Clinical Outcomes of Osteomyelitis Patients Infected With Methicillin-Resistant *Staphylococcus aureus* USA-300 Strains

Paula Peyrani, MD, Marty Allen, MD, David Seligson, MD, Craig Roberts, MD, Anne Chen, MD, Nadia Haque, MD, Marcus Zervos, MD, Timothy Wiemken, PhD, MPH, CIC, Julie Harting, PharmD, Diana Christensen, MD, and Julio Ramirez, MD

Abstract

Methicillin-resistant *Staphylococcus aureus* (MRSA) USA-300 strains have emerged as an important cause of community-acquired infections. These strains have been recognized as an etiology of osteomyelitis but data on their incidence and outcomes are limited.

We retrospectively studied the incidence and clinical outcomes of MRSA USA-300 osteomyelitis in patients at the University of Louisville Hospital and the Henry Ford Health System between January 2007 and March 2008. Pulsed-field gel electrophoresis was used to determine USA type. Clinical outcomes were defined as management success versus failure at 12 months. Chi-square tests, Fisher exact tests, and Mann-Whitney tests were used to compare patient characteristics on the basis of clinical outcomes and USA type.

Of the 50 patients with MRSA osteomyelitis, 27 (54%) had the USA-300 strain. Clinical failure was identified in 22% (6/27) of the patients with MRSA USA-300 and in 30% (7/23) of the patients with MRSA non–USA-300 osteomyelitis (*P* = .509).

Our results showed that MRSA USA-300 is a significant etiology of MRSA osteomyelitis. With current surgical and medical management, outcomes of patients with MRSA USA-300 osteomyelitis are similar to those of patients with MRSA non–USA-300 osteomyelitis.

Dr. Peyrani is Instructor of Medicine and Director of Clinical Research, Division of Infectious Diseases, University of Louisville, Louisville, Kentucky.
Dr. Allen is former Assistant Professor of Medicine, Dr, Seligson is Professor and Vice-Chairman, and Dr. Roberts is Professor of Medicine, Department of Orthopaedic Surgery, University of Louisville.
Dr. Chen, Dr. Haque, and Dr. Zervos are Infectious Diseases Physicians, Henry Ford Health System, Detroit, Michigan.
Dr. Wiemken is Instructor of Medicine, and Dr. Harting and Dr. Christensen are Assistant Professors of Medicine, Division of Infectious Diseases, University of Louisville.
Dr. Ramirez is Professor of Medicine and Chief, Division of Infectious Diseases, University of Louisville, and Professor of Medicine and Chief, Division of Infectious Diseases, Robley Rex Veterans Affairs Medical Center, Louisville, Kentucky.

Address correspondence to: Julio Ramirez, MD, FACP, Division of Infectious Diseases, University of Louisville, 501 E Broadway, MedCenter One, Suite 380, Louisville, KY 40202 (tel, 502-852-7844; fax, 502-852-1147; e-mail, j.ramirez@louisville.edu).

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is increasingly recognized as an etiologic agent in osteomyelitis.[1,2] MRSA osteomyelitis is traditionally considered a hospital-acquired infection. Over the past decade, however, cases of bone and joint infections caused by community-associated MRSA have been reported.[3-5] These infections are produced by MRSA strains with genetic characteristics different from those of the traditional hospital-associated MRSA strains. The molecular biology that characterizes these new strains indicates that they belong to the USA-300 pulsed-field gel electrophoresis (PFGE) type.[6,7]

MRSA contains the *mec*A gene, which encodes for penicillin-binding protein 2A. This protein has a very low affinity for all β-lactam antibiotics. The *mec*A gene is located on a mobile genetic element, Staphylococcal cassette chromosome *mec* (SCC*mec*). Several types of SCC*mec* have been described. Hospital-associated MRSA strains contain SCC*mec* type I, II, or III. These genes carry resistance not only to β-lactam antibiotics but also to several non–β-lactam antibiotics.[8] On the other hand,

