The Role of Panton-Valentine Leukocidin in *Staphylococcus aureus* Musculoskeletal Infections in Children

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### Abstract:
Infections caused by Panton-Valentine leukocidin (PVL)-producing strains of *Staphylococcus aureus* have been reported with increasing frequency. However, the role of PVL in the pathogenesis of invasive staphylococcal infection is controversial. It is interesting to note that the role played by PVL may depend on the site of infection; although an association between PVL and severity has been reported in lung and bone infection, this is not the case for skin and soft tissue infection. A number of recent reports describe severe complications associated with PVL-producing strains in musculoskeletal infections. This review summarizes the current evidence on the influence of PVL on musculoskeletal infections caused by *S. aureus* in children and highlights areas of uncertainty relating to management.

### Key Words:
*Staphylococcus aureus*, Panton-Valentine leukocidin, toxin, bone and joint, musculoskeletal, children, pediatric

The majority of musculoskeletal infections in children are caused by *Staphylococcus aureus*. In the last decade, infections caused by Panton-Valentine leukocidin (PVL)-producing strains of *S. aureus* have been reported with increasing frequency. However, the role of PVL in the pathogenesis of invasive staphylococcal infection is controversial. It is interesting to note that the role played by PVL may depend on the site of infection; although an association between PVL and severity has been reported in lung and bone infection, this is not the case for skin and soft tissue infection. A number of recent reports describe severe complications associated with PVL-producing strains in musculoskeletal infections. This review summarizes the current evidence on the influence of PVL on musculoskeletal infections caused by *S. aureus* in children and highlights areas of uncertainty relating to management.

### DETECTION OF PANTON-VALENTINE LEUKOCIDIN
PVL-producing *S. aureus* strains are identified either by detection of the genes encoding PVL or the toxin itself. Standard techniques for detecting the pvl gene include nucleic acid amplification using polymerase chain reaction with *lukF-PV* and *lukS-PV*-specific primers. PVL toxin can be detected by an enzyme-linked immunosorbent assay using antibodies against *lukS-PV*.

Approximately 90% of *S. aureus* strains that possess *pvl* produce toxic concentrations of PVL in vitro. PVL presence is more common in methicillin-resistant *S. aureus* (MRSA) than in methicillin-sensitive *S. aureus* (MSSA). However, PVL concentrations produced are not different between *pvl*-positive MSSA and *pvl*-positive MRSA.

### EPIDEMIOLOGY AND CLINICAL FEATURES
To date, 9 high-quality studies have reported the frequency and/or influence of PVL-producing *S. aureus* in musculoskeletal infections in children. Publications describing only case reports or case series were not included in this review. Six of the 9 studies are from the same tertiary pediatric hospital in Texas; only 2 studies (from France and Greece) have investigated this issue outside the United States. There is considerable variability in the selection of patients included in these studies. Four studies included only patients with osteoarticular infections caused by *S. aureus*. 4 studies included patients with all types of invasive *S. aureus* infections and the remaining study included patients with infections caused by PVL-producing *S. aureus* only. In the studies from the United States, the proportion of MRSA causing musculoskeletal infections was high, ranging from 19% to 87%.
53% to 68% with the exception of 1 study investigating primarily patients with septic arthritis in which the proportion of MRSA was lower (36%). The only study outside the United States that included osteoarticular infections caused by both MSSA and MRSA, reported a considerably lower proportion of MRSA (26%). Regardless of the location of the study, the proportion of PVL-producing S. aureus was consistently higher in infections caused by MRSA (74–100%) than those caused by MSSA (9–46%). The overall reported proportion of PVL-producing S. aureus is therefore dependent on the prevalence of MRSA in the respective region and ranged from 37% in Greece to 78% in Texas (Fig. 1).

