Mortality Risk Factors with Nosocomial *Staphylococcus aureus* Infections in Intensive Care Units: Results from the German Nosocomial Infection Surveillance System (KISS)

P. Gastmeier, D. Sohr, C. Geffers, M. Behnke, F. Daschner, H. Rüden

Abstract

Introduction: As the number of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infections in German intensive care units increases, the problem of MRSA infection as such is becoming ever more serious. The aim of this study was to investigate whether mortality rates from nosocomial MRSA pneumonia and primary bloodstream infections (BSI) differ significantly from those of nosocomial pneumonia and primary BSI caused by methicillin-susceptible *S. aureus* (MSSA).

Methods: For the analysis data from the ICU component of the German nosocomial infection surveillance system (KISS) were used (January 1997 to June 2002). To identify mortality risk factors a logistic regression analysis with step-wise variable selection was conducted including all cases of nosocomial *S. aureus* pneumonia and primary BSI. The possible risk factors that were evaluated were age > median, male gender, time in the ICU before infection > median, type of ICU, type and size of hospital, intubation, CVC use, total parenteral nutrition, year of investigation, infection caused by MRSA.

Results: Data from 274 ICUs and 505,487 ICU patients were recorded and a total of 6,888 cases of nosocomial pneumonia and 2,357 cases of primary BSI identified, of which 1,851 cases of *S. aureus* pneumonia and 378 cases of *S. aureus* primary BSI were considered for analysis. 59 of the 349 patients with MRSA pneumonia (16.9%) and 105 of the 1,502 patients with MSSA pneumonia (7.0%) died. 16 of the 95 patients with primary MRSA BSI (16.8%) and 17 of the 283 patients with primary MSSA BSI died (6.0%). Four factors were significantly associated with mortality from *S. aureus* pneumonia, one of them being pneumonia caused by MRSA (OR = 2.62; CI95 1.69–4.02). Only MRSA was significantly associated with death from *S. aureus* primary BSI (OR = 3.84; CI95 1.51–10.2).

Conclusion: Nosocomial pneumonia and primary BSI from MRSA may be associated with death, but the cause-effect relationship of severity of illness and MRSA remains to be determined due to the limitations of surveillance data.

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Introduction

Staphylococcus aureus is the most frequent pathogen in intensive care units (ICUs) [1, 2]. It causes not only pneumonia and primary bloodstream infections (BSI) but also intra-abdominal infections, mediastinitis, meningitis and deep tissue infections which are significant clinical diseases. However, if a patient dies with a nosocomial *S. aureus* infection it often remains an open question as to whether it was the infection or the underlying disease which was the actual cause of death.

According to data from the German nosocomial infection surveillance system (KISS), 16.3 % of all nosocomial ICU infections are due to *S.aureus*. This percentage has been relatively constant over the years, however, during the last 6 years the percentage of methicillin-resistant *S. aureus* (MRSA) infections has increased dramatically – from 8% in 1997 to 30% in the first 6 months of 2003.

The relative morbidity and mortality of nosocomial infections caused by MRSA compared with those caused by methicillin-susceptible *S. aureus* (MSSA) remains an issue of controversy. Some investigators have suggested that MRSA infections lead to greater mortality than those from MSSA. For bacteremia this was even shown in two meta-analyses [3, 4]. However, such comparisons may be confounded by concomitant conditions and effects from the treatment of patients infected with MRSA, for instance, the length of time in hospital before bacteremia [5]. However, other authors did not find that MRSA infections significantly influenced the mortality rate [6–10].

P. Gastmeier *(corresponding author)*
Institute of Medical Microbiology and Hospital Epidemiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, Phone: (+49/511) 532-5147, Fax: -8174, e-mail: Gastmeier.Petra@mh-hannover.de
D. Sohr D, C. Geffers, M. Behnke, H. Rüden
Institute of Hygiene and Environmental Medicine, Charité – University Medicine Berlin, Germany
F. Daschner
Institute of Environmental Medicine and Hospital Epidemiology, University Hospital Freiburg, Germany

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We did a risk factor analysis so as to identify factors significantly associated with the outcome of death from *S. aureus* infection in ICU patients from the German nosocomial infection surveillance system.

