Prevalence and regional variation in methicillin-resistant *Staphylococcus aureus* (MRSA) in the USA and comparative *in vitro* activity of tigecycline, a glycylcycline antimicrobial

Debra A. Goff¹ and Michael J. Dowzicky²

Correspondence

Debra A. Goff
debbie.goff@osumc.edu

¹The Ohio State University Medical Center, Department of Pharmacy, Columbus, OH 43210, USA

²Wyeth Pharmaceuticals, Collegeville, PA, USA

The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) is a surveillance study established in 2004 to monitor the activity of tigecycline, the first glycylcycline, and comparator agents [β -lactams (including penicillins, cephalosporins and carbapenems), glycopeptides, tetracyclines, fluoroquinolones and oxazolidinones] against Gram-positive and Gram-negative pathogens worldwide. This report examines 1692 isolates of *Staphylococcus aureus* collected in the continental United States between January 2004 and September 2005. Methicillin-resistant *S. aureus* (MRSA) accounted for 52.0 % of isolates. Prevalence of MRSA by state ranged from 12.5 % in New Hampshire to 100 % in Kentucky. All isolates were susceptible to tigecycline, linezolid and vancomycin. *In vitro*, tigecycline was potent against both methicillin-susceptible *S. aureus* (MSSA) (MIC₅₀ and MIC₉₀=0.12 μ g ml⁻¹) and MRSA (MIC₅₀=0.12 μ g ml⁻¹; MIC₉₀=0.25 μ g ml⁻¹). Only a single isolate was resistant to three or more antimicrobial classes. Ninety-six isolates (5.7 %) were susceptible to the complete antimicrobial panel.

Received 10 May 2006

Accepted 13 February 2007

INTRODUCTION

Staphylococcus aureus is an opportunistic pathogen and is the causative agent of infections such as bacteraemia, sepsis, toxic shock syndrome, bone and joint infection and skin and skin-structure infections (SSSIs), which can result in significant morbidity and mortality (Cunha, 2005; Padmanabhan & Fraser, 2005; Weber, 2005). Methicillin-resistant *S. aureus* (MRSA) isolates have been a source of serious infections in hospitals (healthcare-acquired MRSA; HA-MRSA) since the 1960s and are frequently resistant to other antimicrobial classes, complicating treatment and reducing therapeutic options (Padmanabhan & Fraser, 2005).

Isolates of community-associated MRSA (CA-MRSA) have also been identified in recent years, which often possess fundamentally different genetic characteristics and risk factors from HA-MRSA. One important example is the Panton–Valentine leukocidin toxin gene, which has been associated with necrotizing pneumonia (Weber, 2005; Moran *et al.*, 2005).

Future monitoring of the epidemiology of HA-MRSA and CA-MRSA will depend in part on microbial surveillance studies. These provide up-to-date information on the emergence, dissemination, frequency and consequences of microbial resistance and are essential tools in aiding the decision-making process for physicians (Koeth & Miller, 2005). T.E.S.T. (the Tigecycline Evaluation and Surveillance Trial) is a global surveillance study initiated in 2004 to examine the *in vitro* activity of tigecycline and comparator agents against recent isolates of key Gram-negative and Gram-positive pathogens [including methicillin-susceptible *S. aureus* (MSSA) and MRSA] from hospitals and the community.

Tigecycline is the first of a new class of antimicrobial agents, the glycylcyclines, which are structurally derived from the tetracycline nucleus. Tigecycline possesses activity against Gram-positive and -negative pathogens, binding to the 30S ribosomal subunit and inhibiting protein synthesis (Bouchillon *et al.*, 2005). Tigecycline does not demonstrate co-resistance with known mechanisms of resistance, including tetracycline resistance (Bergeron *et al.*, 1996). Tigecycline has *in vitro* activity against drug-resistant phenotypes including vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae* (PRSP), MSSA and MRSA and extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* (Fritsche *et al.*, 2005; Hoban *et al.*, 2005). It is

Abbreviations: cIAI, complicated intra-abdominal infection; MRSA, methicillin-resistant *Staphylococcus aureus*; CA-MRSA, community-associated MRSA; HA-MRSA, healthcare-acquired MRSA; MSSA, methicillin-susceptible *S. aureus*; SSSI, skin and skin-structure infection.

All MIC testing was done locally following a standard protocol.

bacteriostatic against most pathogens, although bactericidal activity has been reported against *Streptococcus pneumoniae* and *Haemophilus influenzae* (Zinner, 2005).

This study reports on the relative prevalence of MRSA and MSSA and the occurrence of multidrug resistance (resistance to three or more antimicrobial classes) among *S. aureus* isolates collected in the continental United States as part of T.E.S.T. This report will also compare the activity of tigecycline and several comparator antimicrobials against these strains of MSSA and MRSA.

