MAJOR ARTICLE

Community-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections in France: Emergence of a Single Clone That Produces Panton-Valentine Leukocidin

Philippe Dufour,[1] Yves Gillet,[2] Michèle Bes,[1] Gerard Lina,[1] François Vandenesch,[1] Daniel Floret,[2] Jerome Etienne,[1] and Hervé Richet[3]

[1]Centre National de Référence des Toxémies à Staphylocoques, INSERM E0230, Faculté de Médecine, and [2]Service des Urgences et Réanimation Pédiatrique, Hôpital Edouard Herriot, Lyon, and [3]Laboratoire de Bactériologie, Institut de Biologie des Hôpitaux de Nantes, Nantes, France

To characterize the clinical and bacteriologic characteristics of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections, we reviewed 14 cases that were diagnosed in previously healthy patients during an 18-month period in France. Eleven patients had skin or soft-tissue infections. Two patients died of CA-MRSA necrotizing pneumonia. A case of pleurisy occurred in a child who acquired CA-MRSA from his mother, who had a breast abscess. The Panton-Valentine leukocidin genes and the *lukE-lukD* leukocidin genes were detected in all 14 isolates. The clonal origin of all of the isolates was demonstrated on the basis of their pulsotypes and antibiotic resistance profiles. All isolates had an *agr*3 allele. The combination of the Panton-Valentine leukocidin determinant (which encodes a virulence factor for primary skin infection and pneumonia) with the *mecA* gene (which confers antibiotic resistance and epidemicity) appears to have created a superadapted *S. aureus* strain that is spreading in the community.

Resistance to antimicrobial agents is a major concern worldwide and is exemplified by the global spread of methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. MRSA emerged in Europe 40 years ago, shortly after the introduction of methicillin. During the mid-1980s, epidemic strains spread to hospitals throughout the world. Infection-control measures were implemented tardily, allowing these strains to become endemic, with a large reservoir of colonized and infected patients [2]. The recent emergence of community-acquired MRSA (CA-MRSA) infections in Australia, Canada, France, and the United States in patients with no recognized risk factors for MRSA infection is particularly worrisome [3–12]. A low prevalence (<1%) of CA-MRSA in the United States among cases of community acquired *S. aureus* infection was reported in children and their guardians in New York City [13] and in an adult population in Chicago [14]; however, at the University of Illinois Hospital (Chicago), CA-MRSA accounted for up to 22% of all MRSA isolates [15]. CA-MRSA generally causes skin lesions, such as abscesses and cellulitis [3–12], but deaths have occurred among children with necrotizing CA-MRSA pneumonia [16]. Most *S. aureus* strains responsible for primary skin infections and necrotizing pneumonia harbor the Panton-Valentine leukocidin (PVL) determinant [17, 18]. PVL genes were detected in 93% of strains associated with furunculosis, 55% of strains associated with cellulitis, 50% of strains associated with cutaneous abscess, and 13% of strains associated with finger-pulp infection, and these genes

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Reprints or correspondence: Jerome Etienne, Centre National de Référence des Toxémies à Staphylocoques, INSERM E0230, IFR62, Faculté de Médecine, 7 rue Guillaume Paradin, 69372 Lyon cedex 08, France (jetienne@univ-lyon1.fr).

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were absent in strains associated with superficial folliculitis and impetigo [17]. Despite reports of CA-MRSA infection in France [3], little is known about the epidemiological and strain characteristics in this country.

The first CA-MRSA isolate in France was reported to the French Reference Center for Staphylococcal Toxemia (FRCST; Lyon) in January 1999. From that date up to December 2001, clinical microbiologists forwarded 13 additional CA-MRSA isolates to the FRCST. The purpose of our study was to describe the demographic and clinical features of these 14 cases of infection, to evaluate the relatedness of the isolates by PFGE, and to screen for toxin production, including PVL.

PATIENTS AND METHODS

Patients. The study population consisted of patients from whom MRSA was isolated and sent to the FRCST in Lyon. The attending physicians were contacted by the reference laboratory and sent a questionnaire to collect demographic and clinical data and to determine the type of infection, whether it was acquired in the community or the hospital, the treatment received, and the outcome. CA-MRSA infection was defined by culture positivity for MRSA for individuals with no history of hospitalization, surgery, or outpatient care, as well as no family member who works at a health care facility. If the MRSA strain was isolated only after admission to the hospital, CA-MRSA infection was diagnosed only when the signs of infection were present at admission.

