Antibiotic Treatment in Acute Pancreatitis

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ABSTRACT

Infection of pancreatic necrosis seriously aggravates the course of pancreatitis. Gram-negative bacilli and anaerobes from the intestinal flora were the most common pathogens involved in the infection of pancreatic necrosis in the past. Gram-positive flora became more important recently because of antibiotic prophylaxis and prolonged course of the disease. In most cases, infection of necrosis develops in the second phase of the disease. In addition to infection of pancreatic necrosis, extra-pancreatic infections may complicate the course of diseases in critically ill patients with severe pancreatitis. Infection of pancreatic necrosis can be definitively diagnosed with fine needle aspiration and culture of the aspirate. Contrast-enhanced CT showing extra-luminal air in the necrosis is helpful when fine needle aspiration is not indicated. Procalcitonin level may be used as another diagnostic tool. Routine antibiotic prophylaxis of infection of pancreatic necrosis is currently not recommended, but further studies are needed. The choice of antibiotics for the infection of pancreatic necrosis depends upon the antimicrobial spectrum, local antimicrobial susceptibility of the potential causative agents and the penetration of antibiotics in the pancreatic tissue. The duration of antibiotic treatment in patients with infected pancreatic necrosis is not well defined and depends upon the feasibility of the source control.

INTRODUCTION

The annual incidence of acute pancreatitis ranges from 13 to 45 per 100,000 people (1). The incidence is increasing probably as a consequence of obesity epidemics and related increase in gallstones. Most cases are mild and improve spontaneously. Severe necrotizing form develops in 15–20% of patients (2, 3). Overall mortality has decreased in recent years to 2%, but it remains above 30% in most severe forms of disease. Severe forms are defined primarily with systemic inflammatory response and organ failure. In most severe cases, the so-called critical pancreatitis, organ failure is combined with infection of pancreatic necrosis (2). Overall, a half of deaths in patients with pancreatitis are caused by infected necrosis (4). Necrosis affecting 30% of pancreatic tissue on contrast-enhanced CT increases the risk of infection (5).

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MICROBIOLOGY AND PATHOGENESIS OF INFECTED PANCREATIC NECROSIS

Typical gastrointestinal flora with predominance of Gram-negative bacilli and anaerobes was reported as causative agent of infected pancreatic necrosis in the past. More recently, it was found that Gram-positive microorganisms prevail probably because of frequent preceding antibiotic treatment and prolonged survival. Enterococci and coagulase-negative staphylococci became common isolates from pancreatic necrosis. Multiple microorganisms are isolated in most cases (6). The isolated flora is often resistant to antibiotics which limits the choice of antibiotic treatment and further complicates the course of the disease (3). Fungal infections, another consequence of broad-spectrum antibiotics and intensive care (bacteriology), are also clearly linked to increased hospital stays cost, reoperations, as well as overall morbidity and mortality (3). The incidence of fungal infections of pancreatic necrosis varies from 5 to 8%, but it may increase to 15 or even 70% in patients who need surgical intervention and is higher in patients with prior antibiotic exposure (7). The pathogenesis of infection in pancreatic necrosis is not fully elucidated, but the flora and the benefit of enteral nutrition or selective digestive decontamination suggest translocation of bacteria because of its altered permeability caused by systemic inflammation and local situation in the abdominal cavity (5).

CLINICAL COURSE OF INFECTION IN PATIENTS WITH SEVERE PANCREATITIS

The course of severe pancreatitis may be divided in two phases. The first phase is characterized by systemic inflammatory response related to pancreatic inflammation rather than infection. Extra-pancreatic foci of infection such as cholecystitis, cholangitis, bacteremia or pneumonia may be present in some cases (5). The second phase that develops 7–14 days later is dominated by infectious complications, most often infected pancreatic necrosis (4). The development of infected pancreatic necrosis has been shown to peak between weeks 2 and 4 (5). Other types of infection may develop in the second phase as well as complications of prolonged diseases and intensive care treatment (5). The types of infections and their usual timing are presented in Table 1.

DIAGNOSIS OF INFECTION IN PANCREATIC NECROSIS

Definitive diagnosis of infection requires positive culture or Gram stain from CT- or US-guided fine needle aspiration (FNA) biopsy or open surgery. FNA is a safe method with minimal risk for false positivity; false negative results appear in 10%. If infection is highly suspected, the FNA may be repeated (5). Some authors do not recommend routine FNA because of insufficient proof that possible

Table 1. Infections in patients with severe pancreatitis (8)

Type of infection	Frequency (%)	Timing (days)
Infected necrosis	47	17.6
Pneumonia	28	10.7
Bacteraemia	11	13.7
Gastrointestinal infections	8	16.8
Urinary tract infections	6	20.5

shortening of the diagnostic procedure improves the outcome (9). Instead, FNA should be used selectively when there is no clinical response to adequate therapy, or when the clinical and imaging features of infection are uncertain (10). However, in the settings with high prevalence of antimicrobial resistance and especially in patients previously treated with broad-spectrum antibiotics, FNA may become a more important diagnostic tool. Contrast-enhanced CT may be highly suggestive for infection if there are extra-luminal air bubbles found in necrotic tissue (5), but some authors warn against solely relying on the presence of extra-luminal gas, which may lead to overtreatment in a patient who is doing clinically well without antibiotics or any intervention (3). Procalcitonin (PCT) has been investigated as a tool for the diagnosis of infected pancreatic necrosis. In an older study, a cut-off value at 1.8 ng/mL was suggested with sensitivity and specificity above 90%. A larger more recent study found that at PCT concentration ≥ 5.6 ng/mL infected necrosis and multiple organ dysfunction can be diagnosed with 90% sensitivity and 89% specificity. The distinction between infected and non-infected necrosis can be made at PCT level ≥ 4.0 ng/mL with 65% sensitivity and 89% specificity (11, 12).

