Increased mortality associated with methicillin-resistant Staphylococcus aureus (MRSA) infection in the ICU: Results from the EPIC II study

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Summary: The attributable mortality associated with methicillin-resistant *S. aureus* (MRSA) infection is debated. In 999 ICU patients with *S. aureus* infection, MRSA infection was associated with an increased risk of ICU and hospital mortality compared to infection with methicillin-sensitive *S. aureus*.

Abstract

Background: Controversy continues regarding whether the presence of methicillin resistance increases mortality risk in *Staphylococcus aureus* infections. We assessed the role of methicillin resistance on survival of patients with *S. aureus* infection in the EPIC II study cohort.

Methods: The EPIC II point-prevalence study of infection in critically ill patients was performed on May 8, 2007. Demographic, physiological, bacteriological and therapeutic data were collected for 13,796 adult patients in 1,265 participating ICUs from 75 countries on the study day. ICU and hospital outcomes were recorded. We compared characteristics of patients with methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *S. aureus* infection. Co-morbidities, age, SAPS II score and MRSA/MSSA were entered into a multivariable model and odds ratios (OR)[95% CI] for ICU and hospital mortality rates were calculated.

Results: On the study day, 7,087 of the 13,796 patients (51%) were classified as infected. There were 494 patients with MRSA and 505 patients with MSSA infections. There were no significant differences between the two groups in use of mechanical ventilation or hemofiltration/hemodialysis. Cancer and chronic renal failure were more prevalent in MRSA than in MSSA patients. ICU mortality rates were 29.1% and 20.5%, respectively ($p<0.01$) and corresponding hospital mortality rates were 36.4% and 27.0% ($P<0.01$). Multivariable analyses of ICU and hospital mortality for MRSA infection showed an OR of 1.39[1.02-1.9], $P=0.04$ for ICU mortality and 1.37[1.03-1.83], $P=0.03$ for hospital mortality.

Conclusion: In ICU patients, MRSA infection is associated with an almost 40% increase in adjusted ICU and hospital mortality risk compared to MSSA.

Introduction

Staphylococcus aureus is a common cause of infection in intensive care patients [1], and in many cases, the *S. aureus* will be resistant to methicillin [1]. However, whether methicillin resistance increases mortality in patients with *S. aureus* infection remains controversial. Some investigations and meta-analyses have reported that methicillin resistance does increase the mortality risk [2-7], whereas other have been unable to demonstrate any difference in mortality between methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) *S. aureus* infections [8-15]. The conflicting results may be explained by differences in settings, sample sizes, case mix, strain virulence, minimum inhibitory concentrations (MIC), antibiotic choice, antibiotic dosage, and timing of appropriate antimicrobial therapy. The Extended Prevalence of Infection in the ICU (EPIC II) showed that half of all ICU patients on the study day were infected [16]. *S. aureus* was the most frequently isolated pathogen, present in 21% of positive isolates; 50% of the *S. aureus* cultures were methicillin resistant (MRSA) [16]. The purpose of this study was to assess the independent role of methicillin resistance on outcome in patients with *S. aureus* infection in the EPIC II study cohort.

Methods

The EPIC II one-day point prevalence study of infection in critically ill patients was performed on May 8, 2007 [16]. Demographic, physiological, bacteriological and therapeutic data were collected from 13,796 adult (>18 years) patients in 1,265 participating ICUs from 75 countries on the study day as previously described [16]. Local ethical committee approval at each participating center was expedited or waived due to the purely observational nature of the study. Infection was defined according to the criteria of the International Sepsis Forum [17] and classified by the attending physician. Microbiological analyses, including methicillin susceptibility testing, were performed locally.

Patients who had undergone surgery in the four weeks preceding admission were considered surgical admissions. Elective surgery was defined as surgery scheduled more than 24 hours in advance, and emergency surgery as that scheduled within 24 hours. Trauma admissions were defined as ICU admissions directly related to, or occurring as a complication of, a traumatic event in the 30 days preceding admission. All other admissions were considered medical. We did not differentiate between community-acquired, healthcare-acquired or ICU-acquired infections. Participating ICUs were asked to provide patient follow-up until hospital discharge or for 60 days (until July 9, 2007), and ICU and hospital outcomes were recorded.

For the purposes of this study, we selected the patients with positive *S. aureus* isolates.

