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Nosocomial infections due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci at a university hospital in Taiwan from 1991 to 2003: resistance trends, antibiotic usage and in vitro activities of newer antimicrobial agents

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Abstract

A rapid increase of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection (from 39% in 1991 to 75% in 2003) and vancomycin-resistant enterococci (VRE) (from 1.2% in 1996 to 6.1% in 2003) at a university hospital in Taiwan was found. The noticeable rise of MRSA and VRE was significantly correlated with the increased consumption of glycopeptides, β-lactam–β-lactamase inhibitor combinations, extended-spectrum cephalosporins, carbapenems and fluoroquinolones (Pearson's correlation coefficient, $P < 0.05$). Minimum inhibitory concentrations (MICs) of 100 non-duplicate blood isolates of MRSA (in 2003) and of 25 non-duplicate isolates of vancomycin-resistant *Enterococcus faecalis* and 172 vancomycin-resistant *Enterococcus faecium* (in 1996–2003) causing nosocomial infection recovered from various clinical specimens of patients treated at the hospital to nine antimicrobial agents were determined by the agar dilution method. All of these isolates were susceptible to linezolid and were inhibited by 0.5 mg/L of tigecycline, and all MRSA isolates were inhibited by daptomycin 1 mg/L, including two isolates of MRSA with heteroresistance to vancomycin. Daptomycin had two-fold better activity against vancomycin-resistant *E. faecalis* (MIC_{90}, 2 mg/L) than against vancomycin-resistant *E. faecium* (MIC_{90}, 4 mg/L). Decreased susceptibilities of vancomycin-resistant *E. faecium* and MRSA to quinupristin/dalfopristin (non-susceptibility 25% and 8%, respectively) were found. Telithromycin had poor activity against the isolates tested (MIC_{90}, 8 mg/L). Linezolid, daptomycin and tigecycline may represent therapeutic options for infections caused by these resistant Gram-positive organisms.

Keywords: Methicillin-resistant *Staphylococcus aureus*; Vancomycin-resistant enterococci; Antibiotic consumption; In vitro activities

1. Introduction

Antimicrobial drug resistance has become a great public health problem worldwide. Among the resistant Gram-positive pathogens, methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate or -resistant *S. aureus* (VISA or VRSA) and vancomycin-resistant enterococci (VRE) are of great concern because of the importance of these organisms in causing various types of nosocomial infections [1–5]. Increases in the prevalence of these resistant pathogens in hospitals are frequently related to the high selective pressure of antibiotics, including extended-spectrum cephalosporins, fluoroquinolones and glycopeptides [1,3,6–14]. Newer antimicrobial agents (oxazolidinones, daptomycin and streptogramins) with novel antimicrobial mechanisms have been developed to

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treat infections caused by these resistant Gram-positive bacteria [15–26]. Among these agents, linezolid was introduced in Taiwan in 2002, and quinupristin/dalfopristin and daptomycin will be available within the next few years.

In Taiwan, the prevalence of MRSA in hospitals has been steadily increasing over the past decade [5,18,27]. Moreover, MRSA strains with reduced susceptibility to vancomycin, i.e. VISA and heterogeneously resistant VISA, and VRE, causing invasive nosocomial infections have been reported recently [4,14]. This study aimed to describe the trend of increasing prevalence of MRSA and VRE at National Taiwan University Hospital (NTUH) from 1991 to 2003, to elucidate the relationship between annual antibiotic consumption at the hospital and the trends of resistance, and to determine the potential roles of some newer agents in the treatment of infections caused by these resistant pathogens.

2. Materials and methods

2.1. Setting

NTUH is a 1800-bed university hospital located in northern Taiwan. The Nosocomial Infection Control Committee of the hospital was established in 1980 [5]. Definitions for nosocomial infection followed the National Nosocomial Infections Surveillance Guidelines [28]. The number of annual patient-days at the hospital increased from 360 210 in 1991 to 672 676 in 2002, but slightly decreased in 2003 (629 168) owing to the severe acute respiratory syndrome epidemic in Taiwan. The antimicrobial agent teicoplanin was introduced into the hospital in 1995 and the antibiotic linezolid in 2002. Quinupristin/dalfopristin, telithromycin and daptomycin were not available in the hospital during the study period.

