Rational Use of Antimicrobials in Patients with Severe Acute Pancreatitis

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ABSTRACT

Infectious complications in severe acute pancreatitis are associated with considerable morbidity and mortality. The course of the disease is often protracted, and patients often stay in the hospital for several weeks. Diagnosis of infected pancreatic necrosis is difficult, and the treatment consists of source control and antibiotic treatment. Antibiotic use should be rational in terms of a rational indication, a rational spectrum, and a rational duration. Prophylactic antibiotics are not effective in reducing the incidence of (peri)-pancreatic infection in patients with severe disease (or even documented necrotizing pancreatitis). The only rational indication for antibiotics is documented infection. The spectrum of empirical antibiotics should include both aerobic and anaerobic gram-negative and gram-positive microorganisms. Also, fungal infections are often present in these patients, and antifungal coverage or even prophylaxis should be considered, especially if multiple risk factors for invasive candidiasis are present. Although initiation of antibiotics may be a difficult decision, stopping antibiotic therapy often proves to be even more difficult. Currently, no tools are available to guide antimicrobial treatment. Antibiotic use is only effective if proper source control has been established.

KEYWORDS: Acute pancreatitis, infected pancreatic necrosis, necrotizing pancreatitis, severe acute pancreatitis, walled-off necrosis

Pancreatic infection is one of the most challenging infections to manage in the intensive care unit (ICU). Infection can complicate the various stages of pancreatitis and its local complications, including infected pancreatic necrosis (IPN), acute postnecrotic fluid collections, and walled-off necrosis. IPN, which occurs within the first weeks after the onset of pancreatitis, is the most significant problem in terms of diagnosis and treatment. When pancreatic necrosis becomes infected, the course is often protracted; often multiple source control procedures are necessary, and morbidity and mortality are significantly increased. The diagnosis of IPN is as challenging as the treatment because the inflammatory process observed in severe acute pancreatitis is indistinguishable from infection and because concomitant extrapancreatic infection is a frequent problem.

The treatment of IPN, an unpredictable condition, is typically multidisciplinary and requires experience and dedication from gastroenterologists, intensivists, surgeons, and interventional radiologists.

IPN has received a lot of interest in recent years, but the focus was not so much the management of established infection and the problems related to diagnosis and different treatment options, but the use of preventive strategies, in some cases the prophylactic use of antibiotics. Although several studies have been conducted and multiple meta-analyses have been performed,

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this remains a controversial and highly institutionalized issue, with believers and nonbelievers essentially adhering to established habits.

This article reviews the rational use of antimicrobials, both antibiotics and antifungals, in patients with severe acute pancreatitis. Rational use of antibiotics applies to indication, spectrum, and duration in a context of appropriate sepsis management, including source control.

INFECTION IN SEVERE ACUTE PANCREATITIS

IPN complicates approximately one third (range 16 to 47%) of severe acute pancreatitis patients.[1] Because mortality in this disease is bimodal, with ~30 to 50% of patients dying within the first weeks, a survivor bias may be present given that these patients may not live long enough to develop infection. Therefore, if patients survive the initial phase, infection is a likely complication. The probability of infection is also related to the extent of pancreatic necrosis: up to 50% of patients with more than half of the pancreas develop infection.[2] The reported incidence of IPN has seemed to decrease in recent years; in prospective studies on the use of preventive strategies that have been performed in the past 10 years, only about half (or fewer) of the patients expected to develop infection did so.[3] This may be due to improvements in the general ICU care for these patients,[4] the use of preventive strategies such as enteral nutrition,[5] or the recognition of problems such as intraabdominal hypertension that may facilitate translocation.[6]

The timing of infection is variable and unpredictable and peaks in the second to fourth week after the onset of pancreatitis.[7] This underappreciated aspect of the disease may explain much of the difficulties in prediction of, diagnosis of, and therapy for IPN; also, it exemplifies how fundamentally different pancreatitis in humans is compared with animal models of pancreatitis, where necrosis and infection are usually induced within 24 hours. This affects all interventions aimed at reducing IPN and should be considered when designing studies in acute pancreatitis.

