Panton-Valentine Leukocidin: A Marker of Severity for *Staphylococcus aureus* Infection?

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(See the article by Gonzalez et al. on pages 583–90)

Until recently, *Staphylococcus aureus*–associated pulmonary infections have been indistinguishable with respect to the toxin-associated genes in the strains associated with each case. The recent emergence and worldwide spread of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) clones containing the genes encoding Panton-Valentine leukocidin (PVL) has led to an increase in the number of pulmonary lung infections associated with PVL-positive CA-MRSA and the recognition of more-specific clinical conditions. The diffusion of CA-MRSA within certain communities is now impressive. In Texas, for example, 76% of infections due to community-acquired *S. aureus* at Texas Children’s Hospital (Houston) are caused by MRSA [1, 2].

In this issue of *Clinical Infectious Diseases*, Gonzalez et al. [3] compared the clinical characteristics of 92 children with invasive CA-MRSA infection with those of 68 children with invasive community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) infection. The major difference between the 2 groups was the greater frequency of abnormal pulmonary imaging findings in the CA-MRSA group (67% of patients), compared with the CA-MSSA group (28% of patients) (*P* = .00008). Overall, among 47 patients with CA-MRSA infections and abnormal pulmonary imaging findings, the primary diagnoses were pneumonia (21 patients [45%]), osteomyelitis (20 [43%]), deep-seated abscess (5 [11%]), and septic arthritis (1 [2%]). Patients with CA-MRSA and pneumonia were rarely bacteremic, in contrast to patients with osteomyelitis, among whom the frequency of metastatic pulmonary disease was accordingly higher.

Cases of pneumonia associated with PVL-positive *S. aureus* strains have been described by Gillet et al. [4], and other cases have since been reported worldwide [5–11]. The clinical description of the cases reported by Gonzalez et al. [3] differs from the description reported by Gillet et al. [4]. Classic severe necrotizing pneumonia, which presents as a rapid extensive pneumonia evolving towards an acute respiratory distress syndrome with hemoptysis (or blood secretions) and leukopenia, is reported in the study by Gonzalez and colleagues for only 3 patients. Pulmonary manifestations associated with PVL-positive MRSA clones were much more diverse in the Texas patients and included classic lobar pneumonia, pneumonia with pneumatoceles, empyema, and septic emboli. No explanation can be given for these differences. The high incidence of CA-MRSA among the patients of Gonzalez and colleagues, in contrast to the low incidence of necrotizing pneumonia, suggests that specific host factors (which might be related to a specific host genotype) are associated with the development of the disease.

*S. aureus* can access the lung parenchyma by the following 2 routes: aspiration of flora from the upper respiratory tract and hematogeneous spread. Influenza virus is known to increase respiratory colonization by *S. aureus* and to impair ciliary function (and, therefore, the clearance of *S. aureus*). Influenza is still commonly complicated by *S. aureus* pulmonary infection, with methicillin resistance currently observed in the majority of *S. aureus* isolates from both children and adults in the United States [12]. In the classic scenario of PVL-associated necrotizing pneumonia, a patient develops a flu-like respiratory illness and then, after few days, deteriorates rapidly with fever and dyspnea. In the study by Gonzalez et al. [3], necrotizing pneumonia was observed at the time of initial presentation in 2 patients with viral infection due to influenza A virus (in one) and parainfluenza virus 1 (in the other). The mortality rate as-
associated with typical PVL-positive \textit{S. aureus} necrotizing pneumonia is high. Gillet et al. [4] reported 16 cases with a crude mortality rate of 75%. The fatal outcome is rapid, with a survival rate of 62.5% within 48 h after admission to the hospital [4]. The same severe outcome has been described in other patients in the literature: 2 of the 3 patients described by Bousaud et al. [13] died, as did 1 of the 4 patients described by Francis et al. [5]. Hematogenous seeding of the lungs with \textit{S. aureus} follows embolization from an intravascular nidus of infection. Septic pulmonary embolization commonly presents as a complication of right-side endocarditis, a disease that has been observed in patients with PVL-negative \textit{S. aureus} infection but not in those with PVL-positive CA-MRSA infection, a finding that was confirmed by Gonzalez and colleagues.

