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CONCISE ARTICLE

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Clinical Impact of Nosocomial *Klebsiella* Bacteremia in Critically Ill Patients

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Abstract In order to determine the clinical impact of *Klebsiella* bacteremia on critically ill patients, a matched cohort study was conducted between January 1992 and December 2000. During the study period, all intensive care unit (ICU) patients with nosocomial *Klebsiella* bacteremia were defined as cases (*n*=52), but two of these patients were excluded from the matched cohort due to incomplete medical records. The remaining 50 patients were matched at a ratio of 1:2 with control patients (*n*=100) on the basis of the APACHE II severity of disease classification system. Patients with *Klebsiella* bacteremia experienced acute renal failure and hemodynamic instability more often than controls. They also had a longer ICU stay and longer ventilator dependence. In-hospital mortality rates for cases and controls were nearly equal (36% vs. 37%, respectively; *P*=0.905). In conclusion, after adjusting accurately for severity of underlying disease and acute illness, no difference in mortality was found between ICU patients with *Klebsiella* bacteremia and their matched control subjects.

Introduction

Bacteremia involving gram-negative bacilli poses a significant threat to critically ill patients [1, 2]. In this context, *Klebsiella* species are important nosocomial pathogens, not only because of their tendency to develop antibiotic resistance [3, 4], but because of their association with a fatal outcome [5]. The objective of this study was to evaluate the clinical impact of nosocomial *Klebsiella* bacteremia in terms of survival in intensive care unit (ICU) patients by means of a matched cohort study.

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Materials and Methods

The study was conducted at the Ghent University Hospital, which is a 1,060-bed tertiary care centre with a 54-bed ICU including a surgical and medical ICU, an ICU for cardiac surgery and a burns unit. No significant changes in the average patient age, length of ICU stay or acute physiology and chronic health evaluation (APACHE) II scores [6] were observed during the study period.

In the retrospective, matched cohort study (1:2 ratio) all ICU patients with nosocomial, microbiologically documented *Klebsiella* bacteremia were defined as cases. Every case was matched with two other ICU patients without clinical or microbiological evidence of bacteremia (with the exception of coagulase-negative staphylococci) or candidemia (matched controls). The study population included adult, critically ill patients admitted to the ICU over a 9-year period (January 1992–December 2000). A hospital-wide case-based surveillance programme for bloodstream infections was used to search retrospectively for ICU patients with nosocomial bacteremia involving *Klebsiella* spp. Bacteremia was considered nosocomial when diagnosed 48 h after hospital admission. Every patient whose ICU stay was complicated by *Klebsiella* bacteremia was included in the analysis.

Control patients were selected during the same 9-year study period. They were matched with cases using the APACHE II classification system, based on an equal APACHE II score (±1 point) and an equal principal diagnosis leading to ICU admission [6, 7]. The APACHE II system is a recognised standard for comparing the severity of illness in ICU patients. Each patient's score is calculated on the basis of a chronic health evaluation and a set of acute physiologic parameters obtained during the first 24 h of ICU observation. The expected in-hospital mortality of patients can be calculated using the APACHE II score and a factor attributed to a precise diagnostic category (e.g., surgical vs. nonsurgical admission, elective or urgent surgery, failure of major vital organ system, and the principal diagnosis leading to ICU admission). Since expected mortality can be derived from the APACHE II system (APACHE II score and diagnostic category), our matching procedure for cases and controls resulted in the expected mortality for both groups being equal. Controls were selected without prior knowledge of the patient's outcome. When more than two potential controls were available, selection was based on the date of admission nearest to that of the case patient.

