The Epidemiology, Clinical Characteristics, and Outcomes of Patients With Nosocomial Pneumonia Caused by Community-Acquired Methicillin-Resistant *Staphylococcus aureus*

D.B. Huang,[1] G.R. Corey,[2] V.G. Fowler Jr[2]

[1]*Formerly of Pfizer Inc, Collegeville, PA, USA;* [2]*Division of Infectious Diseases, Duke University School of Medicine, Durham, NC, USA*

Ernesto G. Scerpella, MD
Infectious Diseases
Specialty Care Medicines
Development Group
Pfizer Inc
500 Arcola Road
Collegeville, PA 19426
Tel: +1 305 790 7523
Fax: +1 646 441 6224
E-mail: ernesto.scerpella@pfizer.com

ABSTRACT (UPDATED)

Background: Little is known about the characteristics and outcomes of patients who develop NP caused by CA-MRSA.

Methods: We identified all patients with NP caused by CA-MRSA enrolled in an international, double-blind, randomized, controlled trial of linezolid (LZD; 600 mg twice daily) vs. vancomycin (VAN; 15 mg/kg twice daily) for NP caused by MRSA. We defined CA-MRSA as a baseline MRSA isolate from an adequate respiratory specimen that was SCC*mec* type IV, PVL+. Non–CA-MRSA was defined as a baseline MRSA isolate that was SCC*mec* type I, II, III, or IV, PVL–. Outcomes at end of study (EOS) were assessed 7–30d after end of therapy.

Results: In total, 48/385 (12.5%) patients in mITT population with confirmed MRSA had CA-MRSA NP. Patient characteristics and outcomes varied by CA-MRSA status (**Table**). At EOS, mITT patients with CA-MRSA had numerically lower clinical success (total CA-MRSA 41.9%, LZD 36.4%, VAN 47.6%) vs. patients with non–CA-MRSA (total non–CA-MRSA 54%; LZD 60.6%, VAN 48.1%).

Conclusions: CA-MRSA is a cause of NP. Clinical success rates were numerically lower and Day 28 mortality were similar among patients with CA-MRSA compared with those with non–CA-MRSA.

Table. Demographics, Clinical and Microbiologic Characteristics, and Outcomes of Patients With NP Caused by CA-MRSA and Non–CA-MRSA

Characteristic	CA-MRSA (N=48)	Non–CA-MRSA (N=337)	*P* Value
Age (y), mean (SD)	53.6 (17.8)	62.7 (18.0)	0.001
African American, n (%)	12 (25.0)	34 (10.1)	0.004 (race, overall)
Chest X-ray, n (%)			0.62
Bilateral	31 (64.6)	231 (68.5)	
Unilateral	17 (35.4)	105 (31.2)	
Pleural effusion, n (%)	17 (35.4)	156 (46.3)	0.166
Pulmonary disease, n (%)	39 (81.3)	224 (66.5)	0.046
Cardiac disease, n (%)	21 (43.8)	209 (62.0)	0.018
APACHE II ≥15, n (%)	30 (62.5)	220 (65.3)	0.744
Bacteremia, n (%)	5 (10.4)	29 (8.6)	0.786
Ventilated at baseline, n (%)	37 (77.1)	238 (70.6)	0.398
Vancomycin MIC, n (%)[a]			0.247
≤0.5	6 (12.5)	24 (7.1)	
1	40 (83.3)	281 (83.4)	
≥2	2 (4.2)	31 (9.2)	
Unknown	0	1 (0.3)	
Clinical success at EOS, n (%)[b]	18 (41.9)	163 (54.0)	12.1 (–3.7 to 27.9)[c]
Mortality at day 28, n (%)	7 (14.6)	61 (18.1)	–3.5 (–14.3 to 7.3)[c]

[a] Baseline vancomycin MIC data shown for all baseline isolates, irrespective of treatment assignment.
[b] Unknown/missing values were included in the calculation.
[c] Risk difference and 95% confidence intervals calculated for difference in percentage success and mortality.

INTRODUCTION

- Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important healthcare-associated pathogen.
- Community-acquired MRSA (CA-MRSA) was first described in the 1990s. It was initially recognized by its ability to cause infections in patients without healthcare risk factors.[1]
  - CA-MRSA is the predominant cause of skin and soft tissue infections in the United States.[2]
  - Recent studies have shown that CA-MRSA can be an important cause of MRSA healthcare-acquired infections including ventilator-associated pneumonia (VAP), surgical-site infections, and bacteremia.[3]
  - In areas of high prevalence (eg, USA300 in the United States), CA-MRSA is beginning to overtake traditional healthcare-associated MRSA strains as causes of healthcare-associated infections.[4]
- In this analysis, we evaluated patient characteristics, pathogen identification, and outcomes of patients with nosocomial and healthcare-associated pneumonia (HCAP) caused by CA-MRSA enrolled in an international phase 4 study that compared linezolid with vancomycin.