INFLUENCE OF PANTON-VALENTINE LEUKOCIDIN ON CLINICAL OUTCOME

There was considerable variability in the reported outcome associated with PVL-producing S. aureus (Table 1). Four of 5 studies reported longer duration of fever, and higher maximal C-reactive protein and erythrocyte sedimentation rate.1,9,10,12 A shorter duration is associated with PVL-producing S. aureus in the 3 studies providing this information.1,9,11 In the only study to report the number of interventions per child, PVL-producing S. aureus was associated with a higher number of interventions.16

CHOICE OF ANTIBIOTIC TREATMENT

Certain antibiotics increase or decrease PVL production in vitro.18,19 For example, oxacillin in subinhibitory concentrations increases PVL production whereas clindamycin, linezolid, fusidic acid and rifampicin have all been shown to decrease PVL production. Although prompt administration of antibiotics associated with decreased PVL production has been advocated20,21 and is common clinical practice, no study has shown clinical benefit or compared different regimens. A few guidelines give recommendations for the management of infections caused by PVL-producing S. aureus strains, including the use of clindamycin, linezolid or intravenous immunoglobulin.21,22 Some experts suggest including empiric treatment for PVL-producing S. aureus strains for all suspected staphylococcal infections once the local prevalence of MRSA is higher than 10–15%.23 This approach does not account for the fact that in some regions, a large proportion of PVL-producing S. aureus strains are MSSA. It is important to note, however, that clinical studies comparing the effectiveness of different therapeutic regimens in infections caused by PVL-producing S. aureus are lacking.

INVESTIGATIONS FOR DEEP VENOUS THROMBOSIS

An association between DVT and musculoskeletal infections caused by PVL-producing S. aureus has been described.10,24 The incidence of DVT in this setting has been reported as up to 6%, but is likely to be higher as most studies have not routinely included investigations for this complication.24 Of particular concern is the possibility that children with infection-associated DVT may develop septic pulmonary emboli with life-threatening consequences.24–26 Some authors speculate that septic emboli from a local DVT are responsible for dissemination of infection to the lung and brain.26 Investigations for thrombophilia are rarely helpful.26 Most commonly, DVT develops close to the site of infection and therefore the majority of cases are detected incidentally on magnetic resonance imaging studies performed to investigate the extent of the infection or presumed abscess.24,27,28 Other modalities that have been used to detect DVT in this setting include computed tomography scans, ultrasound with Doppler flow or magnetic resonance venography.23,25,28–29 Although 1 study suggests that the preferred imaging modality is ultrasound with Doppler flow,24 this investigation may be unreliable as surrounding inflammation may change the venous flow.

The high incidence of DVT in musculoskeletal infections caused by PVL-producing S. aureus and the potential for life-threatening complications warrant careful clinical evaluation and perhaps systematic screening. However, no study has compared the relative sensitivity and specificity of magnetic resonance imaging and ultrasound with Doppler flow for the presence of DVT in this setting, and therefore, the optimal diagnostic approach is unknown.