Patients with severe acute pancreatitis are often severely ill, requiring mechanical ventilation, renal replacement therapy, and other advanced life-supporting interventions, which predisposes them to nonpancreatic nosocomial infections as well. Not only is the incidence of concomitant infections considerable, there also appears to be an interaction between pneumonia and acute pancreatitis in animal models, where it was found that acute pancreatitis affects clearance of bacteria from the lungs, and pneumonia prolongs the course of pancreatitis.[8]

As already suggested, the development of infection is an important determinant of the prognosis. IPN often requires multiple source control procedures, and although minimally invasive techniques and strategies are increasingly described to control the source of infection, open surgical procedures are still most often used to treat these infections. Rarely, the source can be controlled with a single procedure, and often complications from the surgical procedure such as gastrointestinal tract perforation and bleeding arise.

There has been an ongoing discussion as to whether infection of multiple organ dysfunction syndrome (MODS) is the most important determinant of mortality in these patients. In a recent meta-analysis it was demonstrated that IPN and MODS have a comparable effect on mortality, with around 30% of patients with either IPN or MODS dying from the disease; when both IPN and MODS were present, the risk of mortality was doubled.[9]

To prevent IPN or to optimize the treatment, early and adequate prediction of infection is desirable. However, early risk stratification remains problematic, and so far, no reliable predictor for IPN is available, despite the efforts to identify clinical or biochemical parameters. One of the limitations in our current thinking of complicated severe acute pancreatitis and the search for predictors is that MODS, infection, and other complications have been combined to describe "complicated pancreatitis." Instead, it may be better to look for specific tools to identify patients at risk for infection. Severity scores such as the Ranson,[10] POP (pancreatitis outcome prediction),[11] or BISAP (bedside index for severity in acute pancreatitis)[12] score are often used to predict severity, but they actually quantify the degree of physiological derangement and are comparable to the APACHE (acute physiology and chronic health evaluation) II[13] score in predicting complications in recent studies.[14] Radiological scoring systems have been proposed to predict the severity of pancreatitis, but none of them appears to be useful for the prediction of IPN.[15] The risk of developing IPN is obviously related to severity of pancreatitis, and the development of pancreatic necrosis per se is a prerequisite for the development of infection of the necrosis. The larger the extent of pancreatic necrosis, the higher the risk is for subsequent infection. Biomarkers have been intensively studied in recent years, with procalcitonin (PCT) receiving a lot of interest. In a meta-analysis, Mofidi et al found a diagnostic odds ratio for the development of infection of 28, with a pooled sensitivity of 0.80 and specificity of 0.91[16]; however, differences in timing of the sampling and cutoffs used preclude drawing clear conclusions from this article.

Diagnosis of IPN is equally challenging due to the clinical picture that cannot be distinguished from other infectious complications and the inflammatory status caused by acute pancreatitis per se; clinical signs may be very sensitive yet are not specific enough. Similar results were reported for white blood cell (WBC) count;

combining clinical parameters and WBC count increased the specificity, but sensitivity decreased markedly.[17] A limited number of smaller studies evaluated C-reactive protein (CRP) and PCT; diagnostic performance was found to be comparable. The diagnostic tool of choice remains computed tomographically (CT)-guided fine-needle aspiration (FNA) of the pancreatic necrotic areas; on average, sensitivity and specificity exceed 0.90 in several studies. The presence of gas in the retroperitoneal area is considered indicative of IPN in the context of severe acute pancreatitis, but it is only present in a limited number of patients. A practical approach to the diagnosis of IPN is to start with non-contrast-enhanced CT scan of the abdomen; if gas is present, the presence of IPN is confirmed; when gas cannot be detected but necrotic areas are identified that are amenable to FNA, immediate direct examination and culture are the diagnostic strategies of choice.

