Contribution of Genetically Restricted, Methicillin-Susceptible Strains to the Ongoing Epidemic of Community-Acquired \textit{Staphylococcus aureus} Infections

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Background. Within the current worldwide epidemic of community-acquired \textit{Staphylococcus aureus} infections, attention has focused on the role of methicillin-resistant strains. We characterize methicillin-susceptible strains that also contribute to this epidemic.

Methods. We tracked cultures from abscess specimens submitted to the microbiology laboratory at St. Louis Children’s Hospital and examined Panton-Valentine leukocidin (PVL) genes in methicillin-susceptible \textit{S. aureus} (MSSA) isolates. We further characterized some isolates by multilocus sequence typing, pulsed-field gel electrophoresis, antibiotic susceptibility, accessory gene regulator (\textit{agr}) allele, and presence of the \textit{arcA} gene of the arginine catabolic mobile element.

Results. From 1999 to 2007, we detected a 250-fold increase in cultures of abscesses yielding methicillin-resistant \textit{S. aureus} (MRSA) and a 5-fold increase in abscess cultures yielding MSSA. MSSA isolates from abscesses and wounds were more likely to encode PVL than isolates from other sources. In contrast to PVL-negative isolates of MSSA, which were genetically diverse, PVL-positive isolates were predominantly multilocus sequence typing type 8 and \textit{agr} type 1. More than half of PVL-positive MSSA isolates were resistant to erythromycin and susceptible to clindamycin with the absence of inducible resistance, a pattern uncommon in PVL-negative MSSA but frequent in the USA300 clone of MRSA. In addition, pulsed-field gel electrophoresis of PVL-positive MSSA strains revealed the USA300 pattern.

Conclusions. In addition to methicillin-resistant strains, the current epidemic of \textit{S. aureus} infections includes infections caused by methicillin-susceptible strains that are closely related genetically and share phenotypic characteristics other than susceptibility to methicillin. These findings suggest that factors other than methicillin resistance are driving the epidemic.

Before the late 1990s, methicillin-resistant \textit{Staphylococcus aureus} (MRSA) infections occurred almost exclusively in association with hospitals, nursing homes, and other health care institutions. In the last decade, community-acquired (CA) MRSA infections have become prevalent in many locations around the world [1–3]. Circulating CA strains of MRSA are genetically distinct from those that were traditionally detected in health care–associated infections. In the United States, traditional health care–associated MRSA strains typically possess the type II staphylococcal chromosomal cassette (SCC) \textit{mec}, a mobile element carrying the \textit{mecA} gene that encodes penicillin-binding protein 2a, a cell-wall transpeptidase with low affinity for methicillin and other \textit{β}-lactamase–resistant semisynthetic penicillins [4]. In contrast, strains typically detected in the current epidemic of CA-MRSA infections carry smaller SCCs,
MSSA Strains’ Contribution to Epidemic of CA-MRSA Infections

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Figure 1. Characterization of 214 consecutive methicillin-susceptible Staphylococcus aureus (MSSA) isolates submitted to the St. Louis Children’s Hospital Bacteriology Laboratory. Panton-Valentine leukocidin (PVL) detection was performed on all isolates, whereas the 81 isolates with source listed as “abscess” or “wound” were subjected to further molecular typing and analysis. MLST, multilocus sequence typing; PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis.

Figure 2. Number of Staphylococcus aureus isolates from abscess specimens examined at the St. Louis Children’s Hospital by year. Although the number of methicillin-resistant S. aureus (MRSA) isolates increased nearly exponentially during the period studied, there was also a 5-fold increase in methicillin-susceptible S. aureus (MSSA) isolates from abscesses.

other US cities, cutaneous infections caused by CA-MRSA strains at our center have risen markedly in the last decade; however, cutaneous infections with MSSA at our center also have increased. In this study, we sought to determine the prevalence of PVL genes among isolates of MSSA recovered in our laboratory and to define the clinical and molecular features of PVL-positive MSSA in our community.