METHODS

Bacterial isolates. Consecutive isolates of *S. aureus* were collected from 72 centres in 38 states (Table 1) across the continental United States between January 2004 and September 2005. Each participating centre was requested to provide at least 25 *S. aureus* isolates. All isolates were collected from patients aged 1 to 98 years with documented blood, respiratory tract, urine, skin, wound or body fluid infections or infections from other defined sources. Isolates from urine accounted for no more than 25% of isolates from any one centre. One isolate only was accepted per patient. All isolates were identified on-site by the participating laboratory. Laboratories International for Microbiology Studies, a division of International Health Management Associates, Inc. (Schaumburg, IL, USA), was responsible for organism collection, transport and identification confirmation as well as database development and management.

Antimicrobial susceptibility testing. Minimum inhibitory concentrations (MICs) were determined locally using Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) -approved broth microdilution methodology (NCCLS, 2003). Antimicrobial agents included in the testing panel and the testing ranges used in this study (in $\mu\text{g ml}^{-1}$) are presented in Table 2. The MIC interpretive criterion for tigecycline (susceptible breakpoint $\leq 0.5 \mu\text{g ml}^{-1}$) was derived from the recent US Food and Drug Administration product insert for tigecycline. Determination of intermediate or resistant breakpoints is prevented by the current absence of clinical *S. aureus* isolates resistant to tigecycline (Wyeth Pharmaceuticals, 2005). *S. aureus* strains ATCC 25923 and ATCC 29213 were used for quality control of standardized laboratory procedures.

Multidrug resistance is defined for this report as resistance to three or more antimicrobial classes.

RESULTS

A total of 1692 isolates of *S. aureus* were collected across the continental United States during the study period. Of these, 879 (52.0%) were identified as MRSA. Geographical distributions of *S. aureus*, MRSA and MSSA isolates are reported in Table 1. MRSA occurred infrequently in the participating hospital(s) in some states (i.e. $\leq 20\%$ in NH, VT and VA) but was prevalent in others (i.e. all 25 *S. aureus* isolates collected in KY were MRSA). Although MRSA accounted for $\geq 50\%$ of *S. aureus* isolates in 21 states (IL, MI, OH, KS, ND, NE, DC, FL, GA, MD, NC, AL, KY, TN, AR, LA, OK, TX, AZ, NM and WA), the proportion of MRSA and MSSA isolates is approximately equal in many states, with MRSA representing 40–60% of isolates in 25 states.

Table 1. Geographical distribution of *Staphylococcus aureus*, MSSA and MRSA collected across the continental United States between January 2004 and September 2005

State	<i>S. aureus</i> (n)	MSSA (n)	MRSA (n)
New England			
Connecticut (CT)	24	13	11
Massachusetts (MA)	40	27	13
New Hampshire (NH)	24	21	3
Vermont (VT)	25	21	4
Middle Atlantic			
New Jersey (NJ)	96	49	47
New York (NY)	213	110	103
Pennsylvania (PA)	24	14	10
East North Central			
Illinois (IL)	25	11	14
Indiana (IN)	25	13	12
Michigan (MI)	74	33	41
Ohio (OH)	141	68	73
Wisconsin (WI)	22	13	9
West North Central			
Kansas (KS)	25	11	14
Minnesota (MN)	25	16	9
Missouri (MO)	25	15	10
North Dakota (ND)	22	10	12
Nebraska (NE)	25	10	15
South Atlantic			
District of Columbia (DC)	21	6	15
Florida (FL)	66	16	50
Georgia (GA)	91	31	60
Maryland (MD)	45	18	27
North Carolina (NC)	45	15	30
Virginia (VA)	24	20	4
West Virginia (WV)	25	14	11
East South Central			
Alabama (AL)	24	11	13
Kentucky (KY)	25	0	25
Mississippi (MS)	22	12	10
Tennessee (TN)	62	27	35
West South Central			
Arkansas (AR)	22	11	11
Louisiana (LA)	45	22	23
Oklahoma (OK)	24	10	14
Texas (TX)	68	28	40
Mountain			
Arizona (AZ)	40	12	28
New Mexico (NM)	25	12	13
Utah (UT)	25	15	10
Pacific			
California (CA)	68	46	22
Oregon (OR)	45	23	22
Washington (WA)	25	9	16
Totals	1692	813	879

Susceptibility data for all *S. aureus* isolates as well as MSSA and MRSA are presented in Table 3. All isolates were susceptible to tigecycline, linezolid and vancomycin. Minocycline was also highly active: 99.2% of isolates were

Table 2. Antimicrobial testing panel and test ranges ($\mu\text{g ml}^{-1}$) for *S. aureus*

