Short Communication

Prevalence of Methicillin-Resistant Staphylococcus aureus among Children in a Region with Controlled Antimicrobial Use

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SUMMARY: Since 2002, we have conducted a series of intervention programs in Sado Island, Japan, to increase awareness of the appropriate use of antimicrobials among public and health-care staff. The objective of our study was to determine the antimicrobial susceptibility of Staphylococcus aureus among children in a semi-closed geographic region with controlled antimicrobial use. The average hospital visit-based rate for antimicrobial drug prescription drastically decreased from 535 per 1,000 clinic visits before the intervention programs to 45–75 per 1,000 clinic visits after the intervention programs (P < 0.0001). We obtained 1,260 clinical isolates of S. aureus from 957 pediatric outpatients aged 0–15 years between 2002 and 2010 at Sado General Hospital. The prevalence of methicillin-resistant S. aureus (MRSA) in the final year of the study (2010, 7.9%) was significantly lower than that in the early period of the study (2003, 23.6%; P < 0.001). All tested S. aureus isolates were susceptible to trimethoprim/sulfamethoxazole, teicoplanin, linezolid, and vancomycin. The prevalence of gentamicin-resistant S. aureus in isolates from skin lesions was significantly higher than in isolates from other lesions (41.3% versus 28.5%; P < 0.05). In conclusion, prevalence of MRSA in children in our study population could be decreased by eliminating unnecessary antimicrobial drug prescriptions.

Staphylococcus aureus colonizes the human nasal mucosa and can cause skin and soft-tissue infections (SSTIs), pneumonia, endocarditis, bacteremia, and toxin-associated diseases. Methicillin-resistant S. aureus (MRSA) has been considered a nosocomial pathogen since it was first reported in 1961. In addition, community-associated MRSA, which can carry genes for Panton-Valentine leukocidin, has also become a major concern worldwide since the late 1990s (1,2).

It is generally accepted that the rates of antimicrobial resistance are higher in countries with higher rates of antimicrobial consumption (3). Excessive antimicrobial use also increases the risk of dissemination of MRSA clones. The prevalence of MRSA in hospitalized patients varies among countries and ranges from 0.6% in the Netherlands to 60–70% in Japan (4,5), where there is concern over the excessive use of antimicrobials. Knowledge of the prevalence of MRSA in the community is an important factor for controlling its spread. Because community-associated MRSA mainly affects children and young adults (6), understanding of these MRSA infections is essential. However, there have been few longitudinal studies on antimicrobial resistance in S. aureus isolated from communities in Japan (7–10). Sado Island, which is located 60 km off the Japanese mainland, has a population of approximately 66,000, of whom 8.5% are aged 0–15 years. Since 2002, we have been conducting a series of intervention programs for children aged 0–15 years in Sado Island to increase awareness among public and health-care staff about the appropriate use of antimicrobials and the risks of antimicrobial resistance caused by inappropriate use of antimicrobials (11,12). The program involved encouraging adherence to the following principles among clinicians: (i) antimicrobials should not be prescribed for viral diseases and uncomplicated upper respiratory infections; (ii) narrow-spectrum antimicrobials (i.e., penicillin) should be prescribed where possible; and (iii) parents should be educated to understand and accept the treatment process. As a result of adherence to the above-mentioned principles, the rate of antimicrobial prescriptions decreased from 535 per 1,000 clinic visits to 70 per 1,000 clinic visits at our hospital (11).

To assess the success of the interventions, we initiated a retrospective surveillance of potential pathogens and antimicrobial resistance. Because of the limited movement of people between Sado Island and the Japanese mainland, Sado Island can be considered as a controlled environment for investigating antimicrobial usage and resistance in potential pathogens such as S. aureus. The objective of our study was to determine the antimicrobial susceptibility of S. aureus in a semi-closed geographic region. Data analyses were performed using chi-square test, and P < 0.05 was considered significant. For all significant cases, multiple comparisons were carried out by using Bonferroni correction. All statistical calculations were performed with PASW Statistics 18.0 (SPSS Inc., Chicago, Ill., USA). The study protocol was ap-
proved by the Ethics Committee of our hospital.

The hospital visit-based rate of antimicrobial prescription was defined as the average number of antimicrobial drug prescriptions recorded for subjects divided by the average number of outpatient clinic visits by subjects (11–13). In comparison with older children, children aged 0–3 years were more likely to have visited doctors and been prescribed antimicrobials (14). Therefore, we assumed that the antimicrobial prescribing rates of these age groups best represented the antimicrobial pressure observed between 2002 and 2010. Subjects for prescription rate were grouped according to their year of birth (7 groups, Group-2002 to -2008). All subjects were born at Sado General Hospital, which is the only hospital with a maternity ward on Sado Island. The subjects had also received outpatient treatment (routine health checks and immunization visits were excluded) at least once a year, and their medical records from 0–3 years of age (from 0 to part of 2nd year of age in Group-2008) were evaluated retrospectively. The prescription rates in Group-2002 to Group-2004 have been previously reported (11). The average hospital visit-based rate of antimicrobial prescription decreased from 75 per 1,000 clinic visits in Group-2002 (11) to 45 per 1,000 clinic visits in Group-2008 (P < 0.0001). The morbidity or mortality rates caused by invasive bacterial infections from 2002–2010 were not significantly different from the corresponding values before 2002 (data not shown).