S. aureus *identification.* The species was identified on the basis of colony and microscopic morphology, the results of coagulase testing with rabbit plasma (bioMérieux), and the results of Staphyslide agglutination testing (bioMérieux).

Antimicrobial susceptibility testing. The MICs of oxacillin, gentamicin, tobramycin, kanamycin, chloramphenicol, tetracycline, minocycline, erythromycin, lincomycin, pristinamycin, fusidic acid, rifampicin, pefloxacin, trimethoprim-sulfamethoxazole, vancomycin, and teicoplanin were determined for selected isolates by use of the standardized agar dilution technique recommended by the French Society for Microbiology [19]. The *mecA* gene coding for methicillin resistance was detected by PCR, as described by Murakami et al. [20].

Toxin detection. Strains were grown on brain-heart infusion agar or in brain-heart infusion broth at 37°C overnight. Genomic DNA was extracted by use of a standard procedure, and its concentration was estimated spectrophotometrically [21]. Sequences specific for staphylococcal enterotoxin genes *(sea-e, seg-j,* and *sem-o),* the toxic shock syndrome toxin gene *(tst),* exfoliative toxin genes *(eta* and *etb),* PVL genes (*lukS*-PV–*lukF*-PV), the LukE-LukD leukotoxin gene *(lukE-lukD),* the class F LukM leukocidin gene *(lukM),* and accessory gene regulator alleles (*agr*1–4) were detected by PCR, as described elsewhere [17, 22]. Amplification of *gyrA* was used to confirm the quality of each DNA extract and the absence of PCR inhibitors [23]. All PCR products were analyzed by electrophoresis through 1% agarose gel (Sigma).

Fingerprinting by PFGE. *Sma*I macrorestriction patterns were obtained by use of a contour-clamped homogeneous electric field system on a contour-clamped homogeneous electric field (CHEF) DR-II apparatus (Bio-Rad), as described elsewhere [24]. Resolved macrorestriction patterns were compared as recommended by Tenover et al. [25]. Strains that differed by up to 3 fragments were considered to be subtypes of a given clonal type. The pulsotypes of *mecA*-positive, PVL-positive strains were compared with those of 8 *mecA*-negative, PVL-positive strains responsible for community-acquired infections (4 strains recovered from patients with furuncles and 4 strains recovered from patients with necrotizing pneumonia) and 8 *mecA*-positive, PVL-negative MRSA strains responsible for hospital-acquired infections in France [26].

RESULTS

Clinical characteristics of CA-MRSA infections. During the period of 1999–2001, 593 *S. aureus* isolates were received by the FRCST from French hospitals for the detection of toxin production, and 83 isolates were found to be PVL positive. Fourteen of these PVL-positive isolates were recovered from patients with CA-MRSA infection. The main characteristics of the patients are shown in table 1. Seven patients (50%) were male, and the median age was 13.5 years (range, 2.5 months to 69 years). Six patients (43%) had furuncles (1 case associated with cellulitis and 2 familial cases), 2 patients (14%) had necrotizing pneumonia with positive blood cultures, 1 breast-fed infant (7%) developed pleural effusion (his mother had a breast abscess), 2 patients (14%) had abscesses, 1 patient (7%) had a burn infection, and 1 patient (7%) had an infected sebaceous cyst. None of the patients had known risk factors for MRSA infection, and all had been in good health. Seven patients (50%) received diagnoses and were treated in the hospital. Twelve patients were cured, whereas 2 patients with necrotizing pneumonia died of acute respiratory distress syndrome. Six patients (43%) lived in or near Lyon, 1 (7%) lived in Paris, 1 (7%) in Nantes, and 1 (7%) in Montbéliard; an additional 2 patients (14%) were admitted to hospital in Lyon but lived in Algiers, Algeria. Initial antibiotic therapy was appropriate for MRSA in 4 of the 10 patients who received antibiotics (table 1).

