

## *Is there a correlation between MRSA virulence and PVL?*

There has been a lot of discussion, and pharmaceutical sales presentations, about methicillin-resistant *Staphylococcus aureus* (MRSA), the Panton-Valentine leukocidin (PVL) and the virulence of community-acquired infections. What is the latest evidence supporting or negating such a correlation?

Studies have indicated that community-acquired MRSA (CA-MRSA) strains are generally more virulent than hospital-acquired MRSA, a finding consistent with the ability of CA-MRSA to cause disease in individuals without predisposing risk factors. Although the molecular basis for the enhanced virulence is not known, there is a strong association between CA-MRSA infections and the presence of PVL.

The majority of isolates causing CA-MRSA infections contain genes encoding PVL and possess the *mecA* gene, which is associated with methicillin resistance. One clone, USA300, has achieved predominance and has spread throughout the country. This organism now accounts for >60% of *S. aureus* isolates in most areas of the United States. USA300 and related PVL-containing clones are capable of causing a variety of very serious infections, among them necrotizing fasciitis, pyomyositis, septic thrombophlebitis of the extremities, Waterhouse-Fredrickson syndrome, rapidly progressive pneumonia, and ocular infections.

Not all CA-MRSA strains carry PVL, and CA-MRSA strains can produce toxins other than PVL. In addition, levels of PVL production in vitro do not necessarily correlate with severity of infection.

It is felt by some authors that PVL may be more important as a marker of a virulent strain than as an essential virulence determinant. In a mouse model of pneumonia, removal of PVL had no effect on mortality caused by USA300. Rather,  $\alpha$ -hemolysin was found to be required for CA-MRSA virulence. Moreover, many infections caused by PVL<sup>+</sup> strains are readily treated, and PVL<sup>-</sup> strains can still cause life-threatening infections.

Strains lacking PVL were as virulent in mouse sepsis and abscess models as those containing the leukotoxin. The PVL<sup>-</sup> strains of USA300 were as lethal as wild-type strains in a sepsis model, and they caused comparable skin disease. Moreover, lysis of human neutrophils and pathogen survival after phagocytosis were similar between wild-type and mutant strains in one study.

CA-MRSA is known for its ability to cause skin and soft tissue infections, manifestations typically associated with PVL. A study assessing the ability of CA *S. aureus* strains to cause abscesses and/or dermonecrosis in a mouse skin-infection model found that the average abscess volume in mice infected with PVL<sup>-</sup> strains was slightly greater than that of mice infected with PVL<sup>+</sup> strains although the data were not significantly different. PVL<sup>-</sup> strains produced, on average, slightly smaller abscesses than PVL<sup>+</sup> strains. There were generally more mice with dermonecrotic abscesses after infection with some PVL<sup>+</sup> strains. However, this was offset by the finding that other PVL<sup>+</sup> strains, caused little or no dermonecrosis.

PVL is almost never found in hospital-acquired MRSA strains. PVL toxin is strongly associated with necrotizing pneumonia and skin and soft-tissue infections, which account for the majority of CA-MRSA infections. The ability of CA-MRSA strains to cause necrosis has been linked to the lysis of neutrophils, which are a primary target of PVL. Given that neutrophils are the main cellular defense against bacterial

infections, the destruction of PMNs by CA-MRSA is likely a key component to disease. Recent studies have provided strong support to this idea. It has been suggested that PVL is the primary cause of neutrophil destruction during human infections and thereby promotes disease such as necrotizing pneumonia.

The study of Voyich et al. (1) gives strong support that multiple factors in the overall genetic makeup of each strain, rather than any single determinant such as PVL, promotes CA-MRSA infection. These observations may explain the results of Genestier et al. (2), who studied the involvement of PVL using a laboratory strain of *S. aureus* unrelated to CA-MRSA. Their data demonstrate directly that the toxin is not the major determinant of disease caused by some CA-MRSA strains. The results of Voyich et al were not unique to mouse models of disease, because they made parallel observations using human neutrophils. It does, however, have to be recognized that these latter findings were made in vitro. It may be that PVL contributes to specific pathologic conditions such as necrotizing pneumonia although that was not part of their study.

What does this mean in the overall scheme of things? The rationale for detecting PVL is to direct clinicians to consider adding a protein (toxin) synthesis inhibitor like clindamycin or linezolid to the therapeutic regimen. This might be considered for patients requiring hospitalization because of a CA-MRSA infection or septicemia.

Finally, three quotes to sum up the present thinking about the significance of PVL in MRSA's virulence:

▶ “Although evidence supporting the involvement of PVL in CA-MRSA infections has been circumstantial, the notion that PVL is critical for disease or is even the cause of these infections is widely accepted.” (1).

▶ “Although the toxin may be a highly linked epidemiological marker for CA-MRSA strains, we conclude that PVL is not the major virulence determinant of CA-MRSA.” (1).

▶ “It has been postulated that this toxin is the principal virulence factor responsible for the epidemic spread of many CA-MRSA strains....Our data on the virulence gene content of ST8:USA300 and other...isolates further identified pvl as the single virulence determinant associated with the evolution of this new virulent strain. It is important to note, however, that pvl is not essential in the evolution of other CA-MRSA strains.” (3).

#### References

1. J. M. Voyich et al. J. Infect. Dis. 194:1761 (2006)
2. A. L. Genestier et al. J. Clin. Invest. 115:3117 (2005)
3. B. A. Diep et al. J. Infect. Dis. 193:1495 (2006)