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Correlation between antimicrobial consumption and resistance among *Staphylococcus aureus* and enterococci causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009

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Abstract This study investigated the correlation between antibiotic consumption and resistance among *Staphylococcus aureus* and enterococci causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. Overall, the trend of total consumption (defined daily dose [DDD] per 1,000 patient-days) of glycopeptides, including vancomycin and teicoplanin, significantly increased during 2000 to 2003 and remained stable during 2004–2009. Vancomycin consumption significantly increased during 2003 and decreased after 2004. A significant decrease in the resistance rate with time was found for oxacillin- and gentamicin-resistant *S. aureus*. In contrast, the rates of vancomycin- and teicoplanin-resistant enterococci increased significantly. A significant correlation was found between the increased use of extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, carbapenems and the decreased prevalence of methicillin-resistant *S. aureus* (MRSA). In contrast, the increased use of teicoplanin, extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, and carbapenems was correlated with the increased prevalence of vancomycin-resistant enterococci (VRE). In conclusion, this 10-year study in a single institution identified different correlations between the prescription of antibiotics and the resistance rates of MRSA and VRE. Strict implementation of infection control policy based on these correlates would be helpful in decreasing the presence of these multidrug-resistant pathogens in hospitals.

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Introduction

In this era of aged populations and increasing numbers of immunocompromised patients the incidence of healthcare-associated infection (HAI) has risen dramatically and is most often caused by multidrug-resistant bacteria [1, 2]. For Gram-positive bacteria in the US, *Staphylococcus aureus* is

the most common pathogen causing HAI, followed by enterococci [3]. Among these pathogens, methicillin (oxacillin)-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are of greatest concern because the resistant pathogens are associated with extended length of hospital stay, higher cost and greater mortality [1, 4].

Although antibiotic use is the most important risk factor for the emergence of bacterial resistance, the nature of this relationship is complicated. Previous studies which examined the relationship between antimicrobial consumption and antibiotic resistance have had inconsistent findings, which may be due to differences in the resistance profiles and antibiotic prescribing practices in different countries [5–10]. The prevalence of MRSA and VRE was shown to be associated with the use of glycopetides, extended-spectrum cephalosporins, and fluoroquinolones [11–18]. This study investigated the correlation between antibiotic consumption and antimicrobial resistance of MRSA and VRE causing healthcare-associated infection from 2000 to 2009 at a medical center in Taiwan.

Materials and methods

Setting and patients

National Taiwan University Hospital (NTUH) is a 2,500-bed, academically affiliated medical center providing both primary and tertiary care in northern Taiwan. The number of annual patient-days at the hospital increased from 624,675 in 2000 to 751,026 in 2009. Linezolid and fusidic acid were introduced in the hospital formulary in 2002. Some of the data analyzed in this study were included in a previous study [5, 6]. Prior to 2004, no specific and well-established antibiotic control polices were implemented at the hospital. All attending physicians at the hospital can prescribe nearly all antimicrobial agents (except for liposomal amphotericin B, voriconazole, caspofungin, linezolid, and ganciclovir) without the permission of the infection disease specialists.

Antimicrobial agents and consumption

Data on annual consumption (defined daily dose [DDD] per 1,000 patient-days) of glycopetides (vancomycin and teicoplanin), linezolid, fusidic acid, extended-spectrum cephalosporins (cefotaxime, ceftriaxone, flumoxef, ceftazidime, cefempime and cefpirome), β-lactam-β-lactamase inhibitor combinations (ticarcillin-clavulanic acid and piperacillin-tazobactam), carbapenems (imipenem, meropenem and ertapenem), aminoglycosides (amikacin and gentamicin), and fluoroquinolones (ciprofloxacin and levofloxacin) from 2000 to 2009 were obtained from the pharmacy department of the hospital.

