Impact of Multiresistance of Gram-negative Bacteria in Bloodstream Infection on Mortality Rates and Length of Stay

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Abstract

Background: Bloodstream infections (BSI) with gram-negative bacteria (GNB) are one of the most serious infections in the hospital setting, a situation compounded by the increasing antibiotic resistance of gram-negative bacteria causing BSI. The aim of the study was to assess the impact of antibiotic multiresistance of GNB in BSI on mortality rates and length of stay (LOS).

Materials and Methods: The setting was the University Hospital Aachen, a 1,500-bed tertiary-care hospital with over 100 ICU beds providing maximal medical care in all disciplines. We performed a 5-year hospital-wide matched cohort study (January 1996 to February 2001) in which 71 cases and 99 controls were enrolled. Matching criteria were sex, age and GNB isolated in blood cultures. Multiresistance was defined as resistance against at least two different classes of antibiotics such as penicillins (+ β-lactamase-inhibitor), third-generation cephalosporins, fluoroquinolones or carbapenems.

Results: BSI were mainly nosocomially acquired, and cases of BSI with multiresistant bacteria were associated with a higher mortality ($p = 0.0418$) and a prolonged LOS in the intensive care unit (ICU) ($p = 0.0049$). Risk factors for BSI with multiresistant GNB were antibiotic treatment ($p = 0.0191$) and mechanical ventilation ($p = 0.0283$).

Conclusion: Multiresistance of GNB causing BSI was associated with higher mortality rates and longer LOS in ICU. The initial antibiotic therapy was significantly more often inadequate and might have had an impact on overall mortality. Thus, an effective strategy to administer an appropriate initial empirical antibiotic therapy, especially in patients with risk factors, must be sought. Moreover, the overall usage of antimicrobials must be limited and infection control guidelines should be followed to reduce the emergence and transmission of multiresistant GNB.

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Introduction

The increasing prevalence of antibiotic multiresistance in bacteria is a major public health threat. This phenomenon is particularly prevalent in nosocomial infection, for which antibiotic-resistant bacteria have emerged worldwide. To counteract this worrisome situation, the selection of the initial empirical antibiotic therapy must therefore be appropriate. Hence, correct antibiotic regimen prescription has become a major challenge in the field of infectious diseases [1–3]. Not surprizingly, there is now growing evidence that severe infections like pneumonia or BSI caused by antibiotic-resistant bacteria are associated with higher mortality and morbidity rates as well as increased hospital costs [4–6]. For example, methicillin-resistance in *Staphylococcus aureus* pneumonia and bacteremia resulted in a significant increase in mortality [7–12]. However, the impact of antibiotic-resistance in BSI with gram-negative bacteria (GNB) still remains controversial.

Here, we evaluate the antibiotic resistance in BSI with GNB on mortality rates, LOS and hospital costs and also report risk factors involved in the acquisition of multiresistant gram-negative bacteria (MRGNB).

Methods

Study Design

The study was conducted from January 1996 to February 2001 at the University Hospital Aachen, which is a tertiary care centre with 1,500 beds. It has ten specialized intensive care units (ICUs) with a total of 101 beds. The study was designed as a hospital-wide matched cohort study including patients in the ICU and in general wards. All patients with positive blood cultures for GNB were identified by the Institute for Medical Microbiology's

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microbiological database and were followed by chart review. Every case was matched with two controls where possible but with at least one.

Multiresistance was defined as resistance against at least two different antibiotic classes like penicillins (amoxicillin/clavulanic acid or piperacillin/tazobactam), third-generation cephalosporins (cefotaxim, ceftazidime or ceftriaxon), fluoroquinolones (ciprofloxacin or levofloxacin) or carbapenems (imipenem or meropenem). When evaluating multiresistance, intrinsic resistance patterns, e.g., for *Pseudomonas aeruginosa, Stenotrophomonas maltophilia* or *Acinetobacter* spp. were taken into consideration. Sensitive gram-negative bacteria (SGNB) were defined as being susceptible to all antibiotics of these classes or as being resistant to only a single class.

