

ORIGINAL ARTICLE

Necrotizing Fasciitis Caused by Community-Associated Methicillin-Resistant *Staphylococcus aureus* in Los Angeles

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ABSTRACT

BACKGROUND

Necrotizing fasciitis is a life-threatening infection requiring urgent surgical and medical therapy. *Staphylococcus aureus* has been a very uncommon cause of necrotizing fasciitis, but we have recently noted an alarming number of these infections caused by community-associated methicillin-resistant *S. aureus* (MRSA).

METHODS

We reviewed the records of 843 patients whose wound cultures grew MRSA at our center from January 15, 2003, to April 15, 2004. Among this cohort, 14 were identified as patients presenting from the community with clinical and intraoperative findings of necrotizing fasciitis, necrotizing myositis, or both.

RESULTS

The median age of the patients was 46 years (range, 28 to 68), and 71 percent were men. Coexisting conditions or risk factors included current or past injection-drug use (43 percent); previous MRSA infection, diabetes, and chronic hepatitis C (21 percent each); and cancer and human immunodeficiency virus infection or the acquired immunodeficiency syndrome (7 percent each). Four patients (29 percent) had no serious coexisting conditions or risk factors. All patients received combined medical and surgical therapy, and none died, but they had serious complications, including the need for reconstructive surgery and prolonged stay in the intensive care unit. Wound cultures were monomicrobial for MRSA in 86 percent, and 40 percent of patients (4 of 10) for whom blood cultures were obtained had positive results. All MRSA isolates were susceptible in vitro to clindamycin, trimethoprim-sulfamethoxazole, and rifampin. All recovered isolates belonged to the same genotype (multilocus sequence type ST8, pulsed-field type USA300, and staphylococcal cassette chromosome *mec* type IV [SCC*mec*IV]) and carried the Panton-Valentine leukocidin (*pvl*), *lukD*, and *lukE* genes, but no other toxin genes were detected.

CONCLUSIONS

Necrotizing fasciitis caused by community-associated MRSA is an emerging clinical entity. In areas in which community-associated MRSA infection is endemic, empirical treatment of suspected necrotizing fasciitis should include antibiotics predictably active against this pathogen.

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STAPHYLOCOCCUS AUREUS IS A UBIQUITOUS pathogen and one of the most common causes of severe community-associated (also referred to as community-acquired) infections of skin and soft tissue.¹⁻⁴ Until recently, *S. aureus* strains from community-associated infections were almost uniformly susceptible to penicillinase-resistant β -lactam antibiotics (i.e., methicillin and oxacillin). However, over the past few years, community-associated infections caused by methicillin-resistant *S. aureus* (MRSA) have become commonplace in multiple locales in the United States and worldwide⁵⁻¹⁰; at our center, 62 percent of community-associated *S. aureus* infections are due to MRSA.¹¹ The majority of community-associated MRSA infections have been skin and soft-tissue infections.^{7,10,12} In urban regions, such as Los Angeles County, such infections appear to have become endemic.^{5,7,12,13} In such settings, it is recommended that empirical therapy for serious community-associated *S. aureus* infections include antibiotics directed against MRSA.¹⁴

Necrotizing fasciitis is a rapidly progressive, life-threatening infection involving the skin, soft tissue, and deep fascia.¹⁵⁻¹⁸ These infections are typically caused by group A streptococcus, *Clostridium perfringens*, or a mixture of aerobic and anaerobic organisms, typically including group A streptococcus, the Enterobacteriaceae, anaerobes, and *S. aureus*.¹⁷⁻²¹ *S. aureus* has not been described as a monomicrobial cause of necrotizing fasciitis in major clinical reviews of the topic or in published microbiologic studies of the disease.^{17,19-22} Owing to the frequently polymicrobial nature of necrotizing fasciitis, most authorities recommend the use of broad-spectrum empirical antimicrobial therapy for suspected cases. However, therapy directed against MRSA, such as vancomycin, is not recommended in current standard guides, presumably because of the rarity of this pathogen as a cause of necrotizing fasciitis.²²⁻²⁴

To date, MRSA has been reported to be associated with necrotizing fasciitis in only one case of subacute, polymicrobial infection²⁵ and as a monomicrobial cause of an iatrogenic, surgery-associated "necrotizing fasciitis-like" infection and bacteremia.²⁶ At our medical center in Los Angeles County, we noted a number of cases of monomicrobial necrotizing fasciitis caused by community-associated MRSA beginning in 2003. Because of the very unusual nature of these infections and their important clinical effect on empirical therapy for necrotizing fasciitis, we sought to identify all cases at our

medical center and to characterize clinical and organism-specific features of these infections.