Methods

KISS (Krankenhaus-Infektions-Surveillance-System) is a national surveillance system for nosocomial infections in Germany [11]. The ICU component was established in 1997, since then the number of ICUs participating has increased continuously. Meanwhile 274 ICUs are sending their data. The method used by KISS is almost identical to the surveillance method of the National Nosocomial Infections Surveillance (NNIS) System [12]. This means that definitions from the Centers for Disease Control and Prevention (CDC) are used for diagnosing nosocomial infections [13] or calculating device-associated infection rates, comparing infection rates and recording complications such as the development of secondary bloodstream infection or, ultimately, death. In the case of a nosocomial infection the pathogens identified are documented.

Only nosocomial pneumonias and primary BSI with *S. aureus* were considered for this analysis. Mortality rates were calculated for patients stratified by the following risk factors: type of ICU, size of hospital, type of hospital, time up to infection, gender, age, ventilation (for pneumonia cases only), central venous catheter (CVC) use, total parenteral nutrition (for primary BSI cases only), other pathogens in relevant specimens from the same patient, bacterial resistance to methicillin.

In addition, multiple logistic regression analysis with stepwise variable selection was performed controlling the ICU and patient characteristics mentioned above, as well as the year of infection using a commercial statistical package (Statistical Analysis System [SAS], Version 6.12, the SAS Institute Inc., Cary, NC, USA). Significance level was set at 0.05.

Results

Up to the end of June 2002 KISS had an overview of 505,487 patients from 274 ICUs observed during 6,966 months. The most frequent nosocomial infection was pneumonia with 6,888 cases observed, followed by urinary tract infections (4,691), primary BSI (2,357), and bronchitis (2,026).

A total of 3,101 nosocomial *S. aureus* infections were recorded, among them 1,851 of pneumonia (59.7%) and 378 of primary BSI (12.2%). The distribution of patients with *S. aureus* pneumonia and primary BSI in various risk groups can be found in table 1. In 825 (44.6%) cases of nosocomial pneumonia only one pathogen was identified, in 36.3% two microorganisms were identified, in 19.1% three or more microorganisms. Only one pathogen was identified in the majority of BSI cases (86.1%) followed by 10.7% with two microorganisms and 2.8% with three or more. The analysis considered all combinations of *S. aureus* with other pathogens. However, due to the identification of *Pseudomomas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and *Candida albicans* as mortality risk factors for pneumonia or BSI respectively in other studies [14–19] only the results for these four microorganisms are presented in table 1. 18.9% of *S. aureus* pneumonia and 25.1% of primary *S. aureus* BSI cases were due to MRSA.

59 of the 349 patients with MRSA pneumonia (16.9%) died and 105 of the 1,502 patients with MSSA pneumonia (7.0%). Accordingly, 16 of the 95 patients with primary MRSA BSI (16.8%) and 17 of the 283 patients with primary MSSA BSI died (6.0%).

For *S. aureus* pneumonia there was a significant mortality risk factor according to the results of the bivariate analysis when patients were treated in an interdisciplinary ICU, in an ICU at a hospital with more than 1,000 beds or in a teaching hospital (other than a university hospital). Treatment in a neurosurgical ICU or a university hos-

Table 1
Distribution of patients with *S. aureus* pneumonia and primary bloodstream infections (BSI) according to risk factors.

Risk factors		Pneumonia (n = 1,851) (%)	Primary BSI (n = 378) (%)
Type of intensive care unit	Interdisciplinary	41.8	45.5
	Surgical	36.7	34.4
	Medical	13.5	16.1
	Neurosurgical	7.9	3.2
	Pediatric	0.1	0.8
Size of hospital	< 400 beds	13.1	20.6
	400 – < 1,000 beds	31.4	26.2
	> 1,000 beds	55.5	53.2
Type of hospital	University affiliated	35.8	32.3
	Teaching hospital	53.1	54.4
	Other	11.0	13.3
Time before infection [a]	> median	45.3	48.4
Gender	Male	64.8	67.7
Age [b]	> median	48.1	48.9
Ventilation	Yes	91.6	No information
Central venous catheter	Yes	No information	96.6
Total parenteral nutrition	Yes	No information	41.3
Other pathogens in relevant specimens from the same patient	*P. aeruginosa*	7.5	1.3
	A. baumannii	3.5	0.5
	S. maltophilia	1.2	0.0
	C. albicans	10.5	1.0
Resistance	MRSA	18.9	25.1