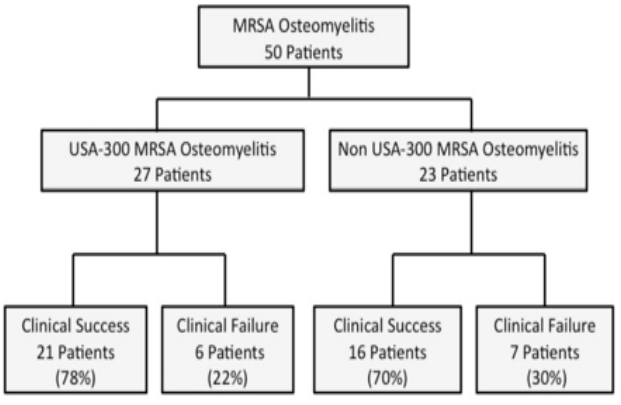

Figure 1. Study flowchart.

Table I. Clinical Characteristics of Patients With Osteomyelitis Caused by Methicillin-Resistant *Staphylococcus aureus* USA-300 (n = 27) Versus Non–USA-300 (n = 23)

Variable	n (%) USA-300	n (%) Non–USA-300	*P*
Demographics			
Mean (SD) age, y	44.5 (11.7)	51.6 (10.9)	.046
Male sex	21 (77.8)	17 (73.9)	.750
Site of Osteomyelitis			
Femur	2 (7.4)	5 (21.7)	.146
Tibia	7 (25.9)	8 (34.8)	.496
Humerus/radius	1 (3.7)	3 (13.0)	.322
Vertebra	1 (3.7)	2 (8.7)	.588
Pelvis	2 (7.4)	0 (0.0)	.493
Foot	3 (11.1)	2 (8.7)	1.000
Hand	1 (3.7)	0 (0.0)	1.000
Sternum	2 (7.4)	2 (8.7)	1.000
Cranium	3 (11.1)	0 (0.0)	.240
Knee	0 (0.0)	0 (0.0)	—
Other	6 (22.2)	2 (8.7)	.260
Type of Osteomyelitis: Acute	18 (66.7)	11 (50.0)	.238
Host Characteristics			
Local Compromise			
Previous surgery (at site)	19 (70.4)	16 (69.6)	.951
Foreign body	13 (48.2)	13 (56.5)	.555
Trauma/fracture (at site)	18 (66.7)	18 (78.3)	.363
Ulcer without healing (at site)	7 (25.9)	6 (26.1)	.990
Peripheral vascular disease (longstanding)	1 (3.7)	2 (8.7)	.588
Neuropathy	4 (14.8)	3 (13.0)	1.000
Systemic Compromise			
Malnutrition	1 (3.7)	2 (8.7)	.588
Diabetes mellitus	(29.6)	7 (30.4)	.951
Renal failure	1 (3.7)	2 (8.7)	.588
Hepatic failure	1 (3.7)	1 (4.4)	1.000
Tobacco abuse	10 (37.0)	11 (47.8)	.441
Immunosuppression	1 (3.7)	0 (0.0)	1.000
Outcome: Clinical Success	21 (77.8)	16 (69.6)	.509

MRSA USA-300 strains contain SCC*mec* type IV, which confers resistance to β-lactam antibiotics and erythromycin but does not regularly carry genes associated with resistance to other non–β-lactam antibiotics.[9] MRSA USA-300 strains are considered more virulent because of the presence of the Panton-Valentine leukocidin (PVL) exotoxin and the global regulatory gene, *agr*.[9]

Patients with community-acquired infections caused by MRSA USA-300 strains may present with severe disease and have poor clinical outcomes. Severe presentation and poor outcome have been found mainly in patients who have skin and soft-tissue infections and present with necrotizing fasciitis and in patients who have pulmonary infections and present with necrotizing pneumonia.[10-12]

Although MRSA USA-300 SCC*mec* type IV strains traditionally have been considered community-associated pathogens, they have been isolated from patients with hospital-acquired bloodstream infections, hospital-acquired pneumonia, and prosthetic joint infections.[13-15] Therefore, the initial characterization of MRSA USA-300 as a unique community-associated pathogen is no longer valid, as MRSA USA-300 is now a well-established hospital-associated pathogen.