Antimicrobial	Class	Test range
Tigecycline (Tig)	Glycylcycline	0.008–16
Amoxicillin/clavulanate (Aug)	β -Lactam (penicillin)	0.03–8
Ampicillin (Amp)	β -Lactam (penicillin)	0.06–16
Penicillin (Pen)	β -Lactam (penicillin)	0.06–8
Piperacillin/tazobactam (Ppt)	β -Lactam (penicillin)	0.25–16
Ceftriaxone (Cax)	β -Lactam (cephalosporin)	0.03–64
Imipenem (Imp)	β -Lactam (carbapenem)	0.12–16
Levofloxacin (Lvx)	Fluoroquinolone	0.06–32
Linezolid (Lzd)	Oxazolidinone	0.5–8
Minocycline (Min)	Tetracycline	0.25–8
Vancomycin (Van)	Glycopeptide	0.12–32

susceptible, including 99.3 % of MRSA and 99.0 % of MSSA isolates. Some 91.0 % of all *S. aureus* isolates were susceptible to imipenem, although in the subset of MRSA isolates only 82.6 % were susceptible by MIC criteria. Four agents (amoxicillin/clavulanate, piperacillin/tazobactam, levofloxacin and ceftriaxone) demonstrated susceptibilities by MIC criteria of between 40 and 90 % against the complete panel of *S. aureus* isolates; against the subset of MRSA isolates, susceptibility to these agents was low (<32 %). For example, 696 (79.2 %) MRSA isolates across the United States were resistant to levofloxacin, ranging from 47.8 % in LA to 100 % in AZ (Table 4).

Tigecycline testing against all *S. aureus* isolates resulted in the lowest MICs reported in this study, with an MIC₅₀ of 0.12 $\mu\text{g ml}^{-1}$ and an MIC₉₀ of 0.25 $\mu\text{g ml}^{-1}$. Low tigecycline MIC₅₀ and MIC₉₀ results were also reported against the MSSA (MIC₅₀ and MIC₉₀ 0.12 $\mu\text{g ml}^{-1}$) and MRSA (MRSA MIC₅₀ 0.12 $\mu\text{g ml}^{-1}$; MIC₉₀ 0.25 $\mu\text{g ml}^{-1}$) subsets. Minocycline testing produced an MIC₅₀ of ≤ 0.25 and an MIC₉₀ of 0.5 $\mu\text{g ml}^{-1}$ against all isolates. Minocycline was also active against both *S. aureus* subsets, resulting in an MIC₅₀ and MIC₉₀ of ≤ 0.25 $\mu\text{g ml}^{-1}$ against MSSA and an MIC₅₀ of ≤ 0.25 $\mu\text{g ml}^{-1}$ and an MIC₉₀ of 0.5 $\mu\text{g ml}^{-1}$ against MRSA. Vancomycin was also active against *S. aureus*, with an MIC₅₀ of 0.5 $\mu\text{g ml}^{-1}$ and MIC₉₀ of 1 $\mu\text{g ml}^{-1}$ against MSSA and MIC₅₀ and MIC₉₀ of 1 $\mu\text{g ml}^{-1}$ against MRSA. The linezolid MIC₅₀ was 2 $\mu\text{g ml}^{-1}$ against both MSSA and MRSA; its MIC₉₀ was 2 $\mu\text{g ml}^{-1}$ for MSSA and 4 $\mu\text{g ml}^{-1}$ for MRSA.

Considerable variation exists between national and state susceptibility/MIC data. For example, the MIC₉₀ for imipenem against all *S. aureus* isolates across the country was 4 $\mu\text{g ml}^{-1}$; however, nine states (IN, OH, ND, DC, FL, NC, LA, UT and WA) reported imipenem MIC₉₀ values ≥ 2 doubling dilutions higher than the national average, while 16 states (NH, VT, NJ, IL, KS, NE, GA, VA, WV, AL, KY, MS, TN, NM, CA and OR) reported MIC₉₀ values ≥ 2

doubling dilutions lower than the national average (data not shown). This wide range was probably due to regional variations in MRSA occurrence, against which a substantially higher MIC₉₀ for imipenem has been reported in this study (16 $\mu\text{g ml}^{-1}$).

Only 96 (5.7 %) *S. aureus* isolates were susceptible to all antimicrobial agents tested; all were MSSA. Multidrug resistance (resistance to three or more antimicrobial classes) was noted in a single isolate in this study. This isolate was collected from a sputum sample collected from a 16-year-old female in New York. It was resistant to all β -lactams (amoxicillin/clavulanate, ampicillin, penicillin, piperacillin/tazobactam, ceftriaxone and imipenem), fluoroquinolones (levofloxacin) and tetracyclines (minocycline) but was susceptible to tigecycline (MIC 0.5 $\mu\text{g ml}^{-1}$), linezolid (2 $\mu\text{g ml}^{-1}$) and vancomycin (2 $\mu\text{g ml}^{-1}$).

DISCUSSION

Isolates of *S. aureus* resistant to methicillin were first reported in 1961 and have been a common cause of outbreaks in hospitals since the 1970s (Cunha, 2005). By 2003, MRSA accounted for 59.5 % of nosocomial *S. aureus* infections in intensive care units (ICUs) in the United States (National Nosocomial Infections Surveillance System, 2004). This ICU result is slightly higher than the MRSA prevalence of 52.0 % reported among all hospital isolates in the United States from the T.E.S.T. study.