The microbiology of IPN has changed significantly in recent years. First of all there has been a shift toward more gram-positive microorganisms causing IPN, both staphylococci and enterococci,[7,18] that now are as often involved in pancreatic infections as gram-negative microorganisms. Also, fungal infections have increasingly been described, with *Candida albicans* most frequently isolated.[19,20] In a series of consecutive patients with IPN, we have described an incidence of multidrug-resistant organisms of more than 50%; most of these patients were in the hospital and ICU for weeks, and often nosocomial superinfection with one of these multidrug-resistant organisms occurred only after prolonged exposure to antibiotics as well.[21] It has often been suggested that these changes in microbiology are due to the widespread use of antibiotic prophylaxis in severe acute pancreatitis patients.[18,21] It is indeed striking that microorganisms that were not covered by the prophylactic antibiotic schemes are indeed found to be pathogens in subsequent infections; multidrug-resistant gram-negatives, resistant gram-positives, and fungi have indeed been on the rise since the introduction of prophylactic antibiotics, which notably are often administered for prolonged periods of time. Moreover, in the few prospective studies on antibiotic prophylaxis, the majority of the infecting microorganisms were resistant to the antibiotics they had been exposed to before infection occurred; in the patients that have been treated with prophylactic antibiotics, *Acinetobacter* spp., *Pseudomonas* spp., and enterococci were more often observed.[22]

RATIONAL USE OF ANTIMICROBIALS IN PANCREATITIS

Rational Indication

There are two distinct situations where antimicrobials are used in pancreatitis patients, therapy and prophylaxis. Prophylaxis refers to the administration of antibiotics in patients when no clinical infection is present with the intent to prevent pancreatic infection; therapeutic use of antibiotics is defined as the use of antibiotic in patients with documented pancreatic infection. As already discussed, infections are frequent in patients with severe acute pancreatitis, most of them extrapancreatic. This article discusses only the use of antimicrobials in the context of pancreatic infection.

Therapeutic use is an obvious and rational use of antimicrobials in patients with pancreatitis. As in other forms of intraabdominal infection (IAI), the goal of antibiotics is to prevent local and hematogenous dissemination as well as to reduce late complications. Due to its anatomical location and lack of capsule, infection easily spreads to surrounding tissue and organs, and surgical elimination of the infectious focus is notoriously difficult and challenging even to experienced surgeons. In this context, the use of antibiotics is probably more important compared with other IAIs where antibiotics are generally considered an adjunct to surgical elimination of the focus. Pancreatic infection is most often suspected based on clinical parameters, but it should be confirmed through sampling of the infected areas using FNA or intraoperative samples. Positive direct examination or culture confirms infected pancreatic necrosis; when direct examination is positive, initiation of antibiotics should not be delayed.

Prophylactic use of antibiotics has intensively been studied in the last two decades. The concept was introduced through several small, unblinded, often uncontrolled, and mostly single-center studies in the 1980s and 1990s that demonstrated significant improvements on outcome, both mortality and pancreatic and extrapancreatic infections.[23,24] These studies led to the widespread adoption of broad-spectrum antibiotic prophylaxis in severely ill patients, often without any evidence of pancreatic necrosis.[25] Because some clinicians still remained skeptical, two major randomized, multicenter studies were organized in the last decade.[3,26] The two studies were comparable in design and used ciprofloxacin and meropenem as prophylactic agents. Neither study demonstrated a significant effect on any relevant outcome parameter in any patient subgroup. It should be added that a considerable number of patients in both placebo groups were switched to open antibiotic treatment, making interpretation of the studies difficult. However, we feel that this should not be used as proof that antibiotics are necessary in all patients because the indications for antibiotics in patients who were switched to open antibiotic therapy were various and often noninfectious. A more recent, smaller study using ciprofloxacin also reported comparable outcomes in intervention and control patients.[27] Results of these studies are summarized in Fig. 1.