Cases were defined as patients with a positive blood culture for MRGNB; controls had a SGNB in the blood culture. To rule out contamination and to document true infection, cases and controls were enrolled in the study only when bacteremia was combined with at least two of the sepsis criteria as defined in *Bone* et al. [13].

Cases and controls were matched for sex and age ± 10 years and species of bacterial isolates. Patients with polymicrobial blood culture results were excluded.

Empirical antibiotic therapy was considered appropriate when the patient received at least one antimicrobial agent with *in vitro* sensitivity against the isolate of the blood culture and when the therapy was started within 24 h after the onset of clinical signs of infection.

Data Collection

The following data were documented: age, sex, species of bacterial isolates and susceptibility pattern, clinical signs of sepsis according to the *Bone* criteria, diagnosis at admission, underlying diseases, follow-up diagnosis during hospitalization, invasive procedures, duration of ICU and hospital stay before and after the onset of BSI, time of ventilation and antibiotic treatment. As severity of illness at admission may differ from severity of illness before onset of BSI, we calculated, whenever possible, an Apache II score on day 3 before the onset of BSI in cases and controls when not more than two parameters were lacking [14].

Microbiological Methods

Isolation and identification of GNB were carried out by standard methods and did not change during the study period. Susceptibility testing was performed according to the criteria of the National Committee for Clinical Laboratory Standards (NCCLS) [15].

Outcome Assessment

Primary outcome parameters were death, LOS in the ICU and general ward. A secondary parameter was appropriateness of the empirical antibiotic therapy.

An analysis of survivors was performed to ensure that outcome parameters were not artificially modified by patients who died in the first days after onset of BSI.

Statistical Analysis

The primary data analysis compared cases and controls, matched 1:1 and if possible 1:2. A second data analysis compared only hospital survivors. All comparisons were unpaired and all tests of significance were two-tailed. Categorical variables were compared using Fisher's exact test. For continuous variables the Wilcoxon rank–sum test for non-normally distributed variables was applied. Values are expressed as the mean ± standard deviation (SD) for continuous variables and as a percentage of the group for categorial variables. All p-values are two-tailed and p-values with $p < 0.05$ indicate statistical significance.

To adjust results for potential confounders a multiple regression analysis was performed.

Results

Seventy-four cases fulfilled the study criteria and 71 could be matched to at least one control patient. Overall, 99 controls could be matched during the study period.

There was no difference either in demographic data, underlying diseases, diagnosis at admission, or invasive procedures before onset of BSI between cases (n = 71) and controls (n = 99) (see Table 1). However, mechanical ventilation and LOS in the ICU before onset of BSI were prolonged in cases compared to controls (24.19 days vs 17.08 days; $p = 0.0283$ and 14.9 days vs 8.9 days; $p = 0.05$, respectively) (see Table 1). 56 Out of 71 cases (79%), in contrast to only 61 out of 99 controls (61%) received antibiotic therapy before onset of BSI ($p = 0.0191$). Only a limited number of patients had a community-acquired BSI (8 vs 14%; $p = 0.3365$). It is of note that the Apache II score on day 3 before onset of BSI was almost identical between cases and controls (10.50 vs 9.42; $p = 0.2249$). The distribution of bacteria isolated in the blood cultures was as follows: *Acinetobacter* sp. (18), *Enterobacter* sp. (15), *P. aeruginosa* (15), *Serratia marcescens* (11), *E. coli* (6), *Citrobacter sp.* (3), *S. maltophilia* (2) and *Klebsiella* sp. (1).

38% of cases with MRGNB were 38%, in contrast to 23% of controls with sensitive GNB ($p = 0.0418$). LOS in the ICU after the onset of BSI was prolonged for cases by an average of 7 days (12.35 days vs 5.79 days; $p = 0.0049$).

There was no difference in LOS before and after the onset of BSI when cases and controls were treated on general wards (see Table 2). Overall, only 42% of cases (30/71) and 62% of controls (61/99) received appropriate empirical antibiotic therapy ($p = 0.0191$).

After adjustment for potential confounders (LOS before BSI, frequency of ICU stay before and ventilation, nosocomial-acquired infections and appropriateness of empiric antibiotic therapy) the only independent factor associated with mortality was MRGNB ($p = 0.013$).

