Frequency and Clinical Association of Panton-Valentine Leukocidin-Positive Staphylococcus aureus Isolates: A Study from Kuwait

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Key Words
Staphylococcus aureus • Panton-Valentine leukocidin • Methicillin resistance

Abstract
Objective: This study was undertaken to determine the frequency of Panton-Valentine leukocidin (PVL)-producing Staphylococcus aureus among strains isolated in our laboratory and to study the association of PVL-positive strains with clinical disease. Materials and Methods: A total of 291 S. aureus isolates obtained from different clinical specimens from June 1, 2009, to March 31, 2010, at the Farwania Hospital Laboratory were investigated for antimicrobial susceptibility, carriage of genes for PVL, and SCCmec elements. Antimicrobial susceptibility testing was performed by standard methods. The presence of mecA genes for PVL SCCmec typing was determined by PCR. Results: Of the 291 S. aureus isolates, 89 (30.6%) were methicillin-resistant S. aureus (MRSA), whereas 202 (69.4%) were methicillin susceptible (MSSA). Genes for PVL were detected in 13 (14.6%) and 24 (12.0%) of the MRSA and MSSA isolates, respectively. The majority of the PVL-producing MRSA and MSSA were isolated from 12 (30.7%) and 19 (21.8%) cases of skin and soft tissue infections (SSTI), respectively. Although both MSSA and MRSA strains were uniformly susceptible to rifampicin, teicoplanin, and vancomycin, multidrug resistance was observed among PVL-producing and nonproducing MRSA isolates. Both MRSA types carried SCCmec type III, IV, IVc, and V genetic elements. Conclusion: This study revealed the presence of genes for PVL in both MSSA and MRSA, associated mostly with SSTI and respiratory tract infections, supporting previous observations that PVL production is widespread among S. aureus strains obtained from different clinical sources.

Introduction
Staphylococcus aureus is an important human pathogen capable of causing a wide spectrum of diseases in the community as well as in the hospital setting [1]. These diseases vary from mild skin lesions to life-threatening invasive infections, such as septicemia, necrotizing pneumonia, endocarditis, and deep-seated abscesses [2]. Pathogenicity is related to the secretion of a number of bacterial factors which include protein A, fibronectin-binding protein, collagen-binding protein, clumping fac-
tors, enterotoxins, toxic shock syndrome toxin, and Panton-Valentine leucocidin (PVL) [3].

Methicillin-resistant S. aureus (MRSA) was previously associated with healthcare facilities. However, since 1991, there have been increasing numbers of reports of MRSA strains causing infections in the community [4]. These MRSA strains have been labeled as community-acquired or community-associated MRSA (CA-MRSA). These strains are typically susceptible to most antibiotic-resistant. Furthermore, genomic sequence analyses of mecA gene, located on the staphylococcal chromosome, have revealed that while HA-MRSA may belong to any of the three SCCmec types (I, II, or III) CA-MRSA carry SCCmec type IV or V elements in their genome [4].

Among the exoproteins elaborated by S. aureus, the role of PVL in the pathogenesis of staphylococcal infections had been uncertain until strains carrying PVL genes were observed to be more often associated with severe skin and soft tissue infections (SSTI), necrotizing pneumonia, and sepsis [2]. PVL is a bicomponent, pore-forming cytotoxin which targets human and rabbit monocytes, macrophages, and human polymorphonuclear leukocytes and causes tissue necrosis [5]. Also, the presence of PVL genes was identified as a possible marker of CA-MRSA strains worldwide [6]. Recently, PVL was also involved in severe diseases and outbreaks among homosexual men, prison inmates, health-care workers, and school children in the USA [7], The Netherlands [8], Switzerland [9], and Scotland [10].

The proportion of S. aureus strains producing PVL has been reported to vary around the world [11–13], ranging from <2% in the UK [3] to 10% in The Netherlands [8]. However, the prevalence of PVL-producing S. aureus, isolated from patients in Kuwait, is unknown. The aim of this study was to determine the frequency of PVL gene carriage among S. aureus strains isolated from clinical samples at the microbiology laboratory of a general hospital in Kuwait. We also sought to establish any association between PVL production and clinical disease.

Materials and Methods

Setting and Patients

This study was conducted at Farwania Hospital, which is a tertiary care facility in Kuwait. It is a university-affiliated hospital with 1,200 acute-care beds, which include medical, surgical, orthopedic, obstetric and gynecologic, pediatrics, and two intensive care units. The clinical specimens from 169 male and 93 female patients were found to be positive for S. aureus, while the gender information from 29 cases was not available. One hundred ninety-four positive samples were received from in-patients and, while the location of 19 cases was not known, the remaining 56 samples were from the out-patient department.