Bacterial isolates

To determine the temporal trend of MRSA and VRE causing health-associated infections at NTUH, data on the disk diffusion susceptibilities of *S. aureus* to oxacillin and of enterococci to vancomycin among isolates recovered from 2000 to 2009 were retrieved from annual summary documents as previously reported [1, 2]. Definitions for health-associated infections followed the National Nosocomial Infection Surveillance guidelines [19]. These isolates were non-duplicate samples, as several isolates of each species from each patient recovered within 7 days were considered as a single isolate. Susceptibility testing for *S. aureus* and enterococci followed Clinical and Laboratory Standards Institute (CLSI) guidelines [20]. *S. aureus* ATCC 25923 and *E. faecalis* ATCC 29212 were used as control strains for routine disk susceptibility testing [20]. Methicillin resistance in *S. aureus* was routinely screened for by growth of the isolate on a trypticase soy agar plate containing oxacillin 6 mg/L plus 2% NaCl and incubation in ambient air at 35°C for 24 h [20, 21]. Vancomycin resistance in enterococci was further confirmed by growth of the isolate on a brain heart infusion (BHI) agar with vancomycin 6 mg/L and incubation in ambient air at 35°C for 24 h [20]. *S. aureus* ATCC 29213, *S. aureus* ATCC 43300, *E. faecalis* ATCC 29212 and *E. faecalis* ATCC 51299 were used as control strains.

Statistical analysis

Linear regression analysis was used to analyze the trends of annual consumption of antimicrobial agents and the trends in the nonsusceptible (including intermediate and resistant) rate of *S. aureus* and enterococci causing all healthcare-associated infections with time. Because of the emergence of severe acute respiratory syndrome (SARS) in 2003, the trends of annual consumption of antimicrobial agents were analyzed with three time periods: 2000–2003, 2004–2009, and 2000–2009, with linear regression analysis. Pearson's correlation coefficient was used to determine the relationship between annual antibiotic consumption and trends in resistance. In order to study the lag-time effect, the relationship of the annual consumption of antimicrobial agents and the next year antimicrobial resistance was further explored in pairs using linear regression and Pearson's correlation analysis. A *p* value <0.05 was considered statistically significant.

Results

Annual antibiotic consumption

In general, the use of each individual antimicrobial agent varied with time period (Table 1 and Fig. 1). During 2000 to

Table 1 Annual consumption of several antimicrobial agents at National Taiwan University Hospital, 2000–2009

Antimicrobial agent	Antimicrobial consumption (DDD/1,000 patient-days) by year										Trend analysis								
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2000–2003			2004–2009			2000–2009		
											r	P	b	r	P	b	r	P	b
Glycopeptides	27.2	31.5	32.2	36.0	36.4	29.5	29.1	29.2	32.6	31.2	0.970	**0.030**	2.708	0.313	0.546	−0.473	0.003	0.993	0.003
Extended-spectrum cephalosporins	42.8	59.6	74.1	81.2	85.7	88	85.8	85.5	127.9	121.1	0.986	**0.014**	12.970	0.797	0.058	8.469	0.915	**<0.0005**	7.612
β-lactam-β-lactamase inhibitor combinations	12.8	14.9	15.4	19.6	18.4	25.1	27.8	26.1	19.8	33.9	0.947	0.053	2.090	0.568	0.239	1.711	0.85	**0.001**	1.873
Carbapenems	20.6	24.6	23.3	29.5	27.3	25.2	26.8	26.7	30.6	33.9	0.880	0.120	2.540	0.814	**0.049**	1.403	0.812	**0.004**	1.021
Fluoroquinolones	76.4	106.7	115.7	170.6	170	171.5	187.3	159.4	155.5	157.4	0.958	**0.042**	29.160	0.617	0.192	−3.969	0.696	**0.025**	8.125
Aminoglycosides	54.7	51.4	48.8	41.2	35.8	30.4	23.8	20.4	21.5	20.7	0.968	**0.032**	−4.310	0.897	**0.015**	−3.017	0.974	**<0.005**	−4.333

r correlation coefficient, b regression coefficient

Statistically significant association (marked in bold type, $P<0.05$). Aminoglycosides included amikacin, and gentamicin; β-lactam-β-lactamase inhibitor combinations included ticarcillin-clavulanic acid and piperacillin-tazobactam; carbapenems included imipenem, meropenem, and ertapenem; extended-spectrum cephalosporins included cefotaxime, ceftriaxone, flumoxef, ceftazidime, cefepime, and cefpirome; fluoroquinolones included ciprofloxacin and levofloxacin