Statistics

Statistical analyses were performed using PASW Statistics 18 for windows (SPSS Inc, Chicago, USA). The Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify if there were significant deviations from the normality assumption of continuous variables. Non-parametric tests of comparison were used for variables evaluated as not normally distributed. Difference testing between groups was performed using Student's t-test, Mann-Whitney test, Chi square test or Fisher exact test as appropriate. Multivariable logistic regression analyses with ICU or hospital mortality as the dependent variables were performed to determine risk factors for mortality in patients with *S. aureus* infection. Data are presented as median (interquartile range [IQR]), or number (%) as appropriate. All tests were two-tailed, and $P<.05$ was considered statistically significant.

Results

Basic characteristics of patients with infections in EPIC II

On the day of the study, 7,087 of 13,796 patients (51%) were classified as infected, and 70% of these had positive cultures: 47% of the positive isolates were Gram-positive. The five organisms most commonly isolated were *S. aureus* (20.5%), *Pseudomonas* species (19.9%), *Candida* spp (17.0%), *Escherichia coli* (16%), and *Klebsiella* spp (12.7%). Fifty per cent of the *S. aureus* isolates were methicillin resistant.

Characteristics of patients with MRSA vs. MSSA infections

The characteristics of patients with MRSA (n=494) vs. MSSA (n=505) infections are shown in Table 1. There were no differences in SAPS II and SOFA scores on admission between groups. Patients with MRSA were slightly older, and had longer ICU stays prior to the study date than those with MSSA (median [IQR] 10 [3-22] versus 7 [3-14], $P<0.001$). Patients with MSSA were more likely to be admitted from the emergency department, whereas patients with MRSA were more likely to be admitted from a hospital ward. Neurological disease was a more common reason for admission in patients with MSSA infection than in those with MRSA, whereas respiratory infection, digestive tract or liver disease were more frequent reasons in MRSA-infected patients. Cancer and chronic renal failure were more prevalent in MRSA than in MSSA patients. There were no differences in use of mechanical ventilation, hemofiltration or hemodialysis between the groups.

Site of infection

The most common site of infection was the respiratory system followed by the bloodstream and renal/urinary tract (Table 2). MRSA isolates were more common than MSSA isolates in patients with abdominal (16.6% vs 7.7%, $P<0.001$) and renal/urinary tract (16.6% vs 11.5%, p=0.02) infections, and less common in patients with central nervous system infections (1.8% vs 5.1%, $P<0.01$).

Antibiotic therapy

Almost all (96%) patients were treated with antibiotics. The distribution of the antimicrobial drugs used on the study day is shown in Table 3. On the study day, 81.4% of MRSA infected patients received at least one antibiotic usually active against MRSA and 87.9% of MSSA infected patients received at least one antibiotic usually active against MSSA.

Factors associated with ICU and hospital mortality

The ICU mortality rates among patients with MRSA and MSSA infections were 29.1% and 20.5%, respectively ($P<0.01$). Corresponding hospital mortality rates were 36.4% and 27%, respectively ($P<0.01$), with corresponding post-ICU proportional mortality rates of 20.1% and 24.0%, respectively ($P=0.42$). The ICU and hospital mortality rates among western European patients with MRSA and MSSA infections were 29.4% vs 16.7% ($p<0.001$) and 39.3% vs 22.8% ($P<0.001$), respectively. Corresponding numbers for other geographic areas were too small to yield any conclusive results.

Multivariable logistic regression analysis showed that age, admission for medical reasons, co-morbid cirrhosis, and MRSA were independently associated with a higher ICU mortality risk (Table 4A). Age, medical admission, chronic renal failure, comorbid cirrhosis, and MRSA were independently associated with a higher hospital mortality risk (Table 4B). MRSA infection was independently associated with a greater risk of ICU (adjusted odds ratio [OR] 1.39, 95% confidence interval [CI] 1.02-1.9, $P=0.04$) and hospital (adjusted OR 1.37, 95% CI 1.03-1.83, $P=0.03$) mortality.

Discussion

The main findings of this study are that, in ICU patients, MRSA infections are more frequent

in patients with underlying co-morbid conditions, such as cancer and chronic renal failure, and are associated with a 40% greater adjusted ICU and hospital mortality risk compared to MSSA infections. These findings are in agreement with several other studies [6, 7] and meta-analyses [2, 4]. However, Kang et al. reported that MRSA infection was only associated with increased mortality in patients with cancer or renal disease and in those with *S. aureus* bacteremia, but not in their total cohort of 4974 patients with *S. aureus* infection [7]. Unlike our study, DeRyke et al. reported no significant difference in attributable mortality between patients with MSSA infection and those with MRSA infection, although this study was limited by the small sample size. In a recent study on healthcare-associated *S. aureus* pneumonia, three of four patients were admitted to the ICU, but there were no significant differences between MRSA and MSSA patients in terms of mortality (17/59 [29%] vs. 19/95 [20%]); again the sample size was very small in this study [14]. The heterogeneity of the patient populations included in the different studies may also explain some of the apparent discrepancies in results [8, 9, 11-14] .