The three most active agents *in vitro* against MRSA identified in this study were tigecycline, vancomycin and linezolid, with 100 % susceptibility reported for each. Recent reports of MRSA resistance to linezolid (Wilson *et al.*, 2003; Anderregg *et al.*, 2005; Peeters & Sarria, 2005) and vancomycin (Bozdogan *et al.*, 2003; Chang *et al.*, 2003) highlight the importance of the development of new agents, such as tigecycline, for the appropriate treatment of infections where highly resistant pathogens are suspected or known.

Tigecycline has previously been shown to be highly active *in vitro* against *S. aureus*. Hoban *et al.* (2005), in an examination of T.E.S.T. database isolates collected globally in 2004, reported an MIC₅₀ of 0.12 $\mu\text{g ml}^{-1}$ and MIC₉₀ of 0.25 $\mu\text{g ml}^{-1}$ for tigecycline against both MRSA ($n=348$) and MSSA ($n=489$), with 98.9 % of MRSA and 99.8 % of MSSA isolates susceptible. Fritsche *et al.* (2004) reported an MIC₅₀ of 0.25 $\mu\text{g ml}^{-1}$ and an MIC₉₀ of 0.5 $\mu\text{g ml}^{-1}$ for tigecycline against oxacillin-susceptible ($n=3196$) and -resistant ($n=1881$) isolates of *S. aureus* in a clinical study of global isolates collected from patients with community-acquired respiratory tract and cutaneous infections. All isolates in this study were susceptible to tigecycline. Fritsche & Jones (2004) showed similar activity for tigecycline against MSSA and MRSA recovered from nosocomial and community-acquired infections. In this study, 3498 isolates of *S. aureus* possessed an MIC₅₀ of 0.25 $\mu\text{g ml}^{-1}$ and an MIC₉₀ of 0.5 $\mu\text{g ml}^{-1}$, with no

Table 3. Antimicrobial activity of tigecycline and comparator antimicrobial agents against clinical isolates of *S. aureus* ($n=1692$), MSSA ($n=813$) and MRSA ($n=879$) across the continental United States

%S represents the percentage of susceptible isolates (susceptibility to β -lactam antimicrobials indicates *in vitro* activity only). %R indicates the percentage of resistant isolates.

Drug	Isolates	MIC ($\mu\text{g ml}^{-1}$)		MIC range	%S	%R
		MIC ₅₀	MIC ₉₀			
Tigecycline	<i>S. aureus</i>	0.12	0.25	0.015–0.5	100	0.0
	MSSA	0.12	0.12	0.015–0.5	100	0.0
	MRSA	0.12	0.25	0.03–0.5	100	0.0
Amoxicillin/clavulanate	<i>S. aureus</i>	2	≥ 16	≤ 0.03 – ≥ 16	61.1	38.9
	MSSA	1	2	≤ 0.03 –4	100	0.0
	MRSA	8	≥ 16	1– ≥ 16	25.1	74.9
Ampicillin	<i>S. aureus</i>	16	≥ 32	≤ 0.06 – ≥ 32	7.6	92.4
	MSSA	4	≥ 32	≤ 0.06 – ≥ 32	15.9	84.1
	MRSA	≥ 32	≥ 32	0.5– ≥ 32	0.0	100
Penicillin	<i>S. aureus</i>	≥ 16	≥ 16	≤ 0.06 – ≥ 16	6.7	93.3
	MSSA	8	≥ 16	≤ 0.06 – ≥ 16	13.9	86.1
	MRSA	≥ 16	≥ 16	0.25– ≥ 16	0.0	100
Piperacillin/tazobactam	<i>S. aureus</i>	4	≥ 32	≤ 0.25 – ≥ 32	64.6	35.4
	MSSA	1	2	≤ 0.25 –8	100	0.0
	MRSA	16	≥ 32	1– ≥ 32	31.9	68.1
Ceftriaxone	<i>S. aureus</i>	16	≥ 128	0.12– ≥ 128	46.7	21.5
	MSSA	4	4	0.12–32	96.9	0.0
	MRSA	32	≥ 128	8– ≥ 128	0.2	41.3
Imipenem	<i>S. aureus</i>	0.25	4	≤ 0.12 – ≥ 32	91.0	7.1
	MSSA	0.25	0.25	≤ 0.12 –2	100	0.0
	MRSA	0.5	16	≤ 0.12 – ≥ 32	82.6	13.7
Levofloxacin	<i>S. aureus</i>	0.5	≥ 64	≤ 0.06 – ≥ 64	51.7	46.0
	MSSA	0.12	4	≤ 0.06 – ≥ 64	87.6	10.1
	MRSA	16	≥ 64	≤ 0.06 – ≥ 64	18.5	79.2
Linezolid	<i>S. aureus</i>	2	4	≤ 0.5 –4	100	0.0
	MSSA	2	2	≤ 0.5 –4	100	0.0
	MRSA	2	4	≤ 0.5 –4	100	0.0
Minocycline	<i>S. aureus</i>	≤ 0.25	0.5	≤ 0.25 – ≥ 16	99.2	0.1
	MSSA	≤ 0.25	≤ 0.25	≤ 0.25 –8	99.0	0.0
	MRSA	≤ 0.25	0.5	≤ 0.25 – ≥ 16	99.3	0.1
Vancomycin	<i>S. aureus</i>	1	1	≤ 0.12 –4	100	0.0
	MSSA	0.5	1	≤ 0.12 –4	100	0.0
	MRSA	1	1	0.25–4	100	0.0

differences in MIC noted between MSSA or MRSA subgroups. All isolates were inhibited by tigecycline at $\leq 1 \mu\text{g ml}^{-1}$.