Bacterial Isolates

A total of 291 S. aureus strains were isolated in the microbiology laboratory of Farwania Hospital and/or the Faculty of Medicine during a period of 10 months, from June 2009 through March 2010. The isolates were collected from cultures of various clinical specimens as part of routine diagnostic care. All isolates were identified as S. aureus by their characteristic growth on manitol salt agar, Gram stain, and positive tube coagulase and DNase tests. The identification of some of the isolates was confirmed by Phoenix (Becton Dickinson, USA). The strains were preserved in 15% glycerol v/v in brain heart infusion broth (Oxoid, Basing-stoke, UK) and maintained at –80 °C. For further characterization these strains were recovered by subculture on brain heart infusion agar and incubated at 37°C for 24 h.

Antimicrobial Susceptibility Testing

Susceptibility to a range of antimicrobial agents was performed by the standard disk diffusion test on Mueller-Hinton agar (Oxoid) according to the criteria of the Clinical and Laboratory Standards Institute (CLSI) [14]. The antibiotic disks (Oxoid) used included methicillin (5 μg), benzyl penicillin (2 U), cefoxitin (30 μg), kanamycin (30 μg), gentamicin (30 μg), amikacin (30 μg), streptomycin (30 μg), erythromycin (15 μg), clindamycin (2 μg), chloramphenicol (30 μg), tetracycline (10 μg), trimethoprim-sulfamethoxazole (2.5 μg), fusidic acid (10 μg), rifampicin (5 μg), ciprofloxacin (5 μg), linezolid (30 μg), and mupirocin (200 μg).

S. aureus ATCC 25923 was used as a quality control strain for susceptibility testing. Susceptibility to vancomycin and teicoplanin was determined by E-test (bioMerieux Diagnostic, France) using the macro method, with an inoculum equivalent to 2 × the McFarland standard according to the manufacturer’s instructions; MIC ≤2 mg/l was regarded as susceptible. Based on susceptibility to cefoxitin the strains were classified as MSSA or MRSA. Further confirmation was done by amplification of the mecA gene by PCR and by detection of PBP2a with a rapid latex agglutination test (Denka-Seiken, Tokyo, Japan) used according to the manufacturer’s instructions.

Urease Production

Urease production was detected on Christensen’s urea agar slope after incubation at 35°C for 48 h.

SCCmec Typing

All S. aureus strains were characterized for their SCCmec types using PCR as described previously [11].

Amplification of PVL Genes

The PVL genes (lukS-PV/lukF-PV) were detected by PCR using the protocol described previously by Lina et al. [15].
The sources of the isolated Staphylococcus aureus strains were: SSTI, n = 126 (43.3%); respiratory tract infections, n = 49 (16.8%); blood, n = 35 (12.0%); urine, n = 15 (5.2%), and miscellaneous, n = 60 (20.6%) (table 1). Cefoxitin susceptibility testing revealed that 202 (69.4%) strains were MSSA and 89 (30.6%) strains were MRSA. All S. aureus isolates (100%) were susceptible to rifampicin, teicoplanin, vancomycin, linezolid, and mupirocin but expressed varying degrees of resistance to aminoglycosides, macrolides, tetracycline, trimethoprim, fusidic acid, and fluoroquinolones (table 2).

Screening for carriage of genes that code for PVL showed that 24 (12%) MSSA and 13 (14.6%) MRSA yielded positive results in each category (table 1). Thirty-one PVL gene-positive (PVL+) S. aureus were isolated from SSTI (83.8%), followed by respiratory tract (n = 3; 8.1%) and blood samples (n = 1; 2.7%). Twelve of the 13 PVL+ MRSA and the majority of the PVL+ MSSA (78.1%) strains were isolated from SSTI samples (table 1).

