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ORIGINAL ARTICLE

An investigation of vancomycin minimum inhibitory concentration creep among methicillin-resistant *Staphylococcus aureus* strains isolated from pediatric patients and healthy children in Northern Taiwan

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Abstract *Background and purpose:* The phenomenon of vancomycin minimum inhibitory concentration (MIC) creep is an increasingly serious problem in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. In this study, we investigated the vancomycin and daptomycin MIC values of MRSA strains isolated from pediatric patients and MRSA colonized healthy children. Then, we assessed whether there was evidence of clonal dissemination for strains with an MIC to vancomycin of $\geq$ 1.5 μg/mL.
Methods: We collected clinical MRSA isolates from pediatric patients and from healthy children colonized with MRSA during 2008–2012 at a tertiary medical center in northern Taiwan and obtained vancomycin and daptomycin MIC values using the Etest method. Pulse-field gel electrophoresis (PFGE) and staphylococcal cassette chromosome (SCC*mec*) typing were used to assess clonal dissemination for strains with an MIC to vancomycin of $\geq$ 1.5 μg/mL.
Results: A total 195 MRSA strains were included in this study; 87 were isolated patients with a clinical MRSA infection, and the other 108 strains from nasally colonized healthy children.

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Vancomycin MIC $\geq$ 1.5 μg/mL was seen in more clinical isolates (60/87, 69%) than colonized isolates (32/108, 29.6%), $p < 0.001$. The PFGE typing of both strains revealed multiple pulsotypes. *Conclusion:* Vancomycin MIC creeps existed in both clinical MRSA isolates and colonized MRSA strains. Great diversity of PFGE typing was in both strains collected. There was no association between the clinical and colonized MRSA isolates with vancomycin MIC creep.

Introduction

Staphylococcus aureus often results in serious infections, including pneumonia, bacteremia, skin and soft tissue infections, and endocarditis. These infections can occur in hospitals, health care institutions, as well as in the community. *S. aureus* has the ability to colonize humans, especially the nose.[1] Colonization plays an important role in the pathogenesis and epidemiology of infections caused by *Staphyloccocus aureus*, including both methicillin-sensitive and methicillin-resistant (MRSA).[1–3] Safdar and Bradley[4] found that there is a greater risk for infection including invasive infections following colonization with MRSA.

Vancomycin has been a front-line drug of choice for treating infections caused by MRSA for the past 60 years.[5] Nevertheless, the association of vancomycin treatment failures with increased vancomycin minimum inhibitory concentration (MIC) is a recent challenge in the current medical circumstances.[6] Even when MRSA isolates are susceptible to vancomycin, treatment failure is frequently seen. In recent years, progressive elevation in glycopeptides MICs for *S. aureus* strains, a phenomenon recognized as vancomycin MIC creep has been discussed. Investigators have reported that an increase in vancomycin MIC for MRSA isolates poses a substantial risk of failure. Sakoulas et al[7] reported that the possibility of treatment success is lower in patients with MRSA infections with a vancomycin MIC of 1–2 mg/mL compared with patients infected with isolates with a vancomycin MIC $\leq$ 0.5 mg/mL. The Infectious Diseases Society of America recommended that the dosage of vancomycin should be at least 60 mg/kg/d to achieve the target vancomycin trough level of 15–20 mg/mL for serious MRSA infections in adults in 2009.[5,8] The guideline for targeting vancomycin trough level for pediatric patients was not discussed. As a result, we obtained more information on MRSA treatment in children. During recent years, community-associated (CA) MRSA infection has become increasingly common. According to reports from Taiwan,[9–11] compared with those reported from America and other nations, CA-MRSA isolates in Taiwan did not always contain type IV staphylococcal cassette chromosome (SCCmec) and were resistant to multiple non-β-lactam antibiotics, including clindamycin and macrolides. There has been no similar study investigating vancomycin and daptomycin MIC values of MRSA strains in children to date.

The aim of this study was to investigate the vancomycin and daptomycin MIC values of MRSA strains isolated from pediatric patients and MRSA-colonized healthy children from 2008 to 2012 at a tertiary medical center using the Etest method. If the vancomycin MIC $\geq$ 1.5 μg/mL, further evaluation with pulsed-field gel electrophoresis (PFGE) and staphylococcal cassette chromosome mec (SCC*mec*) elements typing were used to assess for clonal dissemination.

Methods

Study design and specimen collection

This retrospective study was conducted from 2008 to 2012 at Tri-Service General Hospital, a 1400-bed tertiary medical center in northern Taiwan. All patients were aged $\leq$ 18 years and hospitalized with an MRSA infection identified from medical records and the clinical microbiology laboratory. Eligible healthy children aged $\leq$ 14 years without acute medical problems were enrolled who either visited a healthcare facility for a regular well-child checkup or attended kindergartens in Taipei, Taiwan; this was reviewed and approved by the National Defense Medical Center Institutional Review Board, Taipei, Taiwan. We obtained written informed consent from each child's parents or legal representative before nasal specimen collection or interviews. During the 5-year study period, all children who presented for regular health maintenance visits to our hospital were invited to take part in this study. The kindergartens were chosen based on support for the surveillance investigation by the kindergartens' principals.

The definition of CA-MRSA infection as any MRSA infection which is diagnosed in an outpatient or within 48 hours of admission to hospital, of which the patient has none of the following risk factors for health-care-associated MRSA: hemodialysis; operation; residence in a long-term care facility or treatment in hospital during the previous year; presence of a lasting catheter or percutaneous instrument at the time of culture; or prior isolation of MRSA.[12,13]

Bacterial strains and antimicrobial susceptibility testing

Nasal samples were acquired with a sterile cotton swab, placed in transport medium (Venturi Transystem; Copan Diagnostics, Corona, CA, USA); transported to and processed in our microbiology laboratory within 4 hours. Cotton swabs were plated on mannitol salt agar (BBL Microbiology Systems, Becton Dickinson, Company, Sparks, MD, USA). Distinctive morphotypes of mannitol-fermenting colonies were selected from a mannitol salt agar plate,