METHODS

We identified all wound cultures that were positive for MRSA from January 15, 2003, through April 15, 2004, at Harbor-UCLA Medical Center and reviewed the case records of patients with positive wound cultures that also contained a surgical report. All surgical reports were reviewed to determine the preoperative diagnosis, intraoperative findings, and postoperative diagnosis. If both the intraoperative and postoperative diagnoses were necrotizing fasciitis, myositis, or both, the patient was included in the study.

A single investigator reviewed the 843 cultures positive for MRSA and found that 14 were associated with cases of surgically confirmed necrotizing fasciitis. Two other investigators independently reviewed operative reports for these patients to confirm that there was sufficient information for a diagnosis of necrotizing fasciitis or myositis or both. A standardized instrument was used to abstract information from the medical record of each patient. Information was obtained from several broad categories: demographics, clinical data, microbiologic data, and treatment. The MRSA strains isolated from the patients were obtained from the clinical microbiology laboratory if they were still available. All in vitro susceptibilities were reported as minimal inhibitory concentrations and performed with the VITEK system (BioMerieux), according to the protocols of the National Committee for Clinical Laboratory Standards. The investigation protocol was reviewed and approved by the institutional review board of Harbor-UCLA Medical Center.

All molecular typing was performed at an independent site by an investigator who was unaware of the clinical details of the cases. All isolates were genotyped by means of pulsed-field gel electrophoresis with *Sma*I digestion as previously described.²⁷ The guidelines of Tenover et al. were used to interpret the patterns obtained on pulsed-field gel electrophoresis for genetic relatedness.²⁸ Multilocus restriction-fragment typing (MLRFT) was performed to provide an assessment of the variation in restriction sites in seven housekeeping-gene loci dispersed throughout the genome.^{29,30} We have recently shown the correlation between MLRFT and multilocus sequence typing.³¹ As a validation procedure, we performed multilocus sequence typing

on one of the recovered strains. Sequence types were assigned on the basis of the multilocus sequence typing database (www.mlst.net).

The structural features unique to each of the four major allotypes of the staphylococcal cassette chromosome *mec* (SCC*mec*) element (types I through IV)^{32,33} were determined by means of a previously described polymerase-chain-reaction (PCR)-based multiplex assay.³⁴ Identification of the accessory gene regulator (*agr*) alleles³⁵ and the identification of the Pantone-Valentine leukocidin (*pvl*) genes by coamplification of *lukS-PV* and *lukF-PV* genes were as described by Lina et al.³⁶ Genes for the leukocidins (*lukD* and *lukE*) as well as toxic shock syndrome toxin (*tst*), enterotoxins A through O (*sea*, *seb*, *sec*, *sed*, *see*, *seg*, *seh*, *sei*, *sej*, *sen*, *sem*, and *seo*, respectively), and exfoliative toxin a and b (*eta* and *etb*, respectively) were identified by PCR.^{35,37} The following adhesin genes were defined by PCR: the gene for fibronectin-binding protein A (*fnbA*), bone sialoprotein-binding protein (*bbp*), elastin-binding protein (*ebps*), polysaccharide intercellular adhesin (*icaA*), cell-wall-associated and extracellular fibrinogen-binding proteins (*clfA*, *clfB*, and *efb*), the *sdr* family (*sdrC*, *sdrD*, and *sdrE*), and capsule genes 5 and 8 (*cap5* and *cap8*, respectively).³⁸ As a control for our PCR assay, we used a well-characterized strain collection from the National Institutes of Health Network for Antibiotic Resistance in *Staphylococcus aureus* that contained all specified genes that we examined (www.narsa.org).³⁵

RESULTS

Ten of the 14 patients were men (71 percent), and the median age was 46 years (mean, 43.6) (Table 1). The median length of hospitalization was 10 days (mean, 13.2; range, 2 to 54), and all patients had at least one surgical procedure (range, one to nine). Although all patients survived, they had serious complications, including the need for reconstructive plastic surgery in 3 patients (21 percent) and the need for hospitalization in the intensive care unit in 10 (71 percent). Eleven patients (79 percent) required débridement that was described as either “wide” or “radical,” often with incisions greater than 15 cm, and three required subsequent skin grafting. During the study period, we used *International Classification of Diseases, 9th Revision, Clinical Modification*, discharge coding to identify 31 cases of necrotizing fasciitis at our center, 9 of which were cases of community-associated MRSA necro-

tizing fasciitis (and all of which were included in our study). Thus, during the study period, approximately 9 of 31 cases of community-associated necrotizing fasciitis, or 29 percent, were caused by community-associated MRSA.