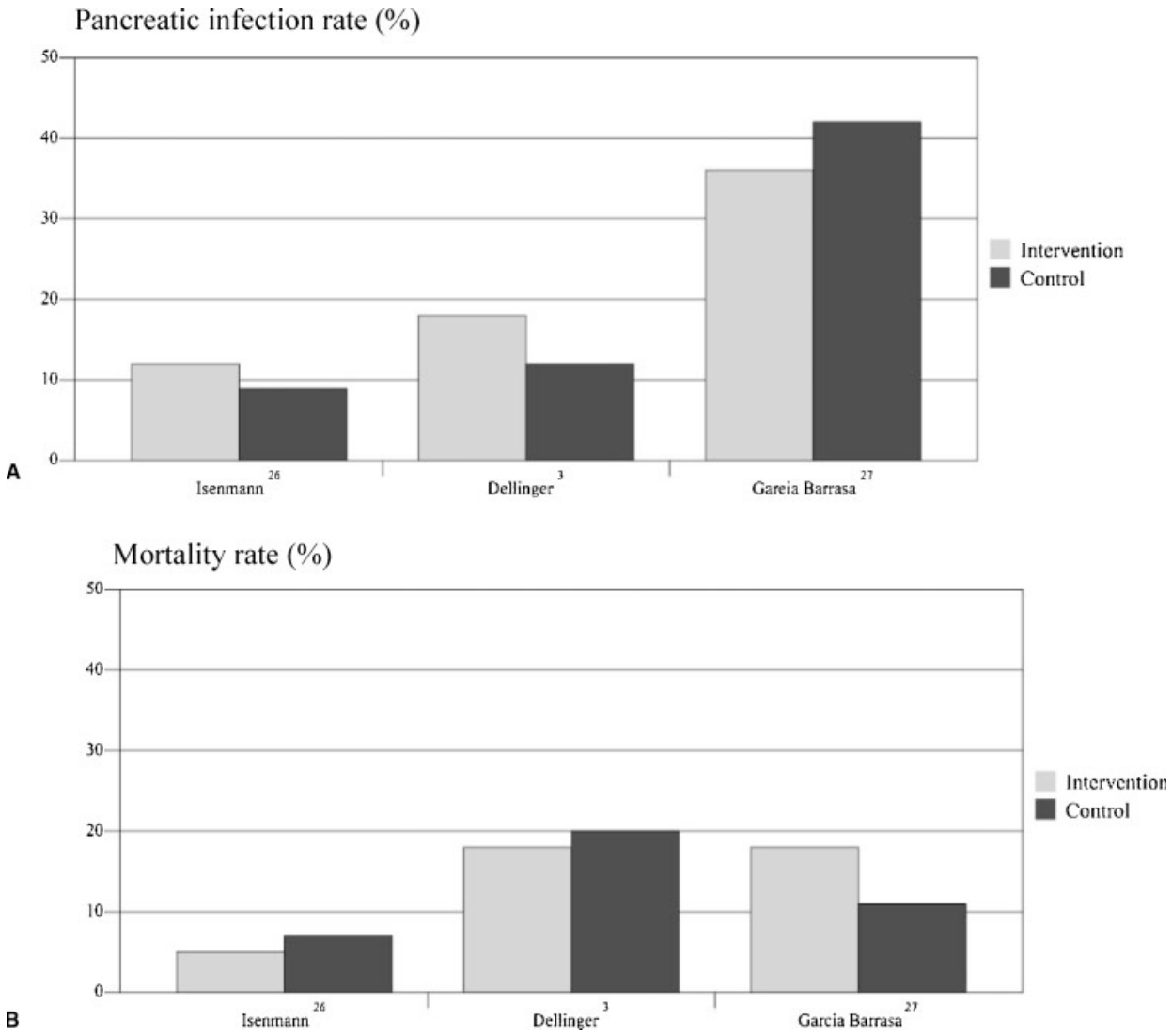

Figure 1 (A) Pancreatic infection and (B) mortality rates in controlled, randomized studies of the use of prophylactic antibiotics in severe acute pancreatitis. None of the differences was statistically significant.

There are probably few topics in infectious diseases that have been subjected to systematic reviews and meta-analysis more often than the use of prophylactic antibiotics to prevent pancreatic infection; the systematic reviews[28–34] published in recent years even outnumber the studies that are included in these reviews. None of them could demonstrate a reduction in infected pancreatic necrosis, need for surgery, or mortality, and if a trend was found toward improved outcome this was solely based on the effect of two unblinded studies.[23,24]