Table 2. Recent meta-analyses on the efficacy of antibiotic prophylaxis in patients with acute pancreatitis. RTC – randomized controlled trial

Author, year (ref.)	**Time of publication of the studies included in the meta-analysis**	**Number of studies included in the meta-analysis**	**Type of studies included in the meta-analysis**	**Results**
Jafri, 2009 (14)	until May 2008	8	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Significant reduction of extra-pancreatic infections
Villatoro, 2010 (15)	November 2008	7	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Extra-pancreatic infection: no effect Fungal infections: no effect Significant reduction in pancreatic infection and no effect on mortality with imipenem
Wittau, 2011 (16)	1980 to December 2009	14	RTC	Infected necrosis: no effect Surgery: no effect Mortality: no effect Extra-pancreatic infection: no effect
Jiang, 2012 (13)	Up to 2009	11	RTC	No effect on mortality.
Lim, 2015 (17)	Up to October 2013	11	Two cohort studies, 9 RTC	Infected necrosis: no effect Mortality: effect was shown in cohort studies and all studies, but not in RTC Surgery and fungal infections: no effect

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis in acute pancreatitis has been a matter of debate for decades. The first studies gave negative results probably because of the spectrum of antibiotics and inclusion of patients with milder forms of pancreatitis. After the introduction of new broad-spectrum antimicrobial agents, there were several studies that showed some benefit of prophylaxis. The studies were small and heterogeneous, and therefore unconvincing; however, their results were confirmed by the first meta-analysis (5). After the year 2000, two well-designed larger studies that followed turned the circle again: none of them was able to show any benefit of antibiotic prophylaxis (5, 13). Several studies and meta-analyses were published after that; their results do not support antibiotic prophylaxis in general. Recent meta-analyses are presented in Table 2.

Based on the existing body of evidence there is a large consensus that antibiotic prophylaxis in severe acute pancreatitis is not recommended (1–3, 5, 9, 10, 18). However, some authors warn against relying on the evidence that is still weak (19). The compliance of the wide-spread guidance is still very poor; a systematic review of studies and patient-based data published in 2016 showed that antibiotic prophylaxis is still given to 41–88% of patients with acute pancreatitis. Partially the poor adherence to guidance is caused by the level of evidence. Further larger well-designed studies are needed to improve the evidence. Currently, for practical purposes, some authors suggest individualized approach (10, 13) with antibiotic prophylaxis in very severely ill patients.

ANTIBIOTIC THERAPY

Antibiotic therapy in acute pancreatitis may be empirical or targeted. The decision for empirical treatment that may also be called the treatment on demand is based on clinical deterioration of patients including signs and symptoms suggestive of infection. The above mentioned diagnostic tools such as CT scan and PCT may be used to guide the decision. Appropriate samples for cultures should be done before the start of the treatment. As in other cases of severely ill patients, empirical antibiotics may be discontinued if relevant cultures (blood cultures, FNA) remain sterile. The choice of antibiotic in empirical treatment should target mixed flora including Gram-negative rods and anaerobes, but also Gram-positive cocci in patients who received antibiotic therapy for prophylaxis or an extra-pancreatic infections. Local susceptibility patterns should be taken into account. Another important factor is the penetration of the drug into the pancreatic tissue. The penetration of aminoglycosides is insufficient. Ureidopenicillins (piperacillin) and higher generation cephalosporins penetrate moderately well, but this may be compensated with their good bactericidal efficacy for the susceptible microorganisms. The best penetration was observed for fluoroquinolones and carbapenems. Fluoroquinolones should be combined with anti-anaerobic agents, usually metronidazole, and another drug with good pancreatic penetration (5). The choice of antibiotics may be complicated in infections with multi-resistant microorganisms. Prudent antibiotic prescribing and infection prevention measures should be undertaken to avoid the colonization and infection of patients with difficult-to-treat microorganisms.

The duration of antibiotic treatment of infected pancreatic necrosis is not well defined. A recent study reports on 14 days therapy with a wide range from 10 to 64 days (20). In the case of adequate source control, there is no need for prolonged treatment. Patients should be followed clinically, with repeated imaging studies and possible additional source control if needed and feasible. Antibiotics may be discontinued if the infection seems to be healed. In clinically stable patients with prolonged antibiotic treatment, the termination of the therapy may be attempted even if the symptoms of inflammation have not completely disappeared (21).

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