METHODS

Patient and isolate identification. All study procedures were approved by the institutional Office of Human Research Protection. To examine the magnitude of increase in abscesses, we queried the result database of the clinical microbiology laboratory at St. Louis Children’s Hospital to ascertain all routine and anaerobic cultures submitted from January 1999 through December 2007 that yielded MSSA or MRSA. From these, we counted S. aureus isolates for which the specimen source was listed as “abscess” or “wound” when the cultures were ordered. Isolates recovered within 30 days of a prior isolate in the same patient were excluded.

Frequency of PVL genes. To examine the frequency of PVL in MSSA, we evaluated 214 sequential isolates of MSSA from clinical specimens from all sources submitted to the St. Louis Children’s Hospital clinical microbiology laboratory from October 2005 through March 2006. Patient data collected for each specimen included date of service and source and body site of the culture. Duplicate isolates (within 30 days in the same patient) were excluded. The presence of the lukF-PV gene was detected by multiplex polymerase chain reaction (PCR) as previously described [27].

PVL was first described in 1932 [10], years before the first appearance in 1961 of methicillin resistance in staphylococci [11]. Intradermal injection of PVL in rabbits produces severe necrotizing skin lesions [12, 13], consistent with the association between PVL-positive staphylococcal strains and the formation of furuncles, cutaneous abscesses, and severe necrotic skin lesions [12, 14–17]. Interestingly, the strains of S. aureus responsible for widespread epidemics in newborn nurseries during the 1950s and 1960s were recently shown to produce PVL [18]. The importance of PVL as a virulence factor has recently been demonstrated in a mouse model of pneumonia [19]; however, it was dispensable for virulence in mouse models of sepsis and skin infection [20]. Recent clinical experience strongly suggests that PVL-positive strains of S. aureus exhibit enhanced virulence [16, 21–24], although it is unclear whether this phenotype is attributable to PVL itself, to linked and yet unidentified virulence determinants, or to altered regulation of toxin expression.

Previous studies of both methicillin-susceptible S. aureus (MSSA) and MRSA isolated sequentially in hospital laboratories from all specimen types indicated that 2%–17% of MSSA strains were positive for PVL [16, 25, 26]. However, the prevalence of PVL genes among MSSA strains isolated from abscesses or furuncles has been as high as 93% [16]. As in many

designated type IV or V [5, 6]. In addition, circulating CA-MRSA strains often carry genes (lukFS-PV) encoding Panton-Valentine leukocidin (PVL), a bicomponent, pore-forming staphylococcal exotoxin [7, 8]. These strains are now also being recognized as causes of health care–associated MRSA infections [9].

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Table 1. Presence of Panton-Valentine Leukocidin (PVL) Genes among 214 Methicillin-Susceptible Staphylococcus aureus Isolates, by Specimen Source

<table>
<thead>
<tr>
<th>Specimen source</th>
<th>No. of isolates tested</th>
<th>No. (%) of PVL-positive isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>31</td>
<td>16 (52)</td>
</tr>
<tr>
<td>Wound</td>
<td>50</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Drainage or discharge</td>
<td>28</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Tissue or aspirate</td>
<td>14</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Blood</td>
<td>7</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urine</td>
<td>4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>66</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>14</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>214</td>
<td>31 (14)</td>
</tr>
</tbody>
</table>