LOS in the ICU before BSI ($p = 0.001$) and MRGNB ($p = 0.027$) were independent risk factors for the prolonged ICU stay after onset of BSI.

Discussion

In this study major risk factors for severe infections with multiresistant bacteria were, prolonged antibiotic therapy and mechanical ventilation before the onset of BSI.

The mortality of patients with BSI with multiresistant GNB was significantly higher in comparison to the control group ($p = 0.0418$). Other studies investigating the impact

Table 1
Patient characteristics, diseases and therapy before onset of bloodstream infection.

	BSI with MGNB n = 71		BSI with SGNB n = 99		p-value
	N (Mean ± SD)	%	N (Mean ± SD)	%	
Age [years]	63.09 ± 15.82		64.16 ± 16.39		0.4565
Sex (males)	50	70	73	74	0.7284
BSI before 48 h after admission	6	8	14	14	0.3365
Apache II score (n = 58, n = 76)	10.50 ± 5.6		9.42 ± 4.15		0.2249
Underlying diseases:					
Cardiovascular	27	38	47	48	0.2725
Respiratory	12	17	9	9	0.1577
Digestive and biliary	16	23	15	15	0.2331
Genitourinary	16	23	19	19	0.7010
Neurologic	12	17	10	10	0.2474
Diabetes	18	25	24	24	1
Infectious	1	1	2	2	1
AIDS and immunodeficiency	14	20	17	17	0.6913
Malignancy	15	21	23	23	0.8524
Initial ward at onset of BSI:					
Patients in ICU [freq]	38	54	45	46	0.3513
Patients on general ward [freq]	33	46	54	54	0.3513
Ventilation:					
Ventilation [freq]	26	37	33	33	0.7442
Ventilation [days]	24.19 ± 17.08		17.09 ± 16.29		0.0283
Antibiotic therapy:					
Penicillin + β-lactamase-inhibitor [freq]	30	42	28	28	0.0715
Third-generation cephalosporins [freq]	16	23	7	7	0.0056
Quinolones [freq]	12	17	13	13	0.5168
Carbapenems [freq]	9	13	8	8	0.4377
Pencillin + β-lactamase-inhibitor [days]	10.27 ± 5.11		9.04 ± 7.10		0.1554
Third-generation cephalosporins [days]	9.69 ± 4.61		9.57 ± 6.27		0.8934
Quinolones [days]	11.58 ± 7.9		5.08 ± 3.23		0.0269
Carbapenems [days]	10.33 ± 6.91		10.88 ± 5.87		0.5307

of antibiotic resistance in GNB-induced BSI on mortality found corresponding results [16–18].

In a prospective cohort study *Schwaber* et al. [19] reported that patients with bacteremia caused by ESBL-producing *Enterobacteriaceae* had a higher mortality rate (30% vs. 16%, p = 0.03). *Kim* et al. [17] compared 49 patients with pneumonia due to ESBL-producing *E. coli* and *Klebsiella pneumoniae* and found that mortality was significantly higher in comparison to the non-ESBL-group (26.7% vs. 5.7%, p = 0.001). Similarly, *Ariffin* et al. [18] reported a higher mortality in neutropenic children with ceftazidime-resistant *K. pneumoniae* bacteremia compared to ceftazidime-sensitive *K. pneumoniae* bacteremia (50.0% vs 13.3%, p = 0.02).

However, there are studies showing no significant impact of antibiotic resistance on mortality [19–21]. In a retrospective hospital-wide cohort study with 231 episodes of multiresistant gram-negative bacteremia, *Harbarth* et al. [19] could not document any difference in mortality. *Blot* et al. [20] also failed to demonstrate an adverse effect of resistance on mortality even in critically ill patients. In addition, in a prospective cohort study *Raymond* et al. [21] has found no difference in mortality with multiresistant gram-negative bacteremia after matching for age, organism and Apache II score (23.6% vs 29.2%, p = 0.35).

