ORIGINAL ARTICLE

Emergence of Antibiotic Resistance in Infected Pancreatic Necrosis

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Background: Overall, the use of antibiotics in the treatment of patients with severe acute pancreatitis has increased owing to the use of antibiotic prophylaxis.

Hypothesis: The incidence of antibiotic-resistant (AB-R) bacteria in infected pancreatitis is related to prolonged antibiotic treatment and may affect outcome.

Design: Case series.

Setting: Fifty-six–bed intensive care unit of a tertiary care center.

Patients: Forty-six consecutive patients with infected pancreatic necrosis.

Main Outcome Measures: Occurrence rate of AB-R organisms in pancreatic infection, overall duration of antibiotic treatment prior to infection, and mortality, defined as inhospital mortality.

Results: Infection with AB-R microorganisms was found in 24 (52%) of 46 patients. Primary infection was present in 7 patients; in 21 patients, nosocomial surinfection with AB-R organisms occurred. Patients with AB-R infections were treated with antibiotics for a longer period (24 vs 15 days, $P<.05$), while disease severity and the incidence of organ failure were not statistically significantly different. The intensive care unit stay was significantly longer in patients with AB-R infections (23 vs 31 days, $P=.02$). Mortality was not statistically significantly different in patients with AB-R infections (37% vs 28%, $P=.23$).

Conclusions: The occurrence rate of infections with AB-R organisms in our patients with severe acute pancreatitis was high and was associated with a longer intensive care unit stay, but no increased mortality could be demonstrated. The duration of antibiotic treatment was increased in patients in whom AB-R infections developed.

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THE USE OF ANTIBIOTICS IN patients with severe acute pancreatitis (SAP) has increased over the last decades, and can, at least partially, be attributed to the use of antibiotic prophylaxis. Although still debated, the use of antibiotic prophylaxis has become standard practice in many hospitals worldwide and is advocated by international societies such as the American College of Gastroenterology.[1]

The emergence of antibiotic-resistant (AB-R) microorganisms has been one of the major concerns for physicians involved in the care of critically ill patients in the last decade. The effect of AB-R infections on outcome and length of hospital stay may be considerable if not treated adequately.[2] Some authors have reported increased mortality in patients in the intensive care unit who have severe infections caused by AB-R bacteria,[3-6] but other studies did not find a difference, a finding that may have been caused by the high rate of adequate therapy in all patients.[7]

Patients with SAP usually have multiple risk factors for developing infection with AB-R bacteria. Among these are the use of broad-spectrum antibiotics and prolonged length of stay, increasing the risk of transmission of hospital pathogens.

Remarkably, the reported incidence of AB-R infections in patients with SAP is low. Gloor et al[8] described 3 patients infected with an AB-R microorganism of 33 patients with infected pancreatitis, although most of the patients had received prophylactic antibiotics for weeks and had multiple drug regimens prescribed. The objectives of this study were to explore the occurrence rate of and risk factors for pancreatic infection caused by AB-R microorganisms in patients with SAP and to study the effect on outcome.

PATIENTS AND METHODS

DATA COLLECTION

Between January 1, 1995, and December 31, 2002, one hundred six patients with SAP were

Table 1. Characteristics of 46 Patients With Infected Pancreatic Necrosis

Characteristic	No. (%) of Patients
Sex, male	29 (63)
Age, mean (range), y	53.7 (27-76)
Cause	
Alcohol	20 (43)
Biliary tract stones	14 (30)
Trauma	5 (11)
Hyperlipemia	1 (2)
Unknown	6 (13)
Use of antibiotic prophylaxis	37 (80)

admitted to the intensive care unit (ICU) of Ghent University Hospital, Ghent, Belgium, a tertiary care facility with a total of 56 ICU beds. Patient names were retrieved from the hospital registry using the *International Classification of Diseases* code 577.0 for acute pancreatitis. All patients met the criteria for severe disease as proposed by the definitions according to the Atlanta consensus meeting.[9]