We wanted to assess the burden of MRSA in a critically ill patient population. The rate of methicillin resistance in the *S. aureus* isolated in this study was 50%, similar to the 42% reported in the large Pan-American and European Sentry surveillance study performed in 2005-2006 [18]. The similarity of these results may be explained by the fact that three fourths of the patients included in our study with *S. aureus* infection were from Europe and America and both studies included community and nosocomial infections. Indeed, one limitation of this study is that the protocol did not distinguish between community-acquired and health-care acquired infections. However, admission from the emergency room was more common among patients with MSSA whereas admission from a hospital ward was more common among patients with MRSA, suggesting that hospital-acquired infections were likely more prevalent among patients with MRSA. This is also supported by the significantly longer

median ICU stay prior to the study day for MRSA-infected patients vs. MSSA patients. This observation is also in agreement with a study on Canadian ICU infections performed in 2005 and 2006 demonstrating that 90.7% of *S. aureus* infections were due to healthcare-associated MRSA strains and 9.3% were community-associated MRSA strains [19]. MRSA rates are known to vary over time in individual units and hospitals, emphasizing the importance of conducting regular surveillance at local, regional and national levels with updated information on MRSA infections.

In our multivariable analysis we were able to demonstrate that age, medical admission, chronic renal failure, cirrhosis and MRSA were independently associated with a higher risk of hospital mortality, while severity of illness, as evaluated by the SAPS II or SOFA scores on admission, was not. Similar findings were also reported by Blot et al. in a smaller number of critically ill patients with bacteremia caused by *S. aureus* where acute renal failure, length of mechanical ventilation, age and methicillin resistance were independently associated with mortality [3].

The strength of our study is the large sample size. The study was not designed to evaluate potential mechanisms at the bacterial level, but to discover global factors associated with the high mortality of MRSA infection. Increased minimum inhibitory concentrations (MIC) to vancomycin [20-22], delay in appropriate antimicrobial therapy [23-28], inferior bactericidal effect of vancomycin and sub-optimal antibiotic dosage [29] are factors and mechanisms that may be involved in the increased mortality of MRSA infections, but that we were unable to assess. Another limitation of this point prevalence study is that antibiotic treatment was only noted on the day of the study and, therefore, data for full therapeutic comparisons are not available

In conclusion, we have demonstrated that in addition to age, admission for medical reasons and cirrhosis, methicillin resistance was independently associated with higher

ICU and hospital mortality rates among critically ill patients with *S. aureus* infections. Active surveillance for MRSA [30] and standard infection prevention measures must be encouraged in this high-risk patient group.

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Table 1. Basic characteristics of patients with MRSA and MSSA infections in the EPIC II Study

		MRSA n = 494	**MSSA n = 505**	***P*-value**
Age, median (IQR), y		63.5 [50-74]	62 [44-72]	0.01
Male		322 (65.3)	343 (67.9)	0.38
SAPS II, median (IQR)		37 [27-49]	37 [27-49]	0.87
SOFA, median (IQR)		6 [4-10]	7 [4-10]	0.64
Days on ICU prior to study date, median (IQR)		10 [3-22]	7 [3-14]	<0.001
Type of admission				0.08
	Surgical: Elective	70 (14.2)	60 (11.9)	
	Medical	151 (30.6)	148 (29.4)	
	Surgical: Emergency	226 (45.8)	223 (44.2)	
	Trauma	46 (9.3)	73 (14.5)	
Admission Source				<0.01
	Operating room /recovery	88 (17.8)	87 (17.3)	
	Emergency department/ambulance	116 (23.5)	168 (33.5)	
	Hospital ward	181 (36.7)	130 (25.9)	
	Other hospital	97 (19.7)	101 (20.1)	
	Other	11 (2.2)	16 (3.2)	
Reason for admission				<0.001
	Surveillance/Monitoring	49 (9.9)	37 (7.3)	
	Neurological	55 (11.1)	118 (23.4)	
	Respiratory	165 (33.4)	122 (24.2)	
	Cardiovascular	101 (20.4)	114 (22.6)	
	Renal	12 (2.4)	10 (2)	
	Digestive/Liver	52 (10.5)	30 (5.9)	
	Trauma	48 (9.7)	63 (12.5)	
	Others*	12 (2.4)	11 (2.2)	
Co-morbidity	Chronic obstructive pulmonary disease	97 (19.6)	91 (18)	0.51
	Cancer	80 (16.2)	53 (10.5)	<0.01
	Hematologic cancer	11 (2.2)	11 (2.2)	0.96
	Insulin-dependent diabetes mellitus	72 (14.6)	66 (13.1)	0.49
	Heart failure (NYHA III-IV))	68 (13.8)	53 (10.5)	0.11
	Chronic renal failure	71 (14.4)	51 (10.1)	0.04
	HIV	3 (0.6)	2 (0.4)	0.64
	Cirrhosis	29 (5.9)	20 (4)	0.16
	Immunosuppression	22 (4.5)	20 (4)	0.34
Number of comorbidties				<0.01
	None	194 (39.3)	249 (49.3)	
	1	158 (32)	160 (31.7)	
	2	94 (19)	60 (11.9)	
	3	36 (7.3)	28 (5.5)	
	>3	12 (2.4)	8 (1.6)	
Mechanical ventilation		341 (69)	353 (70.2)	0.69
Hemofiltration/Hemodialysis		67 (13.6)	61 (12.1)	0.5
Antibiotic treatment		475 (96.2)	485 (96)	0.79

