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Nosocomial bacteremia involving *Acinetobacter baumannii* in critically ill patients: a matched cohort study

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Abstract *Objective:* To determine outcome and attributable mortality in critically ill patients with nosocomial bacteremia involving *A. baumannii*. *Design:* A retrospective matched cohort study in which all ICU patients with microbiologically documented *A. baumannii* bacteremia were defined as cases. Matching of the controls was based on equivalent APACHE II score (±2 points) and diagnostic category. Control patients were required to have an ICU stay equivalent to or longer than the case prior to onset of the bacteremia. *Setting:* The 54-bed ICU of the 1060-bed Ghent University Hospital. *Patients:* 45 ICU patients with *A. baumannii* bacteremia and 90 matched control subjects without clinical or microbiological evidence of blood stream infection. *Measurements:* Population characteristics and in-hospital mortality rates of patients with *A. baumannii* bacteremia and their controls were compared. Attributable mortality is determined by subtracting the crude mortality rate of the controls from the crude mortality rate of the cases. *Results:* Patients with *A. baumannii* bacteremia had significantly more hemodynamic instability, longer ICU stay, and longer length of ventilator dependence than controls. In-hospital mortality rates for cases and controls were, respectively, 42.2% and 34.4%; thus the attributable mortality was 7.8%. *Conclusion:* In critically ill patients *A. baumannii* bacteremia is not associated with a significantly increased mortality rate.

Keywords Intensive care · Bacteremia · *Acinetobacter* · Outcome

Introduction

Mortality associated with *Acinetobacter* bacteremia is approximately 25% but seems to depend strongly on the physical condition of the patients [1, 2]; mortality rates range from as low as 5% in patients in general wards [3] to 54% in patients mostly under intensive care [4]. Despite the increasing incidence of bacteremia involving *A. baumannii* there is a lack of series containing exclusively ICU patients. The main objective of our study was to investigate whether nosocomial *A. baumannii* bacteremia significantly increases the mortality rate in patients under intensive care. The secondary objective was to investigate the longer ICU stay of patients with *A. baumannii* bacteremia.

Materials and methods

Methods

This study was conducted at Ghent University Hospital, a 1060-bed tertiary care center with a 54-bed ICU including a surgical and medical ICU, an ICU for cardiac surgery, and a burn unit. No significant changes in age, length of ICU stay, or Acute Physiology and Chronic Health Evaluation (APACHE) II scores [5] were observed during the study period. We conducted a retrospective matched cohort study (1: 2 ratio) in which all ICU patients with microbiologically documented *A. baumannii* bacteremia were defined as cases. Every case-patient was matched with two other ICU patients (matched controls) without clinical or microbiological evidence of nosocomial blood stream infection (with the exception of bacteremia caused by coagulase-negative *Staphylococci*). The study was performed in adult, non-neutropenic (neutrophil count >500/mm³), critically ill patients admit-

ted to the ICU over a 7–year period (January 1992–December 1998).

A hospital-wide case-based surveillance program for blood stream infections was used for the retrospective search for ICU patients with bacteremia involving *A. baumannii*. Every patient whose ICU stay was complicated by *A. baumannii* bacteremia was included in the analysis. Control patients were selected from the same period. Matching was based upon the APACHE II classification system: an equivalent APACHE II score (±2 points) and equivalent principal diagnosis leading to ICU admission [5, 6, 7]. As expected mortality can be derived from the APACHE II system (APACHE II score and diagnostic category), this matching procedure results in a similar expected mortality in cases and controls. In addition, control patients were required to have an ICU stay equivalent to (or longer than) that of the cases prior to the onset of the bacteremia. Selection of controls was obtained without knowledge of outcome. In the case of more than two potential controls matching was based on the nearest admission date of the case.

Definitions

Bacteremia were considered nosocomial when detected more than 48 h after hospital admission. *A. baumannii* bacteremia was defined as the presence of *A. baumannii* in the blood, documented by at least one positive hemoculture. Hemocultures were taken on a routine basis when the patient's temperature rose above 38.4°C and were processed following the BacT/Alert (Organon Teknika, Durnham, N.C., USA) procedure. All positive hemocultures were judged on their clinical significance in consideration with clinical microbiologists, intensive care physicians, and sometimes infectious diseases specialists. Antibiotic resistance was determined according to methods recommended by the National Committee for Clinical Laboratory Standards for disk diffusion testing [8]. During the study period there were no changes in microbiological laboratory techniques. The source of the bacteremia was determined by both intensivists and microbiologists and based on isolation of *A. baumannii* from the presumed portal of entry and by clinical evaluation.