2.2. Antibiotic consumption and the trend of resistance

Data on annual consumption (defined daily dose (DDD) per 1000 patient-days) of extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, flumoxef, cefepime and cefpirome), β-lactam–β-lactamase inhibitor combinations (ticarcillin/clavulanic acid and piperacillin/tazobactam), carbapenems (imipenem and meropenem), glycopeptides (vancomycin and teicoplanin), aminoglycosides (amikacin, gentamicin and tobramycin), injectable ciprofloxacin, all fluoroquinolones (ciprofloxacin (oral and injectable) and oral levofloxacin and moxifloxacin) and linezolid from 1991 to 2003 were obtained from the Pharmacy Department of the hospital. To determine the temporal trend of MRSA and VRE causing nosocomial infections at NTUH, data on the disk diffusion susceptibilities of *S. aureus* to oxacillin and of enterococci to vancomycin among isolates recovered from 1991 to 2003 were retrieved from the annual summary documents. Susceptibility testing for *S. aureus* and enterococci followed the National Committee for Clinical Laboratory Standards (NCCLS) guidelines [29]. *Staphylococcus aureus* ATCC 25923 and *E. faecalis* ATCC 29212 were used as control strains for routine disk susceptibility testing [29]. Methicillin resistance in *S. aureus* was routinely screened by growth of the isolate on a trypticase soy agar plate containing oxacillin 6 mg/L plus 2% NaCl and incubated in ambient air at 35 °C for 24 h [29–31]. Vancomycin resistance in enterococci was further confirmed by growth of the isolate on a brain heart infusion (BHI) agar with vancomycin 6 mg/L [29–31] and incubated in ambient air at 35 °C for 24 h. *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC 43300, *E. faecalis* ATCC 29212 and *E. faecalis* ATCC 51299 were used as control strains.

2.3. Bacterial isolates

The minimum inhibitory concentrations (MICs) and susceptibility patterns were tested for 100 consecutive, non-duplicate blood isolates of MRSA from 100 patients who developed nosocomial bacteraemia at the hospital in 2003, and for 25 isolates of vancomycin-resistant *E. faecalis* and 172 isolates of vancomycin-resistant *E. faecium* from various clinical specimens of patients treated from 1996 to 2003. Two isolates of heteroresistant VISA from two patients with recurrent bacteraemia found in 2000–2002 were also included in this analysis [14]. The isolates were stored at −70 °C in trypticase soy broth (BBL Microbiology Systems, Cockeysville, MD, USA) supplemented with 15% glycerol before testing.

2.4. Antimicrobial agents

The following antimicrobial agents were provided by their manufacturers for use in this study: penicillin and tetracycline (Sigma Chemical Co., St Louis, MO, USA); oxacillin (Bristol-Myers Squibb, Princeton, NJ, USA); vancomycin (Eli Lilly & Co., Indianapolis, IN, USA); teicoplanin, quinupristin/dalfopristin and telithromycin (Aventis Pharma, Romainville, France); linezolid (Pharmacia, Kalamazoo, MI, USA); tigecycline (Wyeth-Ayerst, Pearl River, NY, USA); and daptomycin (Cubist Pharmaceuticals, Lexington, MA, USA).

2.5. Antimicrobial susceptibility testing

MICs were determined for all isolates using the agar dilution method and the broth microdilution method (daptomycin only) according to the guidelines established by the NCCLS [30,31]. The isolates were grown overnight on trypticase soy agar plates supplemented with 5% sheep blood (BBL Microbiology Systems) at 37 °C for 24 h. Bacterial inocula were prepared by suspending the freshly grown bacteria in sterile normal saline and adjusted to a 0.5 McFarland standard. For susceptibility testing of MRSA and VRE isolates for daptomycin, dry-form microtitre plates containing daptomycin with physiological concentrations of Ca^{2+} (50 mg/L) manufactured by TREK Diagnostic Sys-

tems (Cleveland, OH, USA) were used. For susceptibility testing of MRSA for oxacillin, Mueller–Hinton agar (BBL Microbiology Systems) supplemented with 2% NaCl was used [30]. For susceptibility testing of MRSA for other agents and for VRE, an unsupplemented Mueller–Hinton agar (BBL Microbiology Systems) was used. Using a Steers replicator, an organism density of 10^4 colony-forming units (CFU)/spot was inoculated onto an appropriate plate with various concentrations of antimicrobial agent and incubated at 35 °C for 24 h in ambient air.

