Knowing prior methicillin-resistant *Staphylococcus aureus* (MRSA) infection or colonization status increases the empirical use of glycopeptides in MRSA bacteraemia and may decrease mortality

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Abstract

To compare the management and outcome of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in patients known to be MRSA-colonized/infected (C-patients) with the management and outcome in those not known to be colonized/infected (NC-patients), we conducted a 10-year retrospective review of MRSA bacteraemia in an adult tertiary hospital. Clinical data were obtained by chart review, and mortality data from linked databases. Prior MRSA colonization/infection status was available to treating clinicians at the time of the bacteraemia as a 'Micro-Alert' tag on the patient's labels, in medical charts, and in electronic information systems. C-patients accounted for 35.4% of all MRSA bacteraemia episodes. C-patients were more likely to be indigenous, to be diabetic, or to have a history of previous *S. aureus* infection. Markers of illness severity (Simplified Acute Physiology Score (SAPS)-II, need for admission to the intensive-care unit, length of stay, and metastatic seeding) were similar in both groups. Empirical therapy included a glycopeptide in 49.3% of C-patients vs. 18.9% of NC-patients ($p < 0.01$), and contained an antibiotic to which the MRSA isolate tested susceptible *in vitro* in 56.7% of C-patients vs. 45.1% of NC-patients (p 0.13). All-cause 7-day and 30-day mortality were 7.5% vs. 18.9% (p 0.04), and 22.4% vs. 31.1% (p 0.20), in the C-patient and NC-patient groups, respectively. Knowing MRSA colonization status was significantly associated with lower 30-day mortality in Cox regression analysis ($p < 0.01$). These data suggest that mortality from MRSA bacteraemia is lower in C-patients, which may reflect the earlier use of glycopeptides. The low use of empirical glycopeptides in septic patients known to be previously MRSA-colonized/infected may represent a missed opportunity for infection control to positively impact on clinical management.

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Introduction

Staphylococcus aureus bacteraemia is associated with significant morbidity and mortality [1,2]. Meta-analyses have shown that patients with methicillin-resistant *S. aureus* (MRSA) bacteraemia are more likely to have an unfavourable outcome than those with methicillin-susceptible *S. aureus* bacteraemia [3,4]. This difference may be partly attributable to the administration

of antibiotics without *in vitro* activity against MRSA while susceptibility results are pending; inappropriate therapy given within the first 45–8 h after the blood culture was taken has been shown to be an independent predictor of mortality in MRSA bacteraemia [5,6].

S. aureus colonization often precedes invasive infection [7]. A study on the long-term risk of MRSA colonization has shown that 29% of patients with previous MRSA colonization develop an infection, occurring on average 102 days after the initial isolation of MRSA [8]. Although awareness of prior MRSA colonization status could impact on patient treatment for invasive MRSA infection, data on MRSA colonization status are primarily collated and used for infection control purposes, and are not always available to the treating physician when a patient presents to hospital.

In Western Australia, demographic data, together with outpatient and inpatient visits of patients attending public hospitals, are recorded in a common database. Known carriers of antibiotic-resistant organisms are recorded in this database (Micro-Alert), which helps infection control staff to implement appropriate measures to prevent MRSA transmission.

In this study, we aimed to determine whether information on prior MRSA infection/colonization status (provided by the Micro-Alert system and available to clinicians) impacted on the management and outcome of patients with MRSA bacteraemia.

Materials and Methods

Case ascertainment and clinical data collection

We conducted a 10-year retrospective review of all episodes of MRSA bacteraemia that occurred in a 955-bed adult teaching hospital between June 1997 and June 2007, as previously described [1]. Episodes were identified by use of the Microbiology Department's database. Demographic and clinical data were obtained from chart review. Severity of illness at the time of the bacteraemia was evaluated according to the Simplified Acute Physiology Score (SAPS)-II [9], intensive-care unit (ICU) admission, duration of fever, bacteraemia with positive blood culture for >24 h, and the presence of infective endocarditis (as defined in [10]) or metastatic infection. Additionally, length of hospital stay and time from the first positive blood culture to discharge were determined. All-cause mortality at 7 days and 30 days following the day of MRSA bacteraemia were determined from clinical information systems, which are data-linked to the Western Australian Registry of Deaths.

