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Incidence, Risk Factors, and Outcomes of Panton-Valentine Leukocidin-Positive Methicillin-Susceptible *Staphylococcus aureus* Infections in Auckland, New Zealand▽

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Panton-Valentine leukocidin (PVL) has been linked to invasive community-acquired methicillin-resistant *Staphylococcus aureus* infections. However, the association between disease and PVL-positive methicillin-susceptible *Staphylococcus aureus* (MSSA) has not been widely reported. We aimed to examine the epidemiology of PVL in clinical MSSA isolates from patients presenting to Auckland City Hospital. Four hundred eleven MSSA clinical isolates and 93 nasal carriage isolates were collected and tested for the presence of the *lukSF-PV* genes using PCR. The results were examined in light of host and disease factors. Multilocus sequence typing (MLST) was performed on a random subset of isolates to ensure that there was no single PVL-positive MSSA clone responsible for disease in Auckland. The prevalence of the *lukSF-PV* genes in MSSA isolates associated with disease (124/335; 37%) was not significantly different from the prevalence of the *lukSF-PV* genes in MSSA nasal carriage isolates (29/93; 31% [$P = 0.33$]). PVL-positive MSSA isolates in Auckland are genetically diverse and come from a number of different clonal complexes. PVL-positive infections peaked at between 10 and 20 years of age, with a subsequent decline. Pacific ethnicity, age, diagnosis of skin and soft tissue infection (SSTI), community-onset infection, and the need for surgical intervention were found by multivariate analysis to be independently associated with PVL-positive MSSA infection. More than one-third of MSSA infections in our patient population are caused by PVL-positive strains. Those patients with PVL-positive MSSA infection were more likely to be of Pacific ethnicity, be younger in age, have community-onset infection, have SSTI, and need surgical intervention.

Staphylococcus aureus is a nasal commensal that can be detected in up to 20 to 30% of the general population, one-third of whom are persistently colonized (28). *S. aureus* produces a wide variety of virulence factors that contribute to its ability to colonize, invade, and evade the immune system, which includes Panton-Valentine leukocidin (PVL), a bicomponent, pore-forming toxin encoded by two contiguous genes, *lukF-PV* and *lukS-PV*. PVL can cause either neutrophil lysis or apoptosis and contributes to tissue necrosis (25). PVL has been linked to skin and soft tissue infections (SSTIs), necrotizing pneumonia, and bone and joint infections in humans (3, 11, 17). Rabbit and human leukocytes are highly sensitive to PVL-mediated leukocytosis (18), and animal studies have shown that PVL causes more-severe disease in dermonecrosis (7, 27), osteomyelitis (6), and necrotizing pneumonia models (B. A. Diep, L. Chan, and P. Tattevin, presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 2009).

The presence of PVL has been extensively described for methicillin-resistant *S. aureus* (MRSA), specifically in association with staphylococcal cassette chromosome *mec* (SCC*mec*) type IV and also SCC*mec* type V (4, 25). The epidemiology of PVL-positive methicillin-susceptible *S. aureus* (MSSA) has not been reported as extensively, and the *lukSF-PV* genes are not exclusively linked to the presence of the SCC*mec* element. In the 1950s MSSA ST80 strains, which were associated with outbreaks of SSTI, harbored the *lukSF-PV* genes (22). There have also been recent reports of PVL-positive MSSA causing clusters of SSTI and necrotizing pneumonia (5, 15).

The vast majority of *S. aureus* strains in New Zealand are methicillin susceptible (MSSA); the prevalence of methicillin-resistant *S. aureus* (MRSA) remains low, at about 5% (12). New Zealand has a high incidence of *S. aureus* disease; the incidence of *S. aureus* bacteremia in the late 1990s was 41 cases per 100,000 adults per year (12). We aimed to examine the prevalence of the *lukSF-PV* genes in MSSA isolates responsible for disease and asymptomatic nasal carriage, to determine risk factors for infection with PVL-positive MSSA, and to examine the association between PVL and severity of disease.

