intervention vs. placebo)	Mortality (intervention vs. placebo)
Sainio [15]	60	Cefuroxime	No	9/30 vs. 12/30	1/30 vs. 7/30 *,**
Pederzoli [16]	74	Imipenem	No	5/41 vs. 10/33 $	3/41 vs. 4/33
Delcenserie [63]	23	Ceftazidime, amikacin + metronidazole	No	7/12 vs. 0/11 *, $$	3/12 vs. 1/11
Nordback [64]	58	Imipenem	No	NA	2/25 vs. 5/33
Isenmann[19]	114	Ciprofloxacin + metronidazole	Double blind	7/58vs. 5/56	3/58vs. 4/56
Dellinger [20]	100	Meropenem	Double blind	9/50 vs. 6/50	9/50 vs. 10/50
Rokke [18]	73	Imipenem	No	3/36 vs.7/37	3/36 vs. 4/37

Legend. * p<0.05, ** see text for comment, $ Pancreatic infection rate defined as a combination of infected pancreatic necrosis, pancreatic abscess and infected pseudocyst, $$ Pancreatic infection rate defined as severe sepsis (pancreatic infection and septic shock.

creatic infection or extrapancreatic infection, so the effect of selection may even be underestimated.

These findings, however, contrast with the data published by Luiten et al In their study on the use of selective bowel decontamination [14], a considerable incidence of Pseudomonas and enterococcal infection (50% and 60% in the control group respectively), was found; however, the average number of laparotomies was 3.1 in these patients, with numerous colon resections and intestinal fistulas involved, and it is not clear whether the organisms were present at the first intervention, or only emerged later in the course of the disease.

Prevention of infection: prophylactic antibiotics

Prophylactic antibiotics have been the most intensely debated topic in the treatment of patients suffering from SAP. Although once considered a life saving intervention, based on a number of small unblinded trials, and eagerly adopted by the medical community, in two recent controlled randomized trials, the only blinded studies that have been performed to date, this practice could not demonstrate any benefit.

In the 1980s and 1990s, a number of trials were performed that investigated the use of different antibiotics to reduce the incidence of pancreatic infection. Only one trial showed an effect on mortality. In a small study, Sainio et al studied the use of cefuroxim and reported a reduced mortality rate in treated patients when compared to patients who had not received prophylactic antibiotics (1/30 vs. 7/30, p=0.03) [15]. The incidence of pancreatic infection was no different however, and the high number of patients that did receive antibiotics makes interpretation difficult. Peripancreatic coagulase negative staphylococcal infections were frequent, and also the high number of catheter-related infections suggests problems with intravenous catheter management in these patients.

Similar studies found no effect on mortality, and different end points are used in every single paper. Pederzoli compared imipenem with placebo, and found a decrease in the incidence of pancreatic sepsis, but no effect on mortality [16]. Bassi randomized patients to either treatment with pefloxacin or imipenem, and - not surprisingly - also found no difference in outcome [17]. Another recent trial found no effect on mortality or peripancreatic infection rate, but the overall (pancreatic and non-pancreatic) infection rate was reported to be lower [18]. The total cost of antibiotics in the intervention group was about double of the cost in the placebo groups (20,400 vs. 10,200 Euro)

The beneficial effects of prophylactic antibiotics – albeit on questionable endpoints in most studies – have not been confirmed in the only two blinded randomized controlled trials to have recently been performed. The largest trial, comparing a combination of ciprofloxacin and metronidazole with placebo in predicted severe pancreatitis did not show a difference in incidence of pancreatic infection, extrapancreatic complications or mortality, and was stopped after an interim analysis [19]. More recently, a large multicentre controlled randomized trial has shown no effect of prophylactic meropenem in patients with SAP [20]. Also, the use of meropenem did not delay pancreatic infection. Whereas the early use of non-study antibiotics was very frequent in the placebo group of the Isenmann study, this was not the case in the study by Dellinger et al making the placebo group indeed worth the name.