Antibiotic therapy was considered appropriate if the drugs used at therapeutic doses had in vitro activity against the strain isolated. We considered antibiotic therapy as inappropriate if the drugs used did not have in vitro activity against the *A. baumannii* strain, or if the patient did not receive antibiotic treatment. Delay in the start of antibiotic treatment was calculated from the day of onset of the bacteremia. In five patients no data on antibiotic therapy were available. Acute respiratory failure was defined as ventilator dependence, acute renal failure as dialysis dependence, and hemodynamic instability as the need for vasopressors or inotropics during the ICU stay.

Outcome evaluation was based on the in-hospital mortality of cases and controls. Mortality attributable to the *A. baumannii* bacteremia is the excess mortality caused by the blood stream infection. This was determined by subtracting the crude mortality rate of the control patients from the crude mortality of the cases [9, 10]. Excess length of ICU stay is calculated by subtracting the median ICU stay of the controls from the median ICU stay of the case-patients [10].

Patients

During the study period 22,431 patients were admitted to the ICU. Principal admission diagnosis of cases and controls are in Table 1. Of 90 control subjects five did not meet the criterion of length of ICU stay equivalent to that of the respective case-patient. Population characteristics for cases and controls are presented in Table 1. Bacteremia involving *A. baumannii* was diagnosed in 45 patients. This represents an incidence of 2.0 *A. baumannii* bacteremia on 1000 ICU admissions. The mean length of ICU stay prior to the onset of the bacteremia was 15±12.9 days (median 11 days).

Fifteen bacteremia (33.3%) were of unknown origin. Most detected secondary sources were pulmonary (31.1%) and postsurgical intra-abdominal infections (22.2%). Other sources were contaminated central venous catheters (6.7%), wound infections (4.4%), sinusitis (4.4%), and urinary tract infections (4.4%). Twenty-two bacteremia (48.9%) were polymicrobial. Micro-organisms other than *A. baumannii* involved in these polymicrobial episodes were coagulase-negative staphylococci (*n*=8), enterococci (*n*=5), *Enterobacter* species (*n*=3), *Citrobacter* species (*n*=2), *Escherichia coli* (*n*=1), and *Bacteroides fragilis* (*n*=1).

Sixteen strains (35.6%) were susceptible only to carbapenems and polymyxin B. Thirty-seven strains (82.2%) were ceftazidime-resistant. Antibiotic therapy was administered to 88% of the patients. The mean delay in the start of treatment was 0.8±1.2 days. The mean length of therapy was 11±10.1 days.

Statistical analyses

Continuous variables are described as mean ±standard deviation (SD) and median (range: lower quartile – upper quartile). Comparative analyses used the Mann-Whitney *U* test or the χ^2 as appropriate. For the attributable mortality rate and differences between expected and observed mortality 95% confidence intervals (CI) are reported. Survival curves are prepared by means of the Kaplan-Meier method and univariate survival distributions are compared with use of the log-rank test. A multivariate survival analysis is evaluated according to the Cox proportional-hazards model; here hazard ratios (HR) and 95% CI are reported. Variables entered in the model were required to have a plausible relationship with mortality as well as a significant level of *p*<0.1 in univariate analysis. *A. baumannii* bacteremia was entered in the model irrespective of these requirements as it was the principal variable of investigation. In this analysis continuous variables were handled continuously. Statistical analyses were executed with Statistica 4.5 and SPSS 9.0. All tests were two-tailed, and statistical significance is defined as *p*<0.05.

Results

Mortality rates at 14 and 28 days after the onset of the *A. baumannii* bacteremia were, respectively, 20.0% and 35.6%. The in-hospital mortality rate was 42.2%. There was a trend towards higher in-hospital mortality in bacteremia of secondary origin vs. primary bacteremia (50.0% vs. 26.7%, *p*=0.135). Also, bacteremia treated inappropriately or in which antibiotic therapy was initiated more than 48 h after the onset of the infection (*n*=10) were more likely to have worse prognosis (60.0% vs. 36.7%; *p*=0.196). Patients with *A. baumannii* bacteremia were more likely to have hemodynamic instability. They also had a longer ICU stay and a longer length of ventilator dependence. An excess length of ICU stay of 5 days was found in patients with *A. baumannii* bacteremia since the median length of ICU stay for cases and controls was, respectively, 25 and 20 days.

