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Impacts of a long-term programme of active surveillance and chlorhexidine baths on the clinical and molecular epidemiology of meticillin-resistant *Staphylococcus aureus* (MRSA) in an Intensive Care Unit in Scotland

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ABSTRACT

Evidence is accumulating that active surveillance, when combined with appropriate infection control, is a successful measure for controlling hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA). In this study, the impacts of a long-term control strategy of this type, including the use of chlorhexidine baths, on the clinical and molecular epidemiology of MRSA in the Intensive Care Unit of Aberdeen Royal Infirmary were investigated. Characterisation of 85 sequential index MRSA isolates was performed using phenotypic methods (biotyping), antibiotic susceptibility testing and three genotypic methods (pulsed-field gel electrophoresis, *spa* typing and multilocus sequence typing) over a 4-year period. There was no evidence of loss in effectiveness of the control strategy over the study period. Compliance with screening remained high (>85%) throughout and there was no significant increase in the prevalence of MRSA detected in surveillance ($P = 0.43$ for trend) or clinical cultures ($P = 0.79$). There were no significant trends in rates of other index surveillance organisms ($P > 0.5$). Results of the three typing methods were in general agreement with three prevalent MRSA clones [clonal complex 22 (CC22), CC30 and CC45]. CC22 emerged as the dominant clonal complex alongside a significant decline in CC30 ($P = 0.002$). CC45 was significantly more likely to be positive in glycopeptide resistance screens ($P < 0.001$). There was no increase in antibiotic or chlorhexidine resistance. Long-term chlorhexidine bathing was not associated with any detectable loss of efficacy or increase in resistance in MRSA or with any increase in infection with other organisms. Changing clonal epidemiology occurred with no overall change in the prevalence of MRSA.

1. Introduction

Evidence is accumulating that active surveillance, when combined with appropriate infection control procedures, is a successful measure for controlling hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) [1,2]. A common interventional approach to control MRSA carriage involves rapid screening followed by barrier nursing of positive patients and treatment with anti-MRSA therapy [1,3]. However, a shortage of single rooms and the development of a decrease in susceptibility to antimicrobial agents can pose challenges to such strategies.

Intensive Care Units (ICUs), with their complex patient population, can act as an important reservoir for generating and then disseminating MRSA-colonised patients around the rest of the hospital, therefore making them a primary target for hospitals aiming to lower their infection rates [4].

The emergence of multiply antibiotic-resistant MRSA has been globally reported. MRSA infections have been a major problem in UK ICUs over the last decade and are largely caused by the two prevalent epidemic strains, namely EMRSA-15 and EMRSA-16 [5,6]. Alongside traditional biotyping methods, a number of molecular typing methods have been developed to characterise MRSA strains, which play a crucial role in understanding the evolution, epidemiology and transmission of the pathogen [7–11]. These include three widely used techniques, namely pulsed-field gel electrophoresis (PFGE) of *Sma*I-digested genomic DNA, multilocus sequence typing (MLST) and *spa* typing. PFGE is the most commonly used typing method for studying local and short-term epidemiology of *S. aureus*

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and it has proven useful in nosocomial outbreak investigations [12]. MLST has been extensively used in studying the evolution and population structure of MRSA [8,11]; however, it is not discriminatory amongst local strains and high costs are incurred. *spa* typing offers higher strain resolution and has been preferred over MLST for the study of local epidemiology and transmission tracking in some studies [12,13]. However, the role of *spa* typing in outbreak situations where there is a high prevalence of EMRSA-15, EMRSA-16 or indeed any other local strain may be limited [6].

In this study, we investigated the impacts of a long-term control strategy, including the use of chlorhexidine baths, on the clinical and molecular epidemiology of MRSA in an ICU in North East Scotland. We reveal the dynamics of phylogenetic lineages during the intervention, report on changes in antibiotic and antiseptic (chlorhexidine) resistance, and evaluate the long-term effectiveness of the control measures.

2. Materials and methods

2.1. Design

This descriptive study was designed as a follow-up to a sustained ICU MRSA control programme initiated in May 2001, previously reported to reduce clinical burdens from MRSA in an intensive care setting [1]. To evaluate sustained effectiveness, trends in MRSA colonisation and infection, other index surveillance infections, and screening adherence were investigated over 4 years. The evolving molecular epidemiology was then explored by characterising 85 sequential clinical index MRSA isolates from the same period, combining phenotypic methods (biotyping), antibiotic and antiseptic susceptibility testing, and three genotypic methods (PFGE, *spa* typing and MLST).