Up until now, no data regarding the incidence and clinical outcomes of bone infection caused by MRSA USA-300 were available. We designed an observational study in an attempt to define the incidence and clinical outcomes of MRSA USA-300 as an etiology of osteomyelitis.

Materials and Methods

Study Design

This was a retrospective, observational study of patients who had MRSA osteomyelitis and were hospitalized at 2 academic medical centers between January 2007 and March 2008. Local institutional review board approval was obtained for each participating center. Data were collected on a paper case report form and transferred to an online data collection form located at www.osteosite.net. Data quality was reviewed at the Data and Statistical Coordinating Center, Division of Infectious Diseases, University of Louisville, Louisville, Kentucky. After all queries were completed, the case was entered into the database.

Table II. Comparison of Clinical Success (n = 37) and Clinical Failure (n = 13) in Patients With Osteomyelitis Caused by Methicillin-Resistant *Staphylococcus aureus*

Variable	n (%) Success	Failure	*P*
Demographics			
Mean (SD) age, y	48 (12.3)	47 (10.9)	.684
Male sex	28 (75.7)	10 (76.9)	1.000
Site of Osteomyelitis			
Femur	4 (10.8)	3 (23.1)	.357
Tibia	10 (27.0)	5 (38.5)	.493
Humerus/radius	3 (8.1)	1 (7.7)	1.000
Vertebra	3 (8.1)	0 (0.0)	.558
Pelvis	2 (5.4)	0 (0.0)	1.000
Foot	4 (10.8)	1 (7.7)	.611
Hand	1 (2.7)	0 (0.0)	1.000
Sternum	3 (8.1)	1 (7.7)	1.000
Cranium	2 (5.4)	1 (7.7)	1.000
Knee	0 (0.0)	0 (0.0)	—
Other	6 (16.2)	2 (15.4)	1.000
Type of Osteomyelitis: Acute	23 (63.9)	6 (46.2)	.265
Host Characteristics			
Local Compromise			
Previous surgery (at site)	26 (70.3)	9 (69.2)	1.000
Foreign body	17 (46.0)	9 (69.2)	.148
Trauma/fracture (at site)	28 (75.7)	8 (61.5)	.474
Ulcer without healing (at site)	10 (27.0)	3 (23.1)	1.000
Peripheral vascular disease (longstanding)	3 (8.1)	0 (0.0)	.558
Neuropathy	4 (10.8)	3 (23.1)	.357
Systemic Compromise			
Malnutrition	1 (2.7)	2 (15.4)	.162
Diabetes mellitus	10 (27.0)	5 (38.5)	.493
Renal failure	2 (5.4)	1 (7.7)	1.000
Hepatic failure	1 (2.7)	1 (7.7)	.456
Tobacco abuse	16 (43.2)	5 (38.5)	.764
Immunosuppression	0 (0.0)	1 (7.7)	.260
MRSA Pulsed-Field Gel Electrophoresis Type: USA-300	21 (56.8)	6 (46.2)	.537

Inclusion Criteria

A patient was diagnosed with MRSA osteomyelitis and included in the study when these criteria were met:

- Bone culture positive for MRSA.

Plus at least 1 of the following:

- Evidence of local inflammatory response, manifested as local pain, edema, erythema, warmth, or drainage.
- Evidence of systemic inflammatory response, manifested as fever, elevated C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), or white blood cell count.
- Osteomyelitis-compatible findings on plain radiograph, computed tomography, bone scan, magnetic resonance imaging, or positron emission tomography.
- Pathology report indicative of osteomyelitis.

Exclusion Criteria

A patient was excluded from the study when there was no follow-up visit 12 months after initiation of management.