2003, a significant increase in consumption of glycopetides, extended-spectrum cephalosporins, and fluoroquinolones was found while a decrease in consumption was found for aminoglycosides. From 2004 to 2009, only the prescription of carbapenems and aminoglycosides significantly increased and decreased, respectively. Overall, the consumption of extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, carbapenems, and fluoroquinolones significantly increased while the consumption of aminoglycosides decreased during the study period. Vancomycin consumption significantly increased during 2003 ($r=0.96$, $p=0.03$, b=2.28) and decreased after 2004 ($r=0.84$, $p=0.036$, $b=−1.00$). In contrast, the teicoplanin use remained stable during the study period ($r=0.47$, $p=0.18$, $b=0.28$). In addition, the trend in consumption of linezolid insignificantly increased from 2.2 DDD per 1,000 patient-days in 2002 to 66.5 DDD per 1,000 in 2009, while the trend for fusidic acid use remained stable from 2002 to 2009.

Trend of antimicrobial resistance among *S. aureus* and enterococci isolates

A total of 4,352 non-duplicate *S. aureus* and 3,673 enterococci isolates were identified and tested for susceptibility. Table 2 shows the trends in the resistance rate of *S. aureus* and enterococci isolates. A significant decrease in the resistant rate with time was found for oxacillin- and gentamicin-resistant *S. aureus*. In contrast, a significant increase in resistance rates was found for vancomycin- and teicoplanin-resistant enterococci.

Correlation between antibiotic consumption and rate of resistance

The correlation between the rates of resistant MRSA and VRE causing healthcare-associated infections and the annual consumption of the specific antibiotics are shown in Tables 3 and 4. A significant correlation was found between the increased use of extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, carbapenems and the decreased prevalence of MRSA. In contrast, a significant positive correlation was found between the increased use of teicoplanin, extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, carbapenems and the increased prevalence of VRE. Decreased prescription of aminoglycosides was correlated with the decreased prevalence of MRSA and the increased prevalence of VRE.

Discussion

This study evaluated the association between antibiotic consumption and the antimicrobial resistance of MRSA and

Fig. 1 Portions of annual consumption (defined daily dose (DDD) per 1,000 patient-days) of vancomycin, teicoplanin, linezolid and fusidic acid
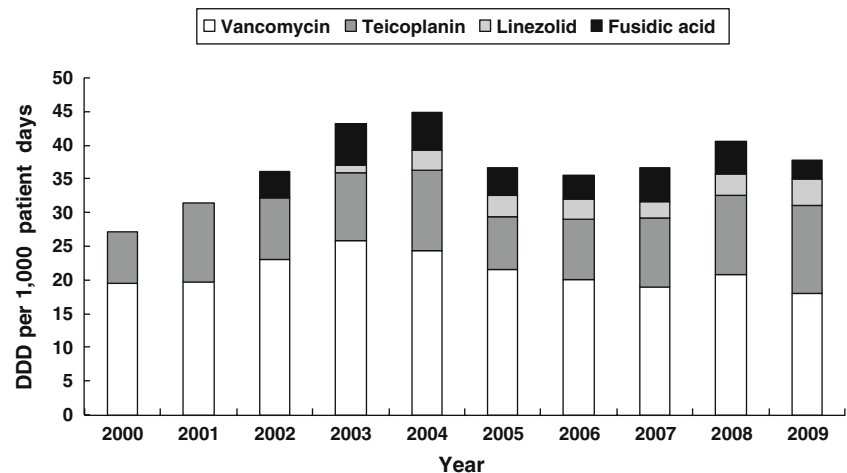
VRE causing healthcare-associated infection in a medical center in Taiwan during a 10-year period. The first noteworthy finding of this study was that the trend in the consumption of extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, carbapenems, and fluoroquinolones significantly increased during the study period; however, the trend for consumption of glycopeptides, with significant increases only during 2000 to 2003, was followed by stable consumption during the next six years. As has been previously documented, the emergence of SARS led to acknowledgement of the need for more stringent infection control measures by physicians and in healthcare-associated infection policy. The revised policies reflected the need for more cautious intervention but not misuse of antibiotics. The slow-down in the increasing use of antibiotics documented in this work thus appears to have resulted from the implementation of

infection control intervention measures after the emergence of SARS. In addition, the consumption of aminoglycosides significantly decreased during this period, which is probably attributable to changes in prescription practices due to the notable side effects of these agents.