MATERIALS AND METHODS

Clinical MSSA isolates. All MSSA isolates isolated from diagnostic specimens submitted to the Microbiology Laboratory of Auckland City Hospital from February to April 2008 were collected. These specimens were generally obtained at the request of the attending physician, midwife, or district nurse for clinical reasons. Duplicate isolates from the same patient were excluded. The isolates were stocked onto nutrient agar (Difco Laboratories, Detroit, MI).

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Nasal carriage isolates. MSSA isolates from nasal carriers were obtained from healthy population volunteers in the Auckland community during a separate study performed to examine the demographic features of nasal carriers in Auckland. These volunteers were recruited in public places spread across the Auckland region between February and November 2008; people with hospital contact in the previous 3 months were excluded.

Detection of the *lukSF-PV* genes. All isolates were cultured onto tryptic soy agar with 5% sheep blood (Difco Laboratories, Detroit, MI) and incubated aerobically overnight at 35°C. Nucleic acid was extracted from MSSA isolates as previously described (20). The PVL and *nuc* probes were synthesized with the nonfluorescent quencher BHQ1 (Biosearch Technologies, CA). Cal Fluor Gold 540 and FAM (6-carboxyfluorescein) were utilized as reporter dyes. Primers were synthesized based on oligonucleotide sequences described previously (20). Data for the duplex PCR (for the simultaneous amplification of the *lukSF-PV* genes and the *nuc* gene) were collected with an ABI 7500 real-time PCR system (Applied Biosystems, CA). Reactions were performed with 1× universal master mix (Applied Biosystems, CA) under the following thermal cycling conditions: 15 min at 95°C, followed by 40 cycles of 95°C for 15 s and 55°C for 1 min. Amplification was confirmed by the generation of a sigmoid amplification plot. A negative control was provided by use of negative blanks and PCR blanks.

MLST. In order to ensure that there was no single dominant PVL-positive MSSA clone that caused disease in Auckland, all of the *lukSF-PV* MSSA carriage isolates were genotyped by using multilocus sequence typing (MLST) (9). A similar number of randomly selected *lukSF-PV*-positive clinical MSSA isolates were also genotyped. To assign a clonal complex (CC), sequences were compared with the sequences in the *S. aureus* MLST database (http://saureus.mlst.net/) (10).

Clinical data. Electronic clinical records were reviewed to ascertain the following demographic data: patient age, gender, ethnicity, and place of domicile. The NZDep2006 (New Zealand Deprivation 2006) score was calculated for each patient; the NZDep2006 score is derived from population data for each neighborhood (23). This score ranges from 1 to 10, where 1 represents the least deprived areas of Auckland and 10 represents the most deprived areas of Auckland. The source of infection was also recorded. In order to evaluate potential risk factors associated with *S. aureus* disease, the following data were ascertained: community versus hospital onset, Charlson weighted index of comorbidity (16), the presence of an implanted medical device, recent trauma with breach of skin within 30 days, the presence of a noninfective chronic skin condition, or a history of alcoholism or intravenous drug use. Disease severity was measured by means of the following data: requirement for surgical intervention, number of surgical procedures, bloodstream invasion, duration of admission, 30-day readmission rate, and 30-day mortality rate.

Definitions used. Skin and soft tissue infection was defined as the presence of a cutaneous abscess or other signs of inflammation and a culture positive for MSSA.

Bone infection was defined as radiologic or surgical evidence of osteomyelitis and MSSA-positive blood or aspirate culture.

Joint infection was defined as pain with, or limitation of, joint movement and MSSA-positive aspirate or blood cultures.

Pneumonia was defined as the presence of fever with radiographic changes consistent with pneumonia and MSSA-positive sputum, tracheal aspirate, bronchial washing, or blood cultures.

Surgical-site infection and catheter-related infection were defined in accordance with the criteria of the Australian Council of Healthcare Standards (1).

Primary bacteremia was defined as the presence of a blood culture positive for MSSA with no identifiable focus of infection.

The diagnosis of endocarditis was based on modified Dukes' criteria (8).

Community-onset, not health care-associated, infections were defined as those episodes with an MSSA-positive culture within 48 h of admission without a history of a health care-associated risk factor.