We recorded demographic characteristics, cause, and disease severity assessed by the Ranson criteria and Acute Physiology and Chronic Health Evaluation (APACHE) II score[10] calculated at admission to the ICU (for patients transferred from other hospitals, the score was calculated using the data from the referring center). The occurrence of organ failure during ICU stay was recorded and defined as follows: cardiovascular failure, hypotension requiring vasoactive medication; acute renal failure, serum creatinine level above 2.0 mg/dL (>178 µmol/L); respiratory insufficiency, the need for mechanical ventilatory assistance or Pao_2/fraction of inspired oxygen concentration ratio below 300.

The use of antimicrobial agents was recorded, as was the duration of therapy before infection occurred. Antibiotics were divided into different groups: carbapenems, broad-spectrum penicillins, cephalosporins, fluoroquinolones, and miscellaneous. Antimicrobial prophylaxis was defined as the use of an antimicrobial agent covering intra-abdominal pathogens, for at least 48 hours before the first operation or diagnosis of infected necrosis.

The number of reoperations and data on the duration of continuous postoperative lavage were retrieved from the hospital records. Length of stay in the ICU and in the hospital was calculated; mortality was defined as inhospital mortality.

PATIENT TREATMENT

All patients were admitted to the ICU before or after surgical treatment and treated by the same surgical team. The use of antibiotic prophylaxis was left to the discretion of the attending ICU physician. Enteral nutrition was started as early as possible. Computed tomographic scan and fine-needle aspirate of the pancreatic necrosis were performed on an individual patient basis, that is, when the clinical condition of the patient was suggestive of infection of the pancreatic necrosis. Indications for surgery were infected pancreatic necrosis (positive fine-needle aspiration or retroperitoneal gas on computed tomographic scan), deterioration of multiple organ dysfunction syndrome despite maximum support in the ICU, and unresolving pancreatitis or suspected pancreatic infection without proof on fine-needle aspirate or computed tomographic scan. Standard surgical intervention consisted of necrosectomy through a midline laparotomy as described by Beger et al.[11] The pancreas was debrided using blunt dissection, and 2 to 4 large-caliber drains were inserted in the retroperitoneum. Continuous postoperative lavage of the retroperitoneum was started initially at a rate of 500 to 1000 mL/h, and progressively decreased, based on the general condition of the patient, inflammatory parameters (C-reactive protein), and the macroscopic aspect of the drain effluent.

MICROBIOLOGY AND ANTIBIOTIC RESISTANCE

Microbiological data were retrieved from the patient file and the hospital laboratory. Microbiological studies were performed by the hospital laboratory according to standard clinical practice.

Primary infection of pancreatic necrosis was defined as the presence of microorganisms in cultures obtained at the first operation or a fine-needle aspirate without previous surgery. Nosocomial surinfection refers to superinfection after surgical treatment. Here, microorganisms and leukocytes were obtained from preoperative cultures at later interventions or from the abdominal lavage fluids in patients with a clinical picture of infection for which antimicrobial and/or antifungal therapy was started.

For gram-negative bacteria, antibiotic resistance was defined as in vitro resistance to ceftazidime. In our hospital, ceftazidime resistance is considered to be an indicator of epidemic extended-spectrum β-lactamase–producing strains or hyperproducers of β-lactamases, and, therefore, it is an indicator of infection with organisms that are resistant to multiple drugs.[7] *Pseudomonas aeruginosa* was considered to be resistant when resistance to one of the following antipseudomonal antibiotics was found: piperacillin, ciprofloxacin, ceftazidime, or imipenem.[7,12] For staphylococcal infections, resistance to methicillin was considered as antibiotic resistance; for enterococci, resistance to vancomycin.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS for Windows version 11.0.1 (SPSS Inc, Chicago, Ill). Continuous variables were compared using the *t* test or the Mann-Whitney test where appropriate. Categorical data were compared using the χ^2 test or Fisher exact test. Data are expressed as mean (SD) unless mentioned otherwise. A double-sided $P<.05$ was considered statistically significant.

