Case–control study to identify factors associated with mortality among patients with methicillin-resistant Staphylococcus aureus bacteraemia

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia is associated with increased mortality. Delay in appropriate antimicrobial therapy (DAAT) is an important risk factor for death, although confounding between carriage of MRSA and DAAT has not been resolved. We studied the association of risk factors with mortality and searched for specific populations vulnerable to DAAT. We conducted a case–control study comparing patients with MRSA bacteraemia who died during hospitalization (cases) with patients with MRSA bacteraemia who survived (controls) in three medical centres in two states. Patients were identified using computerized hospital databases for the years 2001–2005. Medical records were retrieved and various epidemiological data extracted. Bivariate and multivariate logistic regression analyses were performed. Overall, 388 patients with MRSA bacteraemia were included, 164 cases and 224 controls. According to bivariate analyses, cases were significantly more likely than controls to (i) be older (>65 years), (ii) have transferred from an institution, (iii) have stayed in an ICU, (iv) have had more invasive devices, (v) have a poorer prognosis on admission, (vi) have higher disease severity at the time of bacteraemia, and (vii) have a DAAT of ≥2 days. Upon multivariate analysis, among patients >65 years, DAAT was significantly associated with increased mortality (p 0.04). Furthermore, patients >65 years with severe sepsis were much more likely to experience DAAT (p 0.02). In elderly patients with MRSA bacteraemia, DAAT is associated with increased mortality. Moreover, advanced age is a predictor for DAAT. These significant epidemiological associations mandate early coverage of MRSA in septic elderly patients.

Keywords: Bacteraemia, case–control, delay therapy, methicillin, MRSA, risk factors, sepsis, Staphylococcus

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) first emerged in the 1960s, and since then its incidence has risen continually worldwide [1–5]. In recent years, a large increase has been observed among outpatients. It reflects the spread of nosocomial strains outside of the hospital settings and the emergence of novel community-acquired strains, causing infections mostly in otherwise healthy people without any contact with a healthcare institution [1–4,6]. According to recent data from the National Healthcare Safety Network, the pooled MRSA proportion among all S. aureus clinical isolates is 56.2% [7].

Infections caused by MRSA are associated with adverse outcomes compared with methicillin-sensitive Staphylococcus aureus (MSSA) infections [3]. This may be related to: (i) differences in vulnerability of the affected populations [8–14]; (ii) differences in strain virulence; (iii) differences in efficacy of treatment (various studies suggest that vancomycin, the most commonly prescribed agent for MRSA infections, is less effective than semisynthetic penicillins [15]); and (iv) differences in delay of appropriate antimicrobial therapy (DAAT), which could lead to increased mortality, length of hospitalization, and costs [16]. Patients with MRSA infection have been shown to experience DAAT more often than those with MSSA infection [16–22].

Previous studies allowed conclusions to be drawn by comparing mortality in patients with MRSA infections with mortality in patients belonging to other control groups, which may lead to residual confounding associated with risks of MRSA carriage such as older age, comorbidities, and other less well-defined factors. To avoid this likely confounding, we
used a different study design, i.e. a case–control study, to identify reliably factors associated with mortality.

Materials and Methods

Settings

A multicentre case–control study comparing patients with MRSA bacteraemia who died during the index hospitalization (cases) with patients with MRSA bacteraemia who survived (controls) was conducted during the years 2001–2005 in three participating centres: (i) Beth Israel Deaconess Medical Center (Boston, MA, USA); (ii) Duke University Medical Center (Durham, NC, USA); and (iii) Tufts-New England Medical Center (Boston, MA, USA). All centres are large tertiary teaching hospitals.

All *S. aureus* bloodstream isolates submitted to the microbiology laboratories of the participating centres were identified to the species level and tested for susceptibility to antibiotics according to the CLSI criteria [23].

Study design

A retrospective case–control study design was used. Patients with MRSA bacteraemia were identified using the local computerized databases in each hospital. Patients were then classified as cases or controls based on discharge status, i.e. fatality/survival. Medical records were retrieved and data extracted into a prepared questionnaire. The parameters recorded included demographics, comorbidities, severity of illness, functional status, transfer from institution, admission to ICUs, surgical procedures, antibiotic consumption, prosthetic devices, source of bacteraemia, removal of the source of bacteraemia, and the presence of sepsis at the time of diagnosis. The exact delays between onset of symptoms, obtaining blood cultures, and the time appropriate treatment was given were determined. All data were extracted into a uniform questionnaire using a data management system (Access; Microsoft Corp., Redmond, WA, USA).

Definitions

For the purpose of this study we used the following definitions: bacteraemia was defined as the presence of at least one blood culture growing MRSA; previous surgery was defined as an operation within the month prior to the onset of MRSA bacteraemia. The level and severity of comorbidities were assessed according to the Charlson chronic comorbidity score [23]; the severity of illness was calculated according to prognosis as reflected by the McCabe score [24]; and the clinical severity of the bacteraemia episode was assessed according to the Pitt bacteraemia score [25].