MRSA Identification, Antibiotic Susceptibility, and Genetics

Initial identification of isolates and in vitro susceptibilities were determined with automated susceptibility testing methods. Isolates were then screened for inducible clindamycin resistance using D-test methodology. Vancomycin minimum inhibitory concentrations (MICs) were determined using the standard Etest method (AB bioMérieux, Solna, Sweden). The Etest macromethod that uses a higher inoculum to detect the presence of a less susceptible subpopulation was used to screen for heteroresistance. PFGE of MRSA isolates was performed. For PFGE, genomic DNA was prepared with the addition of lysostaphin at a concentration of 30 U/mL, and sample plugs were digested with SmaI 30 U (New England Biolabs, Beverly, Massachusetts) loaded on a 0.8% agarose gel in 0.5× TBE buffer (Tris base, 45 mM; boric acid, 45 mM; ethylenediaminetetraacetic acid, 1 mM) and electrophoresed on a CHEF-DR III apparatus (Bio-Rad, Hercules, California) using these parameters: initial switch time, 5 s; final switch time, 35 s; start ratio, 1; voltage, 200V; run time, 18 h; temperature, 14°C. Lambda ladder PFG marker (New

Table III. Phenotypic and Genotypic Characteristics of Methicillin-Resistant *Staphylococcus aureus* USA-300 (n = 27) and Non–USA-300 (n = 23) Isolates

Variable	n (%)	
	USA-300	Non–USA-300
Global Regulatory Gene, agr		
Type I	22 (100)	0 (0.0)
Type II	0 (0.0)	17 (100)
Panton-Valentine Leukocidin Exotoxin	12 (44.4)	0 (0.0)
Staphylococcal Cassette Chromosome mec		
Type II	0 (0.0)	23 (100)
Type IVa	26 (96.3)	0 (0.0)
Type IVB	1 (3.7)	0 (0.0)
Resistance		
Clindamycin resistance	2 (9.1)	17 (100)
Erythromycin resistance	21 (95.5)	17 (100)
Heteroresistance	0 (0.0)	2 (11.8)
Vancomycin Minimum Inhibitory Concentration, µg/mL		
0.75	0 (0.0)	1 (4.4)
1	5 (18.5)	1 (4.4)
1.5	22 (81.5)	15 (65.2)
2	0 (0.0)	6 (26.1)

Table IV. Phenotypic and Genotypic Characteristics of Methicillin-Resistant Staphylococcus aureus Isolates by Clinical Success (n = 37) and Clinical Failure (n = 13)

Variable	n (%)	
	Success	Failure
Global Regulatory Gene, agr		
Type I	18 (60.0)	4 (44.4)
Type II	12 (40.0)	5 (55.6)
Panton-Valentine Leukocidin Exotoxin	10 (27.0)	2 (15.4)
Staphylococcal Cassette Chromosome mec		
Type II	16 (43.2)	7 (53.9)
Type IVa	21 (56.8)	5 (38.5)
Type IVB	0 (0.0)	1 (7.7)
Resistance		
Clindamycin resistance	13 (43.3)	6 (66.7)
Erythromycin resistance	29 (96.7)	9 (100.0)
Heteroresistance	0 (0.0)	2 (22.2)
Vancomycin Minimum Inhibitory Concentration, µg/mL		
0.75	1 (2.7)	0 (0.0)
1	4 (10.8)	2 (15.4)
1.5	29 (78.4)	8 (61.5)
2	3 (8.1)	3 (23.1)

England Biolabs, Ipswich, Massachusetts) was used as a size standard. All MRSA isolates were entered into a database of isolates using the Gel Doc 2000 gel documentation system (Bio-Rad), and PFGE patterns were compared using BioNumerics software (Applied Maths, Austin, Texas). Polymerase chain reaction analysis was performed to identify MRSA isolates carrying the PVL gene.