[a] the median time up to infection was 6 days for pneumonia and 11 days for primary BSI;
[b] the median age was 62 for patients with pneumonia and 63 for those with primary BSI

pital appeared a protective factor. In addition, a significant difference was found for time before infection above a median of 6 days, age older than a median of 62 years, isolation of *S. maltophilia* in a relevant specimen from the same patient and when the *S. aureus* strain was methicillin resistant. For primary *S. aureus* BSI there was only a difference regarding methicillin resistance (Table 2).

Multivariate analysis identified the teaching hospitals other than university hospitals, patient age above the median, isolation of *S. maltophilia* from a relevant specimen from the same patient, and methicillin resistance as independent predictors of mortality. MRSA was the only independent predictor of mortality for patients with *S. aureus* primary BSI (Table 3).

Discussion

This study using national surveillance data is the largest individual study hitherto dealing with mortality from nosocomial *S. aureus* infections. Four factors were independently linked with death from nosocomial *S. aureus* pneumonia infection, one of them being resistance to methicillin. For nosocomial primary *S. aureus* BSI only MRSA was found to be significant.

Four other studies have also investigated the influence of methicillin resistance on the outcome of *S. aureus* pneumonia (Table 4). However, beside the study of *Rello* et al. [20], the present study is the only one demonstrating differences in outcome for MRSA and MSSA pneumonia. The study of *Ibelings* et al. [6] investigated a subset of patients in the EPIC study (European Prevalence of In-

Table 2
Distribution of deaths among patients with nosocomial primary bloodstream infection or pneumonia caused by *S. aureus*.

Risk factors		Pneumonia					Primary bloodstream infection (BSI)				
		Patient deaths among those with risk factor	%	Patient deaths among those without risk factor	%	P-value	Patient deaths among those with risk factor	%	Patient deaths among those without risk factor	%	P-value
Type of intensive care unit	Interdisciplinary	87/774	11.2	77/1,077	7.2	0.003	16/172	9.3	17/206	8.3	0.72
	Surgical	59/680	8.7	105/1,171	9.0	0.87	13/130	10.0	20/248	8.1	0.57
	Medical	17/249	6.8	147/1,602	9.2	0.28	2/61	3.3	31/317	9.8	0.14
	Neurosurgical	1/146	0.7	163/1,705	9.6	< 0.001	1/12	8.3	32/366	8.7	1.00
	Pediatric	0/2	0.0	164/1,849	8.9	1.00	1/3	33.3	32/375	8.5	0.24
Size of hospital	< 400 beds	12/157	7.6	152/1,694	9.0	0.66	5/51	9.8	28/327	8.6	0.79
	400 – < 1,000 beds	28/376	7.5	136/1,475	9.2	0.31	5/65	7.7	28/313	9.0	1.00
	> 1,000 beds	72/666	10.8	92/1,185	7.8	0.03	10/132	7.6	23/246	9.4	0.70
Type of hospital	University	17/456	3.7	147/1,395	10.5	< 0.001	5/85	5.9	28/293	9.6	0.38
	Teaching hospital[c]	89/676	13.2	75/1,175	6.4	< 0.001	14/143	9.8	19/235	8.1	0.58
	Other	9/140	6.4	155/1,711	9.1	0.35	3/35	8.6	30/343	8.8	1.00
Time up to infection [a]	> median	88/839	10.5	76/1,012	7.5	0.03	16/183	8.7	17/195	8.7	1.00
Gender	Male	98/1200	8.2	66/651	10.1	0.17	20/256	7.8	13/122	10.7	0.44
Age [b]	> median	110/890	12.4	54/961	5.6	< 0.001	20/185	10.8	13/193	6.7	0.20
Ventilation	Yes	148/1695	8.7	16/156	10.8	0.56	–	–	33/378	8.7	–
Central venous catheter	Yes	–	–	164/1,851	8.9	–	32/365	8.8	1/13	7.7	1.00
Total parenteral nutrition	Yes	–	–	164/1,851	8.9	–	15/156	9.6	18/222	8.1	0.71
Other pathogens in relevant specimens from the same patient	*P. aeruginosa*	16/138	11.6	148/1,713	8.6	0.27	1/5	20.0	34/378	9.0	0.38
	A. baumannii	5/65	7.7	159/1,786	8.9	1.00	0/2	0.0	35/381	9.2	1.00
	S. maltophilia	8/23	34.8	156/1,828	8.5	< 0.001	-	-	-	-	-
	C. albicans	21/194	10.8	143/1,657	8.6	0.288	1/4	25.0	34/379	9.0	0.32
Resistance	MRSA	59/349	16.9	105/1,502	7.0	< 0.001	16/95	16.8	17/283	6.0	0.003