Four (40 percent) of the 10 patients who had blood cultures performed had MRSA bacteremia. The sites of necrotizing fasciitis included the buttock, legs, or both in six patients (43 percent); the arms or shoulder in four patients (28 percent); the trunk (back, axilla, or flank) or abdomen in two patients (14 percent); and the head and neck in two patients (14 percent) (Table 1). Intraoperative findings explicitly described necrotizing fasciitis in all but one patient (Patient 7), who was noted to have necrotizing myositis of the neck with probable accompanying necrotizing fasciitis. Wound specimens were obtained intraoperatively from all patients and sent for Gram’s staining and culture. Gram’s staining showed no white cells in three patients, “rare” white cells in one, “occasional” white cells in six, “1+” in two, and “2+” in two. A representative pathological specimen from Patient 4 is shown in Figure 1.

Most patients had documented coexisting conditions or risk factors, most commonly current or past injection-drug use (six patients [43 percent]), a seizure disorder (three [21 percent]), diabetes (three [21 percent]), and chronic hepatitis C (three [21 percent]) (Table 1). Four patients (29 percent) had no serious coexisting conditions or risk factors. Four patients (29 percent) were homeless; six patients (43 percent) had been hospitalized within the year before the current admission. The preoperative diagnosis was “abscess” in eight patients (57 percent), “necrotizing fasciitis” in five patients (36 percent), and “mediastinitis” in one patient (7 percent). Three patients (Patients 1, 5, and 13) had a history of MRSA infection that was not associated with necrotizing fasciitis. Two patients had known exposures to β -lactam antibiotics in the six months before hospitalization; one had received cephalexin just before admission. The median interval between the onset of symptoms and hospitalization was 5 days (mean, 6.2).

Wound cultures were monomicrobial for MRSA in 12 patients (86 percent). Culture of one neck lesion grew MRSA and *Klebsiella pneumoniae*, and culture of one back lesion grew *Pseudomonas aeruginosa* in addition to MRSA. Four patients (29 percent) who had monomicrobial MRSA also had negative anaerobic wound cultures; anaerobic wound cultures

Table 1. Characteristics of the Patients.*

Patient No.	Age	Sex	Race or Ethnic Group†	Duration of Hospitalization	Duration of Symptoms before Hospitalization	Coexisting Conditions	No. of Surgical Procedures during Hospitalization	Homeless	Site of Infection	MRSA Bacteremia	Comments
1	28	M	W	12	NK	DM, history of IDU	1	Yes	Left side of back	Yes	<i>Pseudomonas aeruginosa</i> also isolated from wound; DKA at presentation; skin graft required
2	41	F	H	8	4	Hepatitis C, remote history of IDU	1	Yes	Right buttock, anterior or abdominal wall	No	
3	28	F	W	9	4	Hepatitis C, IDU	2	No	Right side of groin, right thigh	No	
4	46	M	H	10	5	IDU	1	No	Left shoulder	Yes	
5	35	M	B	28	5	HIV/AIDS	4	No	Left buttock, left thigh	Yes	Skin graft required
6	59	M	H	8	10	None	2	No	Right shoulder	ND	Skin graft required
7	40	M	H	10	3	None	1	No	Right side of neck to sternum	ND	
8	45	M	H	54	NK	DM, hypertension	9	No	Left axilla and flank	Yes	Endophthalmitis, nosocomial candidemia
9	49	M	W	8	3	IDU, seizure disorder, hypertension, history of cutaneous abscesses	1	Yes	Left upper arm	No	
10	47	M	H	18	7	Glioblastoma multiforme, seizure disorder, neutropenia	1	No	Right posterior side of neck and cheek	No	<i>Klebsiella pneumoniae</i> also isolated from wound; septic shock
11	30	F	B	4	3	None	2	No	Multiple lesions on left leg	No	
12	46	F	W	2	7	Hepatitis C, seizure disorder, IDU	1	No	Left arm	No	
13	48	M	W	2	3	None (although history of multiple skin abscesses)	1	No	Right side of groin	ND	
14	68	M	W	12	21	Hypertension, DM, CAD, prior MI, vascular dementia, alcoholism	3	Yes	Left buttock	ND	

* W denotes white, NK not known, DM diabetes mellitus, IDU injection-drug use, DKA diabetic ketoacidosis, H hispanic, B black, HIV/AIDS human immunodeficiency virus infection or the acquired immunodeficiency syndrome, ND not done, CAD coronary artery disease, and MI myocardial infarction.