Characterization of MSSA strains. From within the 214 sequential isolates of MSSA, those with specimen source listed as “abscess” or “wound” (n = 81) were further characterized (figure 1). Antimicrobial susceptibility testing, including the D-test for inducible clindamycin resistance, was performed by disk diffusion in accordance with procedures of the Clinical Laboratory Standards Institute [28]. Isolates were tested by PCR for the presence of the accessory gene regulator (agr) allele group as previously described [29] and for the presence of the arcA gene of the arginine catabolic mobile element (ACME) originally identified in a USA300 isolate of MRSA [30]. All PVL-positive MSSA isolates from abscesses and wounds (n = 29) and a subset of PVL-negative isolates from abscesses and wounds (n = 31; selected to represent different body sites) were analyzed by multilocus sequence typing (MLST) performed at the Washington University Genome Center [31]. A subset of the PVL-positive isolates that were MLS type 8 was further analyzed by pulsed-field gel electrophoresis (PFGE) after Smal digestion, performed at the Centers for Disease Control and Prevention. To minimize potential bias toward genetic relatedness, we selected for PFGE 6 of the PVL-positive MSSA strains that represented maximally diverse patterns of antimicrobial susceptibility. The PFGE patterns were analyzed using BioNumerics, version 5.10 (Applied Maths), and grouped into pulsed-field types using Dice coefficients and 80% similarity as previously described elsewhere [32].

Medical record review. To permit assessment of epidemiologic associations with PVL-positive MSSA infection, we reviewed clinical and epidemiologic characteristics of patients with MSSA isolated from abscesses or wounds. Medical records were available for 69 of 81 patients, including 28 whose isolates were PVL positive and 41 whose isolates were PVL negative. Medical record abstraction was performed using a standardized form that captured demographic data, health history information, and illness characteristics, including demonstrated and putative risk factors for CA-MRSA colonization and infection [33] (S.A.F., unpublished data).

Statistical analysis. Differences between proportions were tested for statistical significance using Fisher’s exact test, and differences in means were tested with Student’s t test. A P value of <.05 was considered statistically significant.

RESULTS

Number of MRSA and MSSA cutaneous infections. We counted isolates of MRSA and MSSA from abscesses and wounds recovered annually in the clinical microbiology laboratory at St. Louis Children’s Hospital. In keeping with the current and well-recognized epidemic of CA-MRSA, the number of MRSA isolates from abscesses increased 250-fold from 1999 to 2007, following an approximately exponential curve (figure 2). During the same period, the number of MSSA isolates from abscesses increased 5-fold. A review of medical records data indicated a 5-fold increase in incision and drainage procedures performed from 1999 to 2003 (data not shown), suggesting that the increase in S. aureus isolation was not only attributable to a change in practice (increased culturing of abscesses) but also reflected an actual increase in the incidence of abscesses.

Frequency of PVL genes in MSSA. Of the 214 consecutive MSSA isolates recovered at the St. Louis Children’s Hospital clinical microbiology laboratory during the period from October 2005 to March 2006, 31 (14%) were positive for the lukF-PV gene. Twenty-nine of the 31 PVL-positive MSSA isolates were from specimens with “abscess” or “wound” listed as the source. Isolates from these specimen sources were significantly more likely to carry PVL than isolates from other specimen sources (2 [2%] of 133 isolates; P<.001) (table 1).
Antibiotic susceptibility of MSSA isolates from abscesses and wounds. The antibiotic susceptibility patterns of the 81 MSSA isolates (29 PVL positive and 52 PVL negative) grown from culture of abscess or wound specimens were reviewed. Of the PVL-positive isolates, 55% displayed a susceptibility profile defined by resistance to erythromycin, susceptibility to clindamycin, and a negative D-test result for inducible clindamycin resistance (table 2). This susceptibility profile is consistent with the presence of the msrA gene that accounts for isolated erythromycin resistance and is frequently present in CA-MRSA, specifically USA300 strains, in the United States [24, 34, 35]. In contrast, only 2% of the PVL-negative MSSA isolates displayed this same antibiotic susceptibility pattern.

Molecular typing of MSSA isolates. The 81 isolates from abscesses and wounds were characterized further by agr typing and arcA PCR. Of the 29 PVL-positive isolates, 25 (86%) were of agr type 1 compared with 20 (38%) of the 52 PVL-negative isolates \( (P < .001) \). The arcA gene of the ACME was present in 3 (10%) of the PVL-positive isolates and in 2 (4%) of the PVL-negative isolates.