Confounding Variables

Multiple variables that may influence the association between MRSA type and clinical outcomes were collected. Age and sex data were collected as demographic variables. Osteomyelitis site was classified as femur, tibia, humerus/radius, vertebra, pelvis, foot, hand, sternum, cranium, knee, or other. Osteomyelitis was classified as acute in patients who had signs and symptoms for fewer than 30 days. Host characteristics indicative of a local compromise favoring infection included previous surgery at the osteomyelitis site, foreign body, trauma or fracture at the osteomyelitis site, ulcer at the osteomyelitis site, longstanding peripheral vascular disease, and neuropathy. Host characteristics indicative of a systemic compromise favoring infection included malnutrition, diabetes mellitus, renal failure, hepatic failure, tobacco use, and immunosuppression.

Medical Management

Patients received anti-MRSA antibiotics for at least 6 weeks. Serum bactericidal levels were measured in an attempt to optimize antibiotic management.[16] Antibiotic therapy was discontinued at 6 weeks in patients with documented resolution of local inflammatory response as well as resolution of systemic inflammatory response. Systemic response was evaluated by CRP level and ESR. In patients without resolution of inflammatory response, antibiotic therapy was continued until CRP level and ESR were normalized. In patients who had hardware in place, and in whom MRSA survival in biofilm was likely, suppressive antibiotic therapy with low-dose oral antibiotics was continued during the study period.

Surgical Management

Surgical intervention was classified as primary (primary intervention for management of osteomyelitis with removal of all infected bone within 30 days of antibiotic therapy), adjuvant (surgery performed for aggressive bone debridement with goal of removing all necrotic bone), or salvage (surgery performed because of failure of medical management and after documented failure of antibiotic therapy for MRSA osteomyelitis). If, after bone debridement, a significant local defect persisted, vancomycin-impregnated beads were placed.

Study Outcomes

Clinical outcomes—clinical success and failure—were defined at 12-month follow-up. The following definitions were used.

Clinical Success. (a) *Infection arrested:* patients with no clinical or laboratory evidence of infection with all antibiotics discontinued. (b) *Infection arrested plus suppressive therapy:* patients with no clinical or laboratory evidence of infection but continuing oral antibiotics because of a high risk for relapse.

Clinical Failure. (a) *Failure during antibiotic therapy:* patients experiencing clinical and laboratory deterioration during antibiotic therapy that required surgical intervention. (b) *Relapse of infection:* patients experiencing clinical and laboratory deterioration after discontinuation of antibiotic therapy.

Statistical Analysis

Characteristics of patients with MRSA USA-300 osteomyelitis were compared with those of patients with MRSA non–USA-300 osteomyelitis. Characteristics were also compared between patients who experienced clinical success and those who experienced clinical failure. Continuous variables were compared using the Mann-Whitney test, and categorical variables were compared using the χ^2 test or the Fisher exact test. Ps≤.05 were considered statistically significant. SAS version 9.2 (SAS, Cary, North Carolina) was used for all analyses.

Results

Of the 50 patients with MRSA osteomyelitis enrolled in the study, 27 (54%) had the USA-300 strain. The antibiotics most commonly used for management were vancomycin, daptomycin, and linezolid, and those most commonly used for suppressive therapy were doxycycline and trimethoprim/sulfamethoxazole. Surgical intervention was used in 62% of patients; in the other 38%, surgical intervention was not indicated (eg, vertebral osteomyelitis). Six percent of patients underwent primary surgical therapy, and 56% underwent adjuvant surgical therapy; no patient required salvage surgical therapy. The clinical characteristics of patients with MRSA USA-300 osteomyelitis and patients with MRSA non–USA-300 osteomyelitis are listed in Table I. The only statistically significant characteristic associated with MRSA USA-300 infection was younger age. The clinical characteristics of patients with clinical success and patients with clinical failure are listed in Table II. Bone infection caused by MRSA USA-300 was not associated with increased risk for clinical failure. Clinical failure was documented in 22% of patients with MRSA USA-300 osteomyelitis and 30% of patients with MRSA non–USA-300 osteomyelitis (P = .509). A flowchart (Figure 1) illustrates the study results.