So far, no trial has undeniably shown an effect on mortality, and in the randomized trials, no effect on pancreatic infections was found; therefore, the use of prophylactic antibiotics – although widely practiced and still recommended by some societies [21, 22] and experts in the field [23, 24] – cannot be supported in patients with pancreatic necrosis.

Prevention of infection: selective digestive decontamination

As the bowel is evidently the source of infection in patients with infected pancreatic necrosis, the use of **selective digestive decontamination** (SDD) may be a logical solution to decrease the load of micro-organisms that can potentially infect the peripancreatic tissues.

Luiten et al studied the effect of selective digestive decontamination – a combination of topical antibiotics and antifungal agents, consisting of colistin, tobramycin and amphotericin B, together with intravenous cefotaxim for a mean of 7.4 days. They found that the infection rate of pancreatic necrosis was reduced from 38% to 18% [14]. In particular, the occurrence rate of gram-negative infections was decreased, whereas gram-positive infections did not change significantly [25]. Moreover, mortality in 102 patients included in this trial was reduced from 35% to 22%, which was not statistically significant, but multivariate analysis showed that treatment with SDD had an odds ratio of 0.3 (p=0.048). The question remains however, whether this effect should be solely attributed to the use of SDD, as the patients also received a 7.4 day course of cefotaxim. Also, the high rate of intestinal fistulas and colonic resections may be alternative explanations for the high rate of infections in the control group. It is not clear if this study is still valid, as some things have changed since this trial was completed. The trend towards early enteral nutrition, which has shown to have protective effect on bowel integrity, and therefore decreasing the chances of translocation, has been demonstrated to have a similar effect on pancreatic infection rate, albeit in small underpowered and unblended studies. Recently, a large multicentre trial in the Netherlands could not demonstrate any beneficial effect of SDD in a general ICU population.

Prevention of infection: enteral nutrition

Whereas it was once considered dangerous to feed the patient enterally to avoid stimulation of the exocrine pancreas, the early use of

enteral nutrition is now generally accepted for patients with acute pancreatitis. Apart from the obvious advantages as compared to total parenteral nutrition in critically ill patients, such as reduced cost and lower catheter-related- and other infections [26], it is also considered to reduce morbidity specifically related to pancreatitis. In a recent meta- analysis, McClave et al found that the use of enteral nutrition results in better outcome when compared to parenteral nutrition. Not only is it assumed that enteral nutrition modulates the inflammatory response, but a number of studies demonstrated that enteral nutrition compared to parenteral nutrition decreases the incidence of infectious complications and even mortality associated with it [27, 28]. Although part of the effect may be due to the side effects of parenteral nutrition in the control groups, It is assumed that enteral nutrition improves gut mucosal integrity and therefore reduces the rate of bacterial translocation; however, a recent study in humans did not find any evidence for this [29]. Enteral nutrition also results in a better glucose control that parenteral nutrition, which may also add to the beneficial effect observed [30].

Prevention of infection: what is on the horizon?

Early and adequate risk stratification is of paramount importance if strategies aimed at reducing infection are to be investigated in the future; early because pathophysiological mechanisms leading to pancreatic infection, such as bacterial translocation, should be stopped as soon as possible, and adequate because studies in the past often failed to include patients who are truly at risk for pancreatic infection, and therefore there is an inherent risk for statistical type II error. This has proved to be a difficult issue, but progress is being made. Recently, Rau et al demonstrated that procalcitonin may be helpful in identifying patients at risk for infected pancreatic necrosis and multiple organ dysfunction early after admission [31]. However, procalcitonin could not differentiate between sterile necrosis and infected necrosis without organ dysfunction, and therefore seemed related to MODS rather than to infection.

