Lack of association between genotypes and haematogenous seeding infections in a large cohort of patients with methicillin-resistant *Staphylococcus aureus* bacteraemia from 21 Spanish hospitals

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Abstract

There is increasing concern regarding the association between certain methicillin-resistant *Staphylococcus aureus* (MRSA) genotypes and poor clinical outcome. To assess this issue, a large cohort of 579 subjects with MRSA bacteraemia was prospectively followed from June 2008 to December 2009, in 21 hospitals in Spain. Epidemiology, clinical data, therapy, and outcome were recorded. All MRSA strains were analysed in a central laboratory. Presence of a haematogenous seeding infection was the dependent variable in an adjusted logistic regression model. Of the 579 patients included in the study, 84 (15%) had haematogenous seeding infections. Microdilution vancomycin median MIC (IQR) was 0.73 (0.38–3) mg/L. Most MRSA isolates (n = 371; 67%) belonged to Clonal Complex 5 (CC5) and carried an SCCmec element type IV and agr type 2. Isolates belonging to ST8-agr1-SCCmecIV, ST22-agr1-SCCmecIV and ST228-agr2-SCCmecI—a single locus variant of ST5—accounted for 8%, 9% and 9% of the isolates, respectively. After adjusting by clinical variables, any of the clones was associated with increased risk of haematogenous seeding infections. Higher vancomycin MIC was not identified as an independent risk factor, either. In contrast, persistent bacteraemia (OR 4.2; 2.3–7.8) and non-nosocomial acquisition (3.0; 1.7–5.6) were associated with increased risk.

Keywords: Bloodstream infection, complicated bacteraemia, genotype, methicillin-resistant *Staphylococcus aureus*
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Background

Staphylococcus aureus is one of the microorganisms most frequently involved in bacteraemia worldwide. Compared with other microorganisms, it is associated with higher rates of morbidity and mortality [1].

Haematogenous seeding infections are a frequent feature of *S. aureus* bacteraemia [2]. This clinical scenario is observed in approximately 30–40% of episodes and can be predicted by the presence of factors such as community acquisition, unknown source, suggestive skin lesions, persistent fever and positive follow-up blood cultures [3].

Infective endocarditis (IE) caused by *S. aureus* is probably the most relevant complication due to this microorganism [4]. Notably, with mortality rates between 40% and 50%, methicillin-resistant *S. aureus* (MRSA) IE is associated with worse prognosis than methicillin-sensitive *S. aureus* IE [5].

Higher vancomycin minimum inhibitory concentration (V-MIC), has been described as an independent predictor of treatment failure [6] and complicated bacteraemia [7]. Given that most clinical studies do not include molecular microbiology assessment, it is not known whether certain MRSA genotypes are associated with worse outcome and enhanced risk of complications. However, a few studies have taken into account strain clonality in their analyses of outcome predictors with contradictory results [8–11]. In this study we evaluated the influence of MRSA genotypes on the appearance of haematogenous seeding infections in a large cohort of bacteraemia episodes.

Methods

Study period and patients

The study was conducted from June 2008 to December 2009 in 21 hospitals in Spain. Four hospitals had <500 beds; nine had 500–1000 beds; and eight had >1000 beds. An infectious disease specialist prospectively followed up adult patients (>16 years old) with MRSA blood cultures previously detected at the microbiology laboratory, and excluded those that did not meet the inclusion criteria (lack of signs and symptoms consistent with sepsis). A standardized protocol with demographic and clinical information was applied. Strains were sent to a central laboratory for further studies. The first isolate of each episode was used for the analysis.

Study design

With the data collected, MRSA bacteraemia episodes with and without observed haematogenous seeding infections were compared. To analyse whether there is an association with genetic background, we carried out an adjusted multivariate analysis in which presence of haematogenous seeding infection was the dependent variable and MRSA clonal complex was the independent variable of interest.

Definitions

The MRSA bacteraemia was defined as the presence of at least one positive blood culture for MRSA in a sample from a patient with clinical findings consistent with infection. When a focal infection different from bacteraemia portal of entry was diagnosed, the episode was considered a haematogenous seeding infection. Clinical data were interpreted accordingly with the infectious diseases specialist criteria.

Clinical variables. Co-morbidity was measured using the Charlson score, which stratifies the associated diseases on an ordinal scale. Three acquisition categories were considered: (i) nosocomial bacteraemia was considered when the episode was diagnosed at least 48 h after hospital admission, either to the ICU or to a conventional ward (non-ICU), and when there were no signs or symptoms of infection at admission; (ii) healthcare-related bacteraemia was diagnosed following Friedman's criteria; and (iii) community acquisition was considered when MRSA bacteraemia was diagnosed within 48 h of admission and when no previous contact with the healthcare system was recorded. The bacteraemia portal of entry was defined following CDC criteria [12]. Endocarditis was diagnosed in cases that met modified Duke criteria [13]. The severity of sepsis was determined on the basis of the Pitt score. Initial antibiotic was defined as the antibiotics administered in the first 48 h after bacteraemia onset. Definitive treatment was considered the antimicrobials administered after performing microbiological sensitivity tests. Antibiotic treatment was considered appropriate when the MRSA isolate was susceptible to at least one of the antibiotics administered, following the current CLSI breakpoints, with the exception of aminoglycosides, which were considered inappropriate, regardless of the sensitivity tests. Early intervention was considered when the catheter or foreign body was removed, or when a surgical procedure or drainage of infected source was performed within the first 48 h. Persistent bacteraemia was diagnosed when MRSA was isolated in blood cultures more than 48 h after the first dose of appropriate antibiotic. Relapse was diagnosed within 4 weeks after the end of therapy.

Susceptibility testing and molecular epidemiology of MRSA isolates

Each hospital identified the isolates and performed preliminary susceptibility tests. Further antimicrobial susceptibility testing