Among 80 patients with PVL-positive \textit{S. aureus} infection, Gonzalez et al. [3] observed 41 cases of osteomyelitis, 6 cases of septic arthritis, and 3 cases of pyomyositis. The clinical characteristics related to musculoskeletal infections caused by CA-MRSA in children are not well defined. The presence of the genes encoding PVL is associated with an increased likelihood of complications, more-frequent complications, and more-frequent development of chronic osteomyelitis in children with \textit{S. aureus} musculoskeletal infection [14]. Cases of MRSA infection associated with severe necrotizing fasciitis and/or pyomyositis has also been reported recently [15, 16].

\textit{S. aureus} infections associated with PVL-positive strains are in fact mainly primary skin and soft-tissue infections occurring in patients with no initial skin effraction. PVL toxin was discovered in 1894 by van de Velde [17], who was an assistant at the University of Louvain (Louvain-la-Neuve, Belgium) when he isolated a more “virulent” \textit{S. aureus} strain. van de Velde discovered that the virulent clone secreted an unknown substance that could lyse leukocytes. He named this substance “substance leucocide” (also known as “leukocidin”). The link between PVL and severe abscess was next described in 1932 by Panton and Valentine [18], who noted an association between leukocidin production and styes, carbuncles, and pyemic infection. In 1936, Valentine reported that “\textit{S. aureus} which have succeeded in invading human tissue were found capable of producing in vitro considerable amounts of leukocidin” [19, p. 530].

Interest in staphylococcal leukocidin subsided for several decades, until Cribier et al. [20] demonstrated again in 1992 that PVL was mainly associated with primary cutaneous infections, especially furuncles and abscesses. Cribier and colleagues detected PVL by immunoblotting in 43 \textit{S. aureus} isolates from patients with skin infection. In 1999, Lina et al. [21] used PCR to screen 172 \textit{S. aureus} isolates for PVL genes and confirmed the strong association with furunculosis and necrotizing pneumonia in children and young adults. Clinical investigation by Yamasaki et al. [22] revealed that PVL-positive \textit{S. aureus} strains are involved in the development of multiple furuncles with more intense erythema, particularly in healthy young adults.

Regardless of the localization of the infection, the presence of the PVL appears to be associated with increased severity, ranging from cutaneous infection requiring surgical drainage to severe chronic osteomyelitis and deadly necrotizing pneumonia. With the increased prevalence of CA-MRSA, which usually contain the genes encoding PVL, it is important that clinical laboratories test for detection of this toxin in routine \textit{S. aureus} isolates.

PVL-positive CA-MRSA is easily transmissible within families but also, on a larger scale, in communities with increased promiscuity. Simple skin-to-skin contact with no skin effraction and indirect contact of contaminated objects seem to be the primary routes of transmission. Use of shared bars of soap and presence of preexisting cuts of abrasions, use of a locker near a teammate with skin and soft-tissue infection, use of shared towels, presence of skin abrasions or turf burns, and cosmetic body shaving have all been shown to be associated with CA-MRSA infection in football players [23–25]. Similarly, close contact between military recruits has been reported as a risk factor [26, 27]. Outbreaks of CA-MRSA have been also identified in other individuals, including members of other types of athletic teams and prison inmates [28, 29]. CA-MRSA skin infections can be misdiagnosed as spider bites, and if proper treatment and infection-control measures are delayed, there can be serious consequences for both the patient and the medical community [30, 31]. The exact prevalence of CA-MRSA is still subject to discussion, because of the inherent bias in numerous studies associated with limiting enrollment to patients from emergency departments or to persons requiring hospitalization. Isolates collected at hospitals certainly represent the tip of the iceberg of the entire population of CA-MRSA spreading in each continent.

The ultimate goal is to set up and implement adequate prevention measures to reduce or limit the spread of these strains. In past outbreaks of skin and soft-tissue infections in a limited, close-living community of patients, classic therapeutic and hygiene measures have proven to be successful in curing infected patients and controlling the outbreak. The main question to address is how to prevent transmission of these clones in the open community.

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References

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