RESULTS

In 46 (43%) of 106 patients with SAP, infection of pancreatic necrosis was documented and these are the subject of this analysis. Details of patient characteristics are summarized in **Table 1**. Most patients were referred from other hospitals (n=33 [72%]). Antimicrobial prophylaxis was used in 80% of all patients; the antibiotics used are listed in **Table 2**. Carbapenems and broad-spectrum penicillins were used most frequently (40% and 29%, respectively).

Infection of pancreatic necrosis with AB-R microorganisms was found in 24 (52%) of 46 patients. Primary infection with these AB-R microorganisms was present in 7 patients; in 21 patients nosocomial surinfection with AB-R microorganisms occurred. Both primary and surinfection with AB-R organisms occurred in 4 patients. Gram-negative microorganisms were most often involved (20 infections vs 14 infections with gram-positive microorganisms). Details on the AB-R microor-

Table 2. Forty-Two Antibiotics Used for Prophylaxis in 37 Patients With Severe Acute Pancreatitis

Antibiotic	No. (%) of Patients
Carbapenems	**17** (40)
Imipenem	11
Meropenem	6
Broad-spectrum penicillins	**12** (29)
Piperacillin and tazobactam	7
Amoxicillin and clavulanic acid	3
Piperacillin	2
Cephalosporins	**3** (7)
Cefuroxime	3
Quinolones	**4** (10)
Ciproxin	4
Other	**6** (14)
Vancomycin*	1
Aztreonam*	1
Amikacin*	1
Netilmicin*	1
Metronidazole*	1
Oxacillin	1

*Five antimicrobial agents were used in combination therapy.

Table 3. Antibiotic-Resistant Microorganisms Found in 24 Patients*

Variable	Primary Infection (n = 7)	Nosocomial Surinfection (n = 21)†
Gram-positive microorganisms	3	11
Staphylococcus epidermidis	2	8
Staphylococcus aureus	1	3
Gram-negative microorganisms	4	16
Pseudomonas subspecies	0	9
Stenotrophomonas species	3	1
Acinetobacter subspecies	0	4
Enterobacter aerogenes	1	2

*In 4 patients both primary and nosocomial surinfection with antibiotic-resistant microorganisms occurred.
†In 6 patients 2 antibiotic-resistant microorganisms were involved.

ganisms isolated are summarized in **Table 3**. Antibiotic-resistant *P aeruginosa* and methicillin-resistant *Staphylococcus epidermidis* were cultured most frequently. Antibiotic-resistant infection with multiple AB-R microorganisms occurred in 6 patients (25%).

There was no difference in preoperative factors as age, severity of disease at presentation (APACHE II and Ranson scores), and occurrence rate of organ failure during ICU stay in patients with antibiotic-susceptible (AB-S) and AB-R infections (**Table 4**). Patients with AB-R infections were treated with antibiotics, prophylactic or therapeutic, for a longer period (24 days vs 15 days, $P=.04$) prior to infection than patients with AB-S infections.

The number of surgical interventions was equal in patients with or without AB-R infections, and also the duration of the postoperative lavage was not different (27 vs 23 days, $P=.56$)(**Table 5**). The overall length of ICU stay was prolonged when AB-R organisms were involved in pancreatic infections (53±36.8 days vs 31±20.6 days, $P=.02$), but the total length of hospitalization was not different (78±44.5 days vs 65±43.2 days, $P=.35$). Mortality was not significantly different in patients with AB-R infections (37% vs 23% in patients with AB-S infections, $P=.28$).