Definitions

An episode of MRSA bacteraemia was defined as culture of the organism in one or more sets of blood cultures. If a patient had more than one episode of MRSA bacteraemia, only the first episode was included in the analysis.

Colonization status

In our centre, systematic MRSA screening is performed only on patients at high risk of importing MRSA from another institution, or those in whom MRSA infection is particularly troublesome, such as those undergoing cardiothoracic/orthopaedic surgery or patients in the bone marrow transplant unit or ICU. MRSA screening is performed with a nasal swab and a swab of any wound, ulcer, or skin lesion.

Since 1997, all patients and healthcare workers colonized or infected with MRSA have been notified to the Western Australian Department of Health, and MRSA isolates have been referred to the Australian Collaborating Centre for Enterococcus and Staphylococcus Species (ACCESS) Typing and Research. A Micro-Alert tag is then electronically added to the patient identification label, which is used on subsequent public hospital admissions. The Micro-Alert label remains as long as the patient is not successfully decolonized with documentation of two negative sets of swabs (nose, throat, and perineum) in the absence of ongoing wounds, invasive devices, and/or antimicrobial therapy. Decolonization is performed on patients with MRSA colonization prior to elective orthopaedic or cardiovascular surgery, and on patients transferred to our rehabilitation facility, to avoid transmission via shared physiotherapy equipment.

Episodes of MRSA bacteraemia were considered as occurring in known colonized patients (C-patients) if patients were 'Micro-Alerted' at least 2 days prior to the positive blood culture. All other patients were considered as not known to be colonized (NC-patients).

S. aureus identification and susceptibility testing were performed as previously described [1].

Antimicrobial therapy

Details of antimicrobial therapy administered were obtained from medication charts. Empirical antimicrobial therapy (i.e. therapy administered prior to the susceptibility results being available) was considered to be 'active' if the MRSA isolated was susceptible *in vitro* to one or more of the agents that were administered. This included regimens that were composed of an agent or agents not generally recommended for the treatment of MRSA bacteraemia at our institution (e.g. ciprofloxacin, gentamicin, doxycycline, erythromycin, clindamycin, and azithromycin). The absence of a routine D-test for the detection of inducible resistance to clindamycin did not have any impact, as no patients were treated with clindamycin as the sole active agent. Empirical therapy was considered to

be 'inactive' if it was composed of an agent or agents without *in vitro* anti-MRSA activity.

Statistical methods

Means were compared by use of Student's *t*-test or the Mann–Whitney non-parametric test when appropriate. Percentages were compared by use of Pearson's χ^2-test or Fisher's exact test. Groups were compared by means of the log-rank test. A p-value of <0.05 was considered to be significant. A series of univariate logistic regression models with 30-day mortality as the dependent variable were used to identify potential predictors of mortality risk. The variables chosen were those with at least 90% non-missing observations and a univariate p -value of <0.1. The variables chosen for inclusion on the basis of univariate analysis were nosocomial infection, SAPS-II, metastatic seeding, 'active' empirical treatment, age, dialysis, and Aboriginal heritage. Because of the relatively low number of episodes, the variables entered into the Cox regression model were limited to the most significant. The validity of the proportional hazards model was determined with the phtest based on Schoenfeld residuals. All statistical analyses were performed in SPSS 18.0 for Windows (SPSS, Chicago, IL, USA) and STATA (Version 12; StataCorp LP, College Station, TX, USA).

This study was approved by our institution's ethics committee.

Results

Two hundred and four episodes of MRSA bacteraemia in 194 patients were identified over the study period. Charts were obtainable for 189 patients (97.4%) with 197 episodes of bacteraemia (96.6%). Eight episodes of bacteraemia were removed because they occurred in patients already in the database. All further analyses refer to these 189 episodes. Sixty-seven episodes of MRSA bacteraemia (35.4%) occurred in C-patients, and 122 (64.6%) in NC-patients.