Community-onset, health care-associated infections were defined as those episodes with an MSSA-positive culture within 48 h of admission with a history of a health care-associated risk factor. Health care-associated risk factors were as follows: history of hospitalization in the past year, requirement for renal dialysis, residence in a long-term care facility, and the presence of percutaneous medical devices.

Hospital-onset, health care-associated infections were defined as those episodes with an MSSA-positive culture more than 48 h after admission to hospital.

All other infections were classified following review by an infectious disease physician.

Statistical analysis. Data analyses were undertaken by using JMP 5.1 (SAS Inc., NC) and StatsDirect 2.5.7 (StatsDirect Ltd., Cheshire, United Kingdom) software. For categorical variables, analysis was performed by using chi-square and Fisher's exact tests, and the results were expressed in terms of odds ratios (ORs) and associated 95% confidence intervals (CIs). For continuous variables, the differences between patient groups were investigated by the parametric *t* test or the nonparametric Wilcoxon rank sum test as appropriate. Multivariate analyses were undertaken by using nominal logistic regression and effect likelihood ratio tests, with significance set at a P value of <0.05.

Ethical approval. The regional ethics committee of the New Zealand Ministry of Health provided ethical approval for the study.

RESULTS

MSSA isolates were obtained from 411 patients for whom clinical details were available. The majority of the patients, 335/411 (81.5%), had a clearly identifiable focus of infection; 76/411 (18.5%) patients were not considered to have *S. aureus* infection and were excluded from analysis. We also obtained 93 MSSA isolates from nasal carriers for comparison. The prevalence of the *lukSF-PV* genes among the clinical MSSA isolates, 124/335 (37%), was not significantly different from the prevalence of the *lukSF-PV* genes among the nasal carriage isolates, 29/93 (31%) ($P = 0.33$). MLST confirmed that a diverse range of MSSA genotypes was PVL positive in Auckland: the 29 *lukSF-PV*-positive nasal carriage isolates belonged to eight clonal complexes (CC5, 9/29 isolates [31%]; CC30, 7/29 [24%]; CC1, 6/29 [21%]; CC22, 2/29 [7%]; CC78, 2/29 [7%]; CC15, 1/29 [3%]; CC97, 1/29 [3%]; CC121, 1/29 [3%]), and the 24 randomly selected *lukSF-PV*-positive clinical isolates belonged to six clonal complexes (CC1, 12/24 isolates [50%]; CC121, 6/24 [25%]; CC30, 3/24 [13%]; CC5, 1/24 [4%]; CC8, 1/24 [4%]; CC78, 1/24 [4%]). Several predominant clonal complexes contained the majority of the *lukSF-PV*-positive MSSA isolates: 88% of the clinical isolates belonged to three predominant clonal complexes (CC1, CC30, and CC121), and 76% of the nasal carriage isolates belonged to three predominant clonal complexes (CC1, CC5, and CC30).

The prevalences of PVL-positive MSSA for patients within each infection group were 112/235 (48%) with skin and soft tissue infection, 4/13 (31%) with bone and joint disease, 2/11 (18%) with pneumonia, 2/36 (2%) with surgical-site infection, 1/13 (1%) with catheter-related infection, and 0/6 (0%) with primary bacteremia and endocarditis. Univariate analysis was performed to compare features of the PVL-positive MSSA infections ($n = 124$) to the features of the PVL-negative MSSA infections ($n = 211$) (Table 1). Histories of alcoholism and intravenous drug use were excluded from Table 1, as they were not routinely documented in clinical records. Factors associated with PVL-positive infections in the univariate analysis were investigated further by employing multivariate analysis. A diagnosis of SSTI, Pacific ethnicity, younger age, community-onset infection, and need for surgical intervention were all independently associated with the presence of a PVL-positive MSSA infection. The incidence of PVL-positive MSSA infections over the 2-month study period was 8.7 per 1,000 patients; it peaked for those individuals aged between 10 and 20 years, at 15.4 per 1,000 patients, and steadily decreased to 0.77 per 1,000 patients for those aged between 80 and 90 years ($r = -0.79$; $P = 0.01$). The incidence of PVL-negative infections showed no trend with age ($r = 0.20$; $P = 0.60$).