For the purpose of this study, *Klebsiella* bacteremia was defined as the presence of a *Klebsiella* sp. in blood, documented with at least one positive hemoculture. In our hospital, hemocultures are performed routinely when a patient's temperature rises above 38.4°C or when infection is suspected on clinical grounds. The cultures are processed using the BacT/Alert system (Organon Teknika, USA) in accordance with the manufacturer's instructions. Antibiotic resistance was determined according to the methods

Table 1 Population characteristics of ICU patients distributed for hospital nonsurvivors vs. hospital survivors and for patients with (cases) vs. without (controls) *Klebsiella* bacteremia

Patient characteristic	Hospital nonsurvivors (*n*=55)	Hospital survivors (*n*=95)	*P* value	Cases (*n*=50)	Controls (*n*=100)	*P* value
Female	20 (36.5%)	33 (34.7%)	0.841	18 (36%)	35 (35%)	0.904
Age in years (mean±SD)60±16.8	53±17.5	0.002	52±15.9	56±18.6	0.225	
Median age (range)	62 (56–72)	53 (34–66)	–	56 (37–64)	59 (43–68)	–
APACHE II (mean±SD)	24±7.8	20±7.7	0.005	21±8.1	21±7.9	0.903
Median APACHE II (range)	23 (1830)	21 (17–23)		22 (17–27)	22 (18–27)	–
APACHE II related expected mortality (%) (mean±SD)	45±27.8	30±24.0	<0.001	36±26.4	36±26.5	0.979
Median APACHE II related expected mortality (%) (range)	37 (22–72)	23 (14–43)		26 (16–52)	25 (18–56)	–
Acute renal failure (%)	33	12	0.002	30	14	0.019
Hemodynamic instability (%)	71	53	0.028	30	49	<0.001
Acute respiratory failure (%)	85	80	0.402	88	79	0.176
Ventilator dependence in days (mean±SD)	17±23	13±18.2	0.396	28±25.6	8±13	<0.001
Median ventilator dependence (range)	9 (2–22)	6 (1–19)		21 (14–32)	3 (1–10)	–
ICU stay in days (mean±SD)	18±24.1	21±26.2	0.233	38±31.6	11±14.7	<0.001
Median ICU stay (range)	8 (3–22)	12 (4–28)		25 (16–49)	5 (2–12)	–
In-hospital mortality (%)	100	0		36	37	0.905
Klebsiella bacteremia (%)	33	34	0.904	100	0	–

SD, standard deviation; ICU, intensive care unit

recommended by the National Committee for Clinical Laboratory Standards for disk diffusion testing [8]. The source of bacteremia was determined by both the ICU personnel and the microbiologists based on the isolation of a *Klebsiella* sp. from the presumed port of entry and by clinical evaluation.

Acute respiratory failure was defined as ventilator dependence, acute renal failure as dialysis dependence and hemodynamic instability as the need for vasopressors or inotropic treatment during the ICU stay. Evaluation of patient outcome was based on the in-hospital mortality of cases and controls. For the reporting of statistics, continuous variables were described as the mean±standard deviation and median (range: lower quartile–upper quartile). Comparative analyses were performed using the Mann-Whitney U test or the chi-square test, when appropriate. A multivariate survival analysis was performed according to the Cox proportional-hazards model, whereby hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. To avoid spurious associations, only variables with a plausible connection with mortality were entered in this model. All of the tests performed were two-tailed, and statistical significance was defined as $P<0.05$.

Results and Discussion

During the study period 29,727 patients were admitted to the ICU. *Klebsiella* bacteremia was diagnosed in 52 of these patients, representing a prevalence of 1.7 cases of *Klebsiella* bacteremia per 1,000 ICU admissions. Thirty-four cases were due to *Klebsiella pneumoniae* and 18 were due to *Klebsiella oxytoca*. Eighteen cases were due to ceftazidime-resistant strains. Lower respiratory tract infection was the most common source of *Klebsiella* bacteremia (*n*=15). Other sources of bacteremia were the abdomen (*n*=8), urinary tract (*n*=8), contaminated central venous catheter (*n*=7), nasal sinus (*n*=5) and soft tissue infection (*n*=4). Nine cases were primary in origin. In three cases of bacteremia more than one possible source was identified. Twenty cases were polymicrobial. Of the 52 patients with *Klebsiella* bacteremia, 48 received appropriate antibiotic therapy. The mean delay from the onset of bacteremia until the initiation of antimicrobial treatment was 0.4±0.7 days. Mortality at 14 and 28 days after the onset of bacteremia was 21% (11/52) and 33% (17/52), respectively. In-hospital mortality was 35% (18/52).