TREATMENT FOR DEEP VENOUS THROMBOSIS

Therapeutic approaches for infection-associated DVT include the use of low
<table>
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<th>Citation</th>
<th>Study Group</th>
<th>Study Type (Level of Evidence)</th>
<th>Outcome</th>
<th>Proportion pe1 Presence</th>
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<th>Microbiology</th>
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<td>Martinez-Aguilar et al10</td>
<td>59 children with musculoskeletal infections caused by CA S. aureus: 81% osteomyelitis, 10% septic arthritis, 8% pyomyositis, 2000–2002, USA</td>
<td>prospective cohort (II)</td>
<td>• pe1 presence • clinical course • febrile days • days of positive blood culture • complications (chronic osteomyelitis, DVT)</td>
<td>56% 21% (6) 87% (27)</td>
<td>• febrile days 4.2 vs. 2.1 days (P = 0.02)  • complications 10 vs. 0 (P = 0.002)  • days in hospital 13.5 vs. 14.7 (P = 0.64)  • days of positive blood cultures 3.7 vs. 1.8 (P = 0.16)</td>
<td>47% (28) 53% (31)</td>
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<td>Bocchini et al9</td>
<td>89 children with acute osteomyelitis caused by CA S. aureus, 2001–2004, USA</td>
<td>prospective cohort (II)</td>
<td>• pe1 presence • duration of symptoms • WCC, CRP, ESR • surgical treatment • days in ICU • radiographic studies</td>
<td>66% 9% (3) 100% (56)</td>
<td>• peak CRP 20 vs. 5.7 mg/dL (P &lt; 0.001) • peak ESR 112 vs. 70 mm/h (P &lt; 0.001) • days in ICU 11 vs. 1 (P = 0.01) • initial WCC 13.8 vs. 9.5 cells × 10^9/L (P = 0.03) • pyomyositis on MRI 62% vs. 31% (P = 0.05) • abscess on MRI 76% vs. 47% (P = 0.06) • surgical intervention 92% vs. 84% (P = NS) • days to normalization of CRP 17 vs. 8 (P = 0.008) • days to normalization of ESR 27 vs. 17 (P = 0.006) • febrile days 6.3 vs. 5.4 (P = 0.6) • WCC 12.2 vs. 11.6 cells × 10^9/L (P = 0.6) • surgical intervention 40% vs. 100% (P = 0.63) • number of cellulitis or abscesses 8 vs. 0 (P = 0.02) • peak CRP 18.3 vs. 7.9 mg/dL (P = 0.002) • peak ESR 106 vs. 70 mm/h (P = 0.001) • days to normalization of CRP 17 vs. 8 (P = 0.008) • days to normalization of ESR 27 vs. 17 (P = 0.006) • febrile days 6.3 vs. 5.4 (P = 0.6) • WCC 12.2 vs. 11.6 cells × 10^9/L (P = 0.6) • surgical intervention 40% vs. 100% (P = 0.63) • number of cellulitis or abscesses 8 vs. 0 (P = 0.02) • peak CRP 18.3 vs. 7.9 mg/dL (P = 0.002) • peak ESR 106 vs. 70 mm/h (P = 0.001) • days to normalization of CRP 17 vs. 8 (P = 0.008) • days to normalization of ESR 27 vs. 17 (P = 0.006) • febrile days 6.3 vs. 5.4 (P = 0.6) • WCC 12.2 vs. 11.6 cells × 10^9/L (P = 0.6) • surgical intervention 40% vs. 100% (P = 0.63)</td>
<td>37% (33) 63% (56)</td>
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<td>Sdougkos et al11</td>
<td>19 children with acute osteomyelitis caused by S. aureus, 2005–2006, Greece</td>
<td>prospective cohort (II)</td>
<td>• pe1 presence • clinical course • CRP, ESR • radiographic studies</td>
<td>37% 14% (2) 100% (5)</td>
<td>• peak CRP 18.3 vs. 7.9 mg/dL (P = 0.002) • peak ESR 106 vs. 70 mm/h (P = 0.001) • days to normalization of CRP 17 vs. 8 (P = 0.008) • days to normalization of ESR 27 vs. 17 (P = 0.006) • febrile days 6.3 vs. 5.4 (P = 0.6) • WCC 12.2 vs. 11.6 cells × 10^9/L (P = 0.6) • surgical intervention 40% vs. 100% (P = 0.63) • number of cellulitis or abscesses 8 vs. 0 (P = 0.02) • peak CRP 18.3 vs. 7.9 mg/dL (P = 0.002) • peak ESR 106 vs. 70 mm/h (P = 0.001) • days to normalization of CRP 17 vs. 8 (P = 0.008) • days to normalization of ESR 27 vs. 17 (P = 0.006) • febrile days 6.3 vs. 5.4 (P = 0.6) • WCC 12.2 vs. 11.6 cells × 10^9/L (P = 0.6) • surgical intervention 40% vs. 100% (P = 0.63)</td>
<td>74% (14) 26% (5)</td>
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<td>Carrillo-Marquez et al12</td>