METHODS

- We analyzed information from patients enrolled in a phase 4 randomized, double-blind, multicenter study that compared the clinical and microbiologic efficacy, safety, and tolerability of linezolid with vancomycin in adults with nosocomial pneumonia, including HCAP, due to culture-proven MRSA (study A5951001, ClinicalTrials.gov identifier: NCT00084266).[5]
- We defined CA-MRSA as a baseline MRSA isolate from an adequate respiratory specimen that was staphylococcal cassette chromosome *mec* (SCC*mec*) type IV and positive for the presence of the Panton-Valentine leukocidin genes (PVL+). Non–CA-MRSA was defined as a baseline MRSA isolate that was SCC*mec* type I, II, III, or IV, PVL–.

MRSA Isolate Identification

- MRSA isolates collected in the study were sent to a central reference laboratory.
- Minimum inhibitory concentration (MIC) values for linezolid and vancomycin were determined by broth microdilution following Clinical Laboratory Standards Institute guidelines.
- SCC*mec* types I through VI were characterized using a multiplex polymerase chain reaction (PCR) approach.
- PVL (*lukF-PV* and *lukS-PV*) screening was performed by Real-Time PCR method.
- *Agr* typing (groups I–IV) was performed using a multiplex Real-Time PCR approach. The function of the *agr* operon was determined by the production of delta-hemolysin.

Evaluation of Clinical Outcomes

- Outcomes evaluated included:
  - Clinical response at the end-of-treatment (EOT) visit
  - Clinical response at the end-of-study (EOS) visit
  - All-cause mortality at day 28.
  - Clinical responses were assessed in the following analysis sets:
    - Modified intent-to-treat (mITT) population: patients who received at least 1 dose of study drug and had a positive baseline MRSA culture.
    - Per-protocol (PP) population: patients who achieved key inclusion/exclusion criteria, reported adequate compliance (80% of study drug in patients with documented MRSA), had no prohibited concomitant medications, and had EOT and EOS visits within windows.

Visit	Definition	Investigator Assessment of Clinical Response
End of treatment	≤72 hours after the last treatment dose is completed	• Cure • Improvement • Failure • Unknown
End of study	7–30 days after the end of treatment	• Cure • Failure • Unknown

- Response categories:
  - Clinical success at EOT: cure or improvement
  - Clinical success at EOS: cure
  - Patients that fell within the "unknown" category were excluded from the statistical analysis of response.

Statistical Analysis

- To assess statistical differences in the distribution of baseline characteristics between groups, one-way analysis of variance was used for continuous variables and Fisher's exact test or Chi-square test, as appropriate, was used for categorical variables.
- *P* values <0.05 (2-sided) were considered statistically significant.
- For analysis of clinical outcomes, risk difference and 95% confidence intervals (CIs) were calculated for difference in percentage success and mortality. Overall risk difference was adjusted for treatment using Cochran-Mantel-Haenszel weights.

RESULTS

- In total, 1225 patients were randomized in the clinical study and 385 patients who had CA-MRSA characterization performed on their baseline MRSA isolates were included in the mITT population for the current analysis.
  - The mITT group was used for analysis of baseline patient characteristics and assessment of clinical response at EOT and EOS.
  - 48/385 (12.5%) patients with confirmed MRSA had pneumonia caused by CA-MRSA (SCC*mec* type IV, PVL+).
- The PP population included 325 patients that were only evaluated for clinical response at EOT and EOS.
- Differences in baseline characteristics between groups were observed (**Table 1**).
  - Patients with CA-MRSA pneumonia were more likely to be younger and African American, and to have had a history of pulmonary comorbidities.
  - Patients with non–CA-MRSA pneumonia were more likely to have cardiac comorbidities.
  - VAP was the most common type of pneumonia in both groups, followed by hospital-acquired pneumonia (HAP). HCAP was diagnosed in 15.8% of all patients in the study, with similar percentages in both the CA-MRSA and non–CA-MRSA groups.
  - The percentage of patients with CA-MRSA infection by type of pneumonia was as follows: 11.5% HCAP, 15.8% VAP, and 5.8% HAP.
  - The frequencies of chest radiographic findings, concurrent bacteremia, patients presenting with an initial Acute Physiology And Chronic Health Evaluation II score ≥15, and baseline vancomycin MIC values were similar in both groups.

