Genotypic and Phenotypic Characterization of Methicillin-Resistant *Staphylococcus aureus* Strains Recovered from a Phase IV Clinical Trial for Linezolid versus Vancomycin for the Treatment of Nosocomial Pneumonia

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Abstract

Objective: To characterize methicillin-resistant *Staphylococcus aureus* (MRSA) strains responsible for nosocomial pneumonia collected during an international phase IV trial comparing linezolid to vancomycin.

Methods: 435 MRSA baseline isolates were collected from subjects in Latin America (6 countries, 45 [10.3%] strains), Europe (10 countries, 55 [12.6%] strains), including Turkey and Russia, Asia (5 countries, 67 [15.4%] strains), South Africa (3 strains) and the USA (265 [60.9%] strains). Only one isolate per subject was included. PVL genes and SCC*mec* types were determined by PCR. All strains were subjected to PFGE and *spa* typing. Selected strains were evaluated by MLST. Clonal complexes (CCs) were assigned based on the *spa* and/or MLST results. Susceptibility testing and interpretations were performed by CLSI and EUCAST methods. Inducible clindamycin resistance was assessed by D-test and isolates screened for heterogeneous resistance to vancomycin (hVISA; Etest macromethod).

Results: Overall, most strains were CC5 (56.1%), which originated from the USA (CC5-MRSA-SCC*mec* II/IV; 70.1% [171/244]), Asia (CC5-MRSA-II; 13.9% [34/244]) and Latin America (CC5-MRSA-I/II; 12.3% [30/244]). The second and third most prevalent clones were CC8-MRSA-IV (23.2%) and CC239-MRSA-III (11.3%), respectively. Furthermore, CC5-MRSA-I/II clones predominated in Asia (50.7% within this region) and Latin America (66.7%), followed by CC239-MRSA-III (32.8% and 28.9%, respectively). European strains were CC8-MRSA-IV (34.5%) or CC22-MRSA-IV (18.2%) or CC5-MRSA-I/II/IV (16.4%), while USA MRSA were CC5-MRSA-II/IV (64.5%) or CC8-MRSA-IV (28.7%). Among USA CC8-MRSA-II/IV, 73.7% (56/76) of strains (21.1% of all USA MRSA) clustered within USA300. Overall, strains were PVL-negative, except for one ST80 strain from Greece, one ST96 from Russia, one ST59 from Taiwan, one ST8 from Puerto Rico and USA300 strains from the USA. All strains were susceptible to linezolid and daptomycin, while vancomycin and teicoplanin were active against 96.1-99.8% of strains (EUCAST). Susceptibility to gatifloxacin, clindamycin and tetracycline varied among CCs and regions. hVISA strains (14.5%) were mostly CC5-MRSA-II (63.5%; 40/63) from Asia.

Conclusions: Each region had two predominant clones responsible for nosocomial pneumonia. The rate of USA300 (21.1%) appears high, corroborating previous reports describing increased rates of invasive infections caused by this clone in the USA. The prevalence of hVISA was elevated in Asia and these strains appear to be associated with the CC5 lineage.

Introduction

Staphylococcus aureus is a leading cause of human bacterial infections worldwide, many of which are caused by methicillin-resistant *S. aureus* (MRSA). Bacteremia is one of the most serious syndromes caused by MRSA, especially in healthcare settings. In addition, *S. aureus* is the most common pathogen responsible for hospital- (HABP) and ventilator-acquired bacterial pneumonia (VABP) and accounts for 10 - 40% of these cases. A recent report from the International Nosocomial Infection Control Consortium (INICC) described that 77.5% of *S. aureus* VABP episodes were caused by methicillin-resistant strains [Rosenthal et al., 2008]. These facts, along with complicating risk factors, comorbidity and mortality (between 40 and 60%), result in extended hospitalizations, escalated health care costs, and the requirement of potent, broad-spectrum antimicrobial agents often used in expensive combination regimens.

From October 2004 through January 2010, a phase IV randomized, double-blind, multicenter, international, comparator-controlled study to assess the efficacy, safety and tolerability of fixed-dose linezolid, compared with dose-optimized vancomycin for the treatment of proven MRSA nosocomial pneumonia (NP) in hospitalized adults was performed [Wunderink et al., 2012]. In this clinical trial, a significantly better clinical cure rate was observed with linezolid (58%) when compared with vancomycin (47%). Favorable results were also obtained for linezolid (58%) in terms of microbiological cure rates compared with vancomycin (47%). During this trial, a large collection of geographically diverse MRSA isolates was obtained. This study characterized this MRSA population responsible for NP.