CA-MRSA strain characteristics. The 14 isolates were all positive for *mecA* and had the same antibiotic resistance profile, being resistant to oxacillin (MIC, >32 mg/L), kanamycin (MIC, >32 mg/L), and tetracycline (MIC, 16 mg/L); intermediately

Table 1. Characteristics of patients in France with community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infection.

Patient	Age in years, sex	City of residence	Hospital admission	Site of isolation (date of sampling)	Diagnosis	Initial therapy	Definitive antimicrobial therapy received
1	67, M	Paris	Yes	Blood culture, tracheal aspirate (30 Dec 1999)	Necrotizing pneumonia[a]	Unknown	—
2	17, M	Nantes	Yes	Blood culture, bronchoalveolar lavage specimen (15 Jan 1999)	Necrotizing pneumonia[a]	Ofloxacin, erythromycin	None
3	2, M	Lyon	No	Skin (31 Dec 2000)	Furuncle	Amoxicillin	None
4[b]	9, M	Lyon	No	Skin (24 Mar 2000)	Furuncle	—[c]	—
5[b]	36, F	Lyon	No	Skin (24 Mar 2000)	Furuncle	—[c]	—
6[b]	4, F	Lyon	No	Ear (24 Mar 2000)	Furuncle	—[c]	—
7	7, F	Villeurbanne	Yes	Abdomen (22 Sep 2000)	Abscess	Cefamandol, I + D	None
8	10, F	Algiers, Algeria[d]	Yes	Foot (19 Sep 2000)	Furuncle, cellulitis	Oxacillin	Pristinamycin
9[b]	0.2, M	Montbéliard	Yes	Pleural fluid (14 Mar 2001)	Pleural effusion	Oxacillin, gentamicin	Vancomycin, gentamicin
10[b]	27, F	Montbéliard	No	Maternal milk (09 Jan 2001)	Breast abscess	Oxacillin	None
11	3, M	Lyon	Yes	Thigh (20 May 2001)	Abscess	Amoxicillin–clavulanic acid, I + D	Erythromycin
12	69, F	Algiers, Algeria[d]	Yes	Foot, thigh (13 Jul 2001)	Infected burn	—[c]	—
13	23, F	Lyon	No	Knee (27 Jul 2001)	Furuncle	Pristinamycin	None
14	22, M	Lyon	No	Jaw (26 Jun 2001)	Infected sebaceous cyst	Pristinamycin	None

NOTE. I + D, incision and drainage.

[a] Died of CA-MRSA infection.

[b] Familial transmission (patient 5 is the mother of patient 4 and the aunt of patient 6; patient 9 is the son of patient 10).

[c] No antibiotic therapy received.

[d] Infection acquired when the patient was in France.

resistant to fusidic acid (MIC, 4 mg/L); and susceptible to gentamicin (MIC, ≤0.5 mg/L), tobramycin (MIC, ≤0.5 mg/L), chloramphenicol (MIC, 4 mg/L), minocycline (MIC, ≤0.25 mg/L), erythromycin (MIC, ≤0.5 mg/L), lincomycin (MIC, 1–2 mg/L), pristinamycin (MIC, ≤0.25 mg/L), rifampicin (MIC, ≤0.5 mg/L), trimethoprim-sulfamethoxazole (MIC, ≤5 mg/L), pefloxacin (MIC, ≤0.5 mg/L), vancomycin (MIC, 1 mg/L), and teicoplanin (MIC, 1 mg/L).

All 14 CA-MRSA isolates had the same toxin gene profiles, and all harbored genes encoding PVL and LukE-LukD leukocidin. None of the other toxin genes for which we tested (see Patients and Methods) were detected. All of the CA-MRSA isolates belonged to the *agr*3 allele type. Figure 1 shows schematic DNA restriction profiles obtained by PFGE. Thirteen of 14 CA-MRSA strains (*mecA*$^+$, *lukF*-PV$^+$–*lukS*-PV$^+$) shared the same pulsotype. The remaining strain differed from this pulsotype by a single band and was considered a subtype. The pulsotypes of *mecA*$^-$, *lukF*-PV$^+$–*lukS*-PV$^+$ strains and *mecA*$^+$, *lukF*-PV$^-$–*lukS*-PV$^-$ strains differed markedly from those of the CA-MRSA strains (figure 1).