Table 4. Comparison of Patients With AB-R and AB-S Infections

Characteristic	AB-R Infection (n = 24)	AB-S Infection (n = 22)	*P* Value
Age, mean (SD), y*	52.5 (13.35)	55.0 (13.45)	.53
Gender distribution, M/F	17/7	12/10	.25
APACHE II score, mean (SD)*	19.9 (10.86)	20.4 (8.73)	.86
Ranson score, mean (SD)*	6.4 (1.72)	5.8 (2.0)	.38
Organ failure			
Respiratory insufficiency	18 (75)	17 (77)	.86
Acute renal failure	12 (50)	13 (59)	.54
Cardiovascular failure	16 (67)	15 (68)	.91
Use of antibiotic prophylaxis	20 (83)	17 (77)	.61
Duration of antibiotic treatment prior to infection, mean (SD), d*	24.5 (15.05)	15.4 (9.35)	.04

Abbreviations: AB-R, antibiotic-resistant; AB-S, antibiotic-susceptible; APACHE II, Acute Physiology and Chronic Health Evaluation II.
*Data are given as number (percentage) of patients unless otherwise indicated.

Table 5. Outcome and Length of Stay in Patients With and Without Antibiotic-Resistant (AB-R) Infections*

Variable	AB-R Infection (n = 24)	AB-S Infection (n = 22)	*P* Value
No. of operations	2.25 (1.51)	2.29 (1.48)	.94
Duration postoperative lavage, d	27 (27.1)	23 (16.3)	.56
ICU stay, d	53 (36.8)	31 (20.6)	.02
Hospital stay, d	78 (44.5)	65 (43.2)	.35
Mortality, %	9 (37)	5 (23)	.28

Abbreviations: AB-R, antibiotic-resistant; AB-S, antibiotic-susceptible; ICU, intensive care unit.
*Data are given as the mean (SD) unless otherwise indicated.

COMMENT

The occurrence rate of AB-R microorganisms in infected pancreatic necrosis in this study is high, with mostly gram-negative microorganisms involved. The only factor associated with AB-R infection was the duration of administration of antibiotics prior to infection, which was longer in patients in whom AB-R infections developed. Overall ICU stay was increased in patients with AB-R infections. Mortality was higher in patients who had infected pancreatic necrosis with an AB-R microorganism compared with patients with an AB-S microorganism, although this difference was not statistically significant, which may be attributed to the small sample size.

Antibiotic resistance is an important issue in hospital-acquired infections and has been studied most exten-

sively in ventilator-associated pneumonia and bacteremia. It has been associated with increased length of stay and increased cost,[6,13] and even increased mortality in some reports.[5,13] A possible explanation for this is that the virulence potential of AB-R microorganisms is higher, which has been suggested in methicillin-resistant *Staphylococcus aureus*.[14] Another possibility is that adequate treatment is delayed, which is more likely to occur when AB-R microorganisms are involved. Delayed adequate treatment has been associated with a 3-fold higher mortality in some reports.[15-17]

Data on the incidence of AB-R microorganisms in intraabdominal infections are sparse. In a study on the effect of gram-positive–resistant bacteria in patients with intraabdominal infections, Pelletier et al[18] found an increased mortality rate in 53 patients with resistant bacteria (23% vs 9%, $P = .003$), but antibiotic resistance was not an independent predictor of mortality in multivariate analysis. Montravers et al[19] studied the outcome of 100 patients with postoperative peritonitis and also found an increased mortality rate in patients with AB-R infections (45% vs 23%). Several authors have reported on the effect of individual organisms, such as vancomycin-resistant enterococci[20] and methicillin-resistant staphylococci,[21] and found high mortality rates in patients with abdominal infections with these organisms, although a clear causal relationship was not present.

Also in patients with severe acute pancreatitis, data on the incidence of AB-R infections are limited. Gloor et al[8] found antibiotic resistance in only 3 of 33 patients with infected necrosis; all were methicillin-resistant staphylococci. Howard and Temple[22] evaluated the effect of prophylactic antibiotics on microbiology in patients with infected pancreatic necrosis. They compared 66 patients treated prophylactically with a combination of imipenem and cilastatin with a historical control group, and found an increase in gram-positive and a decrease in gram-negative bacteria involved in pancreatic infection. The incidence of β-lactam resistance was unchanged, but most *S aureus* strains involved (80%) were methicillin resistant.