Regular quality assurance was performed among isolate processing with the American Type Culture Collection (ATCC) as control strains: *S. aureus* ATCC 29213, *S. aureus* ATCC 43300, *E. faecalis* ATCC 29212 and *E. faecalis* ATCC 51299. Isolates were classified as susceptible, intermediate or resistant according to the NCCLS criteria [31]. Phenotypes (VanA, VanB or VanC) of VRE were defined as described previously [4]. There are no NCCLS MIC breakpoints for interpreting susceptibilities to telithromycin for *Enterococcus* species, or for tigecycline both for *Enterococcus* and *Staphylococcus* species [31].

2.6. Statistical analysis

Pearson's correlation coefficient was used to determine the relationship of annual antibiotic consumption and annual rates of MRSA and VRE causing nosocomial infections. A *P*-value <0.05 was considered statistically significant.

3. Results

Fig. 1 shows the annual rates of nosocomial MRSA and VRE infections from 1991 to 2003 at NTUH. A stepwise increase of nosocomial infections due to MRSA (from 39% in 1991 to 78% in 2002) and VRE (from 1.2% in 1996 to 6.1% in 2003) was found. An increased consumption (DDDs per 1000 patient-days; fold of increase of DDDs per 1000 patient-days) from 1991 to 2003 was found for glycopeptides (8.87 to 36.03; 4.1), extended-spectrum cephalosporins (20.20 to 56.25; 2.8), β-lactam–β-lactamase inhibitor combinations (0 to 19.55), all fluoroquinolones (0.49 to 170.59; 348.1), ciprofloxacin (0.32 to 34.36; 107.3) and carbapenems (5.55 to 29.50; 5.13). The consumption of aminoglycosides in 1991 was 38.12, increased to 136.8 in 1998, and declined stepwise to 42.24 in 2003.

After the introduction of linezolid in 2002, the DDDs of this agent increased from 0.23 in 2002 to 1.16 in 2003, and a 3% decrease in the rate of MRSA was seen in 2003 compared with 2002. The increase of nosocomial MRSA (1991–2003) and VRE (1996–2003) infections was significantly correlated (Pearson's correlation coefficient) with the increased consumption of glycopeptides ($R = 0.799$, $P < 0.001$ [MRSA] and $R = 0.929$, $P < 0.001$ [VRE]), extended-spectrum cephalosporins ($R = 0.923$, $P < 0.001$ [MRSA] and $R = 0.906$, $P = 0.002$ [VRE]), β-lactam–β-lactamase inhibitor combinations ($R = 0.761$, $P = 0.003$ [MRSA] and $R = 0.813$, $P = 0.014$ [VRE]), carbapenems ($R = 0.738$, $P = 0.004$ [MRSA] and $R = 0.833$, $P < 0.001$ [VRE]) and all fluoroquinolones ($R = 0.789$, $P = 0.001$ [MRSA] and $R = 0.908$, $P < 0.001$ [VRE]) at the hospital. Increased injectable ciprofloxacin use was significantly associated with an increased rate of MRSA ($R = 0.907$, $P < 0.001$) but not VRE ($R = 0.661$, $P = 0.0075$) nosocomial infections.

MICs of antimicrobial agents tested for the two control strains were within the ranges provided by the NCCLS. MICs