The functional status of patients was defined according to the criteria set by Katz et al. [26]. The source of bacteraemia was determined using the following definitions: a catheter was considered to be the source of bacteraemia if (i) quantitative culture of blood or semiquantitative culture of a catheter segment confirmed catheter-related infection according to CDC criteria [27]; (ii) the culture of a specimen with purulent drainage from the insertion site or from the tip of the removed catheter yielded MRSA that had the same resistance phenotype as the cultured strain from the peripheral blood; and (iii) no other source of bacteraemia existed.

Pneumonia was considered to be the source of bacteraemia if the patient had clinical symptoms and signs of a lower respiratory tract infection, and if there was radiological evidence of pulmonary infiltrates not attributable to other causes [28]. Soft-tissue infection was considered to be the source of bacteraemia when patients had a pure culture of MRSA from a tissue or a drainage specimen from the affected site and had signs of infection [29].

Surgical wound infection was defined according to the definitions of the CDC [29]. Infective endocarditis was defined according to Duke’s criteria [30]. Only in cases where endocarditis was diagnosed together with the bacteraemia was endocarditis designated as the source of bacteraemia. Otherwise, endocarditis was considered to be the result, not the source, of the bacteraemia. If a primary focus of infection could not be determined, it was considered to be unknown. The sources of bacteraemia were divided into two categories: removable and non-removable foci. Removable sources included surgically removable infections or drainable abscesses and indwelling foreign bodies, such as peripheral and central intravenous catheters. Non-removable sources included unknown primary sites, pneumonia, and osteomyelitis or arthritis not related to a prosthetic device infection [31]. DAAT was calculated according to the following equation:

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\text{DAAT} = \text{days of calendar days between the time blood cultures were obtained and appropriate treatment was given}.
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Ethical considerations

The study was approved by the Institutional Review Board of each participating centre. Because no direct patient contact was planned, the requirement for informed consent was waived. The data were de-identified in each centre and only then transferred for analysis.

Statistical analysis

All analyses were performed using SAS software (SAS Institute, Cary, NC, USA). Bivariable analyses were performed using Fisher’s exact test or the $\chi^2$ test for categorical
variables and the independent samples t-test or the Wilcoxon rank sum test for continuous variables.

Multivariable models were constructed using logistic regression. The primary objective of the multivariable analyses was to assess the independent impact of DAAT while controlling for potential confounders. The secondary objective of these analyses was to identify other independent risk factors for mortality. All variables with a p value < 0.20 in bivariate analyses were submitted to multivariate analysis. A stepwise selection procedure was used to select variables for inclusion in the final model. The final selected model was tested for confounding. If a covariate affected the β-coefficient of DAAT or another selected variable in the model by >10%, then the confounding variable was maintained in the multivariable model. All p values were two-sided. In addition to examining statistical significance and confounding, the effect modification among variables was evaluated by testing appropriate interaction terms for statistical significance. When effect modification was detected, subgroup analysis was performed. Co-linearity was examined by replacing variables with each other and examining the effect on the model.

Results

Overall, 388 patients with MRSA bacteraemia were included in the study: 164 (42%) who died, i.e. cases, and 224 (58%) who survived, i.e. controls. There were no significant differences in mortality rates among the three participating centres.

Patient characteristics along with bivariate analysis results are summarized in Table 1. Case patients were significantly older, were more often transferred from another institution, had more invasive devices, and had a poorer prognosis as evident by McCabe score [29] and Charlson score [25]. In addition, cases had a greater severity of acute illness at the time of bacteraemia as evident by parameters of severe sepsis and multiorgan dysfunction, by the Pitt bacteraemia score, and by the frequency of admission to ICUs.

Analysis of modifiable factors, i.e. removal of the source of infection, and of DAAT was performed. A removable source of bacteraemia was evident in 44% of all patients, but the source was less often removed among cases (18% vs. 28% by day 3, and 22% vs. 33% by day 5, among cases vs. controls, respectively). The mean number of days from culturing MRSA in blood to the beginning of antimicrobial therapy of any kind, whether appropriate or inappropriate, did not differ between groups. However, DAAT greater than one calendar day tended to occur more often among cases than controls.

Multivariable analysis revealed that after controlling for potential confounders, including comorbidities before the bacteraemia (Charlson score) and the acute severity of the present illness (represented by the McCabe score, ICU stay at time of bacteraemia, and the presence of severe sepsis), poor functional status was associated with increased mortality risk (OR 1.45; 95% CI 1.05–2.02) as illustrated in Table 2. In addition, both DAAT at day 2 and non-removal of the source of the bacteraemia tended to be associated with mortality, although neither reached statistical significance. However, there was a significant effect modification associated
with increased age, and among the 202 patients who were >65 years of age, DAAT of >1 day was significantly associated with mortality (OR 2.35; 95% CI 1.01–5.44; Table 3).