† Race or ethnic group was self-designated.

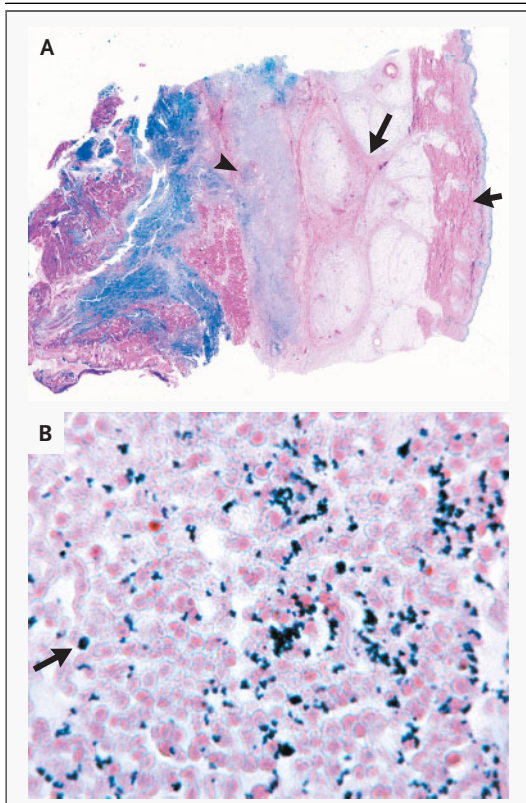


Figure 1. Pathological Findings in a Patient with Community-Associated MRSA Infection.

Pathological findings in Patient 4 include cellulitis (short arrow), panniculitis (long arrow), and fasciitis (arrow-head) of the left-shoulder wound (Panel A), with many gram-positive cocci in clusters (representative cluster at arrow) (Panel B).

were not performed for the remainder of the patients. Gram's staining of specimens from monomicrobial cases showed gram-positive cocci in nine patients and were negative in the remaining three patients. All *S. aureus* isolates were susceptible to clindamycin, trimethoprim-sulfamethoxazole, vancomycin, gentamicin, and rifampin. Ten strains (71 percent) were susceptible to tetracycline, five (36 percent) to levofloxacin, and two (14 percent) to erythromycin. Because of the low prevalence (no more than 15 percent) of the *erm* gene among pulsed-field type USA300 strains and community-associated MRSA isolates in California,^{10,39} our clinical laboratory does not routinely test for the presence of inducible clindamycin resistance.⁴⁰ Ten of the patients (71 percent) received empirical therapy that was active against their infecting strain

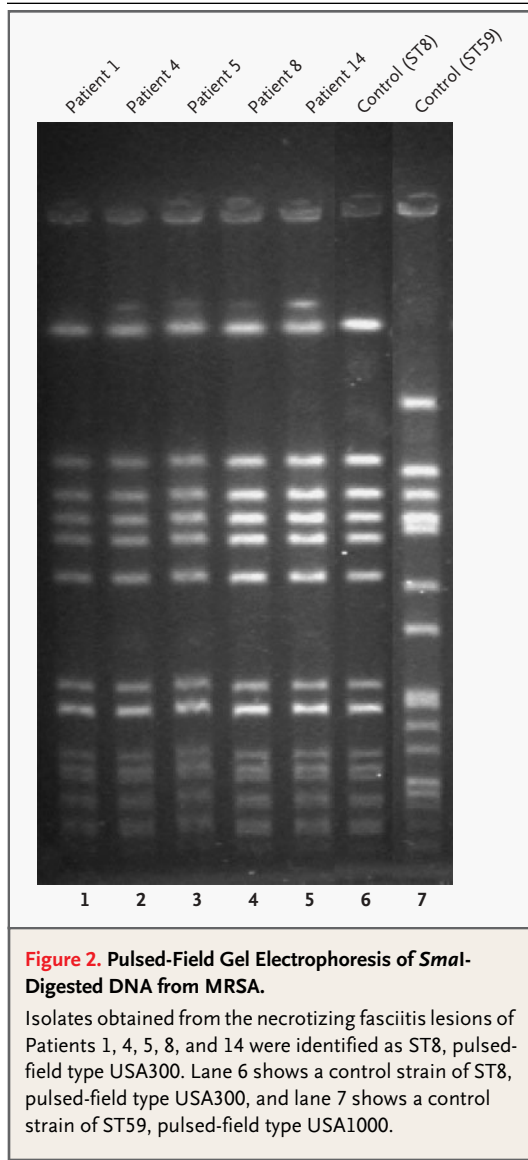
at the time of hospital admission (i.e., clindamycin [7 of 10], vancomycin [7 of 10], or both).