The proponents of the use of prophylactic antibiotics, however, remain insensitive to these findings. Quite often, a multitude of possible explanations are suggested as to why no difference could be found. Antibiotics that are administered too late is among the most frequently cited, but studies that were designed to include only patients early in the course of the disease did not find a difference in outcome. It is also often suggested that prophylactic antibiotics delay the occurrence of infection; this would indeed be desirable given that source control—one of the cornerstones of IPN treatment—is preferably delayed beyond the first 3 weeks after onset of the disease. No study could thus far demonstrate any effect on the timing of infection. It has also been suggested that the duration of antibiotics was insufficient in some studies, but studies that compared prolonged prophylaxis could not find a difference in the incidence of complications.[35]

The use of antibiotics—quite often broad spectrum antibiotics such as carbapenems or quinolones—does have consequences, and adding prophylactic antibiotics in patients without proven benefit should not be taken lightly. Selection of multidrug-resistant microorganisms and fungi is an obvious consequence and has been reported in pancreatic infection as already discussed in the previous paragraph. In patients who often remain in the ICU for longer periods of time and who often develop infections at other sites as well, this may

compromise the availability of effective antibiotics for subsequent infections.

Due to the increased incidence of fungal infections, antifungals are also often administered in a prophylactic strategy. There are no prospective studies that have evaluated the role of antifungals in this specific setting, but one retrospective study found that antifungal use was associated with a decreased incidence of fungal involvement when infection developed.[20] Acute pancreatitis though is often cited as one of the risk factors for invasive fungal infections, and as in these patients often multiple other risk factors for invasive fungal infections are present (antibiotic exposure, multiple indwelling catheters, parenteral nutrition, and prolonged hospitalization, among others), administration of antifungal prophylaxis should be considered when multiple risk factors are present.[36]

Selective digestive decontamination has also been investigated to prevent IPN. In one of the largest randomized, controlled trials to date in acute pancreatitis patients, Luiten et al demonstrated a reduced incidence of bacterial infections (most pronounced gram-positive infections) when a short course of intravenous cefotaxime was combined with enteral colistin, norfloxacin, and amphotericin.[37] Overall mortality was not affected, but when the severity of pancreatitis (as expressed by the Imrie score) was entered in a multivariate analysis, selective decontamination was a significant predictor of outcome. Although this study is almost 20 years old, a similar approach has not been investigated since.

Rational Spectrum

If the first question is *when*, the next will be *what* antibiotic to administer. Adequate spectrum and adequate levels at the site of infection are the prime concerns when selecting an appropriate antibiotic. Empirical antibiotic coverage in this setting should include gram-positive, gram-negative, as well as anaerobic bacteria; empirical choices for established pancreatic infection parallel the options for severe intraabdominal infections. As most of the infections develop after several days of hospital stay, a combination typically prescribed for nosocomial IAI is required, and options include a carbapenem, piperacillin/tazobactam, or a cephalosporin or quinolone combined with an antianaerobic drug (Table 1). Resistant gram-positive organism coverage should be based on the local epidemiology.

Although most human studies on pharmacokinetics focused on penetration into normal pancreatic tissue, adequate penetration of piperacillin, imipenem, meropenem, and quinolones as well as cephalosporins in necrotic pancreatic tissue has been demonstrated or can be assumed based on clinical outcome data.[38–40]

It should be added that the clinical use of antibiotics in this setting has been poorly investigated. Acute pancreatitis or pancreatic infection is an almost universal exclusion criterion in clinical studies evaluating antibiotics for IAIs. No single study has compared different antibiotics in terms of efficacy and safety in this setting. Given the broad spectrum of organisms involved in IPN and the unpredictability of the microbiology, this should be no surprise.

Table 1 Antibiotic Regimens for Empirical Treatment of Infected Pancreatic Necrosis*

Carbapenem
• Imipenem
• Meropenem
• Doripenem
Penicillin plus betalactamase inhibitor
• Piperacillin/tazobactam
Cephalosporin plus antianaerobic
• Cefepime plus metronidazole
• Ceftazidime plus metronidazole
Fluoroquinolone plus antianaerobic
• Ciprofloxacin plus metronidazole
• Levofloxacin plus metronidazole

*Resistant gram-positive coverage to be added based on local epidemiology data.