MLST results were available for 32 MSSA isolates from abscesses and wounds (18 of 29 PVL-positive isolates and 14 of

Table 2. Antibiotic Susceptibility Profiles of 81 Methicillin-Susceptible Staphylococcus aureus Isolates from Abscess and Wound Specimens

<table>
<thead>
<tr>
<th>Disk diffusion interpretation</th>
<th>D-test result</th>
<th>No. (%) of PVL-negative isolates (n = 52)</th>
<th>No. (%) of PVL-positive isolates (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible to both Ery and Clin</td>
<td>Not done</td>
<td>36 (69)</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Resistant to Ery and susceptible to Clin</td>
<td>Negative</td>
<td>1 (2)a</td>
<td>16 (55)a</td>
</tr>
<tr>
<td>Resistant to Ery and susceptible to Clin</td>
<td>Positive</td>
<td>12 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to Ery and susceptible to Clin</td>
<td>Not done</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to both Ery and Clin</td>
<td>Not done</td>
<td>2 (4)</td>
<td>1 (3)b</td>
</tr>
</tbody>
</table>

NOTE. Clin, clindamycin; Ery, Erythromycin; PVL, Panton-Valentine leukocidin.

a \( P < .001 \) by Fisher’s exact test. 
b Disk diffusion test result was intermediate to erythromycin and clindamycin.

Table 3. Data on Patients Whose Abscess Specimens Yielded Methicillin-Susceptible Staphylococcus aureus That Tested Either Positive or Negative for Panton-Valentine Leukocidin (PVL)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with PVL-positive isolates</th>
<th>Patients with PVL-negative isolates</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD</td>
<td>7.7 ± 6.1</td>
<td>9.0 ± 6.4</td>
<td>.390</td>
</tr>
<tr>
<td>Male</td>
<td>17/28 (61)</td>
<td>15/38 (39)</td>
<td>.135</td>
</tr>
<tr>
<td>African American</td>
<td>21/27 (78)</td>
<td>17/38 (45)</td>
<td>.011</td>
</tr>
<tr>
<td>Prior abscess</td>
<td>7/27 (26)</td>
<td>6/40 (15)</td>
<td>.349</td>
</tr>
<tr>
<td>Chronic health problems</td>
<td>8/28 (29)</td>
<td>20/39 (51)</td>
<td>.081</td>
</tr>
<tr>
<td>Hospitalization(s) in the past year</td>
<td>2/28 (7)</td>
<td>6/40 (15)</td>
<td>.455</td>
</tr>
<tr>
<td>Fever at presentation</td>
<td>0/18 (0)</td>
<td>1/23 (4)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Admitted to hospital</td>
<td>4/24 (17)</td>
<td>18/31 (58)</td>
<td>.002</td>
</tr>
<tr>
<td>Leukocytosisa</td>
<td>2/9 (22)</td>
<td>3/21 (14)</td>
<td>.622</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>1/4 (25)</td>
<td>2/15 (13)</td>
<td>.530</td>
</tr>
<tr>
<td>Multiple synchronous abscesses</td>
<td>5/27 (19)</td>
<td>12/39 (31)</td>
<td>.391</td>
</tr>
<tr>
<td>Abscess located on lower body site</td>
<td>13/28 (46)</td>
<td>12/41 (29)</td>
<td>.203</td>
</tr>
<tr>
<td>Mean diameter ± SD of abscess, cm</td>
<td>2.88 ± 1.34</td>
<td>2.77 ± 1.34</td>
<td>.834</td>
</tr>
<tr>
<td>Developed subsequent abscess ( \leq )12 months</td>
<td>4/22 (18)</td>
<td>7/39 (18)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Either a prior or subsequent abscess</td>
<td>10/23 (43)</td>
<td>10/39 (26)</td>
<td>.169</td>
</tr>
<tr>
<td>Both a prior and subsequent abscess</td>
<td>1/21 (5)</td>
<td>3/39 (8)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