Materials and Methods

Bacterial strains: A total of 435 microbiologically evaluable baseline MRSA isolates collected from subjects with NP were further characterized (one strain per subject). These isolates were predominantly collected from enrolled subjects (No., %) in the USA (265, 60.9%), followed by a lower number of subjects from the following countries: Korea (44, 10.1%), Brazil (18, 4.1%), Belgium (18, 4.1%) Taiwan (15, 3.4%), Russia (13, 3.0%), Mexico (10, 2.3%), Portugal (8, 1.8%), Chile (8, 1.8%), France (8, 1.8%), Malaysia (6, 1.4%), Puerto Rico (5, 1.1%), South Africa (3, 0.7%), Colombia (3, 0.7%), Spain (2, 0.5%), Germany (2, 0.5%), and one (0.2%) strain each from Singapore, Greece, Poland, United Kingdom (UK), Argentina, Hong Kong, and Turkey.

Antimicrobial susceptibility testing: Isolates were tested for susceptibility by broth microdilution in cation-adjusted Mueller-Hinton medium according to the Clinical and Laboratory Standards Institute (CLSI) recommendations [CLSI M07-A9, 2012]. Quality assurance was performed by concurrent testing of CLSI-recommended [CLSI M100-S22, 2012] strains: *Enterococcus faecalis* ATCC 29212 and *S. aureus* ATCC 29213. Interpretation of MIC results was in accordance with published CLSI criteria [CLSI M100-S22, 2012].

Inducible clindamycin resistance was detected using the D-test disk diffusion method according to CLSI. Briefly, a 2-μg clindamycin disk was placed 15 mm from the edge of a 15-μg erythromycin disk. Following incubation, isolates that showed flattening of the clindamycin zone were considered D-test positive. The hVISA phenotype was screened by the Etest macromethod.

SCC*mec* typing and detection of PVL genes: SCC*mec* types (I through VI) were characterized using a multiplex PCR strategy [Milheirico et al., 2007]. Strains showing inconclusive SCC*mec* typing results were subjected to a secondary strategy proposed by Oliveira et al. [2006]. PVL (*lukF-PV* and *lukS-PV*) screening was performed by using a multiplex Real-Time (RT) PCR approach as previously described [Mendes et al., 2010].

Epidemiologic typing of MRSA: Chromosomal DNA was subjected to pulsed-field gel electrophoresis (PFGE) after digestion with SmaI [McDougal et al., 2003]. All strains were subjected to *spa* typing [Shopsin et al., 1999]. Clonal complexes (CCs) were assigned based on the *spa* and/or multilocus sequence typing (MLST) results [Enright et al., 2000]. MRSA strains with *spa* typing results previously associated with specific MLST in the MLST-mapping database (http://spa.ridom.de/mlst) or peer-reviewed publications had the CCs assigned accordingly. Strains with new *spa* typing denominations and unknown MLST associations, but clustering within PFGE types containing strains with known CC results, were assigned the same CCs. MLST was performed in a given strain when showing *spa* type with unknown MLST association and a unique PFGE type. The *agr* operon from MRSA isolates were typed (groups 1 through 4) using a multiplex PCR approach [Mendes et al., 2010].