The majority of our MSSA infections, 232/335 (70%), presented as SSTIs, and univariate analysis of this subset was performed to directly compare features of PVL-positive MSSA

TABLE 1. Univariate analysis of patients with PVL-positive MSSA infection versus PVL-negative MSSA infection

Patient characteristic	No. (%) of PVL-positive patients (n = 124)	No. (%) of PVL-negative patients (n = 211)	OR (95% CI) of PVL-positive compared to PVL-negative patients	P value of PVL-positive compared to PVL-negative patients
Female gender	55 (44)	98 (46)	0.92 (0.59–1.44)	0.73
Ethnicity[a]				
European	41 (33)	116 (55)	0.40 (0.25–0.64)	<0.0001
Maori	22 (18)	22 (10)	1.85 (0.98–3.51)	0.09
Pacific	50 (40)	46 (22)	2.42 (1.49–3.94)	0.0007
Asian	4 (3)	17 (8)	0.38 (0.13–1.16)	0.10
Other	7 (6)	10 (5)	1.20 (0.45–3.24)	0.14
Age (yr)[a,b]				
0–9	40 (33)	55 (26)	1.35 (0.83–2.20)	0.21
10–19	27 (22)	23 (11)	2.28 (1.24–4.18)	0.01
20–29	11 (9)	18 (9)	1.04 (0.48–2.29)	0.99
30–39	17 (14)	18 (9)	1.70 (0.84–3.44)	0.14
40–49	13 (11)	18 (9)	1.66 (0.59–2.66)	0.56
50–59	1 (1)	15 (7)	0.11 (0.11–0.81)	0.007
60–69	10 (8)	22 (11)	0.75 (0.34–1.65)	0.57
70–79	1 (1)	23 (11)	0.07 (0.01–0.50)	0.0003
80–89	1 (1)	16 (8)	0.10 (0.01–0.76)	0.008
NZDep2006 score[c]				
1–3 (low deprivation)	22 (18)	52 (25)	0.66 (0.38–1.15)	0.17
4–7 (medium deprivation)	42 (34)	69 (33)	1.05 (0.65–1.68)	0.90
8–10 (high deprivation)	58 (48)	86 (42)	1.28 (0.81–2.00)	0.30
Source of infection[a]				
Skin and soft tissue infection	112 (90)	122 (58)	6.81 (3.54–13.11)	<0.0001
Surgical site infection	2 (2)	34 (16)	0.09 (0.02–0.36)	<0.0001
Catheter-related infection	1 (1)	12 (6)	0.13 (0.02–1.05)	0.04
Bone and joint infection	4 (3)	9 (4)	0.75 (0.23–2.48)	0.78
Pneumonia	2 (2)	9 (4)	0.37 (0.08–1.73)	0.22
Primary bacteremia or endocarditis	0 (0)	6 (3)		
Other	3 (2)	19 (9)	0.25 (0.07–0.86)	0.02
Onset[a]				
Community onset, not health care associated	69 (56)	79 (37)	2.10 (1.34–3.29)	0.001
Community onset, health care associated	43 (35)	52 (25)	1.62 (1.00–2.64)	0.06
Hospital onset, health care associated	12 (10)	80 (38)	0.18 (0.09–0.34)	<0.0001
Comorbidities (Charlson score of <3)	112 (90)	155 (73)	3.37 (1.73–6.58)	0.0002
Implanted medical device	3 (2)	23 (11)	0.20 (0.06–0.69)	0.005
Trauma with breach of skin <30 days	19 (15)	21 (10)	1.64 (0.84–3.18)	0.16
Chronic noninfective skin condition	6 (5)	32 (15)	0.28 (0.12–0.70)	0.004
Required surgical procedure[a]	75 (60)	59 (28)	3.94 (2.47–6.30)	<0.0001
≥2 surgical procedures	4/75 (5)	10/59 (17)	0.28 (0.08–0.93)	0.04
Presence of bacteremia	4/35 (11)	19/92 (21)	0.50 (0.16–1.58)	0.43
Duration of admission (days)				
≤1	45 (36)	72 (34)	1.1 (0.69–1.75)	0.73
2–4	63 (51)	46 (22)	6.00 (3.40–10.59)	<0.0001
≥5	16 (13)	93 (44)	0.19 (0.10–0.34)	<0.0001
Readmitted within 30 days	6 (5)	9 (4)	1.14 (0.40–3.29)	0.79
30-day mortality	1 (1)	10 (5)	0.16 (0.02–1.29)	0.06

[a] Found to be independent associations upon multivariate analysis adjusted for gender, ethnicity, age, deprivation score, onset, comorbidities, implanted medical device, trauma with breach of skin, chronic noninfective skin conditions, surgical requirement, duration of admission, 30-day readmission, and 30-day mortality.
[b] Six patients aged greater than 90 years were excluded from analysis due to low numbers.
[c] NZDep2006 score was not available for six patients.

SSTIs to features of PVL-negative MSSA SSTIs. Of note, 112/232 (48%) of our patients presenting with MSSA SSTI had infection with a PVL-positive strain. Patients with PVL-positive MSSA SSTI were also 7.4 times as likely to required surgical drainage of cutaneous abscesses compared to patients with PVL-negative MSSA SSTI (95% confidence interval, 4.1 to 13.3).

DISCUSSION

We found similar prevalences of *lukSF-PV* genes in both clinical and nasal carriage isolates of MSSA among a diverse genetic range of MSSA in Auckland. The prevalence of PVL-positive MSSA among clinical isolates of MSSA in Auckland,

37%, is similar to that reported in a study conducted in the Arkhangelsk region of Russia (26). However, other studies that used a methodology similar to that of our study reported much lower prevalence rates, ranging from 7 to 12% (13, 21, 29). In Auckland, PVL-positive MSSA was strongly associated with the diagnosis of SSTI; 48% of all MSSA isolates associated with SSTI were *lukSF-PV* positive. The reported incidence of PVL-positive MSSA SSTI in the literature ranges from 6.8% in a teaching hospital in Michigan (14) to 93% in a New York prison endemic with the PVL-positive USA300 MSSA strain (19).

The 2006 New Zealand Census revealed that the total population of Auckland consisted of the following ethnic groups: 61% European, 7% Maori, 11% Pacific, and 21% Asian (24). Compared to this census, Pacific and Maori patients are overrepresented in the MSSA infection group, and European and Asian patients are underrepresented. PVL-positive MSSA infections were also more commonly associated with Pacific people than with people of other ethnic groups. Previous studies have also shown that Maori and Pacific people living in New Zealand are at a higher risk of disease caused by *S. aureus* (12), and socioeconomic deprivation is likely to play an important role in the development of infectious disease in Auckland (2). We found that people with MSSA infection were more likely to live in areas with higher NZDep2006 scores (more deprived) than the general population, but there was no significant association between the prevalence of PVL-positive MSSA infection and increasing NZDep2006 scores.

In this study, we compared the differences in severities of PVL-positive versus PVL-negative infections. We found that patients with PVL-positive MSSA infection were 3.9 times more likely to require surgery than those with PVL-negative MSSA infection. Within the SSTI group, this distinction was even more pronounced: those with PVL-positive MSSA SSTI were 7.4 times more likely to require surgery than those with PVL-negative MSSA SSTI. However, there was no significant difference between the two groups in terms of other measures of disease severity: the number of surgical procedures required, rate of bloodstream invasion, duration of admission, 30-day readmission rate, and crude 30-day mortality rate.

In conclusion, we found that more than one-third of MSSA infections in our region were caused by PVL-positive strains. PVL-positive MSSA infection was strongly associated with patients of Pacific ethnicity, younger age, diagnosis of SSTI, community-onset infection, and need for surgical intervention. This study showed a peak in PVL-positive infections in childhood and young adulthood, with a decline in later years. Further studies are required to elucidate the underlying reasons for this finding.

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