2.2. Setting

This study took place between May 2003 to April 2007 in the mixed surgical–medical ICU of Aberdeen Royal Infirmary, a 900-bed tertiary referral hospital serving a population of 500 000 in North East Scotland. The ICU is a 16-bedded unit, with four isolation rooms and an average annual admission rate of ca. 800 patients.

2.3. Intervention

The MRSA control programme was similar to that previously described [1]. Briefly, all patients were screened for MRSA at multiple body sites on admission, specifically the nose, throat, axilla and groin, and were immediately commenced on 6-hourly topical nasal anti-MRSA preparations and daily bed baths with Hibiscrub cleansing solution (4% chlorhexidine gluconate). This was carried out irrespective of MRSA status until September 2003, after which all decontamination procedures were stopped following receipt of a negative screening result. Three topical nasal preparations were rotated on a weekly basis: 2% fusidic acid (Fucidin cream; Leo Pharma, Risborough, UK); 0.5% neomycin sulphate combined with 0.1% chlorhexidine hydrochloride (Naseptin cream; Alliance Pharmaceuticals, Chippenham, UK); and bacitracin zinc (500 U/g) combined with polymyxin B sulphate (10 000 U/g) (Polyfax ointment; Teva, Castleford, UK), replacing the previously described oxytetracycline. All patients found to be MRSA-positive were subsequently isolated in single rooms (or cohorted if no single rooms were available) and barrier nursed.

Screening samples were processed in the laboratory as previously described [1] with the exception of the introduction of Brilliance™ (Oxoid, Basingstoke, UK) chromogenic medium to replace Oxacillin Resistance Screening Agar Base (ORSAB) (Oxoid) in the laboratory from May 2006. Follow-up or discharge screening was not performed.

2.4. Data collection

Data on MRSA clinical and screening cultures, other index surveillance infections, and screening adherence were retrieved from routine surveillance and monitoring in the ICU following introduction of the MRSA control programme. All clinical MRSA isolates were sent to the Scottish MRSA Reference Laboratory (SMRSARL) at Stobhill Hospital (Glasgow, UK) for phenotyping, antimicrobial and antiseptic susceptibility testing, and genotyping.

2.5. Phenotypic characterisation and antibiotic susceptibility testing

Urease production was tested by inoculating Urea Agar slopes (Oxoid) with 10 μL of a 0.5 McFarland inoculum. After incubation for 48 h at 35 °C, a positive test was indicated by a pink colour and a negative result by a yellow colour.

Pigmentation of isolates was recorded after incubation in air at 35 °C for 48 h on Iso-Sensitest agar (Oxoid). Results were recorded as white, cream or yellow.

2.5.1. Antibiotic susceptibility testing

Susceptibility testing of 10 antibiotics was performed using a Vitek® instrument (bioMérieux, Basingstoke, UK) with GPS-528 cards (bioMérieux) that did not include vancomycin. Sulfamethoxazole and neomycin (Oxoid) were tested using disks (25 μg and 10 mg, respectively) on Iso-Sensitest agar with a 0.5 McFarland inoculum; resistance was defined as growth right up to the disk after 24 h of incubation at 35 °C. For the glycopeptides resistance screen, a 10 μL drop of a 0.5 McFarland suspension was inoculated onto a screening agar plate containing glycopeptide (drops from ten test isolates and four control strains per plate). Mueller–Hinton agar with 5 mg/L teicoplanin (E&O Laboratories, Bonnybridge, UK) was used during most of the period covered by this study, but brain–heart infusion (BHI) agar with 4 mg/L vancomycin was used for part of the period. Incubation was in air at 35 °C for 48 h. Any growth on these plates was counted as a positive screen if it was confirmed to be an MRSA phenotypically resembling the inoculated isolate. Positive isolates were tested by Etest (AB Biotek, Mellbystrand, Sweden) for minimum inhibitory concentrations (MICs) to vancomycin and teicoplanin using either the macro method designed to detect heterogeneous resistance (2 McFarland inoculum, BHI agar and 48 h incubation) or a standard method (0.5 McFarland inoculum, Mueller–Hinton agar, 24 h incubation) or both [14].

2.5.2. Antiseptic minimum inhibitory concentrations and qacA/B and smr gene detection by PCR

Chlorhexidine susceptibility was tested using an agar dilution technique on Mueller–Hinton agar as previously described [15]. The range of concentrations tested was 0.016–32 mg/L and inoculation was performed using a multipoint replicating device delivering 10^4 CFU/spot. Incubation was in air at 35 °C for 20 h. *Staphylococcus aureus* ATCC 29213 and 25923 were used as control strains and both organisms returned MICs of 2.0 mg/L.

PCR was carried out for detection of *qac*A/B and *smr* using previously published primers [16]. Control isolates for each gene were included as described and supplied by Smith et al. [17].