[a] the median time before infection was 6 days for pneumonia and 11 days for primary BSI; [b] the median age was 62 for patients with pneumonia and 63 for those with primary BSI; [c] teaching hospitals other than university hospitals

Table 3
Odds ratios of multiple logistic regression analysis with stepwise variable selection and a 95% confidence interval for significant mortality risk factors.

Risk factors		Odds ratios for mortality (CI_{95})	
		Pneumonia	Primary BSI
Type of hospital	Teaching hospital (other than university hospital)	2.45 (1.53–4.05)	
Age	> median (62 years for pneumonia)	2.08 (1.35–3.26)	
Other pathogens in relevant specimens from the same patient	*S. maltophilia*	7.53 (2.46–22.5)	
Resistance	MRSA	2.62 (1.69–4.02)	3.84 (1.51–10.2)

fection in Intensive Care). This study was performed in 17 hospitals and the data shows enormous variations between different countries in the prevalence of MRSA infections as well as mortality. The third and fourth study included only 86 to 171 patients with *S. aureus* pneumonia, respectively, probably too few to achieve real statistical significance.

With the aim of assessing comparative mortality from *S. aureus* bacteremia whether due to MRSA or MSSA, many studies have been published in the last few years, certainly enough to do meta-analyses [3, 4]. Table 5, therefore, only summarizes the results of the two meta-analyses in question in combination with three other recent studies not included in one of the meta-analyses.

The authors of both meta-analyses underlined the fact that there was remarkable heterogeneity between the studies included. However, all in all, the results show relatively constantly that the risk of dying from *S. aureus* bacteremia is about double if MRSA is the pathogen rather than MSSA.

In addition to methicillin resistance, three other factors were identified as being significantly linked to mortality from nosocomial pneumonia. The identification of age as a significant risk factor is not surprising. The findings associated with ICU patients in teaching hospitals being at risk may possibly reflect the severe underlying diseases of the patients. The higher mortality of patients with *S. aureus* and *S. maltophilia* in a relevant specimen is not difficult to explain. *S. maltophilia* was also identified as a risk factor for mortality from nosocomial pneumonia in other studies, in particular when inadequate empiric antibiotic therapy was given [18, 21, 22].

Our analysis has, nevertheless, some limitations.

First, the variables entered into the database did not allow assessment of other important mortality risk factors. Only a minority of German ICUs, for instance, routinely

Table 4
Studies investigating the effect of methicillin resistance on the outcome of *S. aureus* pneumonia.