Table 1. Baseline Patient Characteristics by CA-MRSA Status in the Modified Intent-to-Treat Population

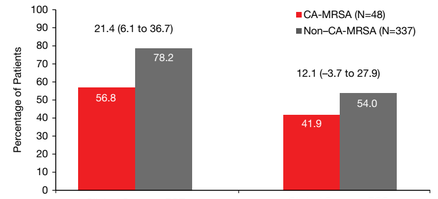
Characteristic	Patients With CA-MRSA (N=48)	Patients With Non–CA-MRSA (N=337)	*P* Value[a]
Mean age ± SD, y	53.6 ± 17.8	62.7 ± 18.0	0.001
Male gender, n (%)	31 (64.6)	216 (64.1)	1.000
Race, n (%)			0.004
White	33 (68.8)	228 (67.7)	
African American	12 (25.0)	34 (10.1)	
Asian	3 (6.3)	59 (17.5)	
Other	0	16 (4.7)	
Mean weight ± SD, kg	81.8 ± 20.0	77.4 ± 22.4	0.195
Comorbidities, n (%)			
Cardiac	21 (43.8)	209 (62.0)	0.018
Pulmonary	39 (81.3)	224 (66.5)	0.046
Gastrointestinal	29 (60.4)	189 (56.1)	0.642
Renal/urinary	15 (31.3)	139 (41.2)	0.210
Vascular	14 (29.2)	116 (34.4)	0.518
Hepatobiliary	10 (20.8)	46 (13.6)	0.192
Neoplastic	5 (10.4)	36 (10.7)	1.000
Chest X-ray, n (%)			0.620
Unilateral infiltrates	17 (35.4)	105 (31.2)	
Bilateral infiltrates	31 (64.6)	231 (68.5)	
Pleural effusion, n (%)	17 (35.4)	156 (46.3)	0.166
Type of pneumonia, n (%)			0.038
HCAP	7 (14.6)	54 (16.0)	
VAP	35 (72.9)	186 (55.2)	
HAP	6 (12.5)	97 (28.8)	
APACHE II score ≥15	30 (62.5)	220 (65.3)	0.744
Ventilated at baseline, n (%)	37 (77.1)	238 (70.6)	0.398
Bacteremia, n (%)	5 (10.4)	29 (8.6)	0.786
Vancomycin MIC values, n (%)[b]			0.247
≤0.5	6 (12.5)	24 (7.1)	
1	40 (83.3)	281 (83.4)	
≥2	2 (4.2)	31 (9.2)	
Unknown	0	1 (0.3)	

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; HCAP, healthcare-associated pneumonia; VAP, ventilator-associated pneumonia; HAP, hospital-acquired pneumonia; APACHE, Acute Physiology And Chronic Health Evaluation; MIC, minimum inhibitory concentration.
[a] *P* value for the comparison CA-MRSA to non–CA-MRSA.
[b] Data for all participants in each group.

Clinical Assessment of CA-MRSA Versus Non–CA-MRSA

- No differences were observed between the CA-MRSA and non–CA-MRSA groups with respect to treatment duration (9.4 vs 10.1 days; *P*=0.256), concomitant Gram-negative coverage (85.4% vs 86.6%; *P*=0.822), and concomitant anaerobic coverage (60.4% vs 51.6%; *P*=0.282).
- Clinical success rates of patients with CA-MRSA pneumonia were lower than those with non–CA-MRSA pneumonia at both EOT and EOS (**Figure 1**).
- We observed no difference in day 28 all-cause mortality between the CA-MRSA and non–CA-MRSA groups (14.6% vs 18.1%; risk difference, –3.5; 95% CI, –14.3 to 7.3).

Figure 1. Clinical Response at EOT and EOS by CA-MRSA Status in the Modified Intent-to-Treat Population.[a]



EOT, end of treatment; EOS, end of study; CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*.
[a] Risk difference and 95% confidence intervals calculated for difference in percentage success. Overall risk difference is adjusted for treatment using Cochran-Mantel-Haenszel weights.

Clinical Assessment of Linezolid and Vancomycin Treatment Outcomes

- CA-MRSA clinical success rates (EOT and EOS) for linezolid and vancomycin are shown in **Table 2**. Clinical success rates for linezolid in non–CA-MRSA were higher than vancomycin at EOT and EOS in both the mITT and PP populations.
- We observed no difference in day 28 all-cause mortality in the various subgroups analyzed.
- No differences were observed in baseline vancomycin MIC values or trough levels in patients with CA-MRSA and non–CA-MRSA pneumonia that were treated with vancomycin (data not shown).