Demographics and risk factors

Demographic data and risk factors are shown in Table 1. Diabetes and dialysis were more frequent in the C-patient group than in the NC-patient group (respectively: 32/67 (47.8%) vs. 33/122 (27.0%), p <0.01; and 16/67 (23.9%) vs. 9/122 (7.4%), p <0.01). Aboriginal/Torres Strait islander ethnicity was also more frequent in the C-patient group (19/67 (28.4%) vs. 17/122 (3.9%), p 0.01). As expected, hospitalization/outpatient clinic attendance in the past year and a history of previous invasive *S. aureus* infection were also more frequent in the C-patient group (Table 1).

TABLE 1. Demographics, risk factors and source of bacteraemia

	Known colonization (C-patients)	No known colonization (NC-patients)	p
No. (%)	67 (35.4)	122 (63.1)	
Male, no. (%)	35 (52.2)	77 (68.8)	0.15
Median age in years (range)	62 (12–95)	68.5 (16–96)	0.27
Aboriginal/Torres Strait islander, no. (%)	19 (28.4)	17 (13.9)	**0.02**
Diabetes, no. (%)	32 (47.8)	33 (27.0)	**<0.01**
Intravenous drug use, no. (%)	0	4 (3.3)	0.13
Solid or haematological malignancy, no. (%)	13 (19.4)	26 (21.3)	0.76
Immunosuppressive treatment, no. (%)	5 (7.53)	14 (11.5)	0.38
Previous invasive *Staphylococcus aureus* infection, no. (%)	21 (31.3)	9 (7.4)	**<0.01**
Dermatological condition, no. (%)	5 (7.5)	4 (3.3)	0.20
Hospitalization/clinic in past year, no. (%)	49 (73.1)	58 (47.5)	**<0.01**
Residence in long-term-healthcare facility, no. (%)	17 (25.4)	31 (25.4)	0.99
Human immunodeficiency virus infection, no. (%)	1 (1.5)	1 (0.8)	0.67
Dialysis, no. (%)	16 (23.9)	9 (7.4)	**<0.01**
Primary bacteraemia[a], no. (%)	7 (10.4)	30 (26.4)	**0.02**
Skin/soft tissue infection, no. (%)	15 (22.4)	19 (15.6)	0.24
Intravascular catheter, no. (%)	18 (26.9)	31 (25.4)	0.83
Bone/joint infection, no. (%)	10 (14.9)	11 (9.0)	0.22
Respiratory tract infection, no. (%)	4 (6.0)	17 (13.9)	0.10
Digestive tract infection, no. (%)	3 (4.5)	1 (0.8)	0.10
Endovascular infection, no. (%)	4 (6.0)	5 (4.1)	0.56
Intravenous drug use, no. (%)	0	1 (0.8)	0.46
Urinary tract infection, no. (%)	2 (3.0)	2 (1.6)	0.54
Surgical site infection, no. (%)	4 (6.0)	5 (4.1)	0.56

[a]No source identified.
The values are in bold to highlight that they are statistically significant.

Source of bacteraemia

When identified, the source of MRSA bacteraemia was similar between C-patients and NC-patients, with a predominance of catheter-related bacteraemia, followed by skin/soft tissue, bones/joints and the respiratory tract as the clinical source of the bacteraemia. No source for the bacteraemia was identified in seven of 67 (10.4%) C-patients, and in 30 of 122 (26.4%) NC-patients (p 0.02) (Table 1).

Severity of infection

SAPS-II was statistically not different between C-patients and NC-patients (median 37 (range 12–77) vs. 41 (range 14–84), p 0.08). There were no significant differences between the two groups regarding ICU admission (8/67 (11.9%) vs. 13/122 (10.7%), p 0.79), length of stay (median 21 days (range 0–137 days) vs. 21 days (range 0–209 days), p 0.79, in C-patients and NC-patients, respectively) or the percentage of patients with positive blood culture for >24 h (15/28 (53.6%) vs. 31/58 (53.4%), p 0.99). Furthermore, the duration of fever (2 days (range 0–19 days) vs. 2 days (range 0–33 days), p 0.32), the presence of endocarditis (2/67 (3.0%) vs. 8/122 (6.6%), p 0.29) and the presence of metastatic seeding (7/67 (10.4%) vs. 21/122 (17.2%), p 0.21) were similar between C-patients and NC-patients.