Reference	Study design	Patient group	Patients included (%)		Patient deaths		OR/RR (CI_{95})
			MRSA	MSSA	MRSA	MSSA	
Rello et al. 1994 [20]	Prospective cohort study	ICU	11	38	54.5	2.6	RR = 20.72 (2.78–154.35) (for mortality directly related to pneumonia)
Ibelings et al. 1998 [6]	International point prevalence study with 6-week follow-up period (EPIC) logistic regression analysis	ICU	112	144	33.3	29.1	NS
Gonzalez et al. 2000 [8]	Cohort study, stepwise logistic regression analysis	All	32	54	56.3	40.7	NS
Combes et al. 2004 [24]	Retrospective cohort study, multivariate logistic regression analysis	ICU	74	97	NA	NA	OR = 1.72 (0.73–4.05)
This study	National cohort study, multivariable analysis	ICU	349	1,502	16.9	7.0	OR = 2.62 (1.69–4.02)

NA: not available; NS: not significant

Table 5
Studies investigating the effect of methicillin resistance on the outcome of *S. aureus* bacteremia.

Reference	Study design	Patient group	Patients included (%)		Patient deaths		OR/RR (CI_{95})
			MRSA	MSSA	MRSA	MSSA	
Whitby et al. 2001 [3]	Meta-analysis of 9 studies	All	778	1,431	29	12	2.12 (1.76–2.57) (fixed effect method) 2.03 (1.55–2.65) (random effect method)
Cosgrove et al. 2003 [4]	Meta-analysis of 31 studies	All	1,360	2,603	Not given	Not given	1.93 (1.54–2.42) (random effect model)
Blot et al. 2002 [25]	Cohort study + multivariate survival analysis 2 case-control studies	ICU	47	38	53	18	1.93 (1.18–3.18) (hazard ratio)
Talon et al. 2002 [26]	Cohort study, multivariate analysis	All	30	69	43.3	20.3	2.97 (1.12–7.88)
Melzer et al. 2003 [27]	Cohort study, logistic regression analysis	All	382	433	11.8	5.1	1.72 (0.92–3.20)
This study	National cohort study, multivariable analysis	ICU	95	283	16.8	6.0	3.84 (1.51–10.2)

record severity of illness scores and so we were not able to take severity of illness scores into account. In general, device use can serve as a surrogate marker for the severity of illness; however, 91.6% of the patients were ventilated and 96.6% had central venous catheterization. Therefore only time before infection, age, gender, type and size of hospital and type of ICU could be used for assessing severity of illness. For primary BSI the necessity for total parenteral nutrition was also brought to bear on our interpretation (41.3% of patients). The factor "time before infection" may reflect severity of illness to a certain extent, but it can not really be regarded as an appropriate surrogate parameter. Therefore it remains open, if severely ill patients die with MRSA or because of MRSA.

Second, the diagnostic quality of microbiology laboratories is generally variable, though for *S. aureus* and methicillin resistance almost all laboratories apply standard procedures and carry out routine evaluation. Identification of *S. aureus* in blood culture shows beyond any doubt that a bloodstream infection is present, so that only careful exclusion of secondary BSI is necessary. This was investigated in a recent evaluation study with KISS, where a specificity of 99.8% was found in diagnosing nosocomial primary BSI according to CDC definitions [23]. In the course of the same study a specificity of 99.7% was found for nosocomial pneumonia diagnosis based on available findings. However, only a subgroup of ICUs routinely perform broncho-alveolar lavage if nosocomial pneumonia is suspected, while others use clinical criteria for diagnosing pneumonia together with identification of *S. aureus* from tracheal secretions. Only in 23% of cases was *S. aureus* identified from broncho-alveolar secretions or blood. Some uncertainty therefore persists as to whether any real cases of pneumonia were in fact recorded.

Third, no information was available on antibiotic use, so we were unable to ascertain the role of antibiotics on outcome. In order to take into account the influence of new antibiotics introduced during the study period on mortality, the data were accordingly adjusted for the year of infection.

Due to the above-mentioned limitations, this study does not prove that pneumonia and primary bloodstream infections from MRSA in ICUs are indeed associated with an increase in the risk of death. However the data at least suggest that methicillin resistance may be associated with death among persons in ICUs who acquire nosocomial *S. aureus* BSI or nosocomial *S. aureus* pneumonia. Thus, hospitals may be able to decrease the mortality rate in ICUs by implementing infection control measures that prevent the spread of MRSA.

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