The phenotypic and genotypic characteristics of MRSA USA-300 and MRSA non–USA-300 isolates are listed in Table III. The PVL gene was identified in 44% of MRSA USA-300 isolates and in none of the MRSA non–USA-300 isolates. There was no association between clinical failure and presence of the PVL gene (P = .48), *agr* type II (P = .465), or vancomycin MIC of 2 μg/mL (P = .173) (Table IV).

Discussion

Our study results indicated that MRSA USA-300 is an emerging pathogen causing bone infection. Fifty-four percent of the MRSA osteomyelitis cases at our institution were caused by MRSA USA-300 strains. Our data showed no significant difference in rate of clinical failure for patients infected with MRSA USA-300 versus MRSA non–USA-300.

MRSA that is resistant to vancomycin remains rare. However, MRSA strains susceptible to vancomycin with increased MICs (eg, 1.5-2 μg/mL) are becoming more common. The literature suggests that MRSA strain infections with vancomycin MIC of 1.5 μg/mL or higher may be associated with poor clinical outcomes.[17-19] Approximately 90% of our MRSA non–USA-300 osteomyelitis cases had a vancomycin MIC of 1.5 μg/mL or higher. Even though MRSA USA-300 strains are likely to have lower MICs to vancomycin, we found that 81% of the strains had a vancomycin MIC of 1.5 μg/mL or higher. Because of the minimal number of MRSA strains with low MICs to vancomycin, we could not evaluate the association between high vancomycin MIC and clinical outcomes. Vancomycin was the initial empiric therapy most commonly used in this study. Our

management approach with vancomycin is to maintain a trough vancomycin level of 15 µg/mL. As antibiotic therapy was not standardized, we could not define the impact of a particular antibiotic on clinical outcomes. In several patients, vancomycin was switched to an alternative anti-MRSA antibiotic. Indications for vancomycin discontinuation were lack of clinical improvement, identification of an MRSA with an MIC to vancomycin of 1.5 µg/mL or higher, and serum vancomycin bactericidal level lower than 1:8.

Aggressive presentation of osteomyelitis caused by MRSA USA-300 with bone necrosis or development of subperiosteal abscess has been reported.[3,4] The pathogenesis leading to bone necrosis in patients with MRSA USA-300 is not well described, but production of exotoxins such as PVL may play a significant role.[20,21] In our study, presence of the PVL gene was identified only in patients infected with MRSA USA-300 strains. Although initial presentation of MRSA USA-300 seems more aggressive, we could not identify any difference in clinical outcomes for patients infected with MRSA USA-300 versus MRSA non–USA-300. Our therapy approach, which includes aggressive removal of necrotic bone, may explain why clinical outcomes were not statistically different between the 2 MRSA types. The suggestion is that, though MRSA USA-300 may have a more aggressive presentation, the clinical response of affected patients to surgical and antibiotic therapy is similar to that of patients with MRSA non–USA-300. A similar clinical response for MRSA USA-300 and non–USA-300 was defined at 12-month follow-up. As 46% of patients with clinical success were on suppressive antibiotic therapy, the possibility exists that late relapse of disease may alter these findings.

An important limitation of this study is that the small sample size did not allow for use of multivariate analysis techniques to better define the association between MRSA phenotypic or genotypic characteristics and clinical outcomes. The only demographic characteristic associated with MRSA USA-300 strains was younger age, but, given the small sample size, clinically important differences between the 2 groups cannot be ruled out. Another limitation is that we combined all osteomyelitis sites, but the pathogenesis at these sites may differ and may influence the clinical course.

Our study results showed that MRSA USA-300 is a significant pathogen in bone infections. With a combination of aggressive surgical intervention and appropriate antibiotic therapy, outcomes of patients with MRSA USA-300 osteomyelitis are similar to those of patients with MRSA non–USA-300 osteomyelitis.

Authors' Disclosure Statement

The authors report no actual or potential conflict of interest in relation to this article.

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