The high incidence of AB-R infections in our patients is worrisome. There are several explanations for the high incidence of AB-R infections when compared with other reports. First, we also studied nosocomial surinfections as well as primary infections with AB-R organisms. The incidence of AB-R organisms in primary infections in our patients is lower than the involvement of AB-R infections in nosocomial surinfections. We believe that these infections should be studied as well to evaluate the role of AB-R infections in these patients. Second, there have been several outbreaks with AB-R gram-negative microorganisms in our ICU during the study period, and there is a constant inflow of patients colonized with methicillin-resistant *S aureus* in the unit, which is an important factor in the spread of antibiotic resistance. The presence of abdominal drains and the need for multiple surgical interventions also may increase the risk of nosocomial infections. Third, the role of the use of prophylactic antibiotics on the emergence of antibiotic resistance is unclear. The duration of antibiotic treatment prior to infection, both in AB-R– and AB-S–infected patients, was very long in this study and consisted in part of antibiotic prophylaxis in most patients. To date, it is unclear how long antibiotic prophylaxis should be continued, and some centers routinely continue treatment up to 4 weeks.[23] A recent trial found no advantage in continuing prophylaxis with meropenem beyond 2 weeks.[24]

The use of prophylactic antibiotics remains one of the most controversial issues in the treatment of SAP. Several small studies suggest a reduction in infectious complications,[25,26] and in a meta-analysis even a reduced mortality was found.[27] The trials included in this meta-analysis, however, used different end points, different classes of antibiotics, and the indication for surgical intervention was not standardized, so it is difficult to draw any conclusions based on the evidence presented. Recently, the first double-blind, randomized trial comparing a regimen of combined ciprofloxacin and metronidazole vs placebo was stopped because no advantage of prophylactic antibiotics could be detected after randomization of 114 patients.[28] Other recent studies, a randomized trial on the duration of prophylaxis[24] and a cohort study on the incidence of fungal infections,[8] failed to reproduce the low incidence of pancreatic infection reported earlier.[29,30]

Also, potential drawbacks of the use of prophylactic antibiotics have not been addressed in the early studies of the effect of antibiotic prophylaxis. Previously, we reported a 50% incidence of fungal infections in patients with SAP who were treated surgically, in case no early therapy with fluconazole was added to the prophylactic antibiotics.[31]

The fact that recent articles could not demonstrate an advantage of antibiotic prophylaxis, together with the emergence of problems as fungal infections[8,32,33] and also infections with AB-R microorganisms as reported herein, demonstrates that antibiotics should be used with caution in these patients if no infection can be demonstrated. Not only is there no proven benefit of prophylactic antibiotics but other problems may be induced by unrestricted antibiotic usage.

In recent years, antibiotic use has been one of the major threats to the development of resistance, and the reduction of antibiotic use has often resulted in a reduction of AB-R infections in patients in the ICU. Carbapenems, which are most often prescribed as antibiotic prophylaxis in patients with SAP, cause important changes in the intestinal flora of patients, which is considered the primary source for bacterial infections of pancreatic necrosis through translocation. Whereas older series describe gram-negative microorganisms as most often involved in pancreatic infections, a shift toward more gram-positive and fungal infections is observed in more recent reports,[34] which is often attributed to antibiotic use. Furthermore, the use of drainage systems and postoperative lavage should be assessed as a possible risk factor.

CONCLUSIONS

In this cohort of critically ill patients, we report a high incidence of AB-R microorganisms in infected pancreatic necrosis, especially in the later stage of the disease.

This seems to be linked to the prolonged use of antibiotic treatment. In this small sample, no difference in mortality could be found, but overall ICU stay was increased in patients infected with AB-R. Future trials studying the effect of antibiotic prophylaxis in this setting should address the occurrence of infection with antibiotic-resistant organisms also at later stages of the disease to fully show the clinical effect of our findings.

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