Management

Initial empirical antimicrobial therapy was 'active' in 38 of 67 (56.7%) C-patients and 55 of 122 (45.1%) NC-patients (p 0.13) (Table 2). Empirical therapy included a glycopeptide in 33 of 67 (49.3%) C-patients and 23 of 122 (18.9%) NC-patients (p <0.01). The time between arrival of the blood culture in the laboratory and the time of the first dose of glycopeptide was significantly shorter in C-patients than in NC-patients (1 day (range −13–5 days) vs. 2 days (range −1–12 days), respectively, p <0.01). Definitive antimicrobial therapy included a glycopeptide in all cases, and the median duration of therapy was 13 days (range 0–217 days) in C-patients, and 14 days (range 0–288 days) in NC-patients (p 0.09).

Outcome

The overall 7-day mortality rate was five of 67 (7.5%) in C-patient episodes, and 23 of 122 (18.9%) in NC-patient episodes (OR 0.35, 95% CI 0.13–0.96, p 0.04). At 30 days, the all-cause mortality rate reached 15 of 67 (22.4%) and 38 of 122 (31.1%), respectively (OR 0.64, 95% CI 0.32–1.27, p 0.20). Cox regression showed a 60% reduction in mortality in C-patient episodes (risk difference −0.58, p <0.01) after adjustment for SAPS-II, aboriginality, and whether active therapy was given (Table 3).

Patients who received active empirical therapy had a lower 7-day mortality rate than those whose initial empirical therapy was not active (9.7% vs. 19.8%, OR 0.43, 95% CI 0.19–1.0, p 0.05). The difference was more marked at 30 days (19.4% vs. 36.5%, OR 0.42, 95% CI 0.22–0.81, p 0.01).

Discussion

This study shows that over one-third of patients with MRSA bacteraemia are known to be colonized with this pathogen when empirical therapy is initiated. Similar findings have been reported previously: 75 of 287 (26.1%) patients with MRSA bacteraemia had a documented history of MRSA colonization or infection [11].

Less than half of C-patients received a glycopeptide as part of their empirical therapy in this study. There are several possible explanations for this. First, the Micro-Alert tag on the patient's identification label is small, and clinicians are not routinely educated as to the meaning of the Micro-Alert tag. Indeed, this system was implemented for infection control purposes, and was not designed to assist clinicians in patient management. Second, glycopeptide use is heavily restricted at our institution, and clinicians require pre-approval from a microbiologist/infectious disease physician, which could have further limited glycopeptide use.

This study showed that C-patients had a lower 7-day all-cause mortality rate than NC-patients. Furthermore, knowing that a patient was colonized remained a significant protective variable in our Cox regression analysis. As C-patients were more likely than NC-patients to be empirically treated with an antibiotic against which the isolate tested susceptible *in vitro*, we postulate that this difference in outcome may be related to the difference in the antimicrobial therapy. These results add to the growing evidence that, in the septic patient, active empirical therapy is associated with a lower mortality rate than therapy without *in vitro* activity against the isolated pathogen: Lodise *et al.* demonstrated that *S. aureus* bacteraemia-attributable mortality was increased when active therapy was delayed beyond 45 h after the blood culture was taken [5]. Similar results have been published from the USA [12] and Spain [13]. However, others have failed to demonstrate a benefit of early active therapy [14,15]. These conflicting results may be attributable to antibiotics other than glycopeptides not being considered as appropriate antimicrobial therapy, despite having *in vitro* activity [15], or an excessively long period (2 days) being considered to be appropriate for the initiation of active therapy [5,14].

TABLE 2. Initial 'active' empirical antimicrobial therapy

Antibiotic	Number of episodes	Number (%) of episodes in which this antibiotic was the single 'active' agent
Known to be colonized (*n* = 38)		
Aminoglycoside	9	4 (44.4)[a]
Glycopeptide	33	28 (84.8)
Quinolone	2	0 (0)
Not known to be colonized (*n* = 55)		
Aminoglycoside	27	22 (81.5)[a]
Clindamycin	1	0 (0)
Doxycycline	1	0 (0)
Glycopeptide	23	20 (86.9)
Macrolide	4	3 (75)
Quinolone	4	2 (50)
Rifampicin	2	0 (0)
Trimethoprim	1	0 (0)

[a]p 0.003 for comparison between episodes where patients are known to be colonized and those where patients are not known to be colonized.