A second noteworthy finding of this study is that the prevalence of MRSA significantly increased from 71.8% in 2000 to 78.2% in 2002 (peak) and finally decreased to 54.9% in 2009. A similar trend was noted for gentamicin-resistant *S. aureus*. As stated above, stricter infection control policy after the emergence of SARS and another simple measure—hand washing—have been intensively carried out since 2003. Therefore, the declining prevalence of MRSA could be partly explained by the aggressive policy of infection control and the resulting decreased risk of hand transmission. However, the prevalence VRE and teicoplanin-resistant enterococci significantly increased up

Table 2 Prevalence trends of Gram-positive bacteria causing healthcare-associated infections not susceptible to the indicated antimicrobial agent at National Taiwan University Hospital, 2000–2009

Organism/antimicrobial agent	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	r	P	b
Staphylococcus aureus													
Number of isolates	524	427	518	465	462	416	448	374	372	346			
Oxacillin	71.8	77.4	78.2	74.6	73.7	71.4	73.4	67.6	59.9	54.9	0.814	**0.004**	−2.021
Gentamicin	68.7	74.2	71.9	69.3	64	64.4	63	60	51.6	44.2	0.905	**0.000**	−2.768
Fusidic acid			6.9	2.9	3.9	5.6	5.5	6.9	7.5	6.2	0.498	0.209	0.321
Teicoplanin							1.6	0.3	0.3	0.9	0.438	0.562	−0.210
Enterococcus spp.													
Number of isolates	241	258	230	328	354	355	346	420	579	562			
Vancomycin	1.7	6.2	3.9	6.1	4	4	6.1	8.9	16.5	25.1	0.787	**0.007**	1.865
Teicoplanin			4.1	5.9	3.7	−	4.9	6.9	12.2	22.4	0.778	**0.040**	1.984
Gentamicin		53.4	46.7	63.7	65.7	62.6	59.5	56.2	55.1	56.6	0.130	0.738	0.280

r correlation coefficient, *b* regression coefficient

Statistically significant association (marked in bold type, *P*<0.05)

Table 3 Relationship between rates of methicillin-resistant *Staphylococcus aureus* (MRSA) causing healthcare-associated infection and annual consumption of several antibiotics at National Taiwan University Hospital, 2000–2009

Antibiotic agents	MRSA			MRSA (one year lag)		
	γ	P	b	γ	P	b
Vancomycin	0.515	0.128	1.526	0.237	0.538	0.783
Teicoplanin	0.508	0.134	−2.081	−0.342	0.368	0.995
Glycopeptides	0.123	0.734	0.312	0.002	0.995	0.006
Extended-spectrum cephalosporins	0.787	**0.007**	−0.235	−0.832	**0.005**	−0.286
β-lactam-β-lactamase inhibitor combinations	0.641	**0.046**	−0.723	−0.532	0.140	−0.797
Carbapenems	0.736	**0.015**	−1.453	−0.668	**0.049**	−1.732
Aminoglycosides	0.707	**0.022**	0.395	0.863	**0.003**	0.517
Ciprofloxacin	0.312	0.380	0.215	0.559	0.117	0.384
Levofloxacin	0.239	0.506	−0.071	−0.526	0.146	−0.156
Fluoroquinolones	0.247	0.492	−0.053	−0.482	0.189	−0.103

r correlation coefficient, *b* regression coefficient

Statistically significant association (marked in bold type, $P<0.05$). Aminoglycosides included amikacin, and gentamicin; β-lactam-β-lactamase inhibitor combinations included ticarcillin-clavulanic acid and piperacillin-tazobactam; carbapenems included imipenem, meropenem, and ertapenem; extended-spectrum cephalosporins included cefotaxime, ceftriaxone, flumoxef, ceftazidime, cefempime, and cefpirome; fluoroquinolones included ciprofloxacin and levofloxacin; glycopeptides included vancomycin and teicoplanin

to more than 20% during the study period. These differences most likely resulted from the character of the bacteria itself as enterococci colonized the gastrointestinal tract of hospitalized patients. Therefore, more effective infection control interventions continue to be needed to prevent the spread of VRE.