<td>44 children with primary diagnosis of septic arthritis caused by CA and HA S. aureus: 38% osteomyelitis, 25% cellulitis, 18% myositis, 11% pyomyositis, 2001–2008, USA</td>
<td>prospective cohort (II)</td>
<td>• pe1 presence • clinical course • laboratory and imaging results</td>
<td>61% 46% (13) 88% (14)</td>
<td>• number of cellulitis or abscesses 8 vs. 0 (P = 0.02) • peak CRP 6.2 vs. 4.6 mg/dL (P = 0.1) • days to normalization of CRP 15 vs. 27 (P = 0.46) • peak ESR 76 vs. 59 mm/h (P = 0.17) • days to normalization of ESR 33 vs. 23 (P = 0.12) • initial WCC 11.8 vs. 12.1 cells × 10^9/L (P = 0.94)</td>
<td>64% (28) 36% (16)</td>
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| Gonzalez et al<sup>1</sup> | 103 children with invasive CA S. aureus infection, 38% osteomyelitis, 25% cellulitis, 18% myositis, 11% pyomyositis, 2001–2004, USA | prospective cohort (II) | • pvl presence  
• changes on CXR and CT scans | 78% (14) 99% (66) | among CA MSSA 50% vs. 9% had an abnormal CXR (P = 0.02) | MSSA (n)  MRSA (n) |
| McCaskill et al<sup>1</sup> | 115 children with invasive CA MSSA infection, 63% osteomyelitis, 11% septic arthritis, 9% pyomyositis, 7% pneumonia, 7% other, 2001–2006, USA | retrospective cohort (II) | • pvl presence  
• clinical course  
• duration of fever  
• duration of positive blood cultures  
• WCC, CRP, ESR | 30% (35) | febrile days 6.7 vs. 3.6 (P = 0.03)  
days in ICU 15 vs. 9 days (P = 0.02)  
peak CRP 15.3 vs. 8.9 mg/dL (P = 0.04)  
peak ESR 95 vs. 69 mm/h (P = 0.002)  
pneumonia 17% vs. 2% (P = 0.01)  
days in hospital 14 vs. 12 days (P = NS)  
initial WCC at presentation 12.6 vs. 11.2 cells x 10<sup>9</sup>/L (P = NS)  
days positive blood culture 3.4 vs. 1.6 (P = NS)  
surgical intervention 100% vs. 94% (P = NS)  
surgical intervention 84% vs. 47% (P = 0.002) | MSSA (n)  MRSA (n) |
| Abdel-Haq et al<sup>13</sup> | 98 children with MRSA infection, 44% skin/soft tissue, 35% bone and joint, 16% bacteremia, 5% not specified, 2006–2007, USA | prospective cohort (II) | • clinical course  
• surgical treatment | 83% (81) | febrile days 28.6 vs. 2.8 (P < 0.001)  
days in hospital 45 vs. 13 days (P < 0.001)  
days of IV antibiotic treatment 48 vs. 11 (P ≤ 0.001)  
days of oral antibiotic treatment 256 vs. 27 (P < 0.001)  
superficial abscess 11 vs. 1 (P < 0.001)  
extension of osteomyelitis 12 vs. 0 (P < 0.001)  
pyomyositis 5 vs. 0 (P = 0.01)  
number of surgical interventions 2.78 vs. 0.52 (P = 0.002)  
visceral abscess 11 vs. 0 (P = 0.012)  
DVT 3 vs. 0 (P = 0.08) | MSSA (n)  MRSA (n) |

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CA, community-acquired; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; CXR, chest radiograph; WCC, white cell count; CT, computed tomography; HA, hospital-acquired; NS, not significant.
molecular weight heparin and intravenous unfractionated heparin. In severe cases, thrombectomy or placement of intravascular filters have been described. In the absence of any comparative studies, it is uncertain which of these approaches provides optimal resolution of thrombus and infection, and best prevents dissemination of infection with the lowest complication rate. The optimal duration of treatment and follow-up for infection-associated DVT is also unclear. One study reported resolution of the thrombus after a average of 11 weeks, but only 30% of the children had follow-up imaging studies done.

CONCLUSION

In summary, the current evidence suggests that musculoskeletal infection in children caused by PVL-producing strains of S. aureus is associated with longer duration of fever, more elevated inflammatory markers, higher frequency of complications, longer intensive care unit admission and more frequent surgical intervention. It currently remains unclear whether this information is useful in guiding the management and choice of antibiotic treatment.

REFERENCES