As the bowel is considered to be the source of micro-organisms involved in pancreatic superinfection, manipulating this pathway may be an interesting alternative way of decreasing pancreatic infection. Several studies have suggested the beneficial effects of enteral nutrition, and two recent meta-analyses found that infectious complications decrease on enteral nutrition [28, 32]. Additionally, adding probiotics to enteral formulas may provide an extra advantage by controlling bacterial overgrowth, as suggested in animal studies, and a small study in humans [33]. A recent, underpowered study by the same group claimed a lower incidence of complications such as pancreatic infection and mortality in the probiotic group, but this difference was not statistically significant [34]. Recently, a large prospective study was completed in the Netherlands [35], the results of which are eagerly awaited.

Diagnosis of infection in acute pancreatitis

The diagnosis of infection in patients with pancreatic necrosis is notoriously difficult. Often, it was only documented at laparotomy when patients underwent necrotomy because of ongoing multiple organ failure, but as this indication for surgery is now generally considered obsolete [36], other means for establishing the diagnosis are used.

Fine needle aspirate, either CT [37, 38] or ultrasound [39] guided, is an elegant method for excluding pancreatic infection. It is very important that Gram staining is immediately performed, but infection cannot be ruled out based on this alone, as, in a considerable number of patients, it may give a false negative. In some extreme cases, retroperitoneal gas may point to infection of the peripancreatic tissue (Figure 1). The occurrence of bloodstream infections has also been associated with intra-abdominal infections in these patients [40].

It is important to realize that clinical criteria such as fever, tachypnoea, or tachycardia are very sensitive, but not very specific in patients with suspected infection, as are elevated leukocytes or C-reactive protein . These should not be used as a guide to start empiric antibiotic treatment, but rather prompt the search for infection using either one of the techniques described above . Infection however is rare in the first 7 to 10 days after the start of symptoms, and as any puncture carries an inherent risk of introducing infection into sterile pancreatic necrosis, FNA should be used judiciously in this setting.

Treatment of established infections

Source control

Infected pancreatic necrosis should be treated according to the principles of source control. Classically, source control should consist of drainage, prevention of ongoing contamination and restoration of premorbid anatomy and function. In acute pancreatitis, this should include proper drainage of pus and proper removal of pancreatic and peripancreatic necrotic tissue - known as debridement. This can be achieved using a variety of surgical techniques, none of which is demonstrably superior [41]. Recently, minimally invasive techniques have proved to be associated with minimal morbidity and mortality [42, 43], but randomized studies, such as the ongoing Dutch multicentre PANTER trial that compares laparotomy to a step-up approach using minimally invasive techniques [44], should be awaited before drawing any conclusions.

In contrast with other intra-abdominal conditions such as abdominal abscess, infected pancreatic necrosis is not usually amenable to percutaneous drainage, as pancreatic necrosis cannot be removed using small bore catheters. Ultrasound and CT-guided drainage may be considered for treating pancreatic abscesses, especially in those patients who have undergone prior debridement for pancreatic necrosis. Patients with infected pseudocysts can be managed adequately using endoscopic cystogastrostomy, depending on both location and extension of the PC.

Some patients with infected pancreatic necrosis have been managed without intervention; these patients did however receive systemic antibiotics. No clear selection criteria exist, but patients who seem to tolerate the infection well, without overt organ dysfunction or deterioration at the moment of diagnosis of the infection may be treated conservatively. Caution should be exercised here, as no definite criteria have been identified to select patients who may be treated without intervention. It can be assumed, however, as the development of infected pancreatic necrosis is a continuum starting with bacterial translocation and ending with a collection of pus in the necrotic pancreatic bed, that some patients, when diagnosed early in this sequence of events, may be spared from developing the classical picture of infected pancreatic necrosis with ensuing severe sepsis and difficult to treat intra-abdominal infection.

In the past, source control meant surgery, but now more than ever, several strategies can be used and a combination of these may be employed. Therefore, diagnosing and controlling infection in patients with pancreatic necrosis is a multidisciplinary process, and early and repeated interaction with surgeons, gastroenterologists and interventional radiologists experienced in the management of pancreatitis, is essential. The variability of the localization, consistency and the extent

of pancreatic necrosis means that any procedure for either diagnosis or treatment, at any stage in any patient should be tailored to the individual patient.