Results

- A great number of isolates included in this study were CC5-MRSA-SCC*mec* type I/II/IV (56.1%; 244/435), which was followed by CC8-MRSA-IV (23.2%; 101/435) and CC239-MRSA-III (11.3%; 49/435; Table 1).
- MRSA strains associated with CC5 (56.1%) originated mostly from the USA (CC5-MRSA-II/IV; 70.1% [171/244]), Asia (CC5-MRSA-II; 13.9% [34/244]) and Latin America (CC5-MRSA-I/II; 12.3% [30/244]). In addition, this lineage comprised the majority of all isolates recovered from the USA (64.5%; 171/265), Latin America (66.7%; 30/45) and Asia (50.7%; 34/67; Table 1).
- CC8 MRSA strains were most commonly observed in the USA (28.7%; 76/265) and Europe (34.5%; 19/55; Table 1). Among CC8 *S. aureus* strains from the USA, 69.7% (53/76) were PVL-positive (Table 2). All PVL-positive strains showed PFGE profiles undistinguishable or similar to that of USA300-0114 strain.
- The vast majority of strains were PVL-negative, except for one ST80 strain from Greece, one ST96 from Russia, one ST59 from Taiwan, one ST8 from Puerto Rico and USA300 strains from the USA (data not shown).
- The third most prevalent MRSA lineage (CC239-MRSA-III) was commonly observed in Asia (32.8%; 22/67) and Latin America (28.9%; 13/45), where these strains represented the second most common clone (Table 1).
- Linezolid, vancomycin, teicoplanin, daptomycin and quinupristin/dalfopristin demonstrated good antimicrobial coverage (>99.0% susceptible) against MRSA strains (Table 3). Trimethoprim/sulfamethoxazole also showed high susceptibility rates (≥95.5% susceptible), except when tested against CC239-MRSA-III strains (Brazilian/Hungarian clone).
- A total of 29.7% (129/435) of the MRSA strains exhibited vancomycin MIC results of >1.5 mg/L by "Etest" and the majority (69.0%; 89/129) originated from the USA (data not shown). These strains (vancomycin MIC, >1.5 mg/L) were mostly represented by CC5-MRSA-I/II/IV (71.3%; 92/129) followed by lower numbers of CC8-MRSA-IV (17.1%; 22/129) and CC239-MRSA-III (6.2%; 8/129).
- Overall, 14.5% (63/435) of isolates were characterized as hVISA (data not shown). The occurrence of a hVISA phenotype was higher among isolates recovered from Asia (44.8%; 30/67), followed by Latin America (22.2%; 10/45), Europe (16.4%; 9/55) and lowest in the USA (5.3%; 14/265).
- The majority of hVISA strains were associated with CC5-MRSA-I/II (63.5%; 40/63), followed by CC239-MRSA-III (17.5%; 11/63) and CC8-MRSA-IV (11.1%; 7/63). A great number of CC5-MRSA-II strains were from Asia (70.0%; 28/40), which clustered within the ASI-A PFGE type (78.6%; 22/28; data not shown).

Conclusions

- The majority (56.1%) of the MRSA strains included in this study belonged to CC5. However, two major clones predominated in each region. In Asia and Latin America, CC5-MRSA-I/II predominated followed by CC239-MRSA-III, while in the USA and Europe the CC5-MRSA-II/IV and CC8-MRSA-IV prevailed, respectively, each followed by the CC8-MRSA-IV and CC22-MRSA-IV clones.
- USA MRSA strains responsible for NP belonged dominantly to clones associated with healthcare-related infections (78.9%; 209/265). All other strains belonged to the USA300 clone (56 strains), initially associated with community-acquired infections, except for one CC1-MRSA-IV strain.
- A greater proportion of USA300 MRSA strains (21.1%; 56/265) were responsible for NP in the USA. This observation corroborates previous reports (16 - 22%) with regards to the increased occurrence of invasive infections caused by this clone in the USA. In addition, higher fluoroquinolone (67.9%) and lincosamide (14.3%) resistance rates were observed among these USA300 strains.
- The prevalence of hVISA among the tested isolates was significant (14.5%). However, this phenotype necessitates confirmation by other reference methodologies, such as population analysis. The strains with a hVISA phenotype were mostly observed in the APAC region, and these strains belonged mostly to a single PFGE cluster (ASI-A).

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Table 1. Clonal distribution of MRSA isolates (unique strains) recovered from patients enrolled in the Phase IV pneumonia clinical trials.