Strains from five patients were available for detailed genotype analyses. Three were from blood cultures (Patients 1, 5, and 8), and two were from wound cultures (Patients 4 and 14). All five strains showed identical profiles on pulsed-field gel electrophoresis and were associated with the ST8 clonal complex (Fig. 2). All carried the type IV SCC*mec* element and the *pvl*, *lukD*, and *lukE* toxin genes. No other toxin genes we tested were identified in any of the strains. All five strains possessed multiple genes encoding adhesins associated with pathogenicity in *S. aureus*, including *fnbA*, *clfA*, *clfB*, *efb*, *icaA*, *sdrC*, *sdrD*, and *sdrE*. All strains were of *agr* type 1 and capsular type 5.

DISCUSSION

Community-associated MRSA has become increasingly endemic in many parts of the world.⁴¹⁻⁴⁴ The most common clinical syndrome has been skin and soft-tissue infections.^{42,45-47} Interestingly, several less common clinical syndromes have been associated with outbreaks of community-associated MRSA infection, including necrotizing pneumonia in children⁴⁸ and a toxic shock-like syndrome.⁴⁹ To our knowledge, only one case of necrotizing fasciitis caused by monomicrobial MRSA infection has been reported.²⁶ This infection occurred nosocomially approximately one week after knee-replacement surgery.

There were substantial common factors among our cases. First, the preoperative diagnosis in 57 percent of the cases was skin or soft-tissue abscess; necrotizing fasciitis and myositis were often an unexpected finding, and surgical procedures were more extensive than anticipated. Second, it was surprising that all patients survived, since the typical mortality rate of necrotizing fasciitis has been reported to be about 33 percent.^{23,50,51} The absence of deaths in our series suggests that necrotizing fasciitis caused by community-associated MRSA may be less virulent than similar infections caused by other organisms. Indeed, the onset of disease in our series was often subacute, with symptoms present an average of 6 days before admission (range, 3 to 21). Nevertheless, in some patients in our series (e.g., Patient 6), infection spread rapidly over a period of several hours. This finding suggests that necrotizing fasciitis caused by community-associated MRSA has the potential to cause



rapidly progressive disease that is clinically indistinguishable from necrotizing fasciitis caused by pathogens such as group A streptococcus. Furthermore, although none of the patients died, serious complications were common, including prolonged stays in the intensive care unit, the need for mechanical ventilation and reconstructive surgery, septic shock, nosocomial infections, and endophthalmitis.

Our observations have important clinical implications. First, because necrotizing fasciitis caused by community-associated MRSA is an emerging clinical syndrome, empirical therapy for community-associated necrotizing fasciitis should include

agents reliably active against the regional MRSA strain. Second, although many of our patients had coexisting conditions or risk factors for MRSA infection (i.e., injection-drug use and diabetes), four patients (29 percent) had none. Therefore, in areas in which community-associated MRSA infection is endemic, empirical therapy for MRSA infection should not be withheld from patients with suspected necrotizing fasciitis on the basis of the absence of clinical risk factors. Because therapy directed against community-associated MRSA is not part of currently recommended therapy for necrotizing fasciitis,^{22,24} the inclusion of antibiotics with good activity against this pathogen represents a major shift in empirical treatment for the infection.