Recent comparative studies have also demonstrated the clinical efficacy of tigecycline in complicated SSSIs and complicated intra-abdominal infections (cIAIs). In a summary of *in vitro* data from Phase 3 clinical trials in cSSSIs and cIAIs, Bradford *et al.* (2005) compared the *in vitro* activity of tigecycline with that of several other antimicrobial agents. Tigecycline was the most active antimicrobial agent in this study, with an MIC₉₀ of $0.25 \mu\text{g ml}^{-1}$ reported for MSSA and MRSA isolates collected from patients with either SSSIs or IAIs. Minocycline was also highly active against MRSA in this

study, but in a direct comparison between these two agents, 11 minocycline-resistant MRSA isolates were identified that were susceptible to tigecycline at low concentrations ($\leq 0.5 \mu\text{g ml}^{-1}$) (Bradford *et al.*, 2005).

McAleese *et al.* (2005) have recently reported a serial passage study in which reduced susceptibility to tigecycline was selected among two strains of *S. aureus*. These strains were grown in increasing concentrations of tigecycline over a period of 16 days, after which MICs increased by 16-fold for *S. aureus* strain N315 and 32-fold for strain Mu3. After passage, both strains showed more than 100-fold increases in expression of the gene cluster *mepRAB*, which encodes the transcription regulator gene *mepR*, the efflux pump gene *mepA* and a third protein of unknown function (*mepB*).

Table 4. Prevalences of MRSA ($n=879$) and fluoroquinolone (FQ)-resistant MRSA ($n=696$) by state collected between January 2004 and September 2005

State	<i>S. aureus</i> isolates (<i>n</i>)	MRSA isolates		FQ-resist- ant MRSA isolates	
		<i>n</i>	%	<i>n</i>	%*
New England					
CT	24	11	45.8	10	90.9
MA	40	13	32.5	9	69.2
NH	24	3	12.5	3	—
VT	25	4	16.0	3	—
Middle Atlantic					
NJ	96	47	49.0	44	93.6
NY	213	103	48.4	94	91.3
PA	24	10	41.7	7	70.0
East North Central					
IL	25	14	56.0	11	78.6
IN	25	12	48.0	9	75.0
MI	74	41	55.4	30	73.2
OH	141	73	51.8	55	75.3
WI	22	9	40.9	9	—
West North Central					
KS	25	14	56.0	13	92.9
MN	25	9	36.0	6	—
MO	25	10	40.0	8	80.0
ND	22	12	54.5	9	75.0
NE	25	15	60.0	12	80.0
South Atlantic					
DC	21	15	71.4	14	93.3
FL	66	50	75.8	38	76.0
GA	91	60	65.9	44	73.3
MD	45	27	60.0	24	88.9
NC	45	30	66.7	27	90.0
VA	24	4	16.7	3	—
WV	25	11	44.0	10	90.9
East South Central					
AL	24	13	54.2	11	84.6
KY	25	25	100	18	72.0
MS	22	10	45.5	5	50.0
TN	62	35	56.5	26	74.3
West South Central					
AR	22	11	50.0	8	72.7
LA	45	23	51.1	11	47.8
OK	24	14	58.3	8	57.1
TX	68	40	58.8	25	62.5
Mountain					
AZ	40	28	70.0	28	100
NM	25	13	52.0	12	92.3
UT	25	10	40.0	9	90.0
Pacific					
CA	68	22	32.4	19	86.4
OR	45	22	48.9	12	54.5
WA	25	16	64.0	12	75.0

*Calculated as percentage of MRSA isolates for states with ≥ 10 MRSA isolates only.

Although several antimicrobial agents possess good *in vitro* activity against MRSA, most are inactive or only sporadically active against HA-MRSA *in vivo*. According to Cunha (2005), the list of antimicrobial agents with *in vivo* activity against MRSA is short, including only quinupristin/dalfopristin, minocycline, daptomycin, linezolid and vancomycin (of these, only daptomycin, linezolid and vancomycin have MRSA indications). These agents are active against HA-MRSA, however; possible treatment options for CA-MRSA include clindamycin and trimethoprim/sulfamethoxazole. Recent clinical studies have shown that tigecycline also demonstrates a high degree of *in vivo* activity against *S. aureus*, both MSSA and MRSA. Ellis-Grosse *et al.* (2005) reported tigecycline microbiological eradication rates of 78.1 and 88.8 % against MRSA ($n=32$) and MSSA ($n=134$), respectively, among medically evaluable patients with SSSIs at the test-of-cure visit; patients treated with vancomycin/aztreonam reported eradication rates of 75.8 % for MRSA ($n=33$) and 90.8 % for MSSA ($n=120$). Similarly, Babinchak *et al.* (2005) recently showed equivalent microbiological eradication at test-of-cure visit among patients treated with tigecycline (92.9 %) or imipenem/cilastatin (91.7 %) for cIAs not infected with MRSA.