Survival curves for patients with *A. baumannii* bacteremia and controls are compared in Fig. 1 (*p*=0.311). The attributable mortality was 7.8% (95% CI: −9.7% to 25.3%) as in-hospital mortality rates for cases and controls were, respectively, 42.2% and 34.4% (*p*=0.378). In

Table 1 Population characteristics of ICU patients with (*cases*) and without *A. baumannii* bacteremia (*controls*) (*IQR* interquartile range)

	Cases (*n*=45)			Controls (*n*=90)			*p*
	Mean ±SD	Median (IQR)	*n* (%)	Mean ±SD	Median (IQR)	*n* (%)	
Age (years)	47±16.9	49 (29–59)	–	49±19.5	52 (27–67)	–	0.466
ICU stay (days)	28±19.9	25 (16–34)	–	23±20.2	20 (8–31)	–	0.043
Acute respiratory failure	–	–	42 (93.3%)	–	–	86 (95.6%)	0.583
Ventilator dependence (days)	25±16.6	22 (15–30)	–	20±18.4	17 (7–25)	–	0.011
Hemodynamic instability	–	–	42 (93.3%)	–	–	71 (78.9%)	0.032
Acute renal failure	–	–	12 (26.7%)	–	–	18 (20.0%)	0.380
APACHE II score	23±8.6	23 (18–27)	–	23±8.6	23 (18–27)	–	0.815
APACHE II related expected mortality (%)	38±24.4	35 (20–59)	–	37±24.3	31 (20–61)	–	0.667
ICU mortality	–	–	14 (31.3%)	–	–	19 (21.3%)	0.203
In-hospital mortality	–	–	19 (42.2%)	–	–	31 (34.4%)	0.378
Admission diagnosis							
Postoperative patients							
Multiple trauma	–	–	11 (24.4%)	–	–	22 (24.4%)	–
Head trauma	–	–	7 (15.6%)	–	–	14 (15.6%)	–
Abdominal surgery	–	–	4 (8.9%)	–	–	8 (8.9%)	–
Gastrointestinal bleeding/obstruction	–	–	2 (4.4%)	–	–	4 (4.4%)	–
Thoracotomy for neoplasm	–	–	1 (2.2%)	–	–	1 (2.2%)	–
Nonoperative patients							
Metabolic/renal disorder	–	–	5 (11.1%)	–	–	10 (11.1%)	–
Respiratory failure due to pneumonia	–	–	4 (8.9%)	–	–	8 (8.9%)	–
Respiratory failure (general)	–	–	3 (6.7%)	–	–	6 (6.7%)	–
Cardiovascular failure due to sepsis	–	–	2 (4.4%)	–	–	4 (4.4%)	–
Respiratory failure due to intoxication	–	–	1 (2.2%)	–	–	1 (2.2%)	–
Seizure disorder	–	–	1 (2.2%)	–	–	1 (2.2%)	–
Cardiac arrest	–	–	1 (2.2%)	–	–	1 (2.2%)	–
Cardiovascular failure (general)	–	–	1 (2.2%)	–	–	1 (2.2%)	–
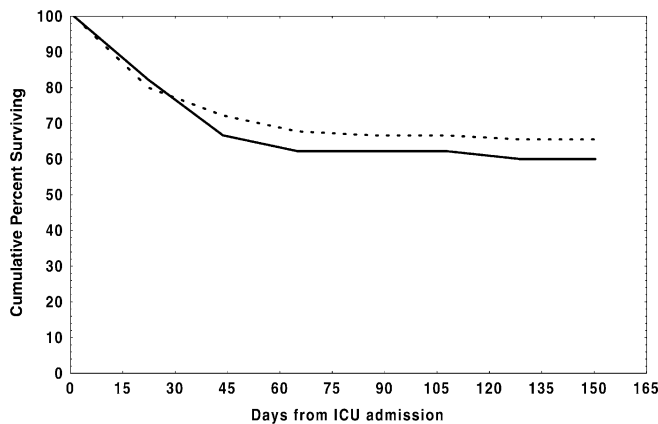
Fig. 1 Survival curves for ICU patients with (cases, *solid line*) and without *Acinetobacter baumannii* bacteremia (matched controls, *broken line*). Log rank test: *p*=0.311

the control group the observed mortality (34.4%) did not differ from the expected mortality (37%) as assessed on APACHE II (95% CI: 24.6–44.2%). In a multivariate survival analysis older age was the only variable reaching a borderline association with in-hospital mortality (HR: 1.01, 95% CI: 1.00–1.02, *p*=0.051). *A. baumannii* bacteremia was no independent predictor of mortality (HR: 0.96, 95% CI: 0.67–1.38, *p*=0.833).