In addition to infection control, we were also interested in the relationship between antibiotic use and the preva-lence of MRSA related healthcare-associated infection. In contrast to previous studies [5, 11, 14, 22] we found a negative correlation between the use of extended-spectrum cephalosporins, β-lactam-β-lactamase inhibitor combinations, and carbapenems and the prevalence of MRSA. We demonstrated that the consumption of extended-spectrum cephalosporins and carbapenems reduced the rate of MRSA with a 1-year lag. On the contrary, the prescription of

Table 4 Relationship between rates of vancomycin-resistant enterococci (VRE) causing healthcare-associated infection and annual consumption of several antibiotics at National Taiwan University Hospital, 2000–2009

Antibiotic agents	VRE			VRE (one year lag)		
	γ	P	b	γ	P	b
Vancomycin	0.455	0.187	−1.287	−0.399	0.287	−1.193
Teicoplanin	0.716	**0.020**	2.802	0.263	0.495	1.170
Glycopeptides	0.056	0.877	0.136	−0.168	0.666	−0.383
Extended-spectrum cephalosporins	0.817	**0.004**	0.233	0.734	**0.024**	0.229
β-lactam-β-lactamase inhibitor combinations	0.658	**0.039**	0.708	0.315	0.410	0.427
Carbapenems	0.854	**0.002**	1.611	0.495	0.175	1.165
Aminoglycosides	0.641	**0.046**	−0.341	−0.687	**0.041**	−0.373
Ciprofloxacin	0.085	0.816	−0.056	−0.531	0.142	−0.331
Levofloxacin	0.213	0.554	0.060	0.276	0.473	0.074
Fluoroquinolones	0.261	0.467	0.053	0.193	0.618	0.037

r correlation coefficient, *b* regression coefficient

Statistically significant association (marked in bold type, $P<0.05$). Aminoglycosides included amikacin, and gentamicin; β-lactam-β-lactamase inhibitor combinations included ticarcillin-clavulanic acid and piperacillin-tazobactam; carbapenems included imipenem, meropenem, and ertapenem; extended-spectrum cephalosporins included cefotaxime, ceftriaxone, flumoxef, ceftazidime, cefempime, and cefpirome; fluoroquinolones included ciprofloxacin and levofloxacin; glycopeptides included vancomycin and teicoplanin

aminoglycosides was positively correlated with the preva-
lence of MRSA with and without a time lag. Most
importantly, all of the MRSA were susceptible to vanco-
mycin and most MRSA remained susceptible to teicoplanin
during the 10-year period.

Besides MRSA, the epidemiology of VRE could be
affected by the use of antibiotics including third-generation
cephalosporins and vancomycin [16]. In this work, we
further confirmed that the consumption of teicoplanin, β-
lactam-β-lactamase inhibitor combinations, and carbape-
nems were positively correlated with an increased rate of
VRE. In addition, aminoglycosides exerted a protective
effect against this resistance, which lasted as long as one
year.

This study had one major limitation. Although we found
a relationship between antibiotic use and the resistance rate
among MRSA and VRE, these results must be interpreted
with care. The cause of emergence of drug resistant bacteria
in the hospital is complex and selective pressure from
widespread use of antimicrobials might only partly explain
investigational results. In fact, the prevalence of MRSA and
VRE are susceptible to several factors such as infection
control measures and hand hygiene, or operational changes
in the hospital (such as shorter length of stay because of the
shift of procedures or rehabilitation to an outpatient setting,
etc.), or even the epidemiology of patients (i.e. shifts
towards an ageing population with more chronic diseases
over a decade-long period). Their effect was not measured
in this study, hence their impact on MRSA and VRE trends
remains unknown. Besides, because this was an ecological
surveillance, we could not analyze the impact of individual
level, duration of exposure to antibiotics or possibility of
clonal spreads of resistant bacteria to determine their further
correlation with the identified associations.

In conclusion, this 10-year study in an institution
provided a profile of the different correlations between the
prescription of antibiotics and the resistant rate of MRSA
and VRE. Strict implementation of infection control policy
including appropriate antimicrobial prescription and simple
infection control measures including hand washing are
positively correlated with a decreased presence of MRSA in
the hospital.

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