Resistance to methicillin among nosocomial *S. aureus* isolates is imparted through acquisition of a genetic element, the staphylococcal cassette chromosome *mecA* (SCC*mecA*), which occurs in several forms. Types I to III impart resistance to β -lactam antimicrobials, while types II and III also impart resistance to numerous non- β -lactam antimicrobials (Padmanabhan & Fraser, 2005; Katayama *et al.*, 2000). Risk factors associated with the acquisition of nosocomial MRSA infections include previous hospitalization, increased length of hospital stay, previous exposure to antimicrobial agents (especially fluoroquinolones), enteral feeding and/or surgery (Graffunder & Venezia, 2002).

Reports of infections caused by MRSA have begun to emerge in recent years among patients not previously exposed to nosocomial MRSA risk factors (Boyce, 2005). Isolates of CA-MRSA possess a novel cassette chromosome, SCC*mecA* type IV, which is smaller than that found in nosocomial isolates and can be transferred horizontally between isolates (Daum *et al.*, 2002). It is dominated by the *ccrAB2* allotype, which is prevalent among emerging community-acquired MRSA strains compared with the less common *ccrAB4* allotype (Oliveira *et al.*, 2006). CA-MRSA isolates are typically susceptible to more antimicrobials than HA-MRSA, including clindamycin, trimethoprim/sulfamethoxazole and the aminoglycosides. CA-MRSA also possesses different gene profiles, including Pantón–Valentine leukocidin, which can result in increased toxicity (Stevenson *et al.*, 2005). Although the name CA-MRSA refers to colonization or infection in the community rather than actual acquisition (Salgado *et al.*, 2003), CA-MRSA strains are often derived from isolates picked up in healthcare facilities on previous visits or through contact with other individuals who have previously been exposed

to HA-MRSA strains. The ability of CA-MRSA to transfer its *SCCmecA* IV gene horizontally might eventually result in the appearance of *SCCmecA* IV among HA-MRSA, making these strains even more difficult to distinguish in the future.

MRSA infections can be problematic to treat compared with MSSA infections in part because of the potentially enhanced virulence of MRSA, potentially decreased efficacy of vancomycin against MRSA and/or delays in initiating appropriate antimicrobial therapy (Cosgrove *et al.*, 2003). Engemann *et al.* (2003) showed that MRSA SSSI patients had significantly longer median durations of hospital stay (8 vs 5 days; $P < 0.001$) and significantly higher mortality (20.7 vs 6.7%; $P < 0.001$) than SSSI patients infected with MSSA. Treatment cost among MRSA patients can also be higher compared with MSSA patients (MRSA mean cost = \$118 415; MSSA mean cost = \$73 165). Similarly, Cosgrove *et al.* (2003) reported a significant increase in mortality associated with MRSA infection compared with MSSA infection (OR = 1.93; $P < 0.001$) in a pooled analysis of 31 studies involving *S. aureus* bacteraemia.

Isolates of MRSA are commonly resistant to multiple antimicrobials, particularly members of the β -lactam family (Chen & Huang, 2005). The selection of empirical therapy for the treatment of suspected MRSA infection should thus be based on as much clinical information as possible, including the presence of coexisting illness, prior antimicrobial therapy, duration of hospitalization, knowledge of local MRSA incidence and/or evidence of patient colonization (Haddadin *et al.*, 2002). The high prevalence of MRSA reported here calls for extreme caution before commencing empirical therapy for any infection potentially caused by MRSA.

Prevalence of MRSA in those hospitals that submitted isolates varied widely by state in this study, ranging from 12.5 % (3/24) in NH to 100 % (25/25) in KY. Regions with high MRSA prevalences may be indicative of localized clonal MRSA outbreaks, as reported previously both in hospitals (Young *et al.*, 2004) and in the community (Stemper *et al.*, 2004). Such outbreaks are usually identified using pulsed-field gel electrophoresis, multi-locus sequence typing and/or staphylococcal cassette chromosome *mec* typing to identify genetically related clonal complexes (Gomes *et al.*, 2005). Genotyping is not currently implemented in the T.E.S.T. study; its introduction would undoubtedly enhance its contribution to epidemiological investigations.