Discussion

Our data revealed that in ICU patients *A. baumannii* bacteremia is associated with high in-hospital mortality (42.2%). However, since the mortality in the control group was high as well (34.4%), we conclude that mortality in the cases is due principally to severity of underlying disease and acute illness. The mortality attributable to *A. baumannii* bacteremia was 7.8% and was not statistically significant. Our findings run counter to those of previous reports stating that bacteremia is associated with high attributable mortality [10, 11]. Crucial in the interpretation of matched cohort studies is the level of coincidence between cases and controls. In the present study matching was based on severity of underlying disease and acute illness (APACHE II) as these are the most important prognostic indicators for death in ICU patients [5, 6, 7] and hence can be considered as basic elements in studies with mortality as principal outcome variable. This matching

procedure makes that the cases and controls have similar risk factors for death and for the acquisition of *A. baumannii* bacteremia at the moment of ICU entry. Additional matching on length of ICU stay prior to the bacteremia includes that control subjects also had an equivalent number of "days at risk" for the development of an *A. baumannii* bacteremia. Matching on severity of disease scoring systems are controversial, precisely because these matching procedures provide a "close match" on risk factors for death as well as risk factors for the acquisition of bacteremia. It can be questioned whether such a procedure does not result in overmatching with loss of statistical validity, in other words, a situation in which there is no difference in mortality as the groups being compared are too similar. However, previous studies have shown important excess mortality rates in patients with nosocomial blood stream infection after matching on APACHE II [11, 12].

In addition to a nonsignificantly increased mortality, an excess length of ICU stay of 5 days was observed. *A. baumannii* bacteremia was responsible for a significantly longer ICU stay, representing an important economic burden.

In our cohort the patients with primary *A. baumannii* bacteremia had better outcomes than those with secondary bacteremia. Although the difference found was not statistically significant (26.7% vs. 50.0%, p=0.135) we investigated the attributable mortality for *A. baumannii* bacteremia stratified for primary vs. secondary bacteremia. In primary *A. baumannii* bacteremia (n=15) no attributable mortality was found as mortality rates for cases and controls were 26.7% and 30.0%, respectively. The attributable mortality for secondary *A. baumannii* bacteremia (n=30) was 13.3% as mortality rates for cases and controls were, respectively, 50.0% and 36.7%. From this it is clear that secondary bacteremia is associated with worse outcome. Although the attributable mortality rate of 13.3% was not statistically significant (95% CI: −8.4–35.0%), it is clinically relevant.

The nonsignificant attributable mortality in *A. baumannii* bacteremia might be the consequence of a high overall rate of appropriate antibiotic therapy (88%) and a short delay in the start of treatment (0.8±1.2 days). This is in accord with previous observations of gram-negative bacteremia in our ICU [7, 13]. However, in ten patients no antibiotic therapy was administrated or initiated with an unacceptable delay of more than 48 h after onset of the bacteremia. The attributable mortality of these badly treated cases of *A. baumannii* bacteremia was 15.0% (60.0% vs. 45.0%; 95% CI: −22.4 to 52.4%). The attributable mortality of the accurately treated *A. baumannii* bacteremia was 5% (36.7% vs. 31.7%; 95% CI: −15.9 to 25.9%). The number patients in these subgroup analyses are small and therefore these results are difficult to interpret. Nevertheless we believe that the attributable mortality of Gram-negative bacteremia can be strongly limited by keeping the delay until appropriate antibiotic therapy as short as possible. In a similar matched cohort study with focus on *Klebsiella* bacteremia no excess mortality was found at all [7]. In this cohort 94% of patients with *Klebsiella* bacteremia were treated appropriate with an average delay in the start of antibiotic therapy of 0.4±0.7 days. In addition, the link between appropriate therapy and more favorable outcomes in nosocomial infections in ICU patients is clear [14, 15, 16, 17, 18].

In summary, our data demonstrate that after adequate adjustment for severity of underlying disease and acute illness and in the presence of early initiation of antimicrobial therapy *A. baumannii* bacteremia does not adversely affect outcome.

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