After initial, empirical antibiotic therapy, an individualized antiinfective treatment can be based on the results of the cultures from the necrosis.

Whereas the involvement of fungi in some forms of IAI can be considered colonization rather than infection, this should not be taken lightly in IPN. Treatment with antifungals is imperative in this setting and should be based on the previous exposure to antifungal agents, colonization status of the patient, and severity of illness. When the patient has been exposed to prophylactic antifungals (most likely fluconazole) or is colonized with *Candida glabrata* or *Candida krusei* or when the patient is hemodynamically unstable, therapy with echinocandins is recommended, as recently advocated by the Infectious Diseases Society of America.[41] When fluconazole is selected for empirical or directed treatment, adequate doses should be administered (6 mg/kg after a loading dose of 12 mg/kg).

Fluconazole remains the most widely used agent for antifungal prophylaxis in this and other high-risk patient groups. Given the increase in *Candida non-albicans* infections in some reports, prophylaxis with echinocandins has been explored in patients with IAIs, and was found to be effective as well.[42]

Rational Duration

Antibiotic therapy should be continued until infecting organisms have been cleared from the focus of infection, but in case of IPN this is not easy to either define or determine from a clinical point of view. Duration is in fact largely determined by the presence and efficacy of

source control. In clinical practice, antibiotics are often continued much longer than in most other indications for antibiotics. When there is no or minimal residual infection left after a source control procedure, a duration of 7 to 10 days is probably sufficient, provided the patient's condition improves. On the other hand, if the source of infection has not been removed completely—often due to anatomical relationships with intestinal and vascular structures that limit the extent of what is surgically feasible—prolonged courses until the residual necrosis has been sterilized are necessary. Care should be taken not to treat colonization when cultures from abdominal drains persistently return positive. Treatment of established fungal infection should be at least 2 weeks. At this moment there is no definite (bio)marker available that may help the decision to stop antibiotics, but procalcitonin may be a helpful tool in this setting.

Sepsis Management and Source Control

As in other infections, early adequate antibiotic treatment is essential when IPN develops. As already suggested, timely diagnosis of infection is challenging, and a low index of suspicion should be maintained at all times. CT-guided FNA of the suspected areas is the preferred diagnostic method because clinical as well as laboratory indicators are not reliable to discern between inflammation related to the pancreatitis, extrapancreatic infection, or pancreatic infection. When present, gas in the retroperitoneum is also a good indicator of IPN. Prompt antibiotic treatment is recommended when infection is diagnosed based on imaging alone; bacteriological sampling may be more difficult to accomplish on short notice, and the lack of samples should not defer antibiotic administration.

Obviously, general measures advocated in the treatment of severe sepsis and septic shock should be readily applied.[43] Whereas most components of sepsis therapy are not different from those for other types of infection, the implementation of source control deserves some extra attention. Source control is a key element in the treatment of IAI, and this also holds true for IPN. It is generally accepted that source control is preferably postponed until the inflammatory process has subsided, and demarcation of infected and necrotic pancreas allows for adequate resection of the infectious focus with reduced risk for collateral damage to the surrounding structures.[44] Recently, a large multicenter study from the Netherlands found that a step-up approach including percutaneous drainage as a temporizing strategy and minimally invasive techniques was as good as a delayed open surgical approach in terms of mortality[45]; the need for surgery and morbidity were significantly reduced. Although some may feel that the decision to operate is a surgical one, the role of the intensivists in determining the appropriate timing and optimal source control method is pivotal.

In conclusion, IPN is a major determinant of outcome in severe acute pancreatitis patients, and antibiotics are an essential element in the treatment of this condition. Although diagnosis of infection in acute pancreatitis patients may be difficult based on clinical parameters, imaging and FNA are reliable tools when infection is suspected. Antibiotics should be rationally used, with documented infection as the sole appropriate indication; antibiotic prophylaxis does not improve patient outcome and should no longer be recommended. Antibiotics penetrate well into the pancreatic necrosis, and different regimens have been used with success. When source control is adequate, treatment duration should be similar as in other IAIs (7 to 10 days), but prolonged courses may be necessary when considerable infected necrotic tissue cannot be debrided.

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