Among 102 patients with severe sepsis, the only predictor for mortality was DAAT, and the effect was most pronounced for a delay of >1 day (delay of 1 day: OR 3.0, p 0.069; delay of >1 day: OR 9.7, p 0.032). We examined the effect of age >65 years on the likelihood of DAAT. We found that among elderly patients with severe sepsis there was a much greater likelihood of DAAT when compared with patients younger than 65 years with severe sepsis (25% among the elderly vs. 6.5% among younger patients; OR 4.78; 95% CI 1.21–5.56; p 0.02). Among the 14 patients over the age of 65 years with severe sepsis who experienced DAAT of >1 day, 13 (93%) died, and among patients over the age of 65 with severe sepsis for whom effective therapy was not delayed for more than 1 day, 29 out of 42 (69%) died (p 0.07).

### Discussion

Bacteraemia caused by MRSA is a common and serious condition, associated with high mortality. Identifying modifiable risk factors for mortality are essential in order to apply effective interventions to reduce mortality. Here, we elected to address specifically the question as to which are the modifiable factors associated with mortality among patients with MRSA bacteraemia, and therefore used the case–control methodology to reduce the risk of residual confounding associated with group ascertainment. Upon bivariate analyses, this large multicentre study identified two modifiable risk factors for mortality: (i) a delay of ≥3 days in removing the source of the bacteraemia; and (ii) DAAT of ≥2 days. Upon multivariate analysis, source removal and DAAT tended to be associated with mortality, although associations were not significant. In the subset of patients older than 65 years, DAAT of ≥2 days was an independent, significant predictor of mortality.

DAAT is considered one of the most important modifiable determinants of survival for patients with bacteraemia [26]. In a study conducted with severe septic patients, each hour of delayed therapy in the first 6 h of infection was associated with an average decrease in survival of 7.6% [17]. Previous studies that assessed DAAT specifically in S. aureus infections in various clinical syndromes and scenarios also showed correlation with increased mortality [16,19–22]. Our study, conducted using a somewhat different methodology, confirms the impact of DAAT on mortality rates.

Removal of the source of the bacteraemia is also a factor that influences mortality in various ways: removal might be as simple as pulling out an intravenous line at bedside, or as complex as removing hardware from infected joints in an operating room. Thus, in some cases removal of hardware might be associated with complex, severe infections and then might be associated with increased risk of mortality. However, in a previous study of S. aureus bacteraemia cases, neither resistance to methicillin nor DAAT had an impact on mortality in patients with a removable source of infection, whereas among patients with a non-removable source or a non-eradicated focus, both MRSA and DAAT became significantly associated with increased mortality [32]. In another observational report, failure to remove lines in catheter-related bacteraemias was associated with increased therapy failures [29]. These studies, in addition to our findings that source removal was independently associated with improved outcome, might reflect an underestimation of the true effect of source removal, since many patients who require hardware removal are severely ill and have poor functional status.

Our analyses demonstrate that age is a strong modifier of the likelihood of DAAT being a risk factor for mortality. In addition, we found that elderly, frail patients experience more DAAT. It was interesting to see that DAAT was not directly associated with the acute severity of illness, as 15–19% of patients in each of the McCabe score groups experienced DAAT, a non-significant difference. However, the difference in DAAT among patients >65 years old was significantly greater in comparison with those <65 years old, and this difference was even more significant among patients older than 80 years in comparison with patients younger than 80 years (p 0.0025 between groups). As far as we know, this study is the first to report DAAT as a function of
age, which has interesting medical and ethical implications, particularly since DAAT in the elderly population was independently associated with increased mortality.

It is important to emphasize that DAAT is difficult to assess since it is usually measured as delay from the time of culture, which is the best available parameter to use for the time of onset of infection. If the actual time of onset of the infection could be recorded, it would better reflect the actual delay between infection onset and administration of effective therapy. In our study 75% of all patients had received appropriate empiric antibiotic therapy directed at MRSA and had experienced no DAAT. This reflects practices where MRSA is often suspected as the causative organism in bacteraemic patients. However, this may have limited our power to investigate the role of DAAT in mortality.

To conclude, this analysis suggests that in-hospital mortality may be prevented by the administration as soon as possible of effective empiric therapy, especially in cases of severe sepsis and in older patients, and by early removal of the source of infection when possible. More than 10% of patients in our cohort did not receive effective therapy even after 3 days of infection, when culture results were available. These patients may have had improved outcome if appropriate therapy had been initiated earlier. Although initiating appropriate therapy early and removing the source of infection may be considered by some to be a matter of ‘common knowledge and practice’ for working physicians, these interventions should be specifically addressed in the management of severe infections, particularly among the elderly. Given the rapid spread of MRSA in healthcare and community settings, our data suggest a significant opportunity for improving healthcare outcomes. Future interventions should incorporate education, rapid diagnostics and established protocols, in order to improve the management of MRSA bloodstream infections.

Transparency Declaration

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References