Clonal complex	Number (%) of strains per region				
	United States	Europe[a]	Latin America[b]	Asia[c]	Total
CC5	171 (64.5)	9 (16.4)	30 (66.7)	34 (50.7)	244 (56.1)
CC5-MRSA-I	0 (0.0)	3 (5.4)	13 (28.9)	0 (0.0)	16 (3.7)
CC5-MRSA-II	160 (60.4)	4 (7.2)	17 (37.8)	34 (50.7)	215 (49.4)
CC5-MRSA-IV	11 (4.1)	2 (3.6)	0 (0.0)	0 (0.0)	13 (3.0)
CC8-MRSA-IV	76 (28.7)	19 (34.5)	1 (2.2)	5 (7.5)	101 (23.2)
CC239-MRSA-III	4 (1.5)	7 (12.7)	13 (28.9)	22 (32.8)	49 (11.3)
CC45-MRSA-II/III	7 (2.6)[d]	6 (10.9)[e]	0 (0.0)	1 (1.5)[f]	14 (3.2)
CC22-MRSA-IV	0 (0.0)	10 (18.2)	0 (0.0)	0 (0.0)	10 (2.3)
CC30-MRSA-II	4 (1.5)	1 (1.8)	0 (0.0)	0 (0.0)	5 (1.1)
CC59-MRSA-IV	1 (0.4)	0 (0.0)	1 (2.2)	3 (4.5)	5 (1.1)
CC1-MRSA-IV	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
CC9-MRSA-II	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.2)
CC72-MRSA-IV	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
CC80-MRSA-IV	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.2)
CC96-MRSA-III	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.2)
CC398-MRSA-III/IV	0 (0.0)	1 (1.8)[e]	0 (0.0)	1 (1.5)[f]	2 (0.4)
Total	265 (60.9)	55 (12.6)	45 (10.3)	67 (15.4)	435 (100.0)

a. Includes isolates from Belgium, France, Germany, Greece, Poland, Portugal, Russia, Spain, Turkey and UK.
b. Includes isolates from Argentina, Brazil, Chile, Colombia, Mexico and Puerto Rico.
c. Includes isolates from Hong Kong, Korea, Malaysia, Singapore and Taiwan.
d. MRSA strains carrying a SCC*mec* type II.
e. MRSA strains carrying a SCC*mec* type IV.
f. MRSA strains carrying a SCC*mec* type III.

Table 2. Epidemiologic data of baseline MRSA isolates (unique strains) recovered from subjects in the USA during the Phase IV pneumonia clinical trial.

No. (%)	SCC*mec*	PVL[a]	*agr*	PFGE	*spa*	CC
56 (21.1)	IV	+	1	USA-A[b]	t008, t024, t121, t211	8
111 (41.9)	II	−	2	USA-B[c]	See footnote "d"	5
17 (6.4)	II	−	2	USA-C	t002, t010, t105, t242, t854	5
1 (0.4)	II	−	2	USA-D	t002	5
5 (1.9)	II	−	2	USA-E	t002, t088, t242, t985	5
10 (3.8)	II	−	2	USA-F	t002, t242, t895	5
4 (1.5)	II	−	2	USA-G	t002, t105, t985	5
1 (0.4)	IV	−	1	USA-H	t008	8
2 (0.8)	II	−	2	USA-I	t002, t2731	5
1 (0.4)	IV	−	1	USA-J	t008	8
1 (0.4)	IV	−	1	USA-K	t024	8
3 (1.1)	II	−	2	USA-L	t002	5
1 (0.4)	II	−	2	USA-M	t1683	5
11 (4.2)	IV	−	2	USA-N[e]	t002, t088, t179, t242, t548, t1062	5
1 (0.4)	II	−	2	USA-O	t242	5
1 (0.4)	IV	−	3	USA-P	t922	1
10 (3.8)	IV	−	1	USA-Q[f]	t008, t064	8
1 (0.4)	IV	−	1	USA-R	t334	8
4 (1.5)	III	−	1	USA-S	t037	239
1 (0.4)	IV	−	1	USA-T	t008	8
1 (0.4)	II	−	2	USA-U	t105	5
2 (0.8)	IV	−	1	USA-V	t008	8
1 (0.4)	II	−	2	USA-W	t1080	5
7 (2.6)	II	−	1/NT	USA-X[g]	t004, t040, t266, t9362	45
4 (1.5)	II	−	3	USA-Y[h]	t012, t018	30
1 (0.4)	IV	−	1	USA-Z	t008	8
1 (0.4)	II	−	2	USA-AA	t1084	5
1 (0.4)	II	−	2	USA-AB	t105	5
1 (0.4)	II	−	2	USA-AC	t105	5
1 (0.4)	IV	−	1	USA-AE[i]	t316	59
1 (0.4)	IV	−	1	USA-AF[j]	t9350	72
2 (0.8)	IV	−	1	USA-AG	t451, t6863	8