SCCmec typing of the 89 MRSA strains showed that 2 of them carried SCCmec II, 30 (33.7%) carried SCCmec III, 40 (44.9%) carried SCCmec IV, and 17 (19.1%) carried SCCmec V genetic elements. Of the 40 SCCmec IV strains, 17 (42.5%) were identified as EMRSA-15, an HA-MRSA strain with the SCCmec IV genotype based on the carriage of the SCCmec IV genetic element and a negative urease test. EMRSA-15 strains usually do not produce urease. All 17 isolates yielded negative results in the urease test. Therefore, SCCmec typing identified 49 HA-MRSA (SCCmec II, SCCmec III, and EMRSA-15) and 40

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**Table 1. Prevalence of PVL among S. aureus isolated from different clinical samples**

| Isolates | Source of the isolate, n | Subtotal |
|----------|-------------------------|----------|
|          | sputum/ETT | SSTI | blood | urine | others |          |
| MSSA a   |            |       |       |       |        |          |
| PVL+     | 3          | 19   | 1     | 0     | 0      | 23       |
| PVL–     | 37         | 68   | 27    | 14    | 30     | 176      |
| Subtotal (a) | 40   | 87   | 28    | 14    | 30     | 199 a    |
| MRSA a   |            |       |       |       |        |          |
| PVL+     | 0          | 12   | 0     | 0     | 0      | 12       |
| PVL–     | 9          | 27   | 7     | 1     | 30     | 74       |
| Subtotal (b) | 9    | 39   | 7     | 1     | 30     | 86 b     |
| Total (a + b) | 49  | 126  | 35    | 15    | 60     | 285      |

ETT = Endotracheal tube aspirate. a Of the 291 isolates, the sources of 3 MRSA (1 PVL+ and 2 PVL–) and 3 MSSA (1 PVL+ and 2 PVL–) were not known.

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**Table 2. Antibiotic resistance profile of S. aureus isolates**

| Isolates | Antibiotic-resistant strains, n (%) |
|----------|-----------------------------------|
|          | P | GM | KA | AK | S | E | CC b | TE | TMP | RIF | FA | CIP | C |
| MSSA (n = 202) | 159 (78.7) | 4 (2.0) | 11 (5.4) | 4 (2.0) | 6 (3.0) | 7 (3.5) | 7 (3.5) | 35 (17.3) | 34 (16.8) | 0 | 1 (0.5) | 5 (2.4) | 2 (1.0) |
| PVL+ (n = 24)  | 16 (66.6) | 0 | 3 (12.5) | 1 (4.2) | 0 | 0 | 6 (25.0) | 7 (29.2) | 0 | 0 | 1 (4.2) | 1 (4.2) |
| PVL– (n = 178) | 143 (80.3) | 4 (2.2) | 8 (4.5) | 3 (1.5) | 6 (3.3) | 7 (3.9) | 7 (3.9) | 29 (16.3) | 27 (15.1) | 0 | 1 (0.5) | 4 (2.2) | 1 (0.5) |
| MRSA (n = 89)  | 89 (100) | 42 (47.2) | 55 (61.8) | 26 (29.2) | 29 (32.5) | 38 (42.7) | 38 (42.7) | 41 (46.0) | 27 (30.3) | 0 | 30 (33.7) | 51 (57.3) | 3 (3.3) |
| PVL+ (n = 13)  | 13 (100) | 5 (38.4) | 9 (69.2) | 2 (15.4) | 3 (23.0) | 3 (23.0) | 3 (23.0) | 4 (30.7) | 5 (38.4) | 0 | 2 (15.4) | 10 (76.9) | 0 |
| PVL– (n = 76)  | 76 (100) | 46 (60.5) | 24 (31.5) | 26 (34.2) | 35 (46.0) | 35 (46.0) | 37 (48.6) | 22 (28.9) | 0 | 28 (36.8) | 41 (53.9) | 3 (3.9) |

a P = Penicillin; GM = gentamicin; KA = kanamycin; AK = amikacin; S = streptomycin; E = erythromycin; CC = clindamycin; TE = tetracycline; TMP = trimethoprim; RIF = rifampicin; CIP = ciprofloxacin; C = chloramphenicol.

b Among MSSA (PVL–) strains 4 exhibited inducible and 2 presented constitutive resistance to clindamycin, whereas among MRSA (PVL+) and (PVL–) strains constitutive and inducible resistance was exhibited by 2 and 1, and 22 and 16 isolates, respectively.

**Results**

The sources of the isolated S. aureus strains were: SSTI, n = 126 (43.3%); respiratory tract infections, n = 49 (16.8%); blood, n = 35 (12.0%); urine, n = 15 (5.2%), and miscellaneous, n = 60 (20.6%) (table 1). Cefoxitin susceptibility testing revealed that 202 (69.4%) strains were MSSA and 89 (30.6%) strains were MRSA. All S. aureus isolates (100%) were susceptible to rifampicin, teicoplanin, vancomycin, linezolid, and mupirocin but expressed varying degrees of resistance to aminoglycosides, macrolides, tetracycline, trimethoprim, fusidic acid, and fluoroquinolones (table 2).