The importance of an early and appropriate antimicrobial therapy [22–24] and its impact on hospital mortality [25–27] is well known. Therefore different outcomes in studies comparing resistant and susceptible bacteria might be explained with delayed administration of an appropriate initial antibiotic therapy. In all of the aforementioned studies assessing a higher mortality rate in antibiotic resistant GNB-induced severe infections, patients received more often, inappropriate initial empirical antibiotic therapy. In contrast, *Blot* [20] showed that administration of appropriate initial empirical antibiotic therapy was extremely high in both groups (93.1% vs 91.1%). Moreover *Harbarth* et al. [19] used an initial

Table 2
Mortality rates, length of stay and antibiotic treatment after onset of bloodstream infection.

	BSI with MGNB n = 71		BSI with SGNB n = 99		p-value
	N (Mean ± SD)	%	N (Mean ± SD)	%	
Mortality rates [freq]	27	38	23	23	0.0418
Length of stay:					
Intensive care unit [days]	12.35 ± 18.81		5.79 ± 11.44		0.0049
General ward [days]	15.49 ± 17.69		18.20 ± 18.65		0.2892
Antibiotic therapy:					
Penicillin + β-lactamase-inhibitor [freq]	23	32	35	35	0.7443
Third-generation cephalosporins [freq]	26	37	24	24	0.0900
Quinolones [freq]	24	34	27	27	0.3984
Carbapenems [freq]	23	32	10	10	0.0004
Penicillin + β-lactamase-inhibitor [days]	6.65 ± 5.42		10.06 ± 6.55		0.0326
Third-generation cephalosporins [days]	7.50 ± 5.84		8.08 ± 3.15		0.2664
Quinolones [days]	6.96 ± 3.50		8.11 ± 5.91		0.7329
Carbapenems [days]	9.74 ± 9.95		5.90 ± 4.09		0.3538
Initial antibiotic therapy:					
Appropriate [freq]	30	42	61	62	0.0191

empirical antibiotic regimen for gram-negative sepsis of a combination of a carbapenem and a quinolone or aminoglycoside; thereby, multiresistant bacteria were covered.

To achieve the aim of an appropriate antimicrobial therapy as early as possible *Depuydt* [28, 29] and *Blot* [30] could demonstrate systemic surveillance cultures to be a promising tool.

During the study period there were no hospital-specific recommendations for the initial antibiotic treatment implemented. This may explain the rate of 38% inadequate initial therapy

In this study, MRGNB-induced BSI was also associated with an increased LOS in the ICU after the onset of infection. We suspect that initial inappropriate empirical antibiotic therapy might have complicated ($p = 0.053$) but did not prolong the clinical course ($p = 0.262$) in these critically ill patients. After adjustment for potential confounders LOS in the ICU before onset of BSI and MRGNB were independent predictors for a prolonged ICU stay.

The matching process of this study did not take into account whether infections were nosocomial acquired or in the community. However, as the numbers of patients in both groups with community-acquired BSI were very low (8% of cases vs 14% of controls, $p = 0.3365$) a probable bias might be negligible. After adjustment, this potential confounder was not associated with mortality ($p = 0.634$) or prolonged LOS in the ICU ($p = 0.683$).

Another weakness of this study might be that the matching did not take into account LOS prior to infection. However, *Blot* et al. [31] could show that the impact of exposure time on attributable mortality caused by GNB did not necessarily have an impact on the outcome. After adjustment for the potential confounders mentioned above an impact could be excluded in this study as well ($p = 0.847$).

As this study is a hospital-wide matched cohort study including patients in the ICU and on general wards the APACHE II Score was only available for 56 of 71 cases (79%) and 76 of 99 controls (77%). Therefore matching for disease severity was not possible; however, the mean score of both groups did not differ.

In conclusion, BSI with MRGNB was associated with a higher mortality rate and a significant prolonged LOS in the ICU. Major risk factors were prolonged antimicrobial therapy and mechanical ventilation prior to the infection. Cases received significantly more often inappropriate initial empirical antibiotic therapy. Especially in the setting with a high prevalence of MRGNB, initial antibiotic therapy for severe infections must be broad enough to cover these bacteria.

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