TABLE 3. Cox regression analysis

Independent variables	Hazard ratio	$LCI_{95\%}$	$UCI_{95\%}$	p
Micro-Alert (yes)	0.58	0.37	0.91	0.02
SAPS-II (standardized)	6.43	1.60	25.9	0.01
Aboriginal (yes vs. no)	0.40	0.22	0.74	<0.014
Effective treatment given, SAPS-II (standardized)	0.26	0.07	1.00	0.05

$LCI_{95\%}$, Lower Confidence Interval; SAPS, Simplified Acute Physiology Score; $UCI_{95\%}$, Upper Confidence Interval.
The model shows a 60% reduction in risk of death for C-patients (risk difference −0.58, p 0.006) after adjustment for SAPS-II, Aboriginality, and whether an effective therapy was given. There is an interaction between SAPS-II and effective therapy that is incorporated in the adjustment.

An alternative explanation for the lower mortality rate among C-patients could be the acquisition of protective immunity to *S. aureus*. However, despite the generation of specific antibodies after invasive infection, it has not been established that this immune response results in protection against re-infection [16]. Furthermore, capsular polysaccharide vaccines, as well as virulence factor-based vaccines and iron-binding protein-based vaccines, have so far failed to demonstrate any reduction in invasive staphylococcal infection [16]. In fact, for the latter, a trial had to be prematurely stopped because of increased mortality among those who did develop an invasive staphylococcal infection after immunization, without any reduction of its incidence [17]. Nevertheless, cell-mediated immunity may play a role, as patients with defects in T-cell immunity, such as those with human immunodeficiency virus infection or Job's syndrome, experience recurrent and often more severe cutaneous infections [16].

This study has important limitations. First, data were collected retrospectively, and possible non-identified confounders may have skewed the data. Second, C-patients are demographically different from NC-patients. Indeed, we have found that patients known to be colonized are more likely to be diabetic, to be on dialysis, to be aboriginal/Torres Strait islanders, or to have had a hospitalization/outpatient clinic visit in the past 12 months. However, if these variables did affect our results, they should have increased mortality in the C-patients, as diabetic or dialysis patients are known to have increased mortality, and aboriginal/Torres Strait islanders have a lower life-expectancy [18,19]. Despite these demographic differences, it is noteworthy that the severity of the infections as measured by SAPS-II, the need for ICU admission, the duration of fever, or the proportion of patients with positive repeat blood cultures, was similar between groups.

Universal MRSA screening on admission has been advocated by some experts [20], and is now compulsory in some US hospitals [21]. However, conflicting results have been reported on the utility of this strategy. In a prospective cross-over cohort study, Harbarth *et al.* failed to demonstrate any reduction in nosocomial MRSA infections, possibly because of the low baseline MRSA infection rate [22]. However, Robicsek *et al.* showed, in an observational study over three consecutive periods, that the introduction of universal MRSA screening on admission was associated with a significant decrease in the prevalence of MRSA infections [23]. These studies were aimed at assessing the usefulness of universal MRSA screening for prevention of MRSA transmission, but they did not investigate the impact of MRSA screening on antimicrobial prescribing. Presurgical screening has been effectively used to identify MRSA colonization, to allow either decolonization prior to surgery or adjustment of perioperative antimicrobial prophylaxis [24]. Our study demonstrates that the lack of clinician awareness regarding the significance of the Micro-alert tag may be a correctable missed opportunity to support appropriate decision-making in antimicrobial prescribing in septic patients. However, this strategy needs prospective validation before it can be recommended to other hospitals, as the systematic use of glycopeptides in patients known to be colonized with MRSA but who ultimately do not have an infection caused by MRSA may lead to unnecessary toxicity and an increase in resistance. Whether a similar process may be equally effective for other pathogens, such as vancomycin-resistant enterococci and multiresistant Gram-negative bacilli, needs to be determined. The use of a 'microbiological passport', similar to the biological passport of some professional athletes, containing the results of previous colonization or infection with multiresistant organisms, could be an attractive strategy, and may help not only in reducing the transmission of these pathogens, but also in improving the initial management and outcome of septic patients.

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Transparency Declaration

The authors declare no conflict of interests.

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