DISCUSSION

The emergence of MRSA in the community is a major public health threat, because these strains are resistant to β-lactam antibiotics, which are used empirically to treat a variety of infections, including pneumonia. The results of the present study are worrisome, because all of the MRSA strains isolated from patients with community-acquired infections harbored the PVL genes. The corresponding toxin is associated with primary skin infections (e.g., furunculosis) and severe necrotizing pneumonia but not with traumatic skin infections, hospital-acquired pneumonia, or infective endocarditis [17, 18]. At the FRCST, PVL genes and the *mecA* gene are examined systematically for all strains received: during the study period, the PVL genes were detected in 83 of 593 strains of *S. aureus* tested, and all PVL-positive and *mecA*-positive isolates were included in the present study. PVL genes were never detected in MRSA isolates associated with hospital-acquired infection. Purified PVL induces severe inflammatory lesions when injected intradermally into rabbits, leading to capillary dilation, polymorphonuclear karyorrhexis, and skin necrosis [27, 28]. No

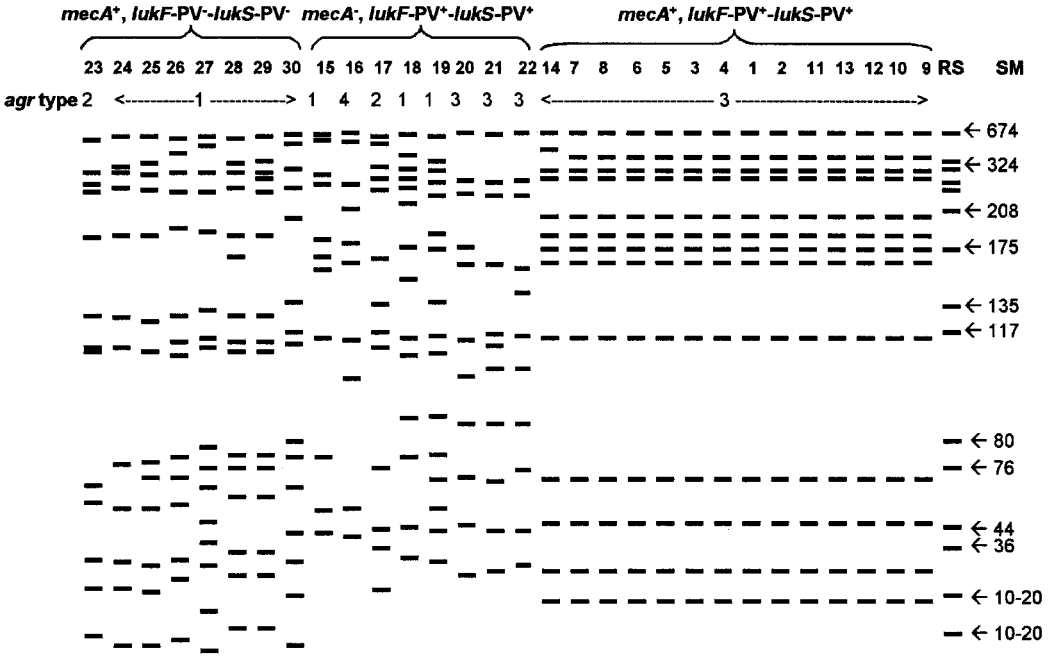

Figure 1. Schematic representation of pulsotypes (*Sma*I restriction enzyme) of *mecA*$^+$, *lukF*-PV$^+$–*lukS*-PV$^+$ *Staphylococcus aureus* strains *(lanes 1–14), mecA*$^-$, *lukF*-PV$^+$–*lukS*-PV$^+$ *S. aureus* strains *(lanes 15–22),* and *mecA*$^+$, *lukF*-PV$^-$–*lukS*-PV$^-$ *S. aureus* strains *(lanes 23–30).* "RS" corresponds to the reference strain *S. aureus* NTCC 8325 (*mecA*$^-$, *lukF*-PV$^-$–*lukS*-PV$^-$). The size markers (SM) are in kilobases.

formal link between PVL and *mecA* genes has been reported in the literature. However, our results suggest that a particular combination of the PVL determinant (which encodes a virulence factor for primary skin infections and pneumonia) and the *mecA* gene (which confers antibiotic resistance and epidemicity) has created a superadapted *S. aureus* strain in the French community.