Table 2. Outcomes by CA-MRSA Status and Treatment Assignment in the mITT and PP Populations[a]

mITT Population	CA-MRSA Patients (N=48) LZD (n=26)	CA-MRSA Patients (N=48) VAN (n=22)	LZD vs VAN RD (95% CI)	Non–CA-MRSA Patients (N=337) LZD (n=165)	Non–CA-MRSA Patients (N=337) VAN (n=172)	LZD vs VAN RD (95% CI)
Clinical success, EOT	12/23 (52.2)	13/21 (61.9)	–9.7 (–38.9 to 19.4)	132/155 (85.2)	119/166 (71.7)	13.5 (4.6 to 22.3)
Clinical success, EOS	8/22 (36.4)	10/21 (47.6)	–11.3 (–40.6 to 18.1)	86/142 (60.6)	77/160 (48.1)	12.4 (1.3 to 23.6)
Mortality at day 28	4/26 (15.4)	3/22 (13.6)	–1.7 (–21.7 to 18.2)	32/165 (19.4)	29/172 (16.9)	–2.5 (–10.8 to 5.7)

PP Population	CA-MRSA Patients (N=48) LZD EOT (n=19) LZD EOS (n=19)	CA-MRSA Patients (N=48) VAN EOT (n=18) VAN EOS (n=18)	LZD vs VAN RD (95% CI)	Non–CA-MRSA Patients (N=337) LZD EOT (n=142) LZD EOS (n=132)	Non–CA-MRSA Patients (N=337) VAN EOT (n=146) VAN EOS (n=141)	LZD vs VAN RD (95% CI)
Clinical success, EOT	12/19 (63.2)	12/18 (66.0)	–3.5 (–34.2 to 27.2)	123/140 (87.9)	106/145 (73.1)	14.8 (5.7 to 23.8)
Clinical success, EOS	8/18 (44.4)	9/18 (50.0)	–5.6 (–38.1 to 27.0)	79/127 (62.2)	68/139 (48.9)	13.3 (1.4 to 25.1)
Mortality at day 28	1/19 (5.3)	1/18 (5.6)	0.3 (–14.3 to 14.9)	26/132 (19.7)	26/141 (18.4)	–1.3 (–10.6 to 8.1)

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; mITT, modified intent-to-treat; LZD, linezolid; VAN, vancomycin; RD, risk difference; CI, confidence interval; EOT, end of treatment; EOS, end of study; PP, per-protocol.
[a] All values n/N (%), where n = patients achieving outcome and N = available data. Percentages are calculated excluding missing data. Unknown/missing values were not included in the calculation.

MRSA Isolate Identification

- The study central microbiology reference laboratory provided us with a report on 434 MRSA isolates (**Table 3**).
- The number of isolates included is more than the number of mITT patients because complete microbiologic and clinical information was not available in all cases. Only 1 baseline isolate per patient, all from respiratory isolates, were included in this evaluation.
- Fifty-five MRSA isolates fulfilled our definition for CA-MRSA (SCC*mec* type IV, PVL+).
  - 48/51 (94.1%) SCC*mec* type IV, PVL+ MRSA isolates came from the United States. Information was not available for 4 isolates.
  - 51/55 (92.7%) of SCC*mec* type IV, PVL+ MRSA isolates also exhibited *agr* expression by delta-hemolysin assay.

Table 3. Distribution of 434 MRSA Isolates by SCC*mec* Type and PVL Status[a]

SCC*mec*	PVL Status	Number of Isolates
Type I	Negative	16
Type II	Negative	230
Type III	Negative	52
Type IV	Negative	80
Type IV	Positive	55
Type VI	Negative	1

MRSA, methicillin-resistant *Staphylococcus aureus*; SCC*mec*, staphylococcal cassette chromosome *mec*; PVL, Panton-Valentine leukocidin.
[a] Isolates from the central reference laboratory.

CONCLUSIONS

- In a clinical study that primarily enrolled patients with nosocomial pneumonia, 12.5% of patients with confirmed MRSA had pneumonia caused by MRSA harboring genetic markers of CA-MRSA genotype (SCC*mec* type IV, PVL+).
  - The spread of CA-MRSA strains into the nosocomial setting may limit the utility of using clinical risk factors or genetic markers alone to assign community- or healthcare-associated status.
- Patients with CA-MRSA pneumonia were more likely to be younger and African American, and to have had a history of pulmonary comorbidities.
  - A high proportion of young, African American patients has been previously described in studies of adult and pediatric patients with CA-MRSA infections and colonization.[6,7]
  - Association with pulmonary comorbid conditions (eg, chronic obstructive pulmonary disease) has been reported in patients with USA300 healthcare-associated infections.[8]
- Clinical success rates for patients with CA-MRSA pneumonia were lower compared with non–CA-MRSA infections. There were no differences in day 28 mortality.
- Linezolid had numerically higher clinical success rates in patients with non–CA-MRSA pneumonia but numerically lower success rates in patients with CA-MRSA compared with vancomycin.
  - These results confirm observations made in clinical studies that predated the era of nosocomial CA-MRSA infections.[9]

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