NOTE. Data are proportion (%) of patients, unless otherwise indicated; the denominator represents the no. of patients for whom the information was available. SD, standard deviation.

a White blood cell count >15,000 cells/\( \mu \)L.
Figure 4. Pulsed-field gel electrophoresis (PFGE) banding patterns of Panton-Valentine leukocidin (PVL)—positive Staphylococcus aureus isolates. Antibiotic susceptibility profiles and D-test results, as measured by standard disk diffusion techniques, are shown to the right of each gel lane. Lanes 1–5 and 7, PVL-positive methicillin-susceptible S. aureus isolates with representative antibiotic susceptibility patterns; lane 6, a PVL-positive community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) isolate (shown for comparison). Bracket, a DNA fragment thought to include the staphylococcal chromosomal cassette mec cassette; arrow, its location in CA-MRSA USA300. The dendrogram to the left of the gel shows the genetic relatedness among the strains; as a group, the seven isolates are >87% similar. Clin, clindamycin; Ery, erythromycin; ND, not done; Neg, negative; Ox, oxacillin; Pen, penicillin; R, resistant; S, susceptible; Tet, tetracycline.

31 PVL-negative isolates (figure 3). An MLST assignment was unable to be made in other strains because of technical issues or lack of an allelic match in the existing type database. Of note, the antimicrobial susceptibilities of the MLST-assignable isolates paralleled those of the entire respective PVL-positive or PVL-negative group (data not shown). Of the 18 PVL-positive isolates for which results were available, 17 (94%) were MLS type 8 compared with 2 (14%) of the 14 PVL-negative abscess isolates for which MLST results were available (P < .001). There was substantial diversity among the PVL-negative isolates because 9 different MLS types were represented in this group of strains.

Six of the 18 PVL-positive MSSA isolates of MLS type 8 were further analyzed by PFGE. For this analysis we chose strains with distinct antibiotic susceptibility patterns in an effort to represent phenotypic diversity. All 6 of these PVL-positive MSSA isolates showed PFGE patterns consistent with that of the USA300 clone of MRSA (figure 4). Interestingly, the 6 isolates varied in the migration of the DNA fragment thought to contain the SCCmec cassette.

**Epidemiologic associations with PVL-positive MSSA infection.** Of the 81 MSSA isolates from abscesses or wounds, 80 (99%) were collected in outpatient settings. When comparing the abscess patients according to the presence or absence of PVL genes in their MSSA isolates, there were more patients in the PVL-positive group who were identified as being African American (P = .011). Differences in the clinical presentation or course between patients with PVL-positive and PVL-negative isolates were not statistically significant, with the exception that patients with PVL-negative isolates were more likely to be admitted to the hospital (P = .002; table 3).

**DISCUSSION**

During the past decade, the emergence and spread of CA-MRSA have been observed in countries throughout the world. This development is a significant departure from the previous pattern of close linkage of MRSA to health care institutions, particularly hospitals and nursing homes. The strains of MRSA associated with community-acquired infection differ from most health care–associated strains in a number of respects, including having the type IV or V SCCmec and possessing genes encoding PVL. In some studies, a close genetic relationship between some strains of CA-MRSA and circulating community strains of MSSA has been demonstrated [36, 37]. We report an increase in detection of disease-causing isolates of MSSA that also possess the genes that encode PVL. Among the 214 MSSA isolates studied, prevalence of PVL was 15%, whereas in the subset of 81 isolates recovered from abscesses and wounds, PVL prevalence was 36%. In comparison, PVL prevalence among MSSA isolates colonizing the nares of healthy children in our community was 2% [33] (S.A.F., unpublished data).