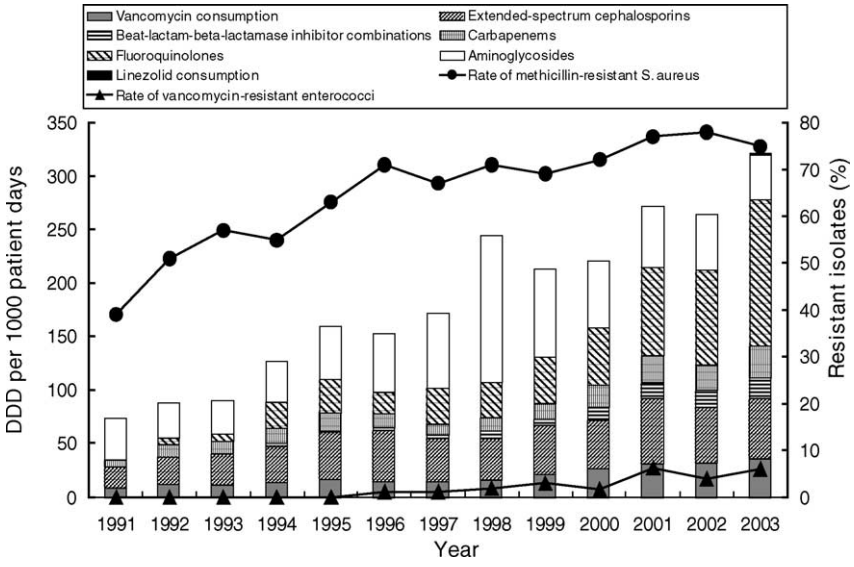

Fig. 1. Association between the prevalence of methicillin-resistant *S. aureus* and vancomycin-resistant enterococci causing nosocomial infections and annual consumption (defined daily dose (DDD) per 1000 patient-days) of extended-spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, flumoxef, cefepime and cefpirome), β-lactam–β-lactamase inhibitor combinations (ticarcillin/clavulanic acid and piperacillin/tazobactam), carbapenems (imipenem and meropenem), glycopeptides (vancomycin and teicoplanin), aminoglycosides (amikacin, gentamicin and tobramycin), injectable ciprofloxacin, all fluoroquinolones (ciprofloxacin (oral and injectable) and oral levofloxacin and moxifloxacin) and linezolid at National Taiwan University Hospital, 1991–2003.

Table 1
In vitro activities of daptomycin, tigecycline and other antimicrobial agents against Gram-positive bacteria

Antimicrobial agent	MIC (mg/L)			Number (%) of isolates		
	Range	MIC_{50}	MIC_{90}	S	I	R
Methicillin-resistant *S. aureus* (*N* = 100)						
Penicillin	2–128	64	64	0 (0)	–	100 (100)
Vancomycin	0.5–4	1	1	100 (100)	0 (0)	0 (0)
Teicoplanin	0.5–16	2	2	99 (99)	1 (1)	0 (0)
Quinupristin/dalfopristin	0.5–4	1	1	92 (92)	7 (7)	1 (1)
Linezolid	1–2	2	2	100 (100)	0 (0)	0 (0)
Telithromycin	0.06–>32	>32	>32	14 (14)	0 (0)	86 (86)
Tetracycline	0.25–>128	>128	>128	15 (15)	0 (0)	85 (85)
Tigecycline	0.12–0.5	0.5	0.5	–	–	–
Daptomycin	0.5–1	0.5	1	100 (100)	–	–
Vancomycin-resistant *E. faecalis* (*N* = 25)						
Penicillin	2–4	4	4	25 (100)	–	0 (0)
Vancomycin	>128	>128	>128	0 (0)	0 (0)	25 (100)
Teicoplanin	8–32	16	32	4 (16)	10 (40)	11 (44)
Quinupristin/dalfopristin	8–32	16	32	0 (0)	0 (0)	25 (100)
Linezolid	2	2	2	25 (100)	0 (0)	0 (0)
Telithromycin	0.25–8	4	8	–	–	–
Tetracycline	0.25–>128	128	>128	3 (12)	0 (0)	22 (88)
Tigecycline	0.06–0.25	0.25	0.25	–	–	–
Daptomycin	1–4	2	2	25 (100)	–	–
Vancomycin-resistant *E. faecium* (*N* = 172)						
Penicillin	0.12–>128	>128	>128	3 (2)	–	169 (98)
Vancomycin	8–>128	>128	>128	0 (0)	2 (1)	170 (99)
Teicoplanin	0.25–128	32	64	9 (5)	2 (1)	161 (94)
Quinupristin/dalfopristin	0.5–16	1	2	129 (75)	27 (16)	16 (9)
Linezolid	0.5–2	2	2	172 (100)	0 (0)	0 (0)
Telithromycin	0.03–8	4	8	–	–	–
Tetracycline	0.06–>128	0.25	32	150 (87)	0 (0)	22 (13)
Tigecycline	0.03–0.12	0.06	0.06	–	–	–
Daptomycin	0.5–8	4	8	155 (90)	–	–

MIC, minimum inhibitory concentration.

of *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212 were 0.25–0.5 mg/L and 2 mg/L, respectively, for daptomycin, and 0.12–0.25 mg/L and 0.06–0.12 mg/L, respectively, for tigecycline. All MRSA isolates were susceptible to vancomycin and linezolid (Table 1). One isolate of MRSA was not susceptible to teicoplanin (MIC, 16 mg/L) and eight isolates (8%) were not susceptible to quinupristin/dalfopristin. Telithromycin and tetracycline had poor activities (>85% were resistant) against the MRSA isolates tested.