This report has shown (using imipenem as an example) that MRSA susceptibility data can vary widely between different states. MIC data for β -lactams against MRSA must be regarded with caution, as several β -lactams (i.e. penicillins, carbapenems, cepheims, β -lactam/ β -lactamase inhibitor combinations) can provide false-positive susceptibility results against MRSA isolates that are not clinically effective (CLSI, 2005). Laboratory-derived MIC values may thus not accurately reflect clinical treatment options for

MRSA infections. Increasing resistance to established anti-MRSA agents such as linezolid and vancomycin confirms the importance of the development of new antimicrobial agents that are effective against resistant organisms. The excellent *in vitro* activity of tigecycline against MSSA and MRSA could make it an important tool in the empirical (and targeted) therapy of nosocomial and community infections caused by resistant pathogens such as MRSA.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the staff of International Health Management Associates, Inc., Schaumburg, IL, USA, for their coordination of the T.E.S.T. study. This study was funded by Wyeth Pharmaceuticals.

REFERENCES

- Anderegg, T. R., Sader, H. S., Fritsche, T. R., Ross, J. E. & Jones, R. N. (2005). Trends in linezolid susceptibility patterns: report from the 2002–2003 worldwide Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program. *Int J Antimicrob Agents* **26**, 13–21.
- Babinchak, T., Ellis-Grosse, E., Dartois, N., Rose, G. M. & Loh, E. (2005). The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: analysis of pooled clinical trial data. The Tigecycline 301 and 306 Study Groups. *Clin Infect Dis* **41**, S354–S367.
- Bergeron, J., Ammirati, M., Danley, D., James, L., Norcia, M., Retsema, J., Strick, C. A., Su, W.-G., Sutcliffe, J. & Wondrack, L. (1996). Glycylcyclines bind to the high-affinity tetracycline ribosomal binding site and evade Tet(M)- and Tet(O)-mediated ribosomal protection. *Antimicrob Agents Chemother* **40**, 2226–2228.
- Bouchillon, S. K., Hoban, D. J., Johnson, B. M., Johnson, J. L., Hsiung, A. & Dowzicky, M. J. (2005). In vitro activity of tigecycline against 3989 Gram-negative and Gram-positive clinical isolates from the United States Tigecycline Evaluation and Surveillance Trial (T.E.S.T. Program; 2004). *Diagn Microbiol Infect Dis* **52**, 173–179.
- Boyce, J. M. (2005). Meticillin-resistant *Staphylococcus aureus*: USA. *Lancet Infect Dis* **5**, 653–654.
- Bozdogan, B., Esel, D., Whitener, C., Browne, F. A. & Appelbaum, P. C. (2003). Antibacterial susceptibility of a vancomycin-resistant *Staphylococcus aureus* strain isolated at the Hershey Medical Center. *J Antimicrob Chemother* **52**, 864–868.
- Bradford, P. A., Weaver-Sands, D. T. & Petersen, P. J. (2005). In vitro activity of tigecycline against isolates from patients enrolled in Phase 3 clinical trials of treatment for complicated skin and skin-structure infections and complicated intra-abdominal infections. *Clin Infect Dis* **41**, S315–S332.
- Chang, S., Sievert, D. M., Hageman, J. C., Boulton, M. L., Tenover, F. C., Downes, F. P., Shah, S., Rudrik, J. T., Pupp, G. R. & other authors (2003). Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. *N Engl J Med* **348**, 1342–1347.
- Chen, C.-J. & Huang, Y.-C. (2005). Community-acquired methicillin-resistant *Staphylococcus aureus* in Taiwan. *J Microbiol Immunol Infect* **38**, 376–382.
- CLSI (2005). *Performance standard for antimicrobial susceptibility testing*, document M100-S15. Wayne, PA: Clinical and Laboratory Standards Institute.
- Cosgrove, S. E., Sakoulas, G., Perencevich, E. N., Schwaber, M. J., Karchmer, A. W. & Carmeli, Y. (2003). Comparison of mortality

- associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis* 36, 53–59.
- Cunha, B. A. (2005). Methicillin-resistant *Staphylococcus aureus*: clinical manifestations and antimicrobial therapy. *Clin Microbiol Infect* 11 (Suppl. 4), 33–42.
- Daum, R. S., Ito, T., Hiramatsu, K., Hussain, F., Mongkolrattanothai, K., Jamklang, M. & Boyle-Vavra, S. (2002). A novel methicillin-resistance cassette in community-acquired methicillin-resistant *Staphylococcus aureus* isolates of diverse genetic backgrounds. *J Infect Dis* 186, 1344–1347.
- Ellis-Grosse, E. J., Babinchak, T., Dartois, N., Rose, G. & Loh, E. (2005). The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind Phase 3 comparison studies with vancomycin-aztreonam. The Tigecycline 300 and 305 cSSSI Study Groups. *Clin Infect Dis* 41, S341–S353.
- Engemann, J. J., Carmeli, Y., Cosgrove, S. E., Fowler, V. G., Bronstein, M. Z., Trivette, S. L., Briggs, J. P., Sexton, D. J. & Kaye, K. S. (2003). Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. *Clin Infect Dis* 36, 592–598.
- Fritsche, T. R. & Jones, R. N. (2004). Antimicrobial activity of tigecycline (GA-936) tested against 3498 recent isolates of *Staphylococcus aureus* recovered from nosocomial and community-acquired infections. *Int J Antimicrob Agents* 24, 567–571.
- Fritsche, T. R., Kirby, J. T. & Jones, R. N. (2004). In vitro activity of tigecycline (GAR-936) tested against 11,859 recent clinical isolates associated with community-acquired respiratory tract and Gram-positive cutaneous infections. *Diagn Microbiol Infect Dis* 49, 201–209.
- Fritsche, T. R., Sader, H. S., Stilwell, M. G., Dowzicky, M. J. & Jones, R. N. (2005). Potency and spectrum of tigecycline tested against an international collection of bacterial pathogens associated with skin and soft tissue infections (2000–2004). *Diagn Microbiol Infect Dis* 52, 195–201.
- Gomes, A. R., Vinga, S., Zavolan, M. & de Lencastre, H. (2005). Analysis of the genetic variability of virulence-related loci in epidemic clones of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 49, 366–379.
- Graffunder, E. M. & Venezia, R. A. (2002). Risk factors associated with nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) infection including previous use of antimicrobials. *J Antimicrob Chemother* 49, 999–1005.
- Haddadin, A. S., Fappiano, S. A. & Lipsett, P. A. (2002). Methicillin resistant *Staphylococcus aureus* (MRSA) in the intensive care unit. *Postgrad Med J* 78, 385–392.
- Hoban, D. J., Bouchillon, S. K., Johnson, B. M., Johnson, J. L. & Dowzicky, M. J. (2005). In vitro activity of tigecycline against 6792 Gram-negative and Gram-positive clinical isolates from the global Tigecycline Evaluation and Surveillance Trial (T.E.S.T. Program, 2004). *Diagn Microbiol Infect Dis* 52, 215–227.
- Katayama, Y., Ito, T. & Hiramatsu, K. (2000). A new class of genetic element, staphylococcus cassette chromosome *mec*, encodes methicillin resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 44, 1549–1555.
- Koeth, L. M. & Miller, L. A. (2005). Evolving concepts of pharmaceutical company-sponsored surveillance studies. *Clin Infect Dis* 41 (Suppl. 4), S279–S282.
- McAleese, F., Petersen, P., Ruzin, A., Dunman, P. M., Murphy, E., Projan, S. J. & Bradford, P. A. (2005). A novel MATE family efflux pump contributes to the reduced susceptibility of laboratory-derived *Staphylococcus aureus* mutants to tigecycline. *Antimicrob Agents Chemother* 49, 1865–1871.
- Moran, G. J., Amii, R. N., Abrahamian, F. M. & Talan, D. A. (2005). Methicillin-resistant *Staphylococcus aureus* in community-acquired skin infections. *Emerg Infect Dis* 11, 928–930.
- National Nosocomial Infections Surveillance System (2004). National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 32, 470–485.
- NCCLS (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*, document M7-A6. Wayne, PA: National Committee for Clinical Laboratory Standards.
- Oliveira, D. C., Milheirico, C. & de Lencastre, H. (2006). Redefining a structural variant of staphylococcal cassette chromosome *mec*, SCCmec type VI. *Antimicrob Agents Chemother* 50, 3457–3459.
- Padmanabhan, R. A. & Fraser, T. G. (2005). The emergence of methicillin-resistant *Staphylococcus aureus* in the community. *Cleve Clin J Med* 72, 235–241.
- Peeters, M. J. & Sarria, J. C. (2005). Clinical characteristics of linezolid-resistant *Staphylococcus aureus* infections. *Am J Med Sci* 330, 102–104.
- Salgado, C. D., Farr, B. M. & Calfee, D. P. (2003). Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis* 36, 131–139.
- Stemper, M. E., Shukla, S. K. & Reed, K. D. (2004). Emergence and spread of community-associated methicillin-resistant *Staphylococcus aureus* in rural Wisconsin, 1989 to 1999. *J Clin Microbiol* 42, 5673–5680.
- Stevenson, K. B., Searle, K., Stoddard, G. J. & Samore, M. H. (2005). Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in rural communities, western United States. *Emerg Infect Dis* 11, 895–903.
- Weber, J. T. (2005). Community-associated methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 41, S269–S272.
- Wilson, P., Andrews, J. A., Charlesworth, R., Walesby, R., Singer, M., Farrell, D. J. & Robbins, M. (2003). Linezolid resistance in clinical isolates of *Staphylococcus aureus*. *J Antimicrob Chemother* 51, 186–188.
- Wyeth Pharmaceuticals (2005). *Tygacil product insert*. Philadelphia: Wyeth Pharmaceuticals.
- Young, L. S., Perdreau-Remington, F. & Winston, L. G. (2004). Clinical, epidemiologic, and molecular evaluation of a clonal outbreak of methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis* 38, 1075–1083.
- Zinner, S. H. (2005). Overview of antibiotic use and resistance: setting the stage for tigecycline. *Clin Infect Dis* 41, S289–S292.