Our data also suggest that the present group of PVL-positive MSSA isolates are genetically restricted and closely related to epidemic strains of community-acquired MRSA. Most of our PVL-positive MSSA isolates were MLS type 8, and the subset analyzed by PFGE all were highly related to USA300. In addition, most carried the agr type 1 allele that has been associated with CA-MRSA [35]. PVL-positive MSSA often exhibited an antibiotic resistance pattern typical of CA-MRSA, characterized by constitutive resistance to erythromycin and susceptibility to clindamycin. This pattern suggests the presence of the msrA gene and is uncommon, in our laboratory, among health care–associated MRSA or in PVL-negative strains of MSSA [34, 35].

In addition, epidemiologic parallels between PVL-positive MSSA and PVL-positive MRSA are apparent. Abscesses caused by PVL-positive MSSA were more frequent in African American patients, similar to our finding in a recent study of increased MRSA colonization in African American compared with white children in the St. Louis area [33]. This finding is also consistent with the finding in other studies that CA-MRSA infection is
observed more frequently in African American patients [38, 39]. Likewise, McCaskill et al [24] found that invasive infections due to MSSA of USA300 clonal origin were more common in African Americans. Although most of the studied PVL-positive MSSA isolates had the same MLS type and were closely related by PFGE, they do not appear to be strictly clonal because of the modest variation among the isolates in antibiotic susceptibility profiles, presence of the arca gene of the ACME, and their agr allele groups. This finding is consistent with a recent examination of the genetic diversity among MRSA USA300 clones [40].

The results of our study are provocative because they have implications for theories regarding the impetus behind the current worldwide outbreak of CA-MRSA infection. If methicillin-susceptible and methicillin-resistant strains are spreading, the driving force is likely unrelated to methicillin resistance and might instead be related to other undefined fitness characteristics of the MLS type 8 USA300 clone. The observation that the emergence of PVL-positive MSSA is occurring several years after the proliferation of PVL-positive MRSA suggests that the mec gene or perhaps a larger portion of the SCCmec element on which it is carried may be unstable, leading to its loss from some strains of MRSA. Indeed, a recent investigation suggested that the SCCmec element does not contribute to staphylococcal pathogenesis in the absence of β-lactam antibiotics [41].

Our study has several limitations. It is based on data from a single center and thus must be replicated at other sites before the findings are considered generalizable. Because PCR for PVL genes was performed only on isolates recovered in 2005 and 2006, it was not possible to quantify the contribution of PVL-positive MSSA to the 5-fold increase in MSSA isolates we observed in the larger period from 1999 to 2007. The conclusion that PVL-positive MSSA isolates are related to the common clone associated with community-acquired MRSA is based on characterization by MLST and PFGE; inclusion of more strains or detailed genomic analysis would further illuminate the genetic relatedness of these strains. Our finding that the PVL-positive MSSA isolates were homogeneous suggests that there may be specific epidemiologic characteristics that would be better characterized by a larger study. We suspect that there are also clinical differences between PVL-positive and PVL-negative MSSA infections, as has been demonstrated in other studies [16, 21–24]. It is likely that studies of larger numbers of strains will allow these differences to be discerned, as they have been for MRSA strains.

The history of staphylococcal infections has been marked by rapid emergence of new strains with distinctive epidemiologic and clinical characteristics. We are currently in such a period. What appeared to be an epidemic of PVL-positive CA-MRSA may now evolve as an epidemic of PVL-positive CA S. aureus infections. Continued epidemiologic surveillance will be important to monitor the course of this development and to anticipate additional changes that are likely to occur.

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Potential conflicts of interest. G.A.S. has served on the medical advisory board of Roche Molecular Diagnostics and received honoraria from Sanofi-Pasteur. S.A.F. has received honoraria from Sanofi-Pasteur. D.A.H. has worked as a consultant for Novartis Vaccines. All other authors: no conflicts.

References