Antibiotics

Generally, little attention has been paid to the choice of antibiotic for established infected pancreatic necrosis. A number of studies have been performed on the penetration of parenteral antibiotics into the normal pancreas, with generally good results for carbapenems and quinolones [45, 46]. The situation is obviously different in pancreatic and peripancreatic necrosis and subsequent superinfection. There is no reason however, why infected pancreatic necrosis should be treated differently from any other complicated intra-abdominal infection, and using any compound or scheme that has proven to be effective in complicated intra-abdominal infections is also a good choice in infected pancreatic necrosis [47].

Fungal infections in acute pancreatitis

In recent years, fungal involvement in infected pancreatic necrosis has increasingly been described, and in the most recent studies, fungal infection was shown to occur in about 30 to 40% of patients who develop IPN [48-50]. *Candida albicans* was isolated from most patients. There seems to be a relationship between the use of prophylactic antibiotics, and the duration of prophylactic antibiotic treatment in a lot of reports. One study showed that early antifungal treatment reduced the incidence of fungal infection without affecting mortality. The impact on mortality of fungal infected pancreatic necrosis is variable with mortality rates reported between 0% [49] and 63% [51], with an overall mortality of 27%. Secondary infections, occurring after one or more surgical procedures for infected pancreatic necrosis are particularly frequent, and in these patients, prophylactic antifungal treatment should be considered.

Pancreatic abscess

Pancreatic abscesses almost exclusively occur in patients with SAP, and incidence ranges from as low as 1% up to 30% [52-55], depending on the report and definitions used. Mortality is considerably lower than in infected pancreatic necrosis, and estimated at around 10-20% [56] whereas in older series mortality rates up to 30-40% have been described [52, 54, 57].

If an SAP patient develops a recurrent episode of sepsis after initial improvement or after surgery for pancreatic necrosis, then pancreatic abscess should be suspected. Typically, diagnosis is confirmed by contrast enhanced CT scan, combined with fine needle aspiration if the presence of infection is unclear. Ultrasound has proved to be less sensitive than CT scan [55]. Caution should be used in the early phase of the disease, where making a distinction between pancreatic necrosis with localized fluid collections and a pancreatic abscess may be difficult; MRI may be helpful in confirming the diagnosis. Anaerobes and gram negatives such as *E. coli* are most often cultured from these abscesses [58], and it can be assumed that microbiology is not different from nosocomial intra-abdominal infections.

These abscesses, like any other intra-abdominal abscess, should be treated by drainage. The initial enthusiasm for percutaneous drainage has recently been questioned. Initial studies included patients with other problems such as pseudocysts or peripancreatic fluid collections, which may have lead to impressive results. The success rate of percutaneous drainage as a primary therapy is low, and should be limited to patients with postoperative infections or as a temporary measure in patients that are too unstable to undergo surgery [59]. On the other hand, successful percutaneous drainage has been reported in a mixed group of infected pseudocysts and abscesses [60]. As the need for surgical intervention varies considerably in patients after percutaneous drainage, it should be decided on a patient-to-patient basis which technique is appropriate. If the collection is unilocular, and is remote from the pancreas, the success rate of percutaneous drainage is presumed to be higher [53].

Alternatively, endoscopic transmural [61] and endoscopic transpapillary [62] drainage has been successfully applied in selected patients. In any case, large catheters should be used in order to drain the contents of the abscess properly. If percutaneous drainage fails, or if the abscess is not amenable to percutaneous drainage, a directed surgical procedure is indicated.

Conclusion

Infected pancreatic necrosis is related to considerable morbidity – largely associated with the surgical procedures required – and mortality. Source control is notoriously difficult in these patients, and the disease often protracted. Therefore strategies aimed at preventing necrosis and infection of established necrosis should be further developed. Currently, enteral nutrition is an easy and elegant way to reduce infectious complications, but the practice of administering systemic prophylactic antibiotics should no longer be condoned.

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