Altogether, 1,260 clinical isolates of S. aureus from 957 pediatric outpatients aged 0–15 years were analyzed between 2002 and 2010 in Sado General Hospital. The isolates were collected from the nasopharynx, skin, abscesses, ear discharge, urine, stools, eye discharge or blood of the subjects. Antimicrobial susceptibilities were determined using commercially available MIC panels (MICrOScan Pos Combo 6.2J, 3.2J, or 3.3J; Siemens Healthcare Diagnostics, Inc., Deerfield, Ill., USA) using the microdilution broth method. The results of analyses were interpreted as susceptible, intermediate, or resistant according to the guidelines issued by the Clinical and Laboratory Standards Institute (15,16). We tested the MICs of the following antimicrobial agents: ampicillin, oxacillin, gentamicin, arbekacin, erythromycin, clindamycin, minocycline, trimethoprim/sulfamethoxazole, fosfomycin, teicoplanin, and vancomycin. MRSA prevalence and antimicrobial susceptibility of all S. aureus isolates from pediatric outpatients. All tested S. aureus isolates were susceptible to trimethoprim/sulfamethoxazole, teicoplanin, linezolid, and vancomycin. MRSA prevalence was indicated both among pediatric outpatients aged 0–15 years and 0–2 years.

Prevalence of MRSA varied with the age of the subjects, ranging from 5.0% among 14-year-old subjects to 24.2% among 11-year-old subjects (Fig. 1). As majority of the samples were collected from younger children, the number of S. aureus isolates was higher in younger children, especially among the 0- and 1-year-old age groups. The MRSA prevalence and antimicrobial susceptibilities of all S. aureus isolates from the pediatric outpatients are summarized in Fig. 2. The prevalence of MRSA was the highest (23.6%) in 2003 and the lowest (5.0%) in 2007 (Fig. 2B). The prevalence of MRSA in the recently collected data in 2010 (7.9%) was significantly lower than that in the early period of the study (23.6% in 2003, P < 0.001). A similar trend of decrease in the prevalence of MRSA was seen among children aged 0–2 years, which was also the age group used for calculating the prescription rate. Overall, the MRSA prevalence tended to decrease between 2002 and 2007, but increased again in 2008 and 2009, and then declined in 2010.

There are few studies describing antimicrobial resistance in S. aureus and the antimicrobial prescribing patterns in children. The prevalence of MRSA among pediatric outpatients with impetigo in Takamatsu, Japan, was 27.8% in 2006 (17). In another longitudinal study in Osaka, the prevalence of MRSA was 55.0% in 1997–2002 and 36.6% in 2003–2007 (7,8), indicating a decrease in the prevalence of MRSA. This decrease correlated with a decrease in antimicrobial prescribing rates from 472 per 1,000 clinic visits in 2002 to 256 per 1,000 clinic visits in 2007 (14). The antimicrobial prescribing rate in Sado General Hospital was lower than the previously reported values in the Japanese mainland (14) and in the United States (252 per 1,000 clinic visits in 1999–2000) (13). Patients aged 0–2 years from the west of Sado Island mainly visited Sado General Hospital (84.3% of their clinic visits), while the remaining 15.7% visited general practitioners’ clinics or otolaryngology clinics. The antimicrobial prescribing rate at these clinics was 138 per 1,000 clinic visits (98 prescriptions per 712 clinic visits) in Group-2008, compared with 45
prescriptions per 1,000 clinic visits at our hospital during the same period. The combined prescribing rates in Group-2008 at both our hospital and other clinics (60 per 1,000 clinic visits) was even lower than that in previous reports. Possible confounding factors (e.g., changes in infection control practices) that may have affected the resistance rates in outpatient clinics were not found during our study period. Therefore, the lower prevalence of MRSA (23.6%-5.0%) in Sado Island during the study period (2002-2010) could be attributed to weak antimicrobial pressure because of lower antimicrobial prescribing rate (45-75 per 1,000 clinic visits). A limitation of the study is that we could not obtain the data for antimicrobial prescribing rates from other clinics in the eastern area of Sado Island. Nonetheless, the medical care zone for children was clearly divided between east and west. Hence, antimicrobial prescription at other clinics may have minimal effects on our results. Moreover, the probability of a spontaneous decrease in the prevalence of MRSA cannot be excluded. We have no explanation as to why the MRSA prevalence temporarily increased during 2008 and 2009.

All tested S. aureus isolates were susceptible to trimethoprim/sulfamethoxazole, teicoplanin, linezolid, and vancomycin, and all tested methicillin-susceptible S. aureus (MSSA) and most of the MRSA isolates were susceptible to arbekin and minocycline (Fig. 2A). Of the 1,260 S. aureus isolates, 370 (29.4%) were susceptible to ampicillin (data not shown).

Topical gentamicin has been frequently prescribed for impetigo over the last 2 decades in Japan, and this has led to a high prevalence of gentamicin-resistant S. aureus in Japan (87% in 1997-2002 and 78% in 2003-2007) (7,8). In this study, we detected a lower rate of gentamicin-resistant strains (41.3%) among the S. aureus isolates from patients with SSTI. Nevertheless, the prevalence of gentamicin-resistant S. aureus isolates obtained from skin lesions was higher than that of isolates obtained from other lesions (41.3% versus 28.5%; \( P < 0.05 \)). Because of the high rate of resistance to gentamicin, we stopped prescribing gentamicin for the topical treatment of SSTI and replaced it with tetracycline, which is effective against most S. aureus strains as shown by the minocycline susceptibility data (Fig. 2A). Thus, tetracycline ointment was prescribed for 69.9% of SSTI cases in 2010, in comparison with 29.6% of the cases in 2002, whereas gentamicin was prescribed for only 3.6% of the cases in 2010, in comparison with 57.4% of the cases in 2002.

In conclusion, the interventions in our hospital and on Sado Island in general have resulted in a decline in both antimicrobial prescribing rate and prevalence of MRSA. However, further studies are required to clarify the effect of antimicrobial prescribing rates in controlling of community-associated MRSA.

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Conflict of interest None to declare.

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