Two patients (both hospital survivors) were excluded from the matched cohort design because of incomplete medical files. Matching was successful in all other patients with *Klebsiella* bacteremia, leading to a comparative study with 50 cases and 100 matched control subjects. Univariate relationships with in-hospital mortality are shown in Table 1. Nonsurvivors were older and experienced acute renal failure and hemodynamic instability more often than survivors; they also had higher APACHE II scores and a higher APACHE II-related expected mortality.

Patient characteristics of cases and controls are presented in Table 1. Patients with *Klebsiella* bacteremia experienced acute renal failure and hemodynamic instability more often than controls. They also had a longer length of ICU stay and longer ventilator dependence. Despite these ominous signs, in-hospital mortality was nearly equal in both groups, with the mortality rate for patients with *Klebsiella* bacteremia being 36% and that of the matched controls being 37% (P=0.905). A multivariate survival analysis demonstrated acute renal failure (HR, 3.7; 95%CI, 1.5–9; P=0.004) and increasing age (HR, 1.02; 95%CI, 1–1.05; P=0.048) to be independent predictors of mortality. The APACHE II-related expected mortality reached borderline significance (HR, 4.3; 95%CI, 0.97–18.78; P=0.055).

Our findings indicate that *Klebsiella* bacteremia does not have a significant impact on the expected survival of critically ill patients after adjusting accurately for severity of underlying disease and acute illness. Although mortality of patients with *Klebsiella* bacteremia and their matched

controls was high, the figures were in accordance with the expected mortality rate determined using the APACHE II system. Based on this finding, we conclude that mortality in ICU patients with *Klebsiella* bacteremia is mostly due to underlying conditions that predict fatality. These findings are in keeping with previous reports, whereby low attributable mortality rates were documented for ICU patients with bacteremia involving *Acinetobacter baumanii* and *Pseudomonas aeruginosa* [9, 10].

Indeed, it has been assumed for decades that the impact of gram-negative bacteremia on patient outcome is negligible when compared with the severity of the patient's underlying illness [11, 12]. Particularly in critically ill patients, for whom death is often the end-point of a cascade of life-threatening complications, distinguishing mortality due to bacteremia from mortality due to severity of underlying disease on clinical grounds is extremely difficult, if not impossible. Thus, matched cohort studies are useful for estimating the actual extent of mortality caused by bacteremia [13].

It remains debatable whether or not matching cases and controls using a scoring system that predicts mortality systematically results in overmatching, thereby reducing the validity of the results. However, since evaluating patient outcome was the principal goal of this study, strict matching of disease severity would seem justified, if not necessary. Moreover, this system allowed us to confirm the absence of a significant clinical impact using multivariate analyses of survival of cases and controls, whereby *Klebsiella* bacteremia was not recognised as a predictor of mortality.

In the group of patients with *Klebsiella* bacteremia, no excess mortality was found, but we cannot prove that none of the deaths were directly attributable to the condition. Since mortality in the control group was equally high, however, we can conclude that if the patients who deceased did not die due to bacteremia, they would have died anyway as a consequence of their dreadful physical condition.

The rate of appropriate antibiotic therapy in our population was high (93%), and the mean time until the start of treatment was short (<1day), even though a considerable percentage of our *Klebsiella* isolates was ceftazidime-resistant. These factors might have played a role in the absence of any excess mortality in the group of patients with *Klebsiella* bacteremia, since a significant delay in the start of antimicrobial treatment has previously been shown to be strongly associated with a negative outcome [14].

The short time until the initiation of antimicrobial treatment may be a result of our hospital's intensive screening policy, which requires that site-specific surveillance cultures be performed thrice weekly for all ICU patients. When clinical signs of infection occur, empirical therapy is started based on the presumed clinical focus of infection and the reported antibiotic susceptibility pattern of the microorganism(s) detected in surveillance cultures. This strategy appears to facilitate the early administration of appropriate antibiotic treatment (<1day) in our ICU [15].

In conclusion, after carefully matching cases and controls using the APACHE II system, which allowed accurate adjustments for severity of underlying disease and acute illness, no excess mortality was found among ICU patients with *Klebsiella* bacteremia compared with their matched control subjects. When appropriate antibiotic therapy is administered quickly, *Klebsiella* bacteremia does not adversely affect the prognosis for ICU patients.

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