Abbreviations: SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; HIV, Human Immunodeficiency Virus; NYHA III-IV, New York Heart Association class III-IV;

Table 2. Site of infection

	MRSA	**MSSA**	***P*-value**
Site of infection	n (%)	n (%)	
Respiratory tract	364 (73.7)	346 (68.5)	0.07
Abdominal	82 (16.6)	39 (7.7)	<0.001
Bloodstream	122 (24.7)	120 (23.8)	0.73
Renal/urinary tract	82 (16.6)	58 (11.5)	0.02
Skin	63 (12.8)	51 (10.1)	0.19
Catheter-related	33 (6.7)	31 (6.1)	0.73
CNS	9 (1.8)	26 (5.1)	<0.01
Others	63 (12.8)	76 (15)	0.29

Table 3. Antibiotic therapy on the study day

	MRSA	**MSSA**	***P*-value**
Cephalosporins	63 (12.8)	127 (25.1)	<0.001
Penicillins	99 (20)	253 (50.1)	<0.001
Other beta-lactams	145 (29.4)	84 (16.6)	<0.001
Aminoglycoside	72 (14.6)	58 (11.5)	0.14
Quinolone	72 (14.6)	89 (17.6)	0.19
Glycopeptides	321 (65)	109 (21.6)	<0.001
Macrolides	15 (3)	28 (5.5)	0.05
Metronidazole	32 (6.5)	28 (5.5)	0.54
Cotrimoxazole	10 (2)	7 (1.4)	0.44
Oxazolidinone	74 (15)	16 (3.2)	<0.001
Daptomycin	5 (1)	0 (0)	0.03
Tigecycline	12 (2.4)	3 (0.6)	0.02
Antifungal	92 (18.6)	58 (11.5)	<0.01
Antiviral	4 (0.8)	7 (1.4)	0.38
Other	51 (10.3)	54 (10.7)	0.85

Table 4A. Multivariable logistic regression analysis with ICU mortality as dependent variable

Variable	**OR (95% CI)**	***P*-value**
Age, per year	1.02 (1.01-1.03)	<0.001
Type of admission		
Elective surgery	Reference	
Medical	1.86 (1.09-3.17)	0.02
Emergency surgery	1.02 (0.62-1.66)	0.95
Trauma	0.99 (0.46-2.11)	0.97
Source of Admission		
Operating room /recovery	Reference	
Emergency department/ambulance	0.91 (0.32-2.61)	0.86
Hospital floor	0.54 (0.32-0.92)	0.02
Other hospital	1.03 (0.65-1.65)	0.9
Other	0.93 (0.55-1.57)	0.78
Chronic renal failure	1.47 (0.95-2.25)	0.08
Cirrhosis	2.65 (1.42-4.94)	<0.01
MRSA	**1.39 (1.02-1.9)**	0.04

Table 4B. Multivariable logistic regression analysis with hospital mortality as dependent variable

Variable	**OR (95% CI)**	***P*-value**
Age, per year	1.02 (1.02-1.03)	<0.001
Type of admission		
Elective surgery	Reference	
Medical	1.95 (1.2-3.15)	<0.01
Emergency surgery	1.31 (0.82-2.08)	0.25
Trauma	1.02 (0.51-2.03)	0.96
Cancer	1.47 (0.97-2.22)	0.07
Chronic renal failure	1.98 (1.31-2.98)	<0.01
Cirrhosis	2.82 (1.52-5.22)	<0.001
MRSA	**1.37 (1.03-1.83)**	0.03