Among the vancomycin-resistant *E. faecalis* isolates, 21 (84%) presented the VanA phenotype and four the VanB phenotype. All were susceptible to penicillin and linezolid. Among vancomycin-resistant *E. faecium* isolates, 161 (94%) exhibited the VanA phenotype and 11 (6%) the VanB phenotype. All of the isolates were susceptible to linezolid, but one-quarter was not susceptible to quinupristin/dalfopristin.

For daptomycin, all MRSA were susceptible (MIC $\leq$ 1 mg/L) and 90% of the vancomycin-resistant *E. faecium* and all vancomycin-resistant *E. faecalis* were susceptible (MICs $\leq$ 4 mg/L). Daptomycin had four-fold better activity against vancomycin-resistant *E. faecalis* (MIC_{90}, 2 mg/L) than against vancomycin-resistant *E. faecium* (MIC_{90}, 8 mg/L). Tetracycline had better activity against vancomycin-resistant *E. faecium* than against MRSA and vancomycin-resistant *E. faecalis*. All isolates tested were inhibited by tigecycline 0.5 mg/L, including MRSA and *E. faecalis* isolates that were highly resistant to tetracycline (MICs $\geq$ 128 mg/L). Tigecycline had 4-fold to 512-fold greater activity against vancomycin-resistant *E. faecium* isolates than tetracycline.

The two isolates of heteroresistant VISA were susceptible to quinupristin/dalfopristin and linezolid but highly resistant to tetracycline (MICs, 128 mg/L) and telithromycin (MICs > 32 mg/L). These two isolates both had daptomycin MICs of 1 mg/L and tigecycline MICs of 0.5 mg/L.

4. Discussion

This study had two important findings. First, among the newer agents developed for the treatment of infections caused by drug-resistant Gram-positive bacteria, linezolid, daptomycin and tigecycline, but not quinupristin/dalfopristin, exhibited excellent in vitro activity both against MRSA and VRE isolates. Second, the stepwise increase of MRSA in the past 13 years and the emergence of VRE in past 7

years were significantly associated with the increasing hospital consumption of several classes of antimicrobial agents, particularly glycopeptides, β-lactam–β-lactamase inhibitor combinations, extended-spectrum cephalosporins, carbapenems and fluoroquinolones ($P < 0.05$).

The relationship between antimicrobial use and the prevalence of MRSA causing nosocomial infections is complex. The positive correlation between the prevalence of MRSA and antibiotic use established at the level of the hospital unit is particularly strong for β-lactam antibiotics and fluoroquinolones [3,6,8,10,11,32]. However, a positive correlation was also found with the use of carboxy- or ureido-penicillin and ceftazidime, cefsulodin, amoxicillin/clavulanic acid, macrolides and fluoroquinolones (levofloxacin or ciprofloxacin) [8,10,32]. Our findings were partly in accordance with previous observations [3,6,8,10,11,32]. Interestingly, despite the vast increase in MRSA rates and the increases in antibiotic consumption, the organisms continued to be fully susceptible to vancomycin.

Antibiotic use is also able to influence nosocomial VRE epidemiology through different mechanisms [9]. High rates of vancomycin or third-generation cephalosporin use have been reported to be associated with increased prevalence of VRE in hospitals [1,2,9,33,34]. The risk of VRE colonisation varies during exposure to different β-lactam antimicrobials, with higher tendency to promote colonisation in cefotetan, ceftriaxone or ceftazidime [7,12,33]. Our study also confirmed that consumption of all fluoroquinolones (but not injectable ciprofloxacin alone) is positively correlated with an increased rate of VRE. Further research should be conducted to clarify this association.