a. PVL reads Panton-Valentine leukocidin.
b. PFGE profiles undistinguishable or similar to USA300.
c. PFGE profiles undistinguishable or similar to USA100.
d. Strains represented by *spa* types t002, t010, t045, t067, t071, t088, t149, t179, t242, t306, t509, t548, t570, t854, t895, t1305, t2516, t2731, t3921, t4255, t5213, t9348.
e. PFGE profiles undistinguishable or similar to USA800.
f. PFGE profiles undistinguishable or similar to USA500.
g. PFGE profiles undistinguishable or similar to USA600.
h. PFGE profiles undistinguishable or similar to USA200.
i. PFGE profiles undistinguishable or similar to USA1000.
j. PFGE profiles undistinguishable or similar to USA700.

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Table 3. Antimicrobial susceptibility testing results of baseline MRSA clinical isolates (unique strains) recovered during the Phase IV pneumonia clinical trial.

Antimicrobial agent	MIC_{50}/MIC_{90} (% susceptible[a]) by CC (No.)					MIC_{50}/MIC_{90} (% susceptible[a]) by USA clone (No.)	
	5 (244)	8 (101)	239 (49)	45 (14)	22 (10)	USA300 (56)	USA100 (111)
Linezolid	2/4(100.0)	2/2(100.0)	2/2(100.0)	2/4(100.0)	2/2(100.0)	2/2(100.0)	2/4(100.0)
Vancomycin	1/1(100.0)	1/1(100.0)	1/1(100.0)	1/1(100.0)	1/1(100.0)	1/1(100.0)	1/1(100.0)
Teicoplanin	0.5/2(99.6)	0.5/1(100.0)	1/2(100.0)	0.5/2(99.6)	0.5/1(100.0)	0.5/1(100.0)	0.5/1(99.1)
Daptomycin	0.5/1(100.0)	0.5/1(100.0)	0.5/1(100.0)	0.5/1(100.0)	0.5/1(100.0)	1/1(100.0)	0.5/1(100.0)
Erythromycin	>64/>64(1.2)	64/>64(8.9)	>64/>64(0.0)	>64/>64(1.2)	>64/>64(40.0)	64/>64(1.8)	>64/>64(0.0)
Clindamycin	>64/>64(4.5)[b]	0.25/64(62.4)[c]	>64/>64(0.0)[d]	>64/>64(57.1)[e]	0.12/>64(40.0)[f]	0.25/0.25(85.7)[g]	>64/>64(0.0)[h]
Gatifloxacin	>16/>16(4.9)	2/16(28.7)	4/16(0.0)	>16/>16(4.9)	8/16(0.0)	2/8(32.1)	8/>16(2.7)
Tetracycline	0.5/64(87.3)	0.25/1(93.1)	32/>64(2.0)	0.5/64(87.3)	0.25/0.5(100.0)	0.25/0.5(98.2)	0.5/1(98.2)
Q/D[i]	0.5/1(99.6)	0.25/0.5(99.0)	0.5/0.5(100.0)	0.5/1(99.6)	0.25/0.25(100.0)	0.25/0.25(100.0)	0.5/0.5(100.0)
TMP/SMX[j]	0.12/0.25(98.0)	0.06/0.5(90.1)	16/>32(18.4)	0.12/0.25(98.0)	0.06/0.06(100.0)	0.06/0.12(100.0)	0.12/0.25(95.5)

a. MIC values were interpreted according to the M100-S22 document.
b. Non-susceptible strains are represented by 73.0% and 22.5% of constitutive and inducible resistance phenotypes, respectively.
c. Non-susceptible strains are represented by 31.6% and 6.0% of constitutive and inducible resistance phenotypes, respectively.
d. Non-susceptible strains are represented by 81.6% and 18.4% of constitutive and inducible resistance phenotypes, respectively.
e. Non-susceptible strains are represented by 42.9% of constitutive resistance phenotypes.
f. Non-susceptible strains are represented by 20.0% and 40.0% of constitutive and inducible resistance phenotypes, respectively.
g. Non-susceptible strains are represented by 10.7% and 3.6% of constitutive and inducible resistance phenotypes, respectively.
h. Non-susceptible strains are represented by 66.7% and 33.3% of constitutive and inducible resistance phenotypes, respectively.
i. Q/D, reads quinupristin/dalfopristin.
j. TMP/SMX, reads trimethoprim/sulfamethoxazole.