Our isolates had a clonal origin, with close or identical pulsotypes, which points to the circulation of a single strain in France (figure 1). Similarly, all but 1 of the CA-MRSA strains described by Nimmo et al. [29] belonged to the same pulsotype, which differed from the French CA-MRSA pulsotype (G. Nimmo and J. Etienne, data not shown). It is not known whether the French epidemic strain emerged through acquisition of the PVL gene by a French MRSA strain or acquisition of the *mecA* gene by a PVL-positive strain.

The genes encoding LukE-LukD leukotoxin were also detected in all of our CA-MRSA isolates. This toxin has been found in MRSA strains isolated from patients with antibiotic-associated diarrhea [30] and in methicillin-susceptible *S. aureus* strains causing impetigo [31]. In our experience, the *LukE-LukD* genes are found in approximately two-thirds (135 of 198) of *S. aureus* strains recovered from patients with all types of staphylococcal infection, and these genes do not appear to be associated with a specific type of infection. All of our CA-MRSA isolates belonged to the *agr*3 allele type, unlike PVL-positive, *mecA*-negative *S. aureus* strains, which belong to the 4 *agr* allele types (figure 1). The *agr* locus controls the expression of most virulence factors in *S. aureus*. It encodes a 2-component signaling pathway whose activating ligand is a bacterial density–sensing peptide (autoinducing peptide) also encoded by *agr* [32]. *S. aureus* strains can be divided into 4 major *agr* groups (*agr*1–4) on the basis of a polymorphism in the amino acid sequence of the autoinducing peptide and its corresponding receptor (AgrC) [33, 34]. All 196 MRSA isolates pooled from worldwide collections and characterized by van Leeuwen et al. [35] belonged to the *agr*1 allele type (like most French MRSA strains) (figure 1), except for a cluster of 7 *agr*3 strains that originated from Ontario, Canada. This suggests that our *agr3* CA-MRSA epidemic strain emerged from a nondominant MRSA clone.

The 14 patients in the present study had a mean age of 13.5 years, confirming that CA-MRSA infections mainly involve children and young adults (the mean ages were 20 years in the study by Naimi et al. [5] and 23 years in the study by Gorak et al. [11]). As in reports elsewhere [5, 11], all of our patients had previously been in good health, and most had skin or soft-tissue infections (i.e., furuncles, abscesses, or cellulitis). The skin infections were all cured, even when antibiotic treatment was inappropriate; incision and drainage were sometimes necessary. Both patients with CA-MRSA necrotizing pneumonia died, which confirms the gravity of this infection [5, 18]; 1 of these cases was described in the series of necrotizing pneumonia reported by Gillet et al. [18]. Another patient, a 3-month-old

infant, developed pleural effusion due to a PVL-producing *S. aureus* strain transmitted by maternal breast-feeding; a similar case was reported in 2001 by Le Thomas et al. [36]. We have no definite explanation concerning the fact that these infants who were exposed by breast-feeding did not develop necrotizing pneumonia. However, we can hypothesize that, in these cases, the staphylococci were ingested, not inhaled, and that they were transferred to the pleural cavity by the lymphatic circulation. Our patients tended to be at the lower end of the socioeconomic scale, as was noted in a report published elsewhere [11]. In Australia, Nimmo et al. [29] reported that most CA-MRSA infections observed in Queensland occurred in native Polynesians, and Maguire et al. [37] likewise reported that most patients in the Northern Territory were aborigines. Like the Australian CA-MRSA isolates, our isolates were susceptible to erythromycin, tetracycline, trimethoprim-sulfamethoxazole, fluoroquinolones, and gentamicin [38].

All 14 CA-MRSA strains sent to the FRCST belonged to the same clone and differed from the MRSA strains that cause hospital-acquired infections in France. The patients lived in different parts of France, which indicates that infection was not directly transmitted from one person to another. The precise incidence of such infections is unknown, because community-acquired infections—especially superficial skin infections—are rarely characterized.

Specific surveillance of MRSA infections in the community is required to monitor and prevent the spread of these strains. Furthermore, CA-MRSA must now be borne in mind as a possible cause of life-threatening community-acquired pneumonia.

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