The great majority of linezolid- and vancomycin-resistant *E. faecium* infections reported have occurred in patients treated with linezolid [35,36]. Patients without prior exposure to linezolid could also acquire linezolid- and vancomycin-resistant *E. faecium* infection via nosocomial transmission [36]. A 17% decline of linezolid susceptibility for vancomycin-resistant *E. faecium* was reported more than 6 months after its introduction into clinical use [35]. At our hospital, linezolid was introduced into clinical use in 2002. Although this drug was allowed in the treatment of VRE infections or in patients with MRSA infections refractory or intolerant to glycopeptide treatment, a five-fold increase in consumption was found in 2003 compared with 2002. Routine testing of linezolid susceptibility among these resistant Gram-positive bacteria, particularly among vancomycin-resistant *E. faecium* isolates, is mandatory and has been performed in this hospital since 2004.

Eighty-six per cent of the MRSA isolates were resistant to telithromycin. This finding is in line with that of a previous global study (82%) [18]. Canton et al. demonstrated that MRSA isolates harbouring constitutive macrolide–lincosamide–streptogramin B mechanism (MLS_B) of resistance phenotype were also resistant to telithromycin [18]. Our previous study indicated that the majority of MRSA isolates in Taiwan were highly resistant to macrolides ($MIC_{50} > 128$ mg/L) and possessed the MLS_B phenotype [3].

Our results on daptomycin susceptibility are generally comparable with other published data on clinical isolates from Europe and North American [19,23,25,26]. All isolates of MRSA and 17 isolates (10%) of vancomycin-resistant *E. faecium* were not susceptible to daptomycin. Bacteraemia due to daptomycin-resistant MRSA (MIC, 2 mg/L) and emergence of daptomycin resistance ($MICs \geq 32$ mg/L) in *E. faecium* during daptomycin therapy have been previously reported [37,38]. Clinicians and microbiologists should be aware of the existence and the potential of the development of daptomycin resistance during therapy, although this agent is not available for clinical use in Taiwan.

Unlike MRSA and vancomycin-resistant *E. faecalis* isolates, the majority (87%) of our vancomycin-resistant *E. faecium* were susceptible to tetracycline. Boucher et al. demonstrated that tetracycline MIC_{90} values of MRSA, vancomycin-resistant *E. faecalis* and vancomycin-resistant *E. faecium* were 1 mg/L, 64 mg/L and 64 mg/L, respectively [17]. These findings were not in agreement with our observations. All our MRSA isolates were inhibited by tigecycline 0.5 mg/L and all VRE isolates were inhibited at concentrations between 0.03 mg/L and 0.25 mg/L, independent of the species of enterococci, susceptibility to tetracycline and phenotype of resistance. Our results were in agreement with previous findings [16–18,22,23].

Tigecycline has been proved to be active against drug-resistant Gram-positive pathogens, including MRSA, VISA and VRE, and had better in vitro activities against these resistant organisms than daptomycin [17,23]. Petersen et al. demonstrated that the activity of daptomycin (MIC_{90}, 0.5 mg/L) could improve and equal that of tigecycline against MRSA strains if the test medium (Mueller–Hinton broth) was supplemented with adequate calcium (50–75 mg/L) [23]. In contrast, MIC_{90} of daptomycin for MRSA and MICs of the two VISA isolates determined in the presence of 50 mg/L calcium in the test medium were two-fold higher than that of tigecycline.

Our report has two limitations. First, our data could not exclude the possibility that the increasing rate of MRSA may have been driving increased consumption, rather than the reverse, because the rate of MRSA was already high (70%) in 1996, when the DDD of glycopeptide was 50% of the consumption in 2003. Furthermore, the increased resistance could be a general trend (as is happening worldwide) and widespread use antimicrobials might contribute partly to this trend. Second, the rate of MRSA and VRE may be overestimated due to the possible hospital-wide dissemination of clonally-related isolates [4,14,39]. Failure to adhere to the guidelines from the Hospital Infection Control Practice Advisory Committee might result in an increase in hospital-acquired VRE [39].

In conclusion, implementation of programmes to improve antimicrobial prescription practices as well as adherence to appropriate infection control measures to control the spread

of MRSA and VRE are essential components of efforts to alleviate the growing prevalence of these multidrug-resistant pathogens in hospitals. Newer agents, such as linezolid, daptomycin and tigecycline, may represent therapeutic options for infections caused by these organisms.

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