The MRSA ST8:S clone seen in our patients was first identified in inmates of San Francisco jails in 2001.⁵² In Los Angeles County, large-scale outbreaks of community-associated MRSA infection associated with this clone have included skin and soft-tissue infections among jail inmates, men who have sex with men, and university athletes.^{53,54} The Centers for Disease Control and Prevention (CDC) also reported the widespread distribution of this clone in correctional facilities in Mississippi, Georgia, Tennessee, and Texas.⁵⁵ As is typical of community-associated MRSA in general, the ST8:S clone carries the *SCC_{mec}* type IV allele and *pvl* genes. It is noteworthy that *pvl* appears in the overwhelming majority of strains belonging to this clone (more than 99 percent), in contrast to its lower prevalence in other strains of community-associated MRSA.⁴² This clone was later described by the CDC as pulsed-field type USA300.³⁹

Our effort to identify known virulence genes revealed a surprising deficiency of toxin genes other than *pvl*, *lukD*, and *lukE*. Of note, *pvl* has been linked to severe necrotizing infections in other settings, such as patients with pneumonia.^{48,56,57} On bronchoscopy and autopsy, severe necrosis of the trachea and alveoli were seen in these patients, along with vascular destruction leading to diffuse alveolar hemorrhage and hemoptysis.^{48,58} Thus, the histologic appearance of necrotizing pneumonia appears to be quite similar to that seen in subcutaneous and fascial tissues in our patients. The second syndrome linked to the expression of *pvl* has been the formation of deep abscesses in skin and soft tissue.^{36,42,47,59} In several series, most isolates causing deep-tissue abscesses have been reported to produce Pantone–Valentine leukocidin, whereas isolates causing other syndromes, such as blood-

stream infections, rarely produce this exotoxin.^{36,59-61} Indeed, intradermal injection of purified or recombinant Pantone–Valentine leukocidin leads to substantial necrosis and purulence in rabbits, mimicking lesions seen in patients infected with community-associated MRSA.^{61,62}

In contrast, other series have reported a lower frequency of *pvl* gene carriage among community-associated MRSA isolates causing skin and soft-tissue infection.⁴⁷ Moreover, the mere carriage of *pvl* in a strain's genome does not necessarily predict the potential for invasive community-associated MRSA infections. In one investigation, 98 percent of community-associated MRSA strains causing nasal colonization carried the *pvl* gene.⁵⁹

All isolates tested in our series were *agr* type 1, differing from the background of *agr* type 3 described in the vast majority of *pvl*-positive strains of community-associated MRSA from several countries but similar to four ST8 isolates from the United States.⁶³ The *agr* operon is critical for regulation of the expression of adhesin and toxin genes (down-regulation and up-regulation, respectively).⁶⁴⁻⁶⁶ The 100 percent carriage rate of 11 major virulence genes by the isolates in our investigation roughly parallels rates in other surveys of recent clinical isolates. For example, in a recent analysis of 29 unselected *S. aureus* clinical isolates, of which approximately one third were MRSA, the following carriage rates for adhesin genes were observed: 45 percent for *fnbA*; 100 percent for *icaA*, *clfA*, *sdnC*, *sdnD*, and capsular type 5; 41 percent for *clfB*; and 72 percent for *sdnE* *fnbA* (Dunman P: personal communication). The high carriage rate of multiple adhesin genes in concert with the low rate of carriage of toxin genes in our strains may have virulence implications, although this possibility will require further investigation.

Our report has limitations. The patients were identified at a single site and may reflect an outbreak of community-associated MRSA infection caused by a locally circulating strain. Hence, the relevance of our findings to areas in which this clone is not circulating is unclear. Regardless, our experience underscores the potential for this syn-

drome to occur in other locales. In addition, our report is limited by its retrospective nature, the lack of consistent reporting about exposures and the presence or absence of certain clinical features (e.g., crepitus and skin necrosis), and the availability of only five (36 percent) of the MRSA strains isolated from the patients. Four of these strains were from patients with bacteremia. Therefore, the strain types and virulence factors identified may reflect only the subgroup of patients who had concomitant bacteremia and not those without bacteremia. Nevertheless, the similarities in the degree of necrosis of fascia and muscle found intraoperatively suggest the presence of common virulence factors among the isolates. Finally, because anaerobic cultures were not always performed, we cannot exclude the possibility that other organisms were involved, but not recovered, from the putatively monomicrobial cases. However, in the cases in which anaerobic cultures were performed, no organisms were isolated, and on Gram's stain, no organisms other than gram-positive cocci were seen.

In summary, we characterize what appears to be a newly described syndrome of necrotizing fasciitis caused by community-associated MRSA. In areas in which this pathogen is endemic, empirical therapy for necrotizing fasciitis should include antibiotics, such as vancomycin, that are reliably active against locally circulating strains of community-associated MRSA. Further investigations building on our findings and focusing on new putative virulence genes and adhesins are required for a better understanding of the pathogenesis of this severe infection.

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