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CA-MRSA (23 SCCmec IV and 17 SCCmec V) strains. The 13 PVL+ MRSA strains consisted of 2 HA-MRSA (SCCmec III) and 11 CA-MRSA (6 SCCmec IV, 4 SCCmec V and 1 SCCmec IVc). Based on SCCmec typing results, 85% of the PVL+ MRSA strains isolated from SSTI were CA-MRSA and 15% were HA-MRSA.

When the PVL+ strains were analyzed for resistance to antibacterial agents, the results showed that none of the 24 PVL+ MSSA strains was resistant to gentamicin, streptomycin, erythromycin, clindamycin, and fusidic acid. However, they exhibited a very low prevalence of resistance to amikacin, chloramphenicol, and ciprofloxacin. In contrast, MRSA strains were more resistant to aminoglycosides, ciprofloxacin, trimethoprim, erythromycin, and clindamycin but there were no significant differences between PVL+ and PVL− strains (table 2).

Discussion

PVL-producing S. aureus strains constitute a major public health threat in the community as well as in healthcare settings [6, 8, 9, 12, 13, 16]. Due to its initial association with CA-MRSA strains, PVL production was suggested to be a genetic marker for CA-MRSA [6, 16]. However, later studies reported genes encoding PVL production in both MSSA and MRSA obtained from different geographical areas, suggesting that PVL production was a poor marker for CA-MRSA [17–19]. The detection of genes for PVL in both MSSA and MRSA in this study confirmed previous reports that PVL production is widespread in S. aureus [18, 19]. In addition, the proportion of S. aureus strains carrying the PVL genes is increasing in some countries [6, 8, 20]. A study of MRSA isolates from The Netherlands showed an increase in the proportion of MRSA strains harboring PVL genes from 5% in 2000 to 15% in 2002 [8]. A recent study from China [21] revealed an overall PVL positivity rate of 12.8% among their S. aureus isolates, which is similar to the results of our study where 12 and 14.6% of the MSSA and MRSA strains, respectively, harbored genes that encode PVL. CA-MRSA are characterized by the carriage of SCCmec types IV and V [22–24]. Infections caused by CA-MRSA are increasing worldwide [6, 20]. Our study, which showed that 40 (44.9%) of the 89 MRSA strains were CA-MRSA, is in agreement with this global trend and with a recent report that CA-MRSA are increasing in Kuwait hospitals [25].

Our results that 83% of the PVL-producing S. aureus strains were obtained from SSTI samples while 8.1 and 7.8% were from respiratory and blood samples, respectively, are similar to those of other studies that have shown an association of PVL-producing S. aureus mostly with SSTI [3, 15, 26, 27]. Our results also reflect the fact as SSTI provided 43.3% of the strains in the study. However, the detection of genes for PVL in S. aureus from respiratory samples and blood confirms the involvement of PVL-producing MRSA in serious infections. As previously noted, PVL production was associated with CA-MRSA causing SSTI and pneumonia [15]. The result that 11 of 13 PVL-producing S. aureus in this study were CA-MRSA is significant and adds to the growing importance of PVL-producing CA-MRSA in serious infections [6, 15, 20]. Also, similar to the detection of PVL genes in a few HA-MRSA strains in this study, PVL-producing MRSA causing hospital-acquired infections have been detected in Algeria [28].

Our results also showed that PVL-producing MRSA were more resistant to gentamicin, erythromycin, clindamycin, tetracycline, ciprofloxacin, and fusidic acid as compared to PVL-producing MSSA strains. However, fusidic acid had excellent activity against our MSSA isolates, being equally effective against PVL-producing and nonproducing strains, whereas rifampicin and chloramphenicol showed consistent activity against all isolates of S. aureus (MSSA and MRSA). Recent studies have suggested that the antimicrobial susceptibility profile, especially ciprofloxacin susceptibility, can be used as a marker for CA-MRSA [29–30]. However, ciprofloxacin resistance was detected in both HA-MRSA and CA-MRSA in this study, making it an inappropriate marker for our CA-MRSA isolates.

Conclusion

The findings showed that both MRSA and MSSA associated with SSTI, respiratory tract infections, and septicemia were more likely to produce